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The ASCRS Textbook of Colon and Rectal Surgery

Third Edition

EXTRAS ONLINE

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Foreword

One given definition of the word *textbook* is "a book used as *a standard* work for the study of a particular subject." Our collective goal for the third edition of the American Society of Colon and Rectal Surgeons' *ASCRS Textbook of Colon and Rectal Surgery* was to make this volume *the standard* for the study of colon and rectal surgery, providing a valuable resource for surgeons and healthcare providers at all stages of their career caring for patients with colorectal disease. In line with previous editions, we aimed to build upon the collective experience and expertise from national and international experts in the field, providing a completely revamped, up-to-date tome covering the wide breadth of colorectal disease. In addition to providing all newly written chapters, we have reorganized the text around the "pillars" of colorectal disease: perioperative (including endoscopy), anorectal disease, benign disease (including inflammatory bowel disease), malignancy, pelvic floor disorders, and a "miscellaneous" section that covers aspects both inside and beyond the operating room that are pertinent to providers at every level. This restructuring coincides effectively with the ASCRS Online Education Portal (www.fascrs.org) and mirrors the configuration of the Society's collection of educational and CME-accredited programs including CREST and CARSEP. In addition, each chapter contains several **Key Concepts** that succinctly depict the major learning objectives for individual sections and are in line with the Core Curriculum for Colon and Rectal Surgery provided by the Association of Program Directors in Colon and Rectal Surgery and the key topics used by the American Board of Colon and Rectal Surgery.

In addition, we have expanded beyond the initial print-only edition to encompass a multimedia platform with the availability of an electronic version of the text along with online videos depicting procedures, tips and tricks, and complications—all easily accessible through desktops, tablets, and smartphones to accommodate the mobile healthcare world in which we live.

While this textbook was originally conceived as a means of providing state of the art information to residents in training and fully trained surgeons, our hope, more than anything, is that this volume continues to support the mission of the American Society of Colon and Rectal Surgeons as the world's most established authority on colon and rectal disease. We are honored to have been a part of this project and wish to thank the leaders of the ASCRS for their continued support of the textbook. We especially would like to recognize the editors of the first and second editions for having the vision and purpose to produce such high-quality, evidence-based texts that have made the *ASCRS Textbook of Colon and Rectal Surgery* the success and reference it remains today. Lastly, we would like to thank our Developmental Editor Elektra McDermott for her extraordinary efforts and thoroughness in overseeing and ensuring its timely completion, and each chapter author and coauthor(s) for their devotion to this task and to the mission of the ASCRS. Since inception, it has been our privilege and pleasure to work with this tremendous gathering of authors and editors, as their unique contributions have come together to make this textbook a reality.

Cleveland, OH — Scott R. Steele, MD
Cleveland, OH — Tracy Hull, MD
Burlington, MA — Thomas Read, MD
Chicago, IL — Theodore Saclarides, MD
Galveston, TX — Anthony Senagore, MD
New Orleans, LA — Charles Whitlow, MD

Preface

The field of Colon and Rectal Surgery has a long and respected tradition of patient service, knowledge expansion, and education. The American Society of Colon and Rectal Surgeons (ASCRS) is the premier professional organization of this specialty. The leaders of our Society (ASCRS) recognized that there were several textbooks in the field of Colorectal Surgery, but none of which could be deemed as truly representative of the collective objective views of the ASCRS. At the inaugural meeting of the senior and associate editors, prior to the 2007 publication of the *ASCRS Textbook of Colon and Rectal Surgery* 1st edition, the group made several fundamental decisions. One of those decisions was to have chapters extensively referenced, authoritatively written, appropriately illustrated, and as unbiased as possible. This very important latter point was strictly enforced by adherence by the chapter authors to ASCRS materials including the evidence-based ASCRS clinical practice guidelines, core subjects, presentations at our annual meeting, questions in the colon and rectal self-assessment program (CARSEP), and material otherwise presented through official society vehicles. In addition, first edition chapters were, in general, written by a "junior" and a "senior" coauthor. A second decision was a rotation schedule for the editors: two to three of the editors would rotate off after each edition. This would provide wider participation and ensure that the text would represent the specialty as a whole and not a select group of individuals.

The overwhelming success of the first edition led to the publication of a second edition in 2011. The second edition expanded upon the first edition, added new authors, supplemented a significant number of color plates, and increased the text itself from 810 to 946 pages. The vision provided by the leaders of our Society was certainly correct, as attested to by the tremendous interest in both editions of the ASCRS textbooks. We are proud that the standardized reference for evidence-based material in Colorectal Surgery is the work product of our Society members, owned by our Society, and has become a source of financial support to our Society. In addition, a corresponding manual (the *ASCRS Manual of Colon and Rectal Surgery*), designed more towards residents in training and physicians desiring a focused reference, has been released for each edition and has also been exceptionally popular.

The continued rapid expansion of knowledge, in part attested by the increased number of pages in each subsequent edition, as well as the new technologies and new techniques has ensured the longevity of our work and has necessitated this third edition. We congratulate the current editors Drs. Scott Steele, Tracy Hull, Thomas Read, Anthony Senagore, Theodore Sacclarides, and Charles Whitlow on their tremendous accomplishment. We also thank all of the chapter authors and coauthors whose dedication, devotion, energy, and expertise have enabled the editors to produce this volume. The third edition has been reorganized and completely rewritten to reflect advances in our specialty and the evolution of our practice. In addition, the current grouping of topics serves as a framework for the ongoing educational efforts of the Society and certification process by the American Board of Colon and Rectal Surgery.

New developments in the management of colorectal diseases and our colleagues' continued search for answers have produced the need for this and future editions of the *ASCRS Textbook*

of Colon and Rectal Surgery. We are gratified that this significant educational endeavor continues to flourish. We commend this work to every practitioner of colorectal surgery throughout the world and eagerly await reports of its success.

New Orleans, LA — Dave Beck, MD
Weston, FL — Steven Wexner, MD

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Part I
Perioperative/Endoscopy

1
Anatomy and Embryology of the Colon, Rectum, and Anus

Joseph C. Carmichael and Steven Mills

Key Concepts

- The dentate line represents a true division between embryonic endoderm and ectoderm.
- The location of the anterior peritoneal reflection is highly variable and can be significantly altered by disease such as rectal prolapse.
- The right and left ischioanal space communicate posteriorly through the deep postanal space between the levator ani muscle and anococcygeal ligament.
- The junction between the midgut (superior mesenteric artery) and the hindgut (inferior mesenteric artery) leads to a potential watershed area in the area of the splenic flexure.
- There is a normal, three-stage process by which the intestinal tract rotates during development beginning with herniation of the midgut followed by return of the midgut to the abdominal cavity and ending with its fixation.

Anatomy of the Anal Canal and Pelvic Floor

Textbooks of anatomy would define the "anatomic" anal canal as beginning at the dentate line and extending to the anal verge. This definition is one defined truly by the embryology and mucosal histology. However, the "surgical" anal canal, as first defined by Milligan and Morgan, [1] extends from the anorectal ring to the anal verge. The surgical definition of the anal canal takes in to account the surrounding musculature that is critical to consider during the conduct of operations from low anterior resection to anal fistulotomy. The surgical anal canal is formed by the internal anal sphincter, external anal sphincter, and puborectalis (Figure 1-1) and is easily identified on digital examination and ultrasound imaging. On average, the surgical anal canal is longer in males than in females. Intraoperative measurements of the posterior anal canal have estimated the surgical anal canal to be 4.4 cm in men compared with 4.0 cm in women [2]. In addition, the anal canal was shown to be a unique muscular unit in that its length did not change with age.

The anatomy of the anal canal has also been characterized using magnetic resonance imaging. MR imaging does not show a difference in the length of the posterior anal canal in men and women, but does show that the anterior and posterior external anal sphincter length (not including the puborectalis) is significantly shorter in women [3].

The anal canal forms proximally where the rectum passes through the pelvic hiatus and joins with the puborectalis muscle. Starting at this location, the muscular anal canal can be thought of as a "tube within a tube." The inner tube is the visceral smooth muscle of the internal anal sphincter and longitudinal layer that is innervated by the autonomic nervous system. The outer muscular tube consists of somatic muscles including the components of the puborectalis and external anal sphincter [4]. It is the outer muscular tube that provides conscious control over continence and is strengthened during Kegal exercises. The external anal sphincter extends distal to the internal anal sphincter and the anal canal terminates at the anal verge where the superficial and subcutaneous portions of the external anal sphincter join the dermis.

Anal Canal Epithelium

The proximal anal canal has a pink appearance and is lined by the columnar epithelium of the rectal mucosa. Six to twelve millimeters proximal to the dentate line, the anal transition zone (ATZ) begins. The ATZ appears purple in color and represents an area of gradual transition of columnar epithelium to squamous epithelium. The columns of Morgagni are noted in this area were redundant columns of tissue are noted with anal crypts at their base. This forms the rippled dentate line (or pectinate line) which may be most easily identified by locating the anal crypts at the base of the Columns of Morgagni. Anal crypts are connected to

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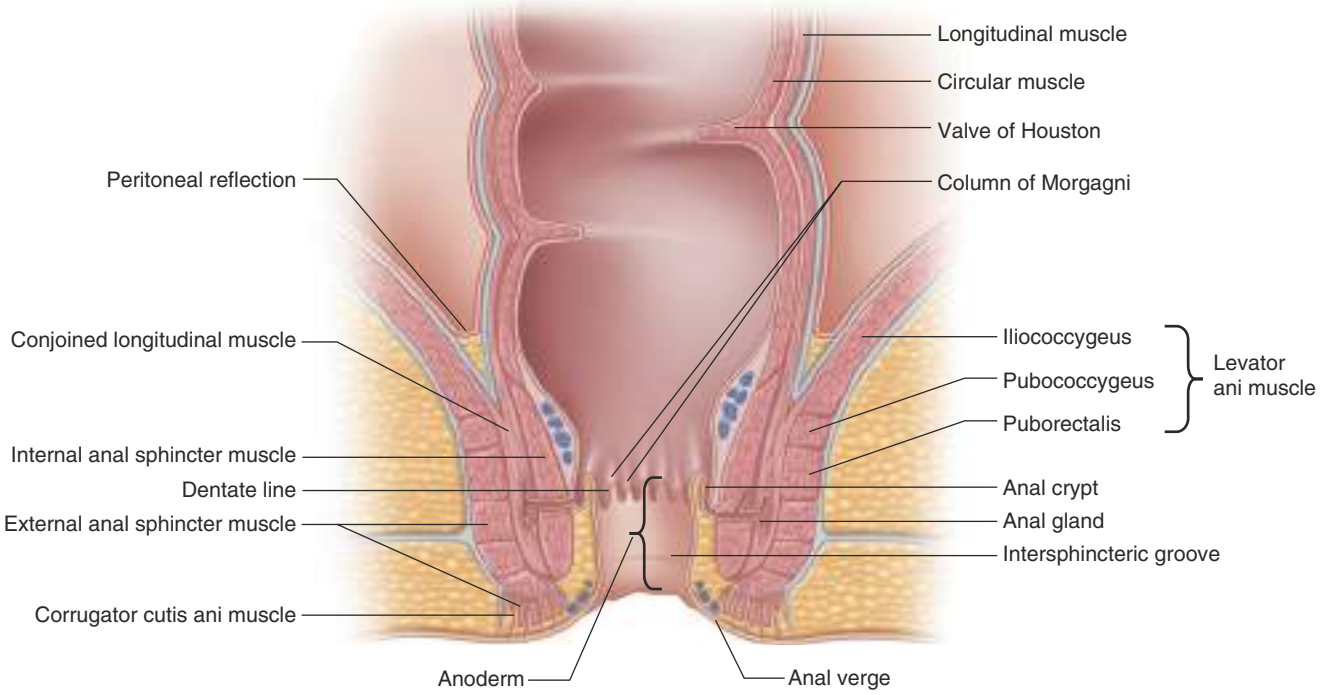

FIGURE 1-1. Anal canal.

underlying anal glands which are the presumed source of sepsis in the majority of anorectal abscesses and fistula. On average, there are six anal glands surrounding the anal canal (range 3–12) [4–6] and they tend to be more concentrated in the posterior quadrants. More than one gland may open into the same crypt and some crypts may not be connected to anal glands. The anal gland ducts proceed inferior and lateral from the anal canal and enter the submucosa where two-thirds enter the internal anal sphincter and half terminate in the intersphincteric plane [5]. It is theorized that obstruction of these ducts leads to anal fistula and abscess [4]. Knowledge of the anatomy also explains why the internal opening of a "cryptoglandular" anal fistula should typically be at the dentate line.

Distal to the dentate line, the anoderm begins and extends for approximately 1.5 cm. Anoderm has squamous histology and is devoid of hair, sebaceous glands, and sweat glands. At the anal verge, the anal canal lining becomes, thickened, pigmented and contains hair follicles—this represents normal skin.

The dentate line represents a true division between embryonic endoderm and ectoderm. Proximal to the dentate line, the innervation is via the sympathetic and parasympathetic systems, with venous, arterial, and lymphatic drainage associated with the hypogastric vessels. Distal to the dentate line, the innervation is via somatic nerves with blood supply and drainage from the inferior hemorrhoidal system.

Internal Anal Sphincter

The internal anal sphincter (IAS) is the downward continuation of the circular smooth muscle of the rectum and terminates with a rounded edge approximately 1 cm proximal to the distal aspect of the external anal sphincter. 3D imaging studies of this muscle demonstrate the overall volume does not vary according to gender, but the distribution is different with women tending to have a thicker medial/distal internal anal sphincter [7]. Overall, the IAS was found to be approximately 2 mm in thickness and 35 mm in length. The authors note that on any study, it is difficult to identify the proximal portion of the IAS as it is a continuation of the wall of the lower rectum.

Conjoined Longitudinal Muscle

The anatomy and function of the perianal connective tissue is often overlooked, but plays a significant role in normal anorectal function. Measuring approximately 0.5–2.0 mm in thickness, the conjoined longitudinal muscle (or conjoined longitudinal coat) lies in between the internal and external anal sphincters. It begins at the anorectal ring as an extension of the longitudinal rectal muscle fibers and descends caudally joined by fibers of the puborectalis muscle [8]. At its most caudal aspect, some of the conjoined longitudinal muscle fibers (referred to as *corrugator cutis ani muscle*)

traverse the distal external anal sphincter and insert into the perianal skin and some enter the fat of the ischiorectal fossa. Fibers of the conjoined longitudinal muscle also pass obliquely and caudally through the internal anal sphincter to interlace in a network within the subepithelial space. These subepithelial smooth muscle fibers were originally described by Treitz in 1853 [9] and have been referred to as Treitz's muscle. They have also been referred to *corrugator cutis ani*, *musculus submucosae ani*, *mucosal suspensory ligament*, and *musculus canalis ani* [10] It has been hypothesized by Thomson that disruption of Treitz's muscles results in anal cushion prolapse, vascular outflow obstruction, and hemorrhoidal bleeding and thrombosis [11]. Haas and Fox have hypothesized that the conjoined longitudinal muscle, along with the network of connective tissue that it supports, plays a role in minimizing anal incontinence after sphincterotomy.

External Anal Sphincter

The external anal sphincter (EAS) is composed of striated muscle that forms an elliptical tube around the internal anal sphincter and conjoined longitudinal muscle. As it extends beyond the distal most aspect of the internal anal sphincter the intersphincteric groove is formed. At its distal most aspect, *corrugator cutis ani muscle* fibers from the conjoined longitudinal muscle traverse the external anal sphincter and insert into the perianal skin. Milligan and Morgan described the external anal sphincter as having three distinct divisions from proximal to distal that were termed: sphincter ani externus profundus, superficialis, and subcutaneus [1]. With time, this theory of three distinct divisions was proven invalid by Goligher who demonstrated that the external anal sphincter was truly a continuous sheet of skeletal muscle extending up to the puborectalis and levator ani muscles [12]. While the external anal sphincter does not have three distinct anatomic layers, it is not uncommon to see the proximal portion of the EAS referred to as deep EAS, the mid-portion referred to as the superficial EAS and the most distal aspect as the subcutaneous EAS. The mid EAS has posterior attachment to the coccyx via the anococcygeal ligament and the proximal EAS becomes continuous with the puborectalis muscle. Anteriorly, the proximal EAS forms a portion of the perineal body with the transverse perineal muscle. There are clear differences in the morphology of the anterior external anal sphincter that have been demonstrated on both MRI and three dimensional endoanal ultrasound studies in normal male and female volunteers [13, 14]. The normal female external anal sphincter has a variable natural defect occurring along its proximal anterior length below the level of the puborectalis sling that was demonstrated in 75% of nulliparous volunteers. This defect correlated with findings on anal manometry and the authors noted that it can make interpretation of an isolated endoanal ultrasound difficult resulting in over-reporting of obstetric sphincter defects [13]. This natural defect of the anterior anal sphincter provides some justification as to why anterior anal sphincterotomy is not routinely recommended in women.

The external anal sphincter is innervated on each side by the inferior rectal branch of the pudendal nerve (S2 and S3) and by the perineal branch of S4. There is substantial overlap in the pudendal innervation of the external anal sphincter muscle on the two sides which enables re-innervation to be partially accomplished from the contralateral side following nerve injury [15].

Perineal Body

The perineal body represents the intersection of the external anal sphincter, superficial transverse perinei, deep transverse perinei, and bulbospongiosus (also referred to as bulbocavernosus) muscles (Figure 1-2). Recent research, based on advanced magnetic resonance and ultrasound imaging, has suggested that the transverse perinei (TP) and bulbospongiosus (BS) muscles contribute significantly to anal continence [16]. It has been proposed that the EAS, TP and BS muscles be collectively referred to as the "EAS complex muscles." In this theory, the EAS complex morphology is "purse string" shaped rather than the typical "donut" shape previously considered. When these muscles are considered as a functional unit, it lends further support to the idea that it is critical to attempt to repair the perineal body during overlapping sphincter reconstructions.

Pelvic Floor Muscles

In addition to the anal sphincter and perineal body, the levator ani (LA) muscles contribute to pelvic organ support. For example, injury to the LA is seen in 55% of women with pelvic organ prolapse, but in only 16% without prolapse [17]. The LA has three subdivisions including the pubococcygeus (aka pubovisceral), puborectalis, and iliococcygeus. Some authors had previously suggested that the puborectalis was part of the deep portion of the EAS [18]; however, a significant amount of evidence has been presented to the contrary. In vivo MRI measurements in women have shown distinct, visible muscle fascicle directions for each of the three LA component muscles [19]. Embryology studies have also demonstrated that the puborectalis muscle is a portion of the LA muscle and shares a common primordium with the iliococcygeus and pubococcygeus muscles [20].

Innervation of the levator ani muscles has been described in detailed cadaveric studies [21]. The contemporary cadaveric studies suggest that the LA muscles are innervated by the pudendal nerve branches: perineal nerve and inferior rectal nerve as well as direct sacral nerves S3 and/or S4 (i.e., levator ani nerve) [22]. The pubococcygeus muscle and

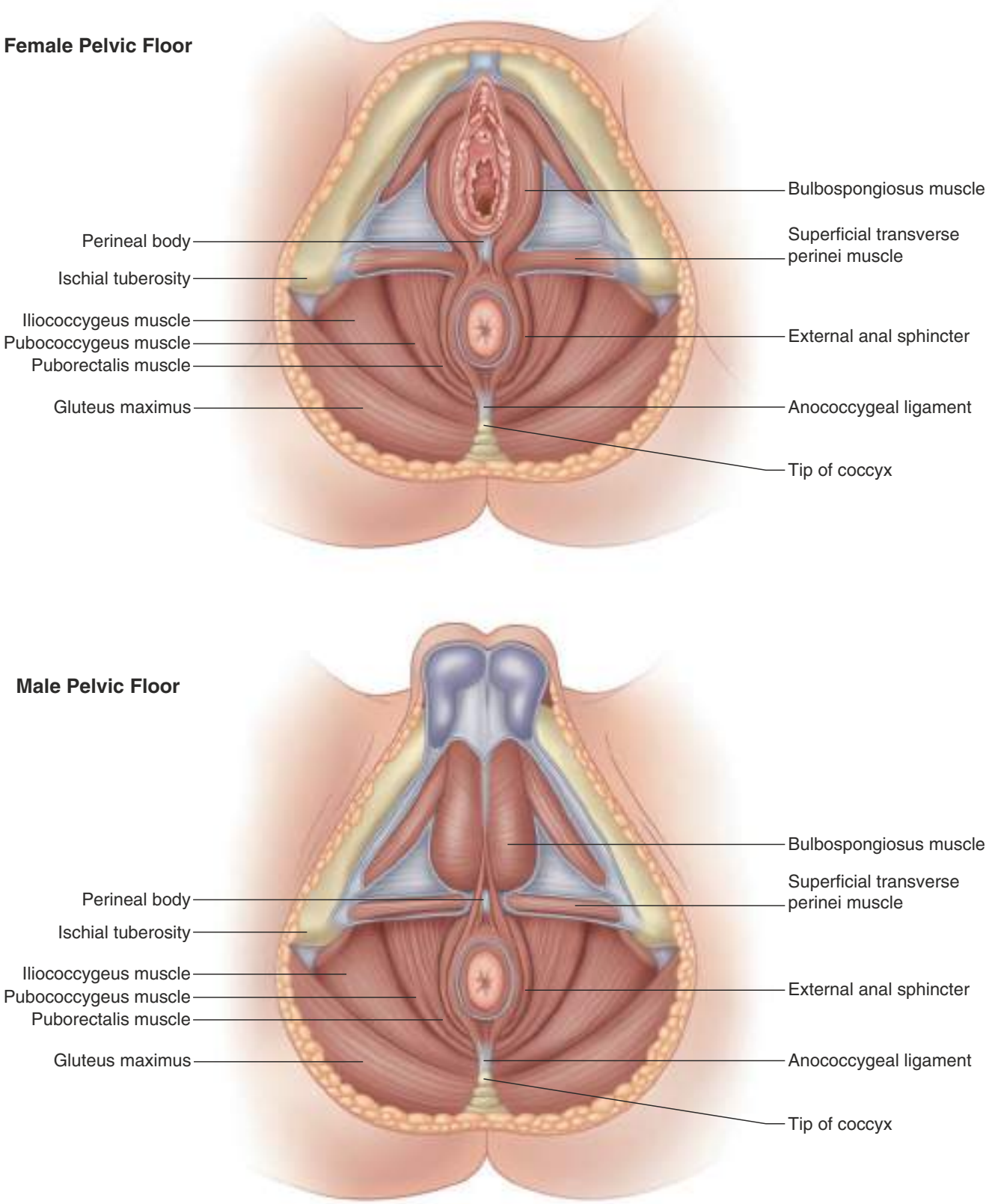

FIGURE 1-2. Pelvic floor muscles.

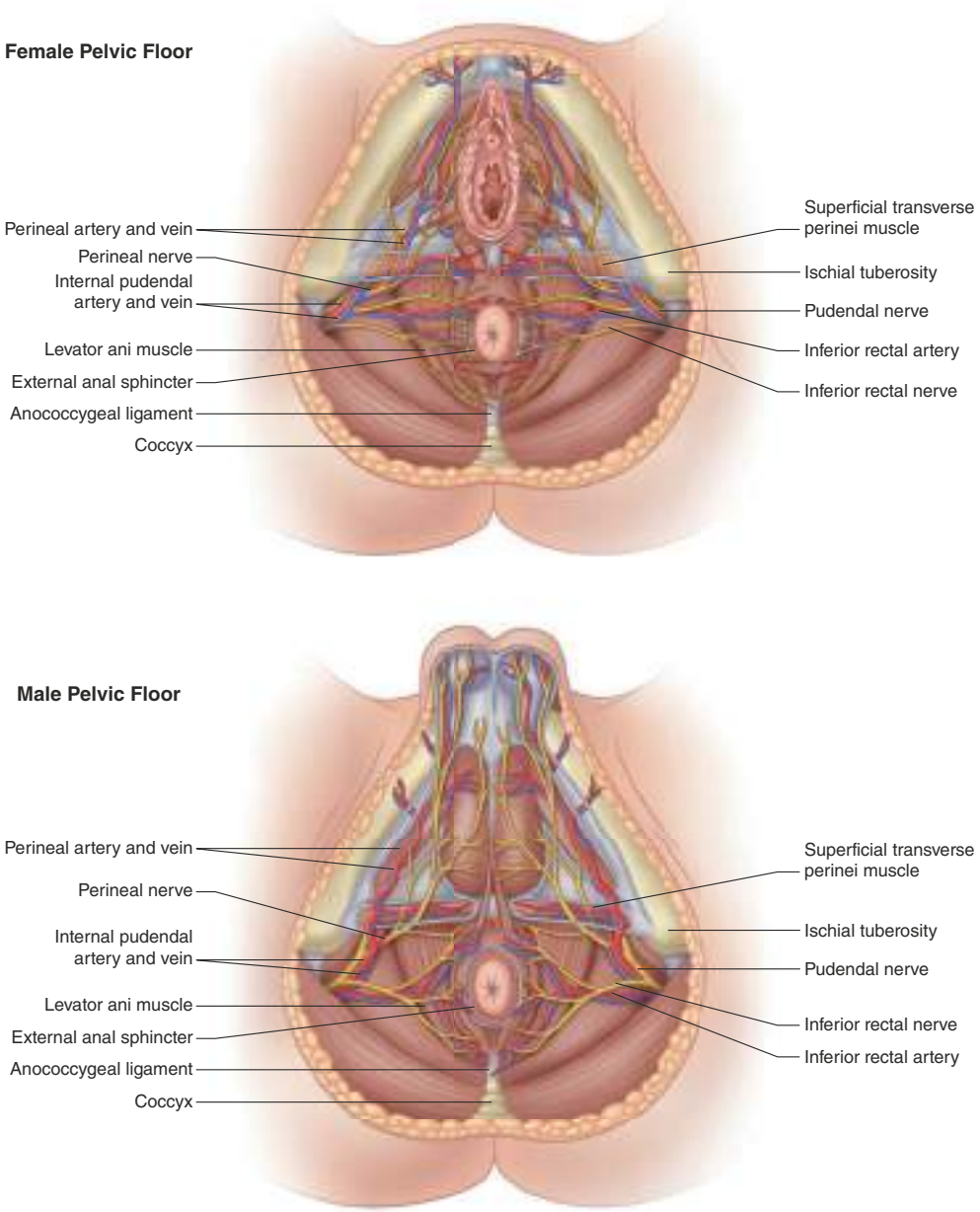

FIGURE 1-3. Pelvic floor nerves and blood supply.

puborectalis muscle are primarily innervated by the pudendal nerve branches while the iliococcygeus muscle is primarily innervated by the direct sacral nerves S3 and/or S4 (Figure 1-3).

Puborectalis Muscle

The puborectalis muscle (PRM) fibers arise from the lower part of the symphysis pubis and from the superior fascia of the urogenital diaphragm and run alongside the anorectal junction. Posterior to the rectum, the fibers join forming a sling. The "anorectal ring" is composed of the upper borders of the internal anal sphincter and puborectalis muscle [1]. Contraction of the PRM sling causes a horizontal force [19] that closes the pelvic diaphragm and decreases the anorectal angle during squeeze. This is widely considered the most important contributing factor to gross fecal continence.

Iliococcygeus Muscle

Iliococcygeus muscle (ICM) fibers arise from the ischial spines and posterior obturator fascia, pass inferior/posterior and medially, and insert into the distal sacrum, coccyx, and anococcygeal raphe. The ICM, along with the pubococcygeus muscle, contributes to "lifting" of the pelvic floor [19].

Pubococcygeus Muscle

The pubococcygeus (PCM) muscle lies medial to the PRM. PCM fibers arise from the anterior half of the obturator fascia and the high posterior pubis. The PCM fibers are directed posterior/inferior and medially, where they intersect with fibers from the opposite side and form the anococcygeal raphe (or anococcygeal ligament). PCM muscle fibers insert in the distal sacrum and tip of the coccyx. Portions of the PCM contribute to the conjoined longitudinal muscle. The PCM forms the "levator hiatus" as it ellipses the lower rectum, urethra, and either the vagina in women or the dorsal vein of the penis in men. The levator hiatus is connected to the intrahiatal organs by a fascial condensation called the "hiatal ligament" (Figure 1-4). The hiatal ligament arises circumferentially around the hiatal margin as a continuation of the fascia on the pelvic surface of the levator muscle [23]. Enlargement of the levator hiatus has been implicated as a cause of female pelvic organ prolapse [24]. The PCM is the portion of the levator ani that is typically injured during traumatic vaginal delivery [25].

Anatomy of the Rectum

The rectum is arbitrarily considered to have three distinct parts: the upper, middle, and lower rectum. Although not anatomically distinct, the upper, mid, and lower rectal divisions are important when considering surgical treatment of rectal cancer. From the anal verge, the lower rectum is 0–7 cm; middle rectum, 7–12 cm; and upper rectum 12–15 cm [26]. However, the rectum is actually variable in length and may extend beyond 15 cm from the anal verge. The upper rectum can be distinguished from the sigmoid colon by the absence of taenia coli and epiploic appendages.

The majority of the rectum lies outside of the peritoneal cavity, although anteriorly and laterally the upper rectum is covered by a layer of visceral peritoneum down to the peritoneal reflection. The location of the anterior peritoneal reflection is highly variable and can be significantly altered by disease such as rectal prolapse. One study sought to identify the location of the anterior peritoneal reflection in 50 patients

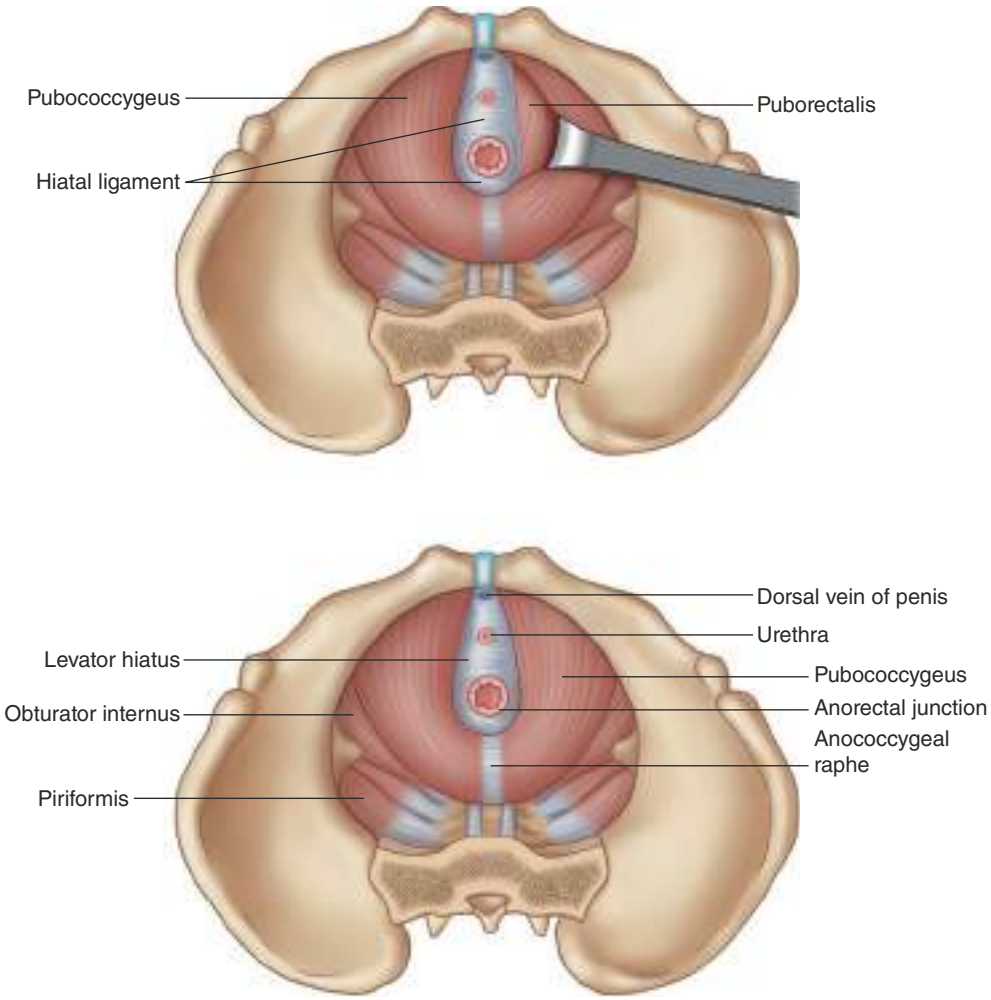

FIGURE 1-4. Pelvic floor anatomy, abdominal view.

who were undergoing laparotomy [27]. It was found that the anterior peritoneal reflection was located on average 9 cm from the anal verge in females and 9.7 cm from the anal verge in males—there was no statistically significant difference based on gender.

Mesorectum

The origin of the word "mesorectum" is difficult to identify and may be attributed to Maunsell in 1892 [28], but was certainly later popularized by Heald [29]. Unfortunately, the term mesorectum is a misnomer that is not generally acknowledged in classic texts of anatomy such as the *Nomina Anatomica* [30]. In anatomic terms, the prefix "meso" refers to two layers of peritoneum that suspend an organ and the suffix applied indicates the target organ (e.g., mesocolon). The term "meso" cannot be assigned to the rectum, as it implies a mobile, suspended rectum, which may only be the case in patients with rectal prolapse.

The mesorectum is a term employed by surgeons to describe the fascial envelope of the rectum that is excised during surgical treatment of rectal cancer. Indeed, failure to completely excise this envelope intact has been associated with an increased incidence of local recurrence of rectal cancer [31]. The mesorectum is contained within the fascia propria. The fascia propria is an upward projection of the parietal endopelvic fascia that lines the walls and floor of the pelvis. The fascia propria encloses the perirectal fat, lymphatics, blood vessels, and nerves and is not considered a barrier strong enough to prevent the spread of infection or malignancy [32].

Presacral Fascia

The presacral fascia is a thickened portion of the parietal endopelvic fascia overlying the sacrum that covers the presacral veins and hypogastric nerves (Figure 1-5). It extends laterally to cover the piriformis and upper coccyx. As the presacral fascia extends laterally, it becomes continuous with the fascia propria and contributes to the lateral ligaments of the rectum. Caudally, this fascia extends to the anorectal junction covering the anococcygeal ligament. During total mesorectal excision, the fascia propria is elevated sharply off the presacral fascia. Leaving the presacral fascia intact eliminates the possibility of causing presacral bleeding.

Retrosacral Fascia

The retrosacral fascia originates at the third and fourth portion [33] of the sacrum and extends anteriorly to the posterior layer of the fascia propria 3–5 cm proximal to the anorectal junction [34]. This tough fascia layer is surgically relevant as it must be sharply incised during total mesorectal excision [32]. The space posterior to the retrosacral fascia is referred to as the supralevator or retrorectal space.

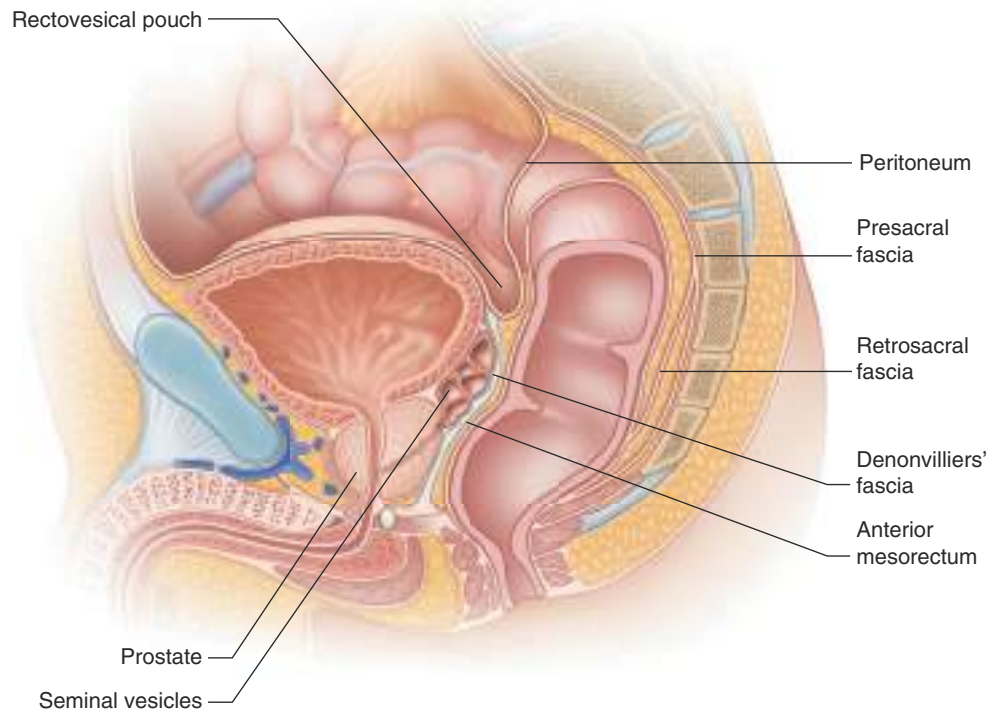

FIGURE 1-5. Fascial relationships of the rectum.

Waldeyer's Fascia

There is significant confusion about what Waldeyer's fascia represents as the eponym has been used to describe the presacral fascia, the retrosacral fascia or all fascia posterior to the rectum. In Waldeyer's original description of pelvic fascia, there was no particular emphasis on the presacral component [32, 34]. While the debate continues regarding "Waldeyer's fascia," it is important to simply understand that the phrase can have the potential to mean presacral fascia, rectosacral, or retrorectal fascia [35].

Denonvilliers' Fascia

Denonvilliers' fascia arises from the fusion of the two walls of the embryological peritoneal cul-de-sac and extends from the deepest point of the rectovesical pouch to the pelvic floor [36]. Originally described by Denonvilliers in 1836 as a "prostatoperitoneal" membranous layer between the rectum and seminal vesicles, Denonvilliers' fascia is also present in females as part of the rectovaginal septum and is sometimes referred to as rectovaginal fascia. It is found immediately beneath the vaginal epithelium and is clearly what most would consider as part of the vaginal wall. It merges superiorly with the cardinal/uterosacral complex in females or the rectovesical pouch in males. It merges laterally with the endopelvic fascia overlying the levator muscle and distally with the perineal body. It contains collagen, some strands of smooth muscle and heavy elastin fibers. Rectoceles represent a defect in this layer that allows the rectum to bulge anteriorly [37].

Microscopically, the Denonvilliers' fascia has two layers; however, it is not possible to discern two layers during pelvic dissection [36]. In the anterior rectal plane, the mesorectum is contained by the fascia propria which lies dorsal to Denonvilliers' fascia. The cavernous nerves run in neurovascular bundles at the anterolateral border of Denonvilliers' fascia.

Lateral Ligaments

While frequently referred to by surgeons, there are two controversial points regarding the lateral ligaments of the rectum. First, do the lateral ligaments exist? Second, what do they contain? Miles refers to division of the lateral ligaments of the rectum in his seminal description of abdominoperineal resection in 1908. Specifically, he notes "In these structures the middle hemorrhoidal arteries are found but seldom require a ligature" [38]. It is interesting to note that at least one modern cadaveric dissection study identified the presence of a middle rectal artery in only 22% of specimens [33] which could be a contributing factor as to why Miles saw no significant bleeding in this area.

Total mesorectal excision, as popularized and described by Heald involves sharp dissection along the fascia propria circumferentially to the pelvic floor. While acknowledging that the middle rectal vessels are "divided as far from the carcinoma as possible," Heald does not mention "lateral ligaments" of the rectum at all [39].

In an extensive review of the anatomy of the lateral ligament, Church notes that it is a common misconception that the lateral ligaments contain the middle rectal artery at all. It appears that the lateral ligaments comprise "primarily nerves and connective tissue" and their division without bleeding attests to the absence of a "significant accessory rectal artery in this location in the majority of patients" [32].

In a separate cadaveric study, the lateral ligaments of the rectum were identified as trapezoid structures originating from mesorectum and anchored to the endopelvic fascia at the level of the midrectum. It was recommended that, as lateral extensions of the mesorectum, the ligaments must be cut and included in the total mesorectal excision (TME) specimen. It was further noted that the lateral ligaments did not contain middle rectal arteries or nerve structures of importance. The urogenital bundle runs just above the lateral ligament at its point of insertion on the endopelvic fascia, the middle rectal artery (if present) runs posterior to the lateral ligament and the nervi recti fibers (which originate from the inferior hypogastric plexus) course transversely under the lateral ligament to the rectal wall [40]. Other modern cadaveric investigations note the rarity of middle rectal arteries and the absence of clinically relevant neurovascular structures in the lateral ligaments [41].

Valves of Houston

The rectum has been classically described to have three distinct, semicircular, inner folds called valves of Houston (Figure 1-1) with the superior and inferior valves located on the left side of the rectum and the more prominent middle rectal valve on the right; however, this is not uniformly the case [42]. Only 45.5% of patients will have the classic three valve rectal anatomy; 32.5% will have only two valves; and, 10.25% may have four valves.

Anorectal Spaces

It is important to acknowledge and understand the anorectal spaces created by the various myofascial relationships in the pelvis as these spaces help us understand how anorectal sepsis can spread throughout the pelvis.

Perianal Space

The perianal space contains external hemorrhoid cushions, the subcutaneous external anal sphincter and the distal internal anal sphincter. The perianal space is in communication with the intersphincteric space (Figure 1-6). The perianal space has its cephalad boundary at the dentate line and laterally to the subcutaneous fat of the buttocks or is contained by fibers

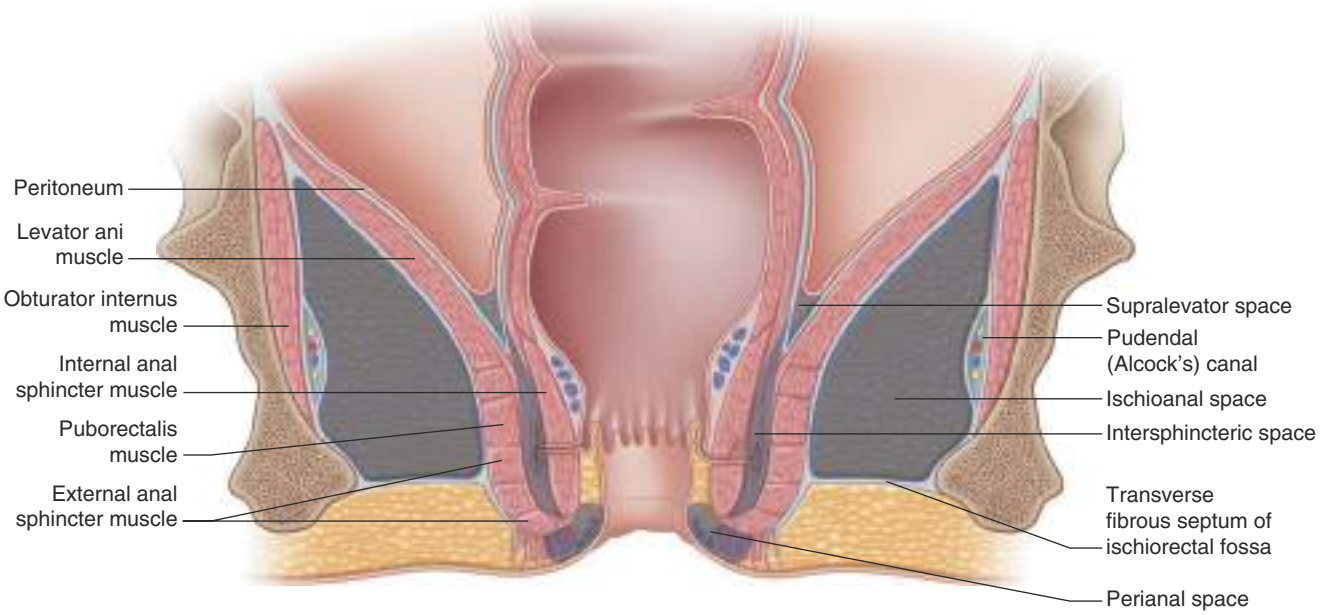

FIGURE 1-6. Perianal and perirectal spaces, coronal view.

extending from the conjoined longitudinal muscle often referred to as *corrugator cutis ani* muscle fibers. Otherwise, the perianal space is contained by anoderm.

Intersphincteric Space

The intersphincteric space is the potential space that lies between the internal and external anal sphincter and is continuous with the perianal space. It is of clinical importance as cryptoglandular infections tend to begin in this area and expand elsewhere to create anal fistula [4].

Submucous Space

This space lies between the medial boarder of the internal anal sphincter and the anal mucosa proximal to the dentate line. It is continuous with the submucosa of the rectum. This area contains internal hemorrhoid vascular cushions.

Ischioanal/Ischiorectal Space

The ischioanal (also referred to as ischiorectal) space is the largest anorectal space. It has been described as a pyramid shape with its apex at the levator muscle insertion into the obturator fascia. The medial boarder is thus the levator ani muscle and external anal sphincter. The obturator internus muscle and obturator fascia make up the lateral boarder of the ischioanal space. The posterior boundary is formed by the lower border of the gluteus maximus muscle and the sacrotuberous ligament. The space is has an anterior boundary formed by the superficial and deep transverse perineal muscles. The caudal boundary is skin of the perineum. The ischioanal fossa contains adipose tissue, pudendal nerve branches and superficial branches of the internal pudendal vessels. The right and left ischioanal space communicate posteriorly through the deep postanal space between the levator ani muscle and anococcygeal ligament (Figure 1-7) [43]. When the ischioanal and perianal spaces are regarded as a single space, it is referred to as the ischioanal fossa [35].

Supralevator Space

The upper boundary of the supralevator space is the peritoneum, the lateral boundary is the pelvic wall, the medial boundary is the rectum and the inferior boarder is the levator ani muscle (Figure 1-8).

Superficial and Deep Postanal Spaces

These spaces are located posterior to the anus and inferior to the levator muscle. The superficial postanal space is more caudal and is located between the anococcygeal ligament and the skin. The superficial postanal space allows communication of perianal space sepsis.

The deep postanal space (retrosphincteric space of Courtney) [44] is located between the levator ani muscle and the anococcygeal raphe. This space allows ischioanal sepsis to track from one side to the other resulting in the so called "horseshoe" abscess.

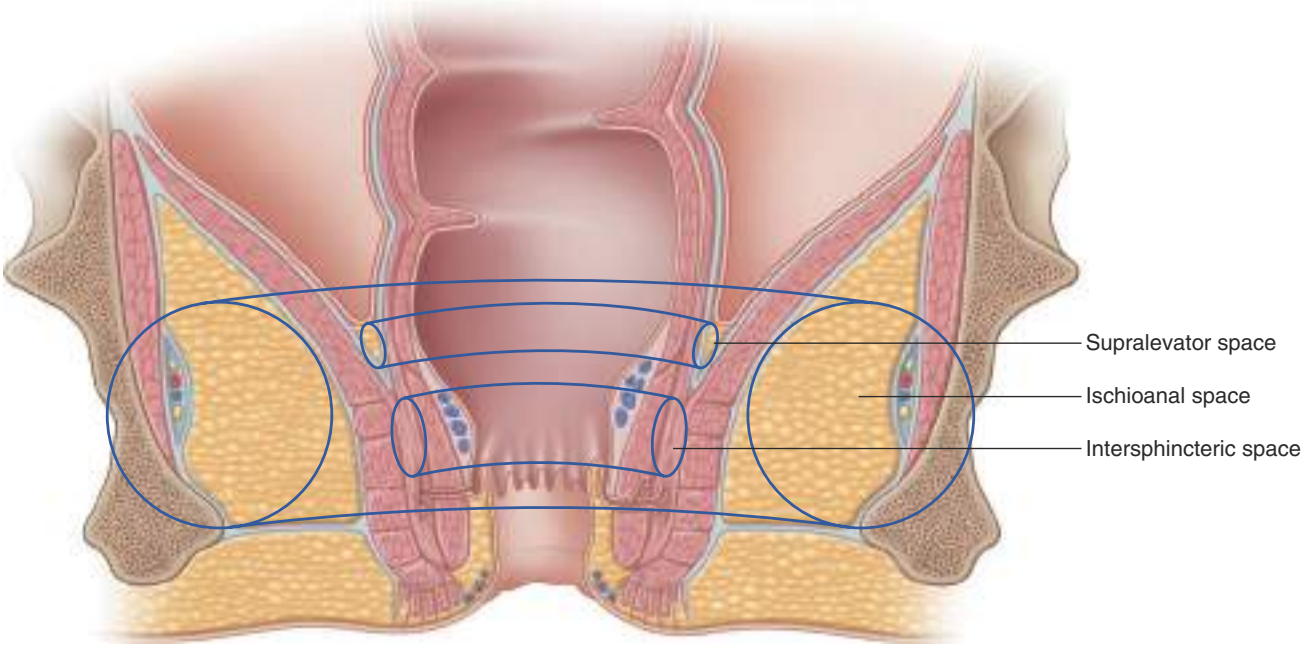

FIGURE 1-7. Communication of the anorectal spaces.

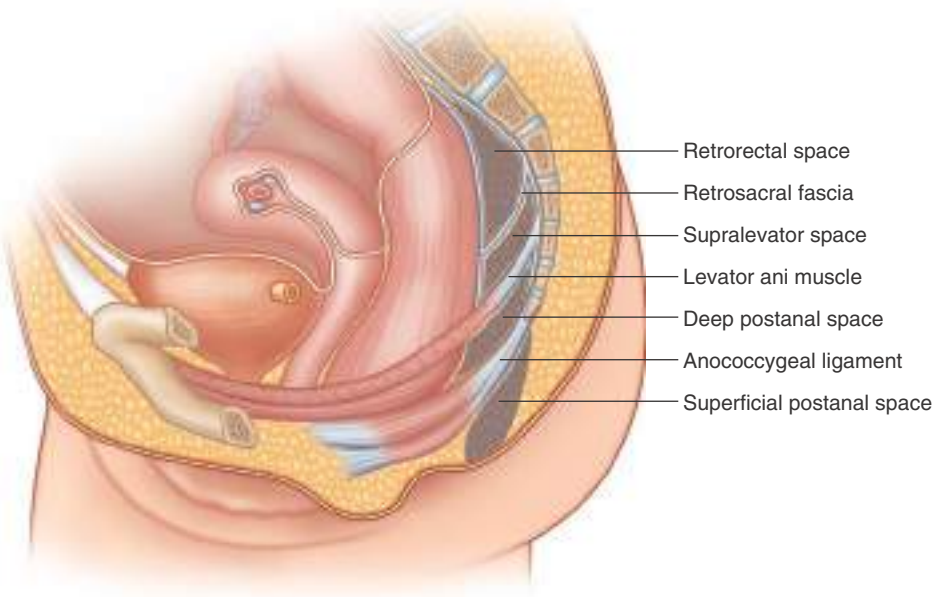

FIGURE 1-8. Perianal and perirectal spaces, lateral view.

Retrorectal Space

The retrorectal space is found between the presacral fascia and fascia propria. It contains no major blood vessels or nerves. It is limited laterally by the lateral ligaments of the piriformis fascia and inferiorly by the retrosacral fascia. The fascia propria and presacral fascia come together at the apex of this space [32].

Rectal Blood Supply

The rectum is supplied by the superior, middle, and inferior rectal (hemorrhoidal) arteries (Figure 1-9). Both the middle and inferior hemorrhoidal vessels are paired arteries and the superior rectal artery is not.

Superior Rectal Artery

The superior rectal artery (SRA) is the continuation of the inferior mesenteric artery and is so named after the inferior mesenteric artery crosses the left iliac vessels. The SRA gives off a rectosigmoid branch, an upper rectal branch, and then bifurcates into right and left terminal branches in 80% [45] of cases as it descends caudally in the mesorectum. On average, eight terminal branches of the SRA have been identified in the distal rectal wall [46].

Middle Rectal Artery

The middle rectal artery (MRA) has been variably noted in many studies. It may be found on one or both sides of the rectum and has been noted to be present 12–28% of the time [41, 47]. At least one study reported the presence of the middle rectal artery in at least 91% of cadaveric specimens [40]. The MRA originates from the anterior division of the internal iliac or pudendal arteries. Please see the "Lateral Ligament" discussion above for more review on the anatomic course of the middle rectal artery.

Inferior Rectal Artery

The inferior rectal arteries (IRA) are paired vessels that originate as branches of the internal pudendal artery which receives its blood supply from the internal iliac artery. The artery originates in the pudendal canal and is entirely extrapelvic (caudal to the levator ani) in its distribution. The IRA

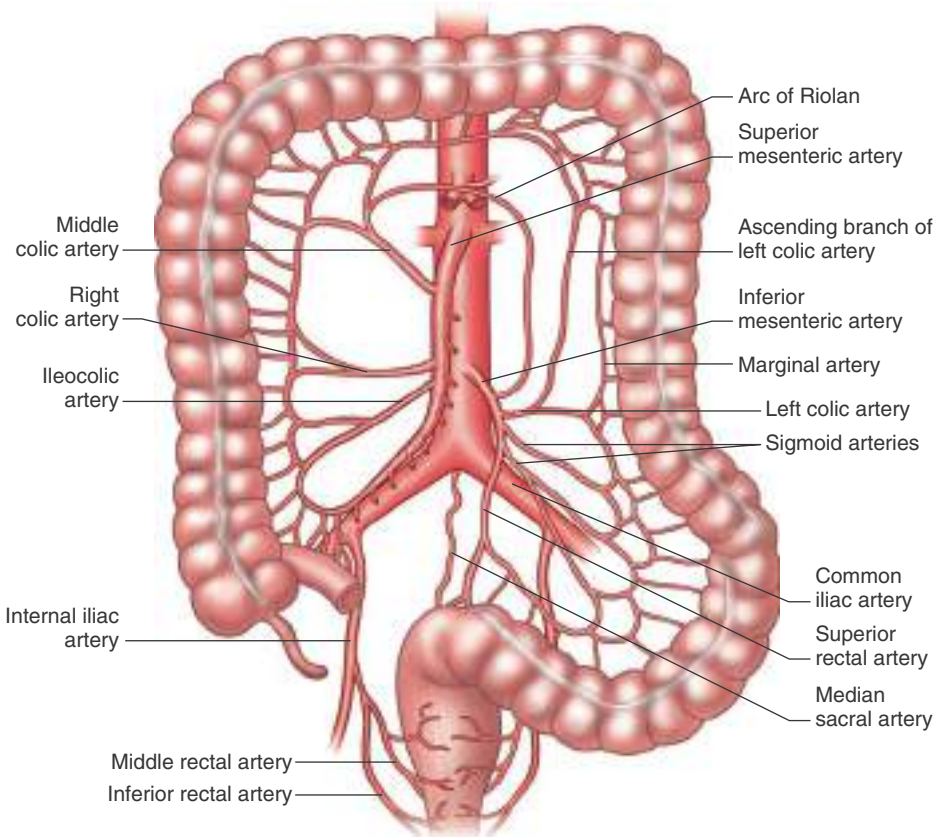

FIGURE 1-9. Arterial anatomy of the colon and rectum.

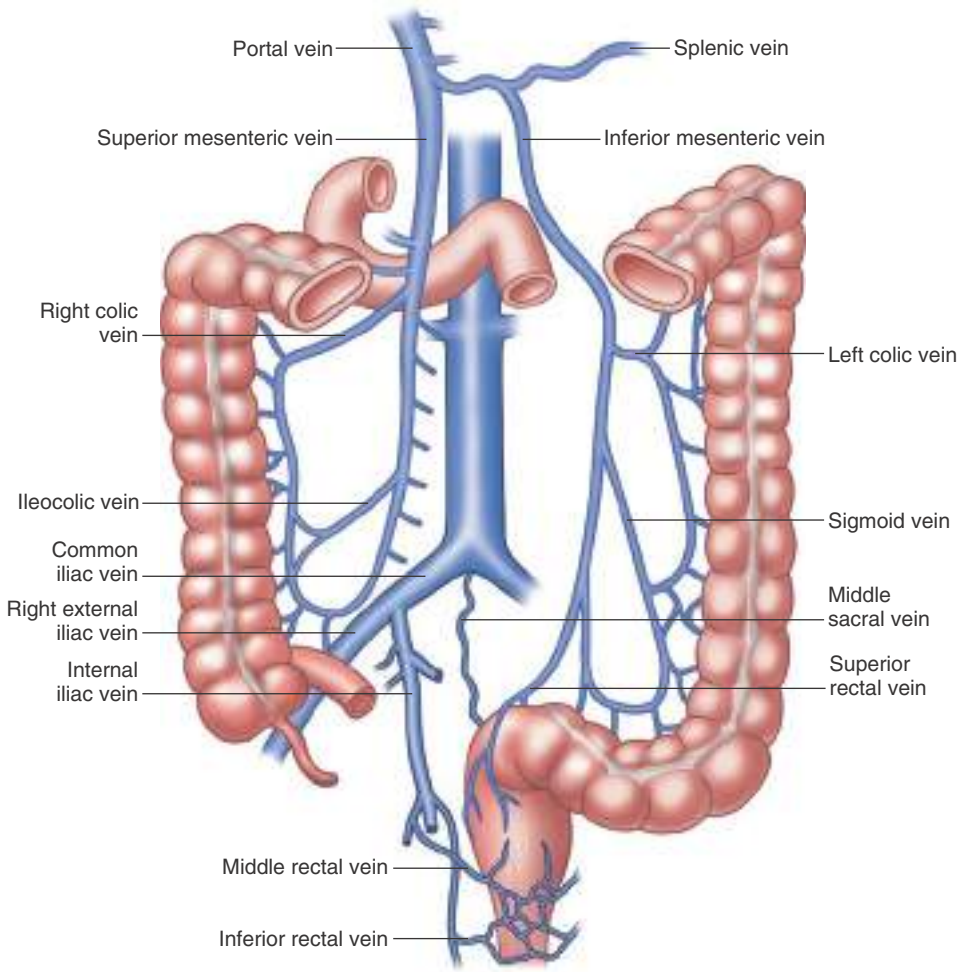

FIGURE 1-10. Venous anatomy of the colon and rectum.

traverses the obturator fascia, the ischiorectal fossa and pierces the wall of the anal canal in the region of the external anal sphincter [32].

Venous and Lymphatic Drainage of the Rectum and Anus

Venous drainage from the rectum and anus occurs via both the portal and systemic systems. Middle and inferior rectal veins drain to the systemic systems via the internal iliac vein while the superior rectal vein drains the rectum and upper anal canal into the portal system via the inferior mesenteric vein (Figure 1-10).

Lymphatics from the upper two-thirds of the rectum drain to the inferior mesenteric lymph nodes and then to the para-aortic lymph nodes. Lymphatic drainage from the lower third of the rectum occurs along the superior rectal artery and laterally along the middle rectal artery to the internal iliac lymph nodes. In the anal canal, lymphatic above the dentate drain to the inferior mesenteric and internal iliac lymph nodes. Below the dentate line lymphatics drain along the inferior rectal lymphatics to the superficial inguinal nodes.

Innervation of the Rectum and Anus

Sympathetic fibers arise from L1, L2, and L3 and pass through the sympathetic chains and join the pre-aortic plexus (Figure 1-11). From there, they run adjacent and dorsal to the inferior mesenteric artery as the mesenteric plexus and innervate the upper rectum. The lower rectum is innervated by the presacral nerves from the hypogastric plexus. Two main hypogastric nerves, on either side of the rectum, carry sympathetic information form the hypogastric plexus to the pelvic plexus. The pelvic plexus lies on the lateral side of the pelvis at the level of the lower third of the rectum adjacent to the lateral stalks (please see discussion of lateral stalks above).

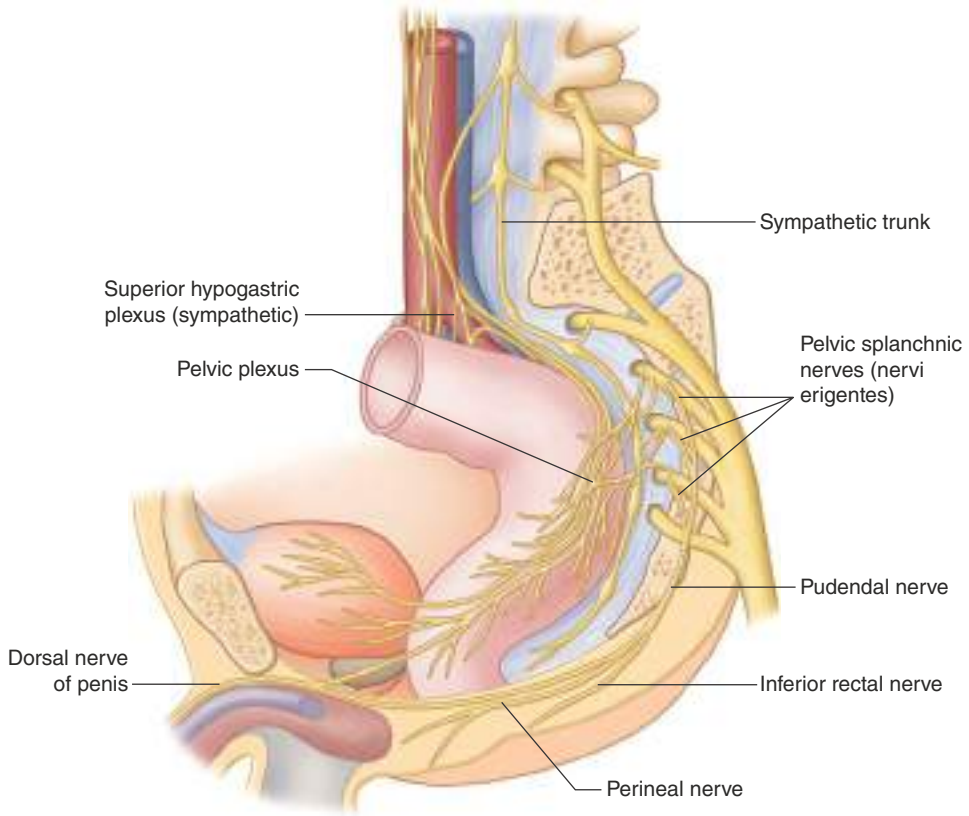

FIGURE 1-11. Nerves of the rectum.

Parasympathetic fibers to the rectum and anal canal originate from S2, S3, and S4 to penetrate through the sacral foramen and are called the nervi erigentes. These nerves course laterally and anterior to join the sympathetic hypogastric nerves and form the pelvic plexus on the pelvic sidewall. From here, postganglionic mixed parasympathetic and sympathetic nerve fibers supply the rectum, genital organs, and anal canal. The periprostatic plexus is considered a subdivision of the pelvic plexus and supplies the prostate, seminal vesicles, corpora cavernosa, vas deferens, urethra, ejaculatory ducts, and bulbourethral glands.

The internal anal sphincter is innervated by sympathetic (L5) and parasympathetic (S2, S3, and S4) nerves following the same route as the nerves to the rectum as noted above. The external anal sphincter is innervated on each side by the inferior rectal branch of the internal pudendal nerve (S2 and S3) and by the perineal branch of S4. Anal sensation is mediated by the inferior rectal branch of the pudendal nerve.

Anatomy of the Colon

The colon is a long tubular organ consisting of muscle and connective tissue with an inner mucosal layer. The diameter of the colon differs depending upon which segment is evaluated, and generally decreases in diameter as one travels proximal to distal (cecum about 7 cm and sigmoid colon about 2.5 cm in diameter). The overall length is variable with an average length approximating 150 cm. The right and left sides of the colon are fused to the posterior retroperitoneum (secondarily retroperitonealized) while the transverse colon and sigmoid colon are relatively free within the peritoneum. The transverse colon is held in position via its attachments to the right/left colon at the flexures (hepatic and splenic, respectively) and is further fused to the omentum. Generally speaking the colon is located peripherally within the abdomen with the small bowel located centrally.

There are three important anatomic points of differentiation between the colon and the small intestine: the appendices epiploicae, the taeniae coli, and the haustra. The appendices epiploicae are non-mesenteric fat protruding from the serosal surface of the colon. They are likely residual from the anti-mesenteric fat of the embryologic intestine which dissipates (unlike the omentum on the stomach). The taenia coli are three thickened bands of outer, longitudinal muscle of the colon. This outer layer of muscle is indeed circumferentially complete [48], but is considerably thicker in three areas represented by the taenia. The three taeniae have been given separate names by some: *taenia libera* to represent the anterior band, *taenia mesocolica* for the

posteromedial band, and *taenia omentalis* for posterolateral band. The bands are continuous from their origin at the base of the appendix until the rectosigmoid junction where they converge (marking an anatomically identifiable differentiation between the sigmoid colon and rectum). Though they run along the full length of the colon, they are not as long as the bowel wall. This difference in length results in outpouchings of the bowel wall between the taenia referred to as haustra. The haustra are further septated by the plicae semilunares.

Cecum

The proximal most portion of the colon is termed the cecum, a sac-like segment of colon below (proximal to) the ileocecal valve. The cecum is variable in size, but generally is about 8 cm in length and 7 cm in diameter. At its base is the appendix. Terminating in the posteromedial area of the cecum is the terminal ileum (ileocecal valve). The cecum is generally covered by visceral peritoneum, with more variability near the transition to the ascending colon (upper or distal cecum). The ileocecal valve is a circular muscular sphincter which appears as a slit-like ("fish-mouth") opening noted on an endoscopic evaluation of the cecum. The valve is not competent in all patients, but when present, its competence leads to the urgency of a colon obstruction as it develops into a closed-loop obstruction. Regulation of ileal emptying into the colon appears to be the prime task in ileocecal valve function [49].

The Appendix

The appendix is an elongated, true diverticulum arising from the base of the cecum. The appendiceal orifice is generally about 3–4 cm from the ileocecal valve. The appendix itself is of variable length (2–20 cm) and is about 5 mm in diameter in the non-inflamed state. Blood is supplied to the appendix via the appendiceal vessels contained within the mesoappendix. This results in the most common location of the appendix being medially on the cecum toward the ileum, but the appendix does have great variability in its location including pelvic, retrocecal, preileal, retroileal, and subcecal.

Ascending Colon

From its beginning at the ileocecal valve to its terminus at the hepatic flexure where it turns sharply medially to become the transverse colon, the ascending colon measures on average, about 15–18 cm. Its anterior surface is covered in visceral peritoneum while its posterior surface is fused with the retroperitoneum. The lateral peritoneal reflection can be seen as a thickened line termed the white line of Toldt, which can serve as a surgeon's guide for mobilization of the ascending colon off of its attachments to the retroperitoneum, most notably the right kidney (Gerotta's fascia) and the loop of the duodenum located posterior and superior to the ileocolic vessels. The right ureter and the right gonadal vessels pass posteriorly to the ascending mesocolon within the retroperitoneum.

Transverse Colon

The transverse colon traverses the upper abdomen from the hepatic flexure on the right to the splenic flexure on the left. It is generally the longest section of colon (averaging 45–50 cm) and swoops inferiorly as it crosses the abdomen. The entire transverse colon is covered by visceral peritoneum, but the greater omentum is fused to the anterosuperior surface of the transverse colon. Superior to the transverse mesocolon, inferior to the stomach, and posterior to the omentum is the pocket of the peritoneal cavity termed the lesser sac, with the pancreas forming the posterior most aspect. The splenic flexure is the sharp turn from the transversely oriented transverse colon to the longitudinally oriented descending colon. It can be adherent to the spleen and to the diaphragm via the phrenocolic ligament.

Descending Colon

The descending colon travels inferiorly from the splenic flexure for the course of about 25 cm. It is fused to the retroperitoneum (similarly to the ascending colon) and overlies the left kidney as well as the back/retroperitoneal musculature. Its anterior and lateral surfaces are covered with visceral peritoneum and the lateral peritoneal reflection (white line of Toldt) is again present.

Sigmoid Colon

The sigmoid colon is the most variable of the colon segments. It is generally 35–45 cm in length. It is covered by visceral peritoneum, thereby making it mobile. Its shape is considered "omega-shaped" but its configuration and attachments are variable. Its mesentery is of variable length, but is fused to the pelvic walls in an inverted-V shape creating a recess termed the intersigmoid fossa. Through this recess travel the left ureter, gonadal vessels, and often the left colic vessels.

Rectosigmoid Junction

The end of the sigmoid colon and the beginning of the rectum is termed the rectosigmoid junction. It is noted by the confluence of the taeniae coli and the end of epiploicae appendices. While some surgeons have historically considered the rectosigmoid junction to be a general area (comprising about 5 cm

of distal sigmoid and about 5 cm of proximal rectum), others have described a distinct and clearly defined segment. It is the narrowest portion of the large intestine, measuring 2–2.5 cm in diameter. Endoscopically, it is noted as a narrow and often sharply angulated area above the relatively capacious rectum, and above the three rectal valves.

In the early nineteenth century, it was proposed that the sigmoid acts as a reservoir for stool, thus aiding in continence [50]. Subsequently, an area of thickened circular muscle within the wall of the rectosigmoid was described and felt to function as a sphincter of sorts. Historically, it has been variably named the *sphincter ani tertius, rectosigmoid sphincter*, and *pylorus sigmoidorectalis* [51–55]. A more recent evaluation of the rectosigmoid junction utilizing anatomic and histologic studies as well as radiographic evaluation concluded that there was an anatomic sphincter at the rectosigmoid junction [56]. Microscopic evaluation of the area does reveal thickening of the circular muscle layer as it progresses toward the rectum. Though not identifiable externally, radiologic evaluation can identify the area as a narrow, contractile segment [56].

Blood Supply

The colon receives blood supply from two main sources, branches of the Superior Mesenteric Artery (SMA) (cecum, ascending, and transverse colon) and branches of the Inferior Mesenteric Artery (IMA) (descending and sigmoid colon) (Figure 1-9). There is a watershed area between these two main sources located just proximal to the splenic flexure where branches of the left branch of the middle colic artery anastomose with those of the left colic artery. This area represents the border of the embryologic midgut and hindgut. Though the blood supply to the colon is somewhat variable, there are some general common arteries. The cecum and right colon are supplied by the terminus of the SMA, the ileocolic artery. The right colic artery is less consistent and, when present, can arise directly from the SMA, from the ileocolic, or from other sources. The transverse colon is supplied via the middle colic artery, which branches early to form right and left branches. The middle colic artery originates directly from the SMA. The left colon and sigmoid colon are supplied by branches of the IMA, namely the left colic and a variable number of sigmoid branches. After the final branches to the sigmoid colon, the IMA continues inferiorly as the superior hemorrhoidal (rectal) artery.

Superior Mesenteric Artery

The superior mesenteric artery (SMA) is the second, unpaired anterior branch off of the aorta (Figure 1-9). It arises posterior to the upper edge of the pancreas (near the L1 vertebrae), courses posterior to the pancreas, and then crosses over the third portion of the duodenum to continue within the base of the mesentery. From its left side, the SMA gives rise to up to 20 small intestinal branches while the colic branches originate from its ride side. The most constant of the colic branches is the ileocolic vessel which courses through the ascending mesocolon where it divides into a superior (ascending) branch and an inferior (descending) branch [57]. A true right colic artery is absent up to 20% of the time and, when present, typically arises from the SMA. Alternatively, the right colic artery can arise from the ileocolic vessels or from the middle colic vessels [45, 57, 58]. The middle colic artery arises from the SMA near the inferior border of the pancreas. It branches early to give off right and left branches. The right branch supplies the hepatic flexure and right half of the transverse colon. The left branch supplies the left half of the transverse colon to the splenic flexure. In up to 33% of patients, the left branch of the middle colic artery can be the sole supplier of the splenic flexure [57, 59].

Inferior Mesenteric Artery

The inferior mesenteric artery (IMA) (Figure 1-9) is the third unpaired, anterior branch off of the aorta, originating 3–4 cm above the aortic bifurcation at the level of the L2 to L3 vertebrae. As the IMA travels inferiorly and to the left, it gives off the left colic artery and several sigmoidal branches. After these branches, the IMA becomes the superior hemorrhoidal (rectal) artery as it crosses over the left common iliac artery. The left colic artery divides into an ascending branch (splenic flexure) and a descending branch (the descending colon). The sigmoidal branches form a fairly rich arcade within the sigmoid mesocolon (similar to that seen within the small bowel mesentery). The superior hemorrhoidal artery carries into the mesorectum and into the rectum. The superior hemorrhoidal artery bifurcates in about 80% of patients.

The Marginal Artery and Other Mesenteric Collaterals

The major arteries noted above account for the main source of blood within the mesentery. However, the anatomy of the mesenteric circulation and the collaterals within the mesentery remain less clear. Haller first described a central artery anastomosing all mesenteric branches in 1786 [60]. When Drummond demonstrated its surgical significance in the early twentieth century, it became known as the marginal artery of Drummond [61, 62]. The marginal artery (Figure 1-9) has been shown to be discontinuous or even absent in some patients, most notably at the splenic flexure (Griffiths' critical point), where it may be absent in up to 50% of patients [63]. This area of potential ischemia is the embryologic connection between the midgut and hindgut. Inadequacy of the marginal artery likely accounts for this area being most severely affected in cases of colonic ischemia. Another potential (though controversial) site of ischemia is at a discontinuous

area of marginal artery located at the rectosigmoid junction termed Sudeck's critical point. Surgical experience would question whether this potential area of ischemia exists; a recent fluorescence study indicates that it does [64], though its clinical importance remains in doubt.

Venous Drainage

Venous drainage of the colon largely follows the arterial supply with superior and inferior mesenteric veins draining both the right and left halves of the colon (Figure 1-10). They ultimately meet at the portal vein to reach the intrahepatic system. The superior mesenteric vein (SMV) travels parallel and to the right of the artery. The inferior mesenteric vein (IMV) does not travel with the artery, but rather takes a longer path superiorly to join the splenic vein. It separates from the artery within the left colon mesentery and runs along the base of the mesentery where it can be found just lateral to the ligament of Treitz and the duodenum before joining the splenic vein on the opposite (superior) side of the transverse mesocolon. Dissecting posterior to the IMV can allow for separation of the mesenteric structures from the retroperitoneal structures during a medial-to-lateral dissection.

Lymphatic Drainage

The colon wall has a dense network of lymphatic plexuses. These lymphatics drain into extramural lymphatic channels which follow the vascular supply of the colon. Lymph nodes are plentiful and are typically divided into four main groups. The *epiploic* group lies adjacent to the bowel wall just below the peritoneum and in the epiploicae. The *paracolic* nodes are along the marginal artery and the vascular arcades. They are most filtering of the nodes. The *intermediate* nodes are situated on the primary colic vessels. The *main* or *principal* nodes are on the superior and inferior mesenteric vessels. Once the lymph leaves the main nodes, it drains into the cisterna chili via the para-aortic chain.

Nervous Innervation

The colon is innervated by the sympathetic and parasympathetic nervous systems and closely follows the arterial blood supply. The sympathetic innervation of the right half of the colon originates from the lower six thoracic splanchnic nerves which synapse within the celiac, pre-aortic, and superior mesenteric ganglia. The post-ganglionic fibers then follow the SMA to the right colon. The sympathetic innervation for the left half originates from L1, L2, and L3. Parasympathetic fibers to the right colon come from the posterior (right) branch of the Vagus Nerve and celiac plexus. They travel along the SMA to synapse with the nerves within the intrinsic autonomic plexuses of the bowel wall. On the left side, the parasympathetic innervation comes from S2, S3, and S4 via splanchnic nerves.

Embryology

The embryologic development of the GI system is complex. That said, however, a working knowledge of the development of the small bowel, colon, and anorectum is critical for a colorectal surgeon as it can aid in understanding pathophysiology and is essential for recognizing surgical planes.

Anus and Rectum

The colon distal to the splenic flexure, including the rectum and the anal canal (proximal to the dentate line), are derived from the hindgut and therefore have vascular supply from the inferior mesenteric vessels (Figure 1-9). The dentate line (Figure 1-1) is the fusion plane between the endodermal and ectodermal tubes. The cloacal portion of the anal canal has both endodermal and ectodermal components which develop into the anal transitional zone [65]. The terminal portion of the hindgut or cloaca fuses with the proctodeum (an ingrowth from the anal pit).

The cloaca originates at the portion of the rectum below the pubococcygeal line while the hindgut originates above it. Before the fifth week of development, the intestinal and urogenital tracts are joined at the level of the cloaca. By the eighth week, the urorectal septum migrates caudally to divide the cloacal closing plate into an anterior urogenital plate and a posterior anal plate. Anorectal rings result from a posterior displacement in the septum and the resultant smaller anal opening. By the tenth week, the anal tubercles fuse into a horseshoe shaped structure dorsally and into the perineal body anteriorly. The external anal sphincter forms from the posterior aspects of the cloacal sphincter earlier than the development of the internal sphincter. The internal sphincter develops from enlarging fibers of the circular muscle layer of the rectum [66]. The sphincters migrate during their development with the internal sphincter moving caudally while the external sphincter enlarges cephalad. Meanwhile, the longitudinal muscle descends into the intersphincteric plane [6]. In females, the female genital organs form from the Müllerian ducts and join the urogenital sinus by the 16th week of development. In contrast, in males, the urogenital membrane obliterates with fusion of the genital folds while the sinus develops into the urethra.

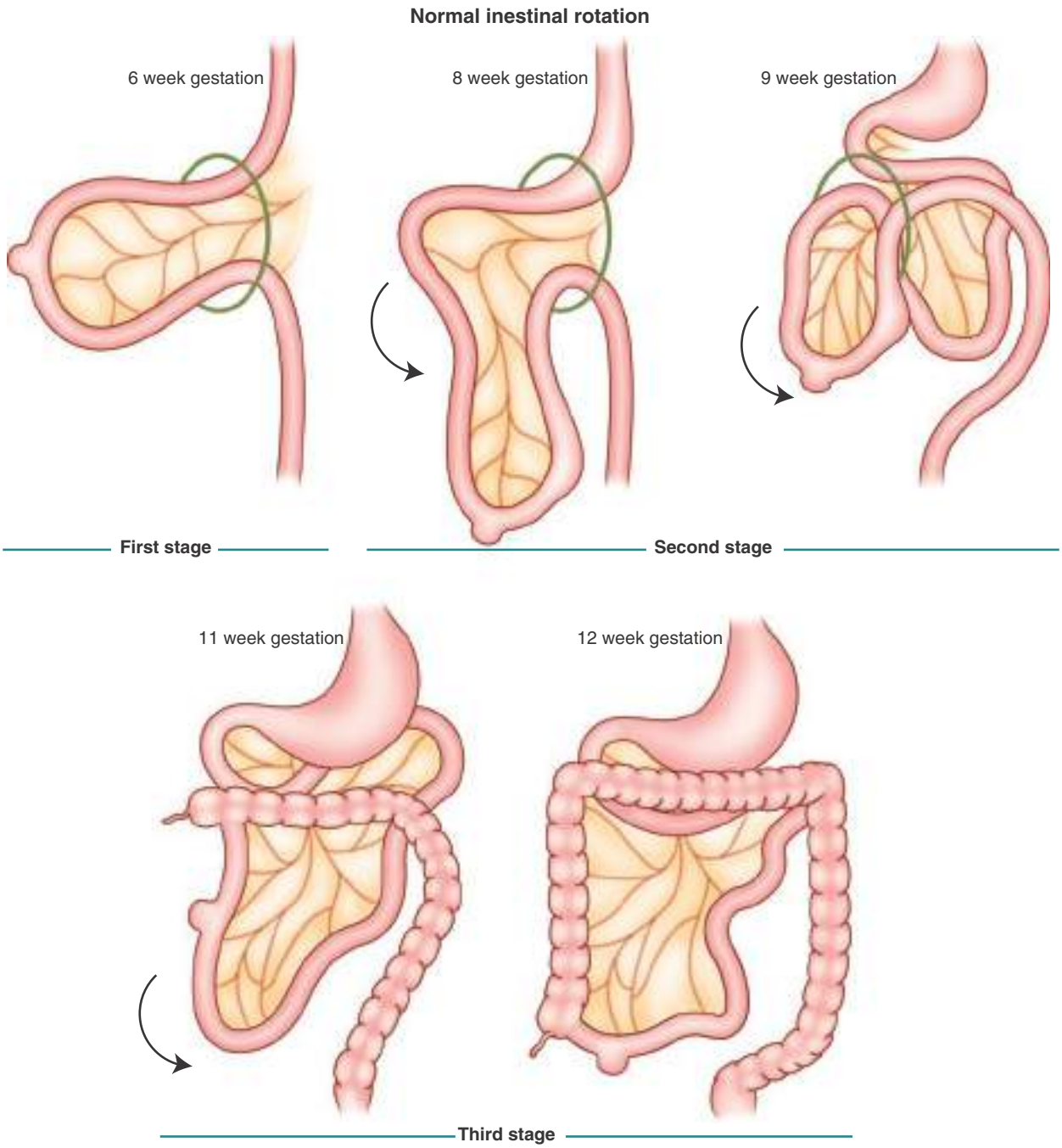

FIGURE 1-12. Summary of normal intestinal rotation during development.

Colon and Small Intestine

The endodermal roof of the yolk sac develops into the primitive gut tube. This initially straight tube is suspended upon a common mesentery. By week 3 of development, it has three discernible segments; namely the foregut, midgut, and hindgut. The midgut starts below the pancreatic papilla to form the small intestine and the first half of the colon (all supplied by the superior mesenteric artery). The distal colon and rectum, as well as the anal canal develop from the hindgut and are therefore supplied by the inferior mesenteric artery.

There is a normal process by which the intestinal tract rotates (Figure 1-12). The first stage is the physiologic herniation of the midgut, the second stage is its return to the abdomen, and the third stage is the fixation of the midgut. Abnormalities in this normal process lead to various malfor-

mations (see below). The physiologic herniation (first stage) occurs between weeks 6 and 8 of development. The primitive gut tube elongates over the superior mesenteric artery and bulges out through the umbilical cord (Figure 1-13). During the eighth week, these contents move in a counterclockwise fashion, turning 90° from the sagittal to the horizontal plane (Figure 1-14). Anomalies at this stage are rare, but include situs inversus, duodenal inversion, and extroversion of the cloaca. During the second stage (tenth week of gestation), the midgut loops return to the peritoneal cavity and simultaneously rotate an additional 180° in the counterclockwise direction (Figure 1-15). The pre-arterial portion of the duodenum returns to the abdomen first, followed by the counterclockwise rotation around the superior mesenteric vessels, resulting in the duodenum lying behind them. The colon returns after the rotation, resulting in their anterior location. Anomalies in this stage are more common and result in nonrotation, malrotation, reversed rotation, internal hernia, and omphalocele. The third stage (fixation of the midgut) begins once the intestines have returned to the peritoneal cavity and end at birth. The cecum migrates to the right lower quadrant from its initial position in the upper abdomen (Figure 1-16). After the completion of this 270° counterclockwise rotation, fusion begins, typically at week 12–13. This results in fusion of the duodenum as well as the ascending and descending colon (Figure 1-17).

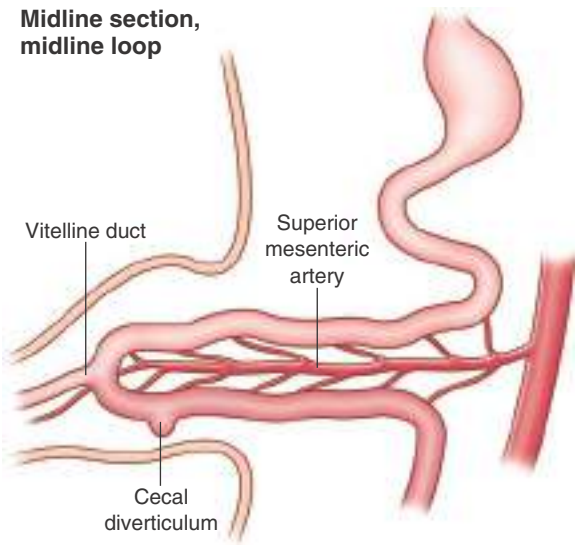

FIGURE 1-13. Elongation of the midgut loop.

Major Anomalies of Rotation

Non-rotation

The midgut returns to the peritoneum without any of the normal rotation. This results in the small intestine being on the right side of the abdomen and the colon on the left side (Figure 1-18). This condition can remain asymptomatic (a finding noted at laparoscopy or laparotomy) or result in volvulus affecting the entirety of the small intestine. The twist generally occurs at the duodenojejunal junction as well as the midtransverse colon.

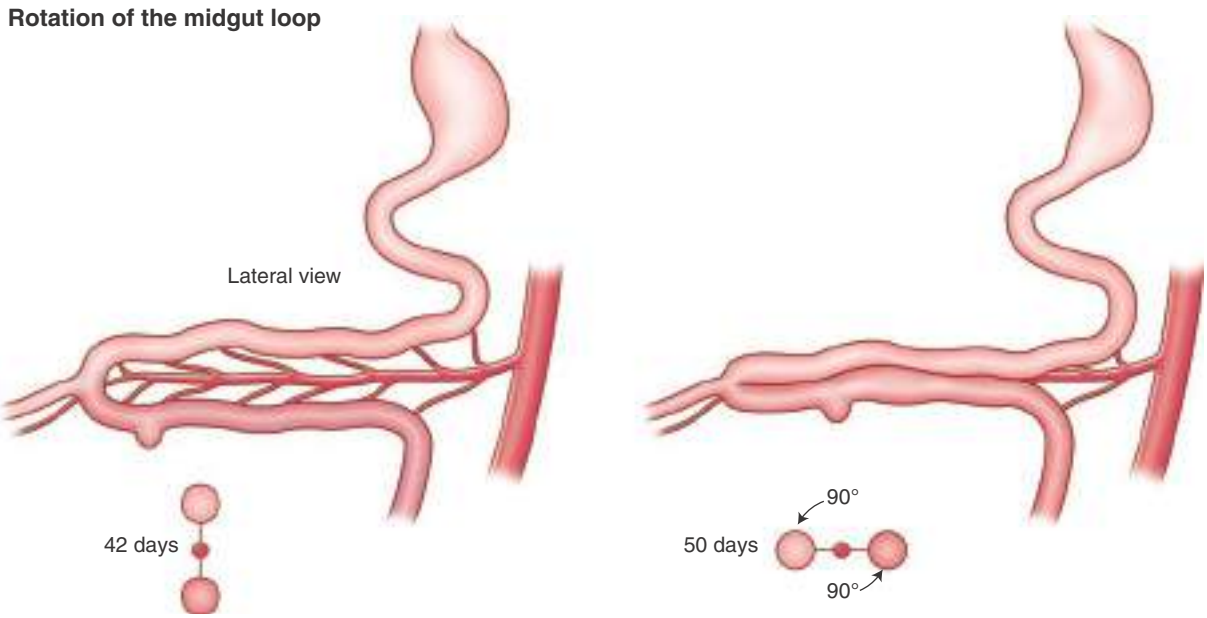

FIGURE 1-14. Rotation of the midgut loop.

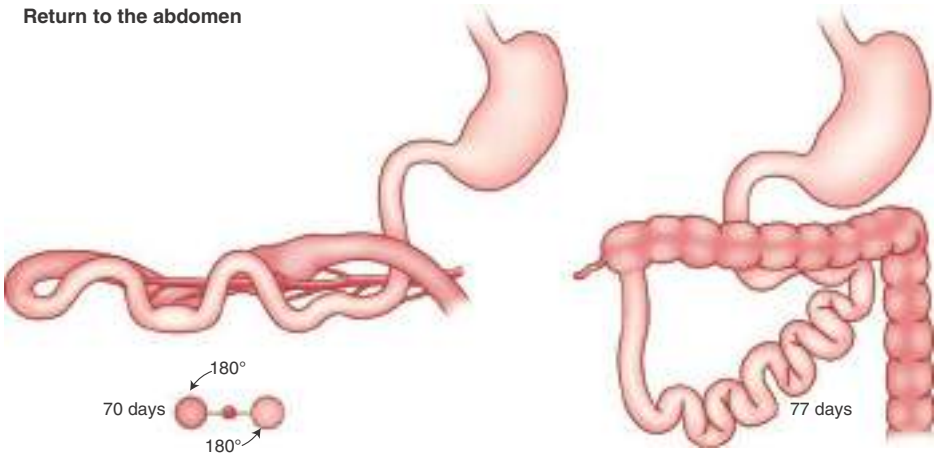

FIGURE 1-15. Return of the intestinal loop to the abdomen.

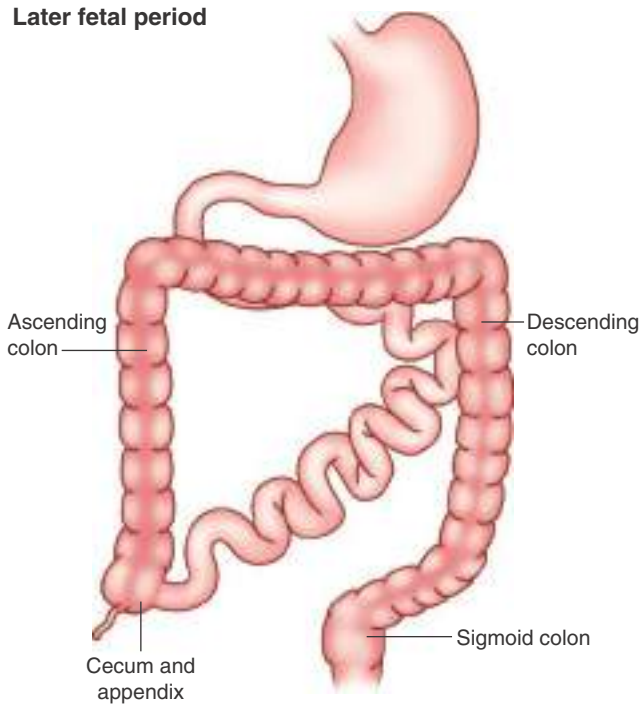

FIGURE 1-16. Later fetal development.

Malrotation

There is normal initial rotation, but the cecum fails to complete the normal 270° rotation around the mesentery. This results in the cecum being located in the mid-upper abdomen with lateral bands (Ladd's bands) fixating it to the right abdominal wall (Figure 1-19). These bands can result in extrinsic compression of the duodenum.

Reversed Rotation

Clockwise (rather than counterclockwise) rotation of the midgut results in the transverse colon being posterior to the superior mesenteric artery while the duodenum lies anterior to it.

Omphalocele

An omphalocele is, basically, the retention of the midgut within the umbilical sac and its failure to return to the peritoneal cavity.

Internal Hernias

Internal hernias, as well as congenital obstructive bands, can cause congenital bowel obstructions. These are considered failures of the process of fixation (the third stage of rotation). This can be the result of an incomplete fusion of the mesothelium or when structures are abnormally rotated. Retroperitoneal hernias can occur in various positions, most notably paraduodenal, paracecal, and intersigmoid.

Other Congenital Malformations of the Colon and Small Intestine

Proximal Colon Duplication

There are three general types of colonic duplication: mesenteric cysts, diverticula, and long colon duplication [67]. Mesenteric cysts are lined with intestinal epithelium and variable amounts of smooth muscle. They are found within the colonic mesentery or posterior to the rectum (within the mesorectum). They may be closely adherent to the bowel

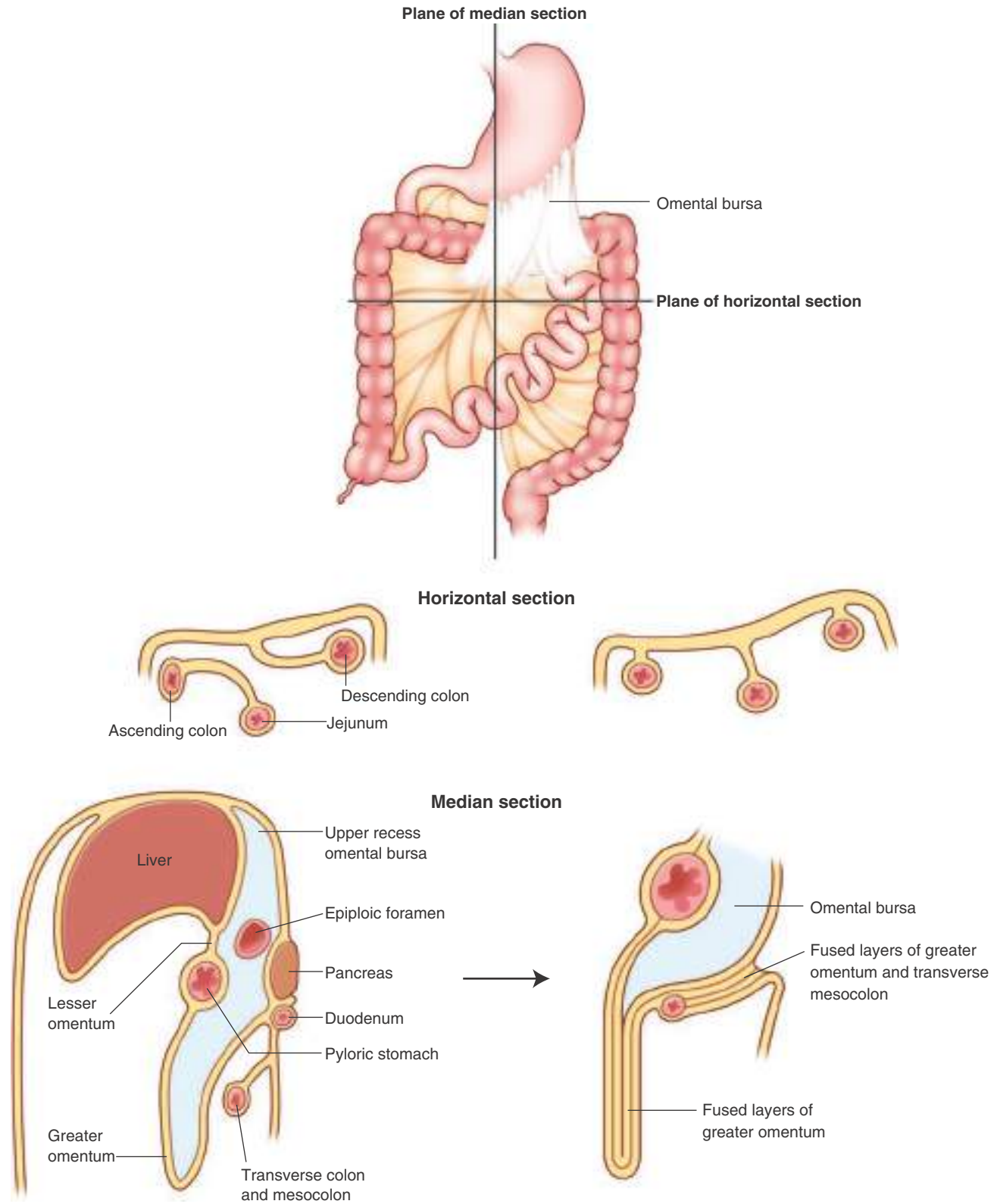

FIGURE 1-17. Development of the mesentery and omental fusion.

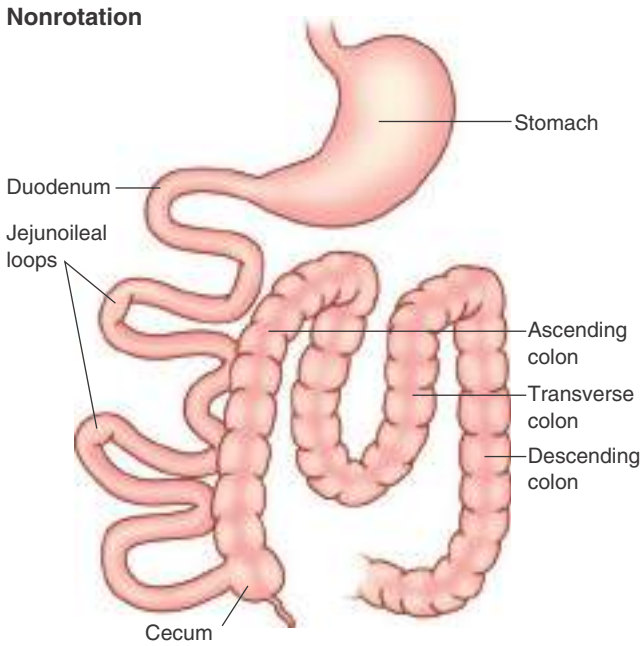

FIGURE 1-18. Intestinal non-rotation.

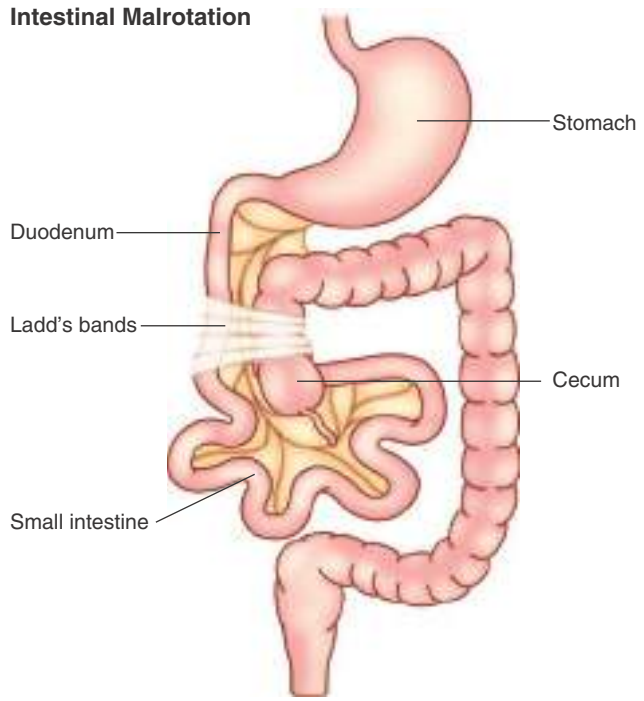

FIGURE 1-19. Intestinal malrotation.

wall or separate from it. They generally present as a mass or with intestinal obstruction as they enlarge. Diverticula can be found on the mesenteric or antimesenteric sides of the colon and are outpouchings of the bowel wall. They often contain heterotopic gastric or pancreatic tissue. Long colonic duplications of the colon are the rarest form of duplication. They parallel the functional colon and often share a common wall throughout most of their length. They usually run the entire length of the colon and rectum and there is an association with other genitourinary abnormalities.

Meckel's Diverticulum

A Meckel's diverticulum is the remnant of the vitelline or omphalomesenteric duct (Figure 1-13). It arises from the antimesenteric aspect of the terminal ileum, most commonly within 50 cm of the ileocecal valve. They can be associated with a fibrous band connecting the diverticulum to the umbilicus (leading to obstruction) or it may contain ectopic gastric mucosa or pancreatic tissue (leading to bleeding or perforation) (Figure 1-20). An indirect hernia containing a Meckel's diverticulum is termed a Littre's hernia. Meckel's diverticulum is generally asymptomatic and, per autopsy series, is found in up to 3% of the population [68]. Surgical complications, which are more common in children than adults, include hemorrhage, obstruction, diverticulitis, perforation, and umbilical discharge. Generally, there is no hard indication for excision of an incidentally discovered Meckel's diverticulum, though its removal is generally safe [69, 70].

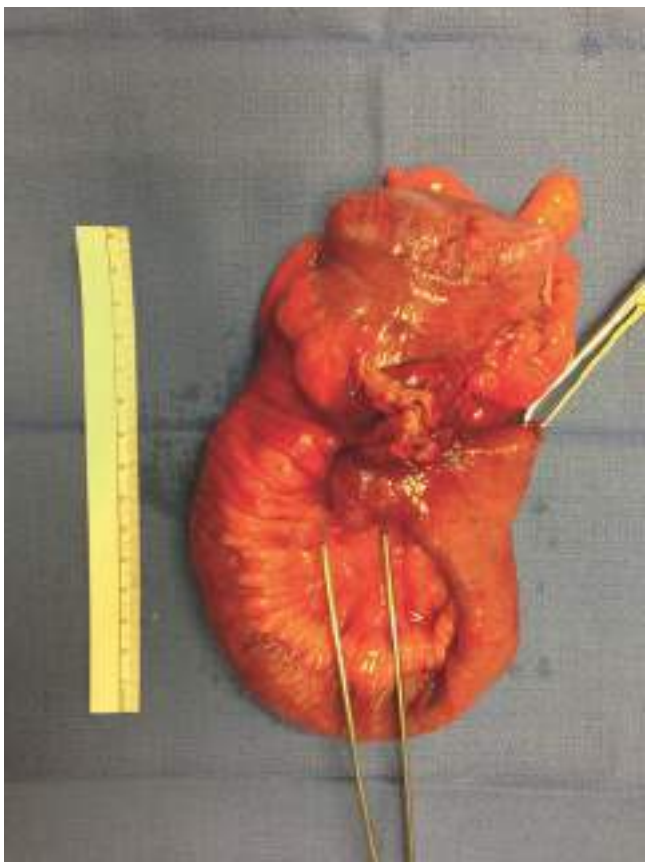

FIGURE 1-20. Perforated Meckel's diverticulum with fistula to ileum.

Atresia of the Colon

Colonic atresia, representing only 5% of all gastrointestinal atresias, is a rare cause of congenital obstruction. They are likely the result of vascular compromise during development [71]. They vary in severity from a membranous diaphragm blocking the lumen to a fibrous cord-like remnant, on to a complete absence of a segment [72].

Hirschsprung's Disease

This nonlethal anomaly, which is more common in males, results from the absence of ganglion cells within the myenteric plexus of the colon. It is caused by interruption of the normal migration of the neuroenteric cells from the neural crest before they reach the rectum. This results in dilation and hypertonicity of the proximal colon. The extent of the aganglionosis is variable, though the internal sphincter is always involved. Its severity is dependent upon the length of the involved segment. It is discussed fully in Chap. 64.

Anorectal Malformations

Abnormalities in the normal development of the anorectum can be attributed to "developmental arrest" at various stages of normal development. These abnormalities are often noted in concert with spinal, sacral, and lower limb defects, as noted by Duhamel and theorized to be related to a "syndrome of caudal regression" [73]. Indeed, skeletal and urinary anomalies are associated in up to 70% [74], while digestive tract anomalies (e.g., tracheoesophageal fistula or esophageal stenosis), cardiac, and abdominal wall abnormalities are also noted in patients with anorectal anomalies. While these are discussed in detail in Chap. 64, a few notable traits are worth pointing out.

Anal Stenosis

While anal stenosis in a newborn is relatively common, noted in 25–39% of infants, symptomatic stenosis is only noted in 25% of these children [75]. The majority of these children undergo spontaneous dilation in the first 3–6 months of life.

Membranous Atresia

This very rare condition is characterized by the presence of a thin membrane of skin between the blind end of the anal canal and the surface. It is also termed the covered anus. It is more common in males.

Anal Agenesis

The rectum develops to below the puborectalis where it either ends in an ectopic opening (fistula) in the perineum, vulva, or urethra, or it ends blindly (less commonly). The sphincter is present at its normal site.

Anorectal Agenesis

Anorectal agenesis is the most common type of "imperforate anus." More common in males, the rectum ends well caudal to the surface and the anus is represented by a dimple with the anal sphincter usually being normal in location. In most cases, there is a fistula to the urethra or vagina. High fistulae (to the vagina or urethra) with anorectal agenesis develop as early as the sixth or seventh week of gestation while the low fistulae (perineal) or anal ectopia develop later, in the eighth or ninth week of development.

Rectal Atresia or "High Atresia"

In rectal atresia, the rectum and the anal canal are separated from one another by an atretic portion. It is embryologically the distal most type of colon atresia, but is still considered an anorectal disorder clinically.

Persistent Cloaca

This rare condition, which only occurs in female infants, is the result of total failure of descent of the urorectal septum. It occurs at a very early stage of development.

Conclusion

It is said that to understand abnormal, you must first understand the normal. No where is that more of a true statement than with human anatomy. Further, to understand the pathophysiology of colorectal and anorectal disease mandates a wide-ranging knowledge base of the underlying anatomy and embryology. To properly care for these patients, one must first have a strong foundation and understanding the anatomical "building blocks" of the human body.

Acknowledgment This chapter was written by José Marcio Neves Jorge and Angelita Habr-Gama in the first and second editions of this textbook.

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2
Colonic Physiology

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Key Concepts

- Colonic innervation is supplied by both extrinsic and intrinsic pathways. The extrinsic pathways are derived from the autonomic nervous system including parasympathetic and sympathetic routes. Parasympathetic input is excitatory while sympathetic input is inhibitory to colonic motor function. The intrinsic colonic nervous system consists of the myenteric plexus.
- Short chain fatty acids are produced by the colon as a result of the fermentation of complex carbohydrates by colonic flora. The SCFA, butyrate, is the primary energy source of the colon.
- The colon absorbs sodium and water and secretes bicarbonate and potassium. Aldosterone mediates the process of active sodium absorption in the colon.
- Colonic contractile events are divided into (1) segmental contractions and (2) propagated contractions (including low-amplitude and high-amplitude propagating contractions, LAPC and HAPC, respectively). The main function of HAPC is to propagate colonic contents towards the anus.
- The Interstitial cells of Cajal (ICC) are the primary pacemaker cells governing the function of the enteric nervous system.

Introduction

The colon plays a central role in gastrointestinal (GI) physiology. There are multiple functions that the colon and rectum serve. The primary role of the colon is one of absorption of excess water and electrolytes, serving to salvage valuable fluid and unabsorbed nutrients as well as to create solid stool. It also plays a central role in bacterial homeostasis, serving as a home to billions of commensal bacteria whose role is symbiotic in maintaining the health of the colonic epithelium. The rectum has evolved complicated and elegant mechanisms to store feces and accommodate it while allowing for the selective egress of stool or gas. Understanding the physiologic and histologic components of the colon and rectum are critical to understanding normal and pathologic states.

Embryology

Understanding the embryology of the colon and rectum provides essential information for understanding its function. During the third and fourth weeks of gestation, the primitive gut arises from the cephalic caudal and lateral foldings of the dorsal endoderm lined yolk sac. The mucosa arises from the endodermal layer, however the muscular wall, connective tissue and outer serosal surface arises from the mesodermal layer. By the fourth week of gestation, three distinct regions have differentiated based on their blood supply. The midgut, supplied by the superior mesenteric artery, begins distal to the confluence of the common bile duct in the third portion of the duodenum and includes the proximal two-thirds of the transverse colon. This portion of the intestine maintains a connection to the yolk sac via the vitelline duct. Absence of its obliteration results in a Meckel's diverticulum. The hindgut, which comprises the rest of the distal GI tract, includes the distal transverse colon, descending colon, sigmoid colon, and rectum. This is supplied by the inferior mesenteric artery (IMA). During the fifth week of gestation, the midgut undergoes a rapid elongation which exceeds the capacity of the abdominal cavity. This results in a physiologic herniation through the abdominal wall at the umbilicus. Through the sixth week, continued elongation results in a 90° counterclockwise rotation around the superior mesenteric artery (SMA). The small intestine continues its significant growth, forming loops, while the caudal end enlarges into the cecal bud. During the tenth week, herniated bowel returns to the abdominal cavity, completing an additional 180° counterclockwise loop which leaves the proximal small bowel on the left, and the colon on the right. The dorsal mesentery of

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the ascending and descending colon shortens and involutes resulting in secondary retroperitoneal fixation [1]. The embryology of the distal rectum is more complex. It initially begins as the cloaca which is a specialized area comprising endodermal and ectodermally derived tissue. The cloaca exists as a continuation between the urogenital and GI tracts, however, during the sixth week it begins to divide and differentiate into the anterior urogenital and posterior anorectal and sphincter components. At the same time, the urogenital and GI tracts become separated by caudal migration of the urogenital septum. During the tenth week, while the majority of the midgut is returning to the abdomen, the external anal sphincter is formed in the posterior cloaca as the descent of the urogenital septum becomes complete. The internal anal sphincter is formed during the 12th week by enlargement and specialization of the circular muscle layer of the rectum [1].

Colonic Anatomy

Introduction

The colonic epithelium has both absorptive and secretory functions. The colon is highly efficient at absorbing sodium chloride, water, and short chain fatty acids. In addition, the colonic epithelium secretes bicarbonate, potassium chloride, and mucus. The colonic epithelium is a typical electrolyte-transporting layer that is capable of moving large quantities of water and salt from the lumen towards the blood. Under normal circumstances, the colon is presented with between 1 and 2 l of electrolyte-rich fluid per day. Under normal physiologic conditions, nearly 90% of this fluid is absorbed. The end result is the excretion of feces that has a sodium concentration that approximates 30 mmol/l and a potassium concentration of approximately 75 mmol/l. Under normal circumstances, fecal and plasma osmolality are similar. Colonic epithelial cells are polarized and equipped with numerous ion channels, carriers, and pumps that are localized on both the luminal and basolateral membranes. Many transport proteins have been identified and their functions elucidated. While an in-depth discussion of these mechanisms is beyond the scope of this chapter, important aspects are highlighted below.

Colonic Wall Anatomy

The luminal surface of the colon is lined by epithelium. Deep to this is the submucosal layer, rich in vascular and lymphatic supply. This is surrounded by the continuous inner circular muscle layer and the outer longitudinal muscle layer which has three condensations known as taenia coli. The serosa, or outer layer of the colon, is surrounded by visceral peritoneum.

Colonic Epithelial Cell Types

Three main cell types are present in the colonic epithelium including columnar epithelial cells, goblet cells, and enterochromaffin cells. Columnar epithelial and goblet cells comprise nearly 95% of the cells in the colonic epithelium. The surface and crypt epithelial cells can be differentiated from one another based on proliferative activity, degree of differentiation, and function. Crypt epithelium is highly proliferative, relatively undifferentiated, and secretes chloride. The surface epithelium in contrast has low proliferative activity, is well-differentiated, and is highly absorptive. In general, epithelial cells become increasingly differentiated the farther they are from the crypt base. Thus, the base of the crypts forms the source of continually regenerating epithelial cells. This polarization provides distinct histologic characteristics, which are easily identified on standard H and E staining (Figures 2-1 and 2-2). Recent evidence, however, indicates that ion absorption and secretion occurs at both the surface and crypt levels [2]. The role of the enterochromaffin cells is discussed below.

The cells responsible for the enteric nervous system, the enteric ganglia, are located in the submucosa, otherwise known as Meissner's plexus. An additional layer of ganglia are located between the inner circular and outer longitudinal muscle layers known as Auerbach's plexus. The interstitial cells of Cajal (ICC), are specialized, c-kit positive cells that are thought to primarily serve as the pacemaker cell of the enteric nervous system, linking the colonic submucosa electrochemically with the myenteric plexi. These are the cells of origin of GI stromal tumors (GISTs) which arise from the colonic wall rather than the mucosa [3].

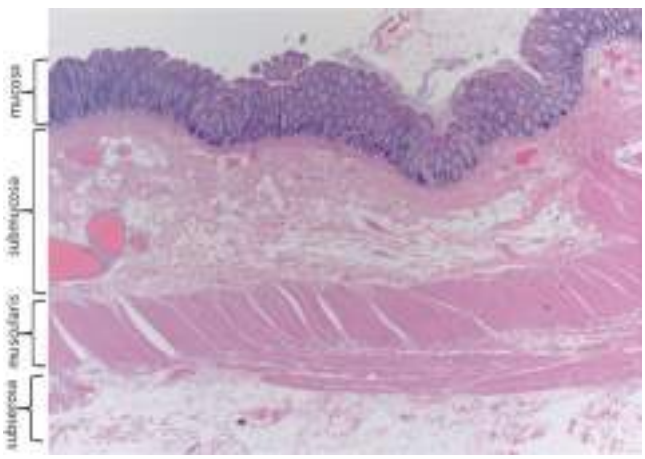

FIGURE 2-1. Normal colonic mucosa. H and E, 250×. The layers of the normal colonic wall are indicated by the *brackets. Courtesy of Julieta E. Barroeta, MD.*

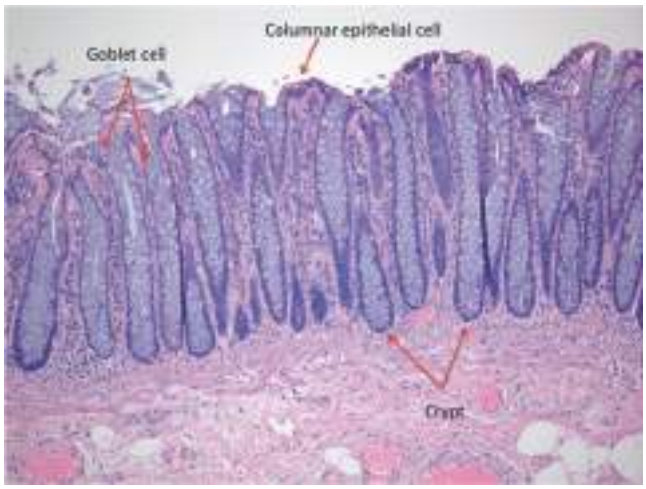

FIGURE 2-2. Normal colonic mucosa. H and E, 1000×. Epithelial cells types are clearly visible including goblet cells and columnar epithelial cells. The crypts are the source of the continually regenerating mucosal cells. *Courtesy of Julieta E. Barroeta, MD.*

Colonic Flora

By the time enteric contents reach the colon, the majority of nutrients have been digested and absorbed by the small intestine. This leaves a fluid rich in electrolytes, bile salts, and undigested starches. These are the primary substrates upon which the colon functions. The colon is home to an enormous quantity of autochthonous flora consisting of more than 400 species of bacteria. Feces contains as many as 10^{11}–10^{12} bacteria/gram of stool, and these bacteria contribute to approximately 50% of fecal mass. The majority of these bacteria are anaerobes which feed on residual proteins and undigested carbohydrates. This microflora contributes several important functions to the host including metabolic support of the colonocyte and gut-associated lymphoid tissue (GALT), which contributes significantly to both innate and adaptive immunity. *Bacteroides* species compose the predominant bacterial type throughout the colon, and they are responsible for almost 2/3 of the bacteria within the proximal colon and 70% of the bacteria in the rectum. The other predominant species are facultative aerobes and comprise *Escherichia*, *Klebsiella*, *Proteus*, *lactobacillus*, and *enterococci*. Unlike the majority of the proximal GI tract, the colonic mucosa does not receive its primary nutrition from blood-borne nutrients. In the colon and rectum, luminal contents provide the primary substrate. The main source of the substrate is undigested dietary fiber. This is metabolized by colonic bacteria through the process of *fermentation*. Cellulose is a partially fermented starch, which leaves behind bulk, whereas fruit pectins are completely metabolized (clarify). The primary end products of this process include short chain fatty acids, including butyrate, and gas. Several of the common dietary complex carbohydrates, including lignin and psyllium, are not metabolized at all, but remain as hydrophilic molecules in stool. These lead to water retention and stool bulking. Butyrate is the main source of energy for the colonocyte. This provides the substrate necessary to maintain epithelial integrity and developmental functions that stimulate epithelial cell differentiation and immune function. Protein fermentation, or *putrefaction*, may result in the formation of potentially toxic metabolites including phenols, indoles, and amines. These toxic end products of bacterial metabolism can lead to mucosal injury, reactive hyperproliferation, and possible promotion of carcinogenesis. Increased stool bulk is felt to provide enhanced colonic transit resulting in decreased time of exposure of the colonic lumen to these toxins, as well as a decreased need for higher intracolonic pressures necessary for segmental motility, a process which may retard the development of diverticular disease. Taken together, these aspects are the reason for many of the recommendations for dietary supplementation with indigestible fiber [4].

Electrolyte Regulation and Water Absorption

Sodium chloride absorption occurs by both electroneutral and electrogenic active transport mechanisms. While electroneutral absorption takes place in both the surface and crypt epithelium, electrogenic absorption appears to be confined to the surface epithelium. A majority of sodium chloride absorption occurs in the proximal colon and is driven primarily through electroneutral absorption by tightly coupled luminal Na^+/H^+ and Cl^-/HCO_3^- exchange. This process is driven by the basolateral Na^+-K^+-ATPase resulting in 1 mol of ATP being hydrolyzed for every 3 mol of NaCl absorbed. Three types of Na^+/H^+ exchangers (NHE) have been identified in colonic epithelium. Similarly, several Cl^- exchange mechanisms have been identified. The luminal Cl^-/HCO_3^- exchange is represented by the anion exchanger type 1 (AE1). A separate Cl^-/OH^- exchange is represented by a protein called DRA (downregulated in colonic adenomas). Human DRA mutations are responsible for congenital chloride diarrhea [2].

Epithelial cells in the distal colon participate in electrogenic absorption of sodium. The epithelial sodium channel (ENaC) mediates this absorption and is located on the luminal surface. Sodium is taken up by the ENaC on the luminal surface and is excreted on the basolateral side by the Na^+-K^+-ATPase. Potassium is secreted on the luminal side and is driven by the electrogenic uptake of sodium. Chloride is absorbed through luminal cystic fibrosis conductance regulator (CFTR) and other chloride channels. Chloride is then excreted on the basolateral side via multiple mechanisms including KCL cotransporter (KCC1), Cl^- channels, and Cl^-/HCO_3^- anion exchangers [2]. The net result is tight regulation of electrolyte secretion in excreted stool (Figure 2-3).

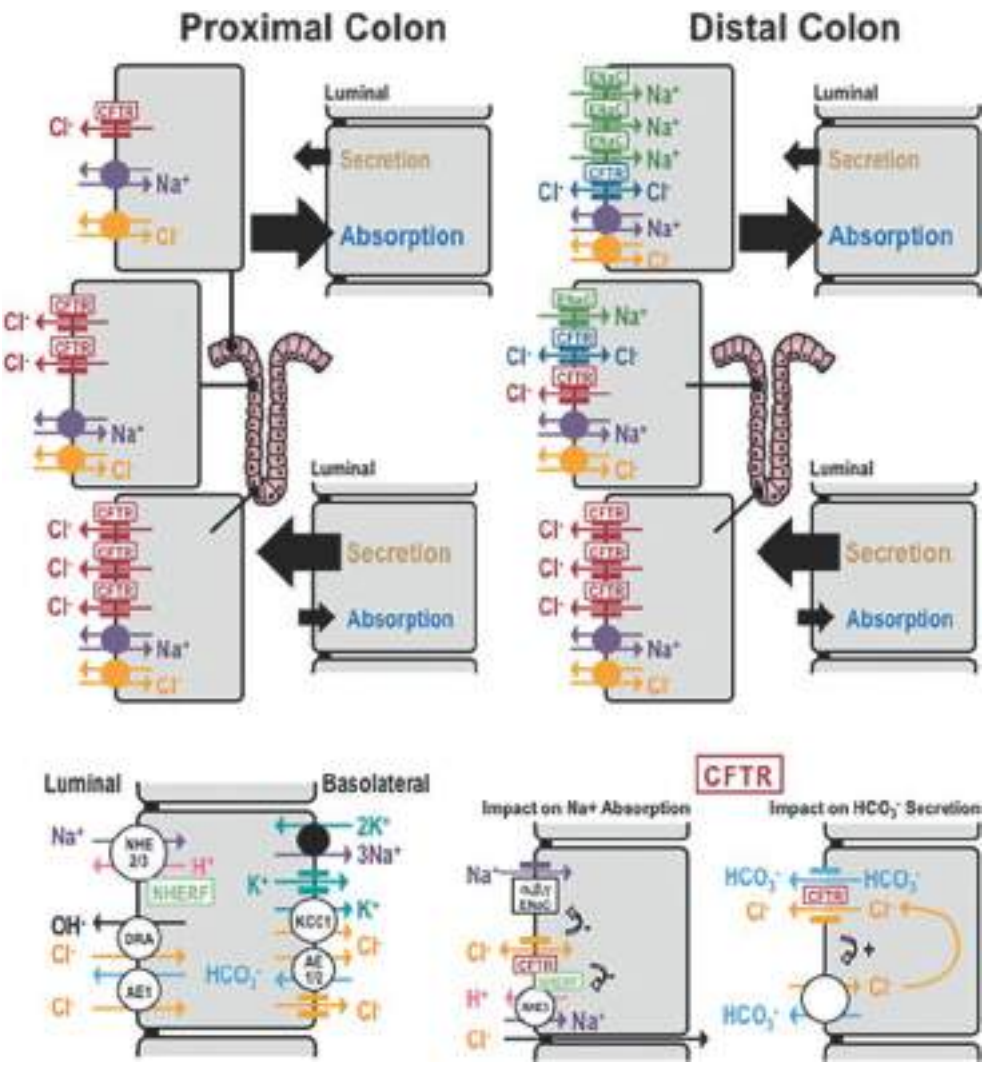

FIGURE 2-3. Schematic of ion-transport channels in proximal and distal colonocytes. *Courtesy of Robin Noel.*

Regulation of sodium absorption is complex and multiple mechanisms are involved. One mechanism of sodium absorption regulation is by feedback inhibition. Namely, changes in intracellular sodium concentration during sodium chloride absorption downregulate ENaC activity. Blood pressure and potassium levels also regulate sodium absorption via angiotensin II. Aldosterone, a mineralocorticoid, is the final endocrine signal in the renin–angiotensin–aldosterone pathway that targets renal and colonic epithelium. Aldosterone is a steroid hormone that is synthesized in the *zona glomerulosa* of the adrenal cortex. Previously, it was thought that aldosterone regulated sodium absorption solely via luminal ENaC. However, aldosterone also increases activity of NHE3. Therefore, aldosterone plays a role in both electrogenic and electroneutral active sodium absorption. Early and late phase aldosterone genomic actions have been identified. In the first 1–6 h, aldosterone-induced proteins including serum and glucocorticoid-inducible kinase (Sgk), corticosteroid hormone-induced factor (CHIF), and K-Ras (KRAS) increase the posttranslational activation of existing ion channels and other proteins involved in ion transport such as ENAc. In the late phase (>6 h), aldosterone acts via the upregulation of nuclear transcription of these receptors. In addition, electroneutral absorption is known to be regulated in response to some G protein-linked receptors, tyrosine kinase-coupled receptors, and protein kinases. For example, activation of protein kinase C, Ca^{2+}/calmodulin-dependent kinase, and increases in cAMP inhibit NHE3 [2, 5].

Evidence also points towards the regulation of sodium absorption by CFTR. ENaC, NHE3, and CFTR are coexpressed in colonic epithelial cells and thus CFTR plays a role in both the electrogenic and electroneutral absorption of electrolytes. CFTR inhibits both electroneutral NaCl absorption as well as electrogenic Na^+ absorption. In the crypts, CFTR is a cAMP-mediated chloride channel that is essential for chloride secretion. In patients with cystic fibrosis, mutations in CFTR result in both impaired chloride secretion and enhanced sodium absorption [2, 6].

Along with the kidneys, the colon assists with potassium homeostasis through the absorption and secretion of potassium. Active potassium absorption is restricted to the distal colon and is mediated by H^+-K^+-ATPase [2].

Water is passively absorbed and can be transported by various pathways including through paracellular shunts and through transcellular flux potentially through aquaporin channels located on luminal and basolateral membrane surfaces [2].

Short Chain Fatty Acid Absorption

As indicated earlier, short chain fatty acids (SCFA) are produced during fermentation of dietary fibers by luminal bacteria. The most common short chain fatty acids include acetate, proprionate, and butyrate. Short chain fatty acids are absorbed by nonionic diffusion and paracellular absorption in the proximal colon. Butyrate is the main energy source for the colonocyte. Butyrate also plays a major role in the stimulation of sodium chloride absorption and inhibition of chloride secretion. Absorption of SCFA plays a significant role in NaCl absorption presumably by the acidification of colonocytes and activation of luminal Na^+/H^+ exchangers. Chloride absorption is also upregulated by increased HCO_3^- production and stimulation of the luminal Cl^-/HCO_3^- exchanger. This HCO_3^- luminal secretion is paramount in regulating luminal intestinal pH. It has been proposed that antibiotic associated diarrhea is secondary to decreased butyrate production resulting in net secretion of fluid [2, 7].

In addition to its role in ionic absorption, butyrate has several other important functions. Butyrate has a trophic effect and stimulates cell proliferation in the crypts. It also reduces the number and size of aberrant crypt foci. This is important as aberrant crypt foci are the earliest precursors of colonic neoplasms. In colon cancer cell lines, butyrate induces apoptosis and cell cycle arrest via inhibition of histone deacetylase. Butyrate also has an anti-inflammatory role primarily by inhibition of nuclear factor kB (NF-kB) in colonic epithelial cells. Some studies have implicated impaired butyrate metabolism in patients with ulcerative colitis. Butyrate stimulates the production of MUC2 mucin and thus may play a role in maintaining the colonic defense barrier. In addition, butyrate may play a role in intestinal motility by regulating gene expression in the enteric nervous system. Finally, butyrate may decrease visceral sensitivity [7, 8].

Despite, the benefits of butyrate discussed above, commercially available butyrate available for oral administration is limited by its short half-life, poor palatability, and side effects such as nausea and anorexia. Rectal formulations are most commonly utilized at this time. Prebiotics and probiotics which produce butyrate are alternative methods of delivery. Prebiotics are nutrients (typically carbohydrates) that support the growth of probiotics bacteria. Probiotics are live bacteria that when consumed in sufficient quantities confer positive health benefits [7, 8].

Secretory Role of the Colonic Epithelium

Another major function of the colonic epithelium is electrolyte secretion. Electrolyte secretion may help transport mucus from the crypts and mucus secretion may be activated by an increase in intracellular cAMP that parallels electrolyte secretion. Chloride secretion occurs predominantly in the crypt cells, but can occur from the surface epithelium as well. Chloride secretion is activated by cAMP-dependent stimulation of CFTR chloride channels. CFTR is the gene product that is affected by any of a number of mutations that cause cystic fibrosis. CFTR is the predominant Cl^- channel in the colon and is responsible for both cAMP- and Ca^{2+}-mediated chloride secretion. CFTR is primarily activated by protein kinase A; however, other second messenger pathways are involved including protein kinase C, cGMP, and calmodulin-dependent kinase [2, 6].

Additional Cl^- channels have been identified in the colonic mucosa that belong to a family of ClC Cl^- channels. The ClC-2 channel is found in colonic epithelium and is regulated by changes in intracellular pH as well as cell volume. They have been localized at tight junction complexes in the crypts [2]. Lubiprostone accelerates colonic transport through the activation of ClC-2 channels on the apical membrane of epithelial cells [9, 10].

As mentioned above, bicarbonate is also secreted to the luminal side of the epithelium and is responsible for the slightly alkaline pH of the colonic lumen [2].

Secretion of electrolytes is often accompanied by secretion of macromolecules. Mucus is probably the most important of these macromolecules and this mucus creates a barrier between the colonic luminal contents and the epithelium [2]. Secreted mucus in the colon forms two distinct layers. The outer loose layer contains bacteria and lubricates feces and protects epithelial cells from abrasion and chemical insult. An inner layer is essentially sterile and is a dense gel that contains antimicrobial peptides, enzymes, and secretory immunoglobulin A (IgA) amongst other substances [3]. Mucus is secreted from goblet cells as well as crypt epithelial cells. Cholinergic stimulation releases preformed mucus. Increased intracellular cAMP induces mucus synthesis. Prostaglandins stimulate mucus secretion from columnar epithelial cells [2].

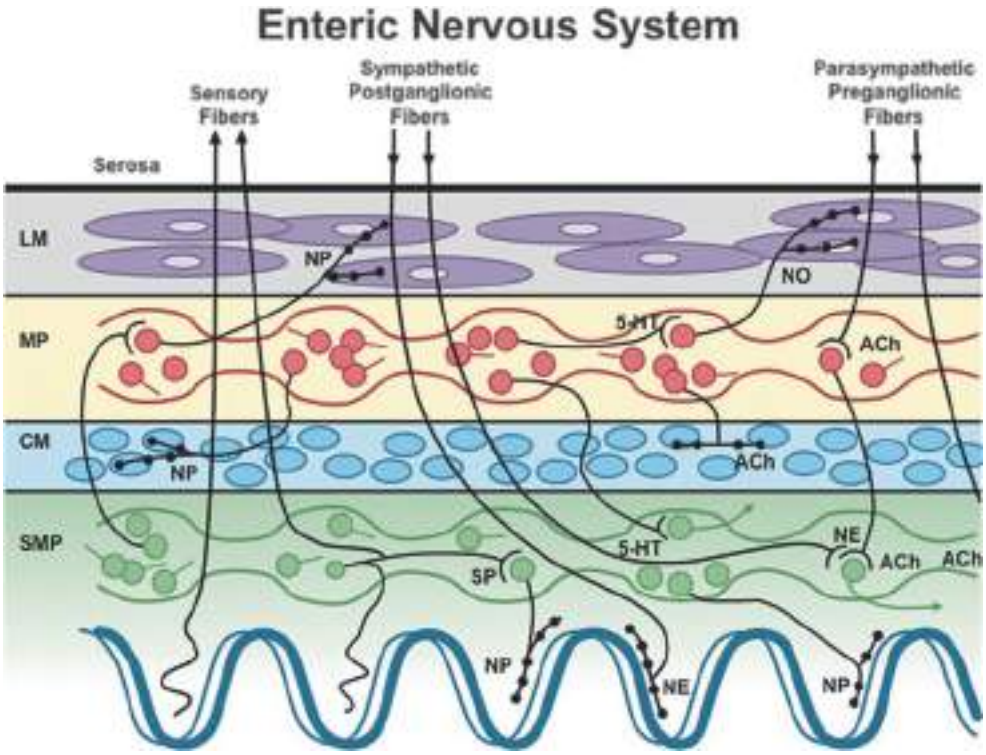

FIGURE 2-4. Schematic representation of the components of the enteric nervous system. *Courtesy of Robin Noel.*

Regulation of Electrolyte and Water Absorption and Secretion

Under normal physiologic conditions, there is a net absorption of sodium chloride and water. Under pathologic conditions, active Cl^- secretion predisposes to the development of diarrhea. Secretion and absorption are mediated by endocrine, paracrine, autocrine, immunologic, and neuronal input [2, 6]. The major neuronal input is via the myenteric (Auerbach's) plexus and the submucosal (Meissner's) plexus. These plexi innervate epithelial as well as vascular smooth muscle cells and regulate colonic blood flow, absorption, and secretion. Food substances, bile acids, and bacterial or viral toxins may act as secretagogues. Secretory hormones and neurotransmitters include vasoactive intestinal polypeptide (VIP), acetylcholine (ACh), histamine, secretin, and serotonin. Substances that inhibit secretion include growth hormone, neuropeptide Y, somatostatin, opiates, and norepinephrine [2]. There is also evidence to suggest that small gaseous molecules, gasotransmitters, also play a role in regulating colonic ion transport. Examples of gasotransmitters include nitric oxide, carbon monoxide, and hydrogen sulfide [6].

Colonic Innervation

Nerves supplying the colon serve to control and modulate colonic motor function. These nerves have a multitude of functions including the following: (1) afferent input via chemoreceptors and mechanoreceptors, (2) efferent output to smooth muscles cells that either stimulate or inhibit contraction by the release of neurotransmitters, (3) modulate the release of neurotransmitters through the release of neuromodulators, (4) control colonic sphincter activity for functions including defecation, and (5) generate signals for the initiation of propagating and nonpropagating motor complexes (see below) [11].

The nerves that control these functions are of both extrinsic and intrinsic origin. The extrinsic pathways originate from the central and autonomic (sympathetic and parasympathetic) nervous systems. Intrinsic innervation consists of the enteric nervous system [11, 12].

It is speculated that central control contributes minimally to baseline colonic tone except as it relates to defecation when voluntary relaxation of the external anal sphincter and contraction of abdominal musculature is required. It is unknown whether the central nervous system provides continuous input to colonic motor control [11].

Autonomic pathways run along parasympathetic and sympathetic chains. Each of these pathways include afferent (sensory) and efferent (motor) innervation. Vagal and pelvic nerves provide parasympathetic input to the colon. Vagal fibers reach the proximal colon along the posterior vagal trunk that follows the arterial blood supply along superior mesenteric arterial branches. The rectum and distal colon receives parasympathetic input from the sacral nerves (S2–S4) through the pelvic plexus. Parasympathetic stimulation stimulates motor activity of the circular and longitudinal muscle throughout the colon. Unlike vagal afferents, the pelvic afferents contain pain fibers and thus convey visceral sensory input (Figure 2-4). Acetylcholine is the major cholinergic parasympathetic neurotransmitter. Noncholinergic neurotransmitters may also play a role [11, 12].

Sympathetic fibers originate from several sources including the lumbar ventral roots (L2–L5), postganglionic hypogastric nerves, and the splanchnic nerves (T5–T12). The lumbar ventral nerve roots provide the main sympathetic supply to the colon. These nerves synapse on the inferior mesenteric ganglia. From there, the post-ganglionic nerves course along the inferior mesenteric artery to synapse on the enteric ganglia. The postganglionic hypogastric nerves also originate from the inferior mesenteric ganglia and then join the pelvic plexus. The hypogastric nerves primarily innervate the anal sphincters. The splanchnic nerves reach the proximal colon as they course along the blood supply. It is speculated that the lumbar nerves innervate the entire colon while the splanchnic nerves likely only innervate the proximal colon. The primary targets of the sympathetic efferent pathways include myenteric ganglia, submucosal ganglia, blood vessels, and sphincters. Sympathetic innervation is inhibitory to the myenteric ganglia and thus inhibits colonic contractions. However, sympathetic input to sphincter muscle is excitatory. Taken together, sympathetic input decreases peristalsis. Amongst numerous other substances, norepinephrine is a neurotransmitter that is known to exert inhibitory effects via a-2 adrenergic receptors in the myenteric plexus [13, 14].

While central and autonomic innervation is important, the intrinsic (enteric) nervous system is unique in that colon can continue to function even when these circuits have been interrupted. Specifically, the colon exhibits reflexes in the absence of extrinsic neural input. This is due to the complex system of 200–600 million ganglia that comprise the enteric nervous system. These ganglia arise from neural crest cells that colonize the gut during embryological development. The enteric nervous system consists of full reflex circuits comprising sensory neurons, interneurons, and motor neurons. This complex system is regulated by a multitude of neurotransmitters and neuromodulators and is responsible not only for controlling colonic motor activity, but also mucosal ion absorption and secretion and intestinal blood flow [3, 11, 12, 15].

Two major sets of ganglia are found in the colon. The myenteric or Auerbach's plexus is located between the longitudinal and circular smooth muscle layers and plays a crucial role in colonic smooth muscle function. The submucosal or Meissner's plexus regulates ion transport [3, 13–15]. The extreme importance of these two plexuses is clear in children with Hirschsprung's disease in which the ganglia of the myenteric and submucosal plexuses are congenitally absent. The aganglionic segments do not relax and peristalsis is disturbed resulting in severe constipation [14]. There is also a mucosal abnormality predisposing to enterocolitis. Nearly 20 types of enteric neurons have been identified and every class of CNS neurotransmitters has been identified in the enteric nervous system. Besides neurotransmitters, other chemicals act in an endocrine or paracrine function to influence the enteric nervous system. While not totally inclusive, substances identified as playing a role in the enteric nervous system include acetylcholine, norepinephrine, 5-hydroxytryptamine (serotonin), dopamine, substance P, neurotensin, vasoactive intestinal peptide, somatostatin, prostaglandins, and neuropeptide Y [11, 12, 16].

Intrinsic primary afferent neurons (IPANs) are the neurons through which enteric reflexes are initiated. These were initially described as Type II neurons with long axonal processes extending to the mucosa and other neurons. However, it has become clear that other non-Type II neurons also play a crucial role in enteric sensation. Nonetheless, these IPANs function to sense changes in luminal chemistry and pressure as well as colonic muscular tone. IPANs are present in the myenteric and submucosal plexi [12, 14, 15]. While the IPANs monitor luminal stimuli, they need to do this transepithelially, since nerve fibers do not directly have contact with the colonic lumen. Therefore, sensory transducer cells in the epithelium are present to respond to mucosal changes. Enterochromaffin (EC) cells represent a type of this sensory transducer cell. EC cells contain large quantities of serotonin. Nearly 95% of serotonin is found in the gut and most of that is stored in the EC cells. When EC cells are stimulated, serotonin is secreted from the basolateral surface of the EC cells of the lamina propria. This is where the serotonin has access to nerve fibers. Serotonin can be excitatory or inhibitory depending on which type of serotonin receptor with which it interacts. Serotonin is not catabolized by enzymes, but is taken up by specific serotonin reuptake transporters (SERT) present in serotonergic neurons. While beyond the scope of this chapter, it is worth mentioning that in patients with irritable bowel syndrome, mucosal expression of SERT is reduced. The importance of serotonin in the enteric nervous system and the role it plays in irritable bowel syndrome has allowed the development of medications to reduce the symptoms of IBS [3, 12, 15]. The 5-HT3 antagonist, alosetron, has been approved for treatment of IBS-associated diarrhea in women [10, 15]. On the other hand, the 5-HT4 agonist, tegaserod, was initially approved for the treatment of IBS-associated constipation. Tegaserod was withdrawn from the market by the FDA in 2007 because of concerns of potential adverse cardiac events [9, 12, 15].

Colonic Motility

Basic colonic motility requirements include slow net caudal propulsion, extensive mixing of semisolid stool, and uniform exposure of luminal contents to the mucosal surface. The colon also needs to rapidly move stool caudally during mass movements. In addition, the colon must be able to store fecal material in the colon until defecation. As reviewed above, most colonic motility is involuntary and is primarily mediated by the enteric nervous system in association with autonomic parasympathetic and sympathetic input.

Cellular Basis of Motility

The muscular apparatus of the colon consists of two distinctive layers of smooth muscle cells including the circular and longitudinal layers. These smooth muscle cells are interconnected by gap junctions that allow electrical signals to spread in coordinated fashion. Very important to this function are the colonic pacemaker cells, also called the interstitial cells of Cajal. The ICC are cells of mesenchymal origin. The ICC generates electrical pacemaker activity that provides the smooth muscle with the mechanism to produce propulsive rhythmic activity. They also appear to serve as conduits for muscle innervation and may transmit sensory information. In colon biopsy specimens, ICC density is able to be measured by c-Kit immunohistochemistry. ICC occur in the submucosa and myenteric borders [3, 17–20]. ICC of the submucosa (ICC-SM) generate electrical stimuli with an oscillatory pattern of 2–4 Hz. Coupling of the ICC-SM to smooth muscle cells triggers large, slow repetitive depolarizations of the smooth muscle referred to as slow waves. Higher frequency oscillations (17–18 Hz) are generated in the ICC of the myenteric border (ICC-MP), but the slow waves from the ICC-SM seem to predominate [17–19].

Motility Patterns and Measurement

Intraluminal colonic motility measurements (manometry and barostat studies) have provided an understanding of colonic motility patterns. Colonic motor activity is not rhythmic, but is characterized by brief (phasic) and sustained (tonic) contractions. At least seven different patterns of human colonic phasic pressure activity have been identified. These include non-propagating and propagating pressure waves and contractions. Non-propagating pressure waves occur randomly for at least 30 s. Simultaneous pressure waves occur simultaneously at least 10 cm apart with an onset time of <1 s. Periodic colonic motor activity also manifests as discrete random bursts of phasic and tonic pressure waves with a frequency of ≥3 per minute and a cycle duration of ≥3 per minute. Similar discrete bursts of phasic and tonic pressure waves also occur in the rectosigmoid and occur predominantly at night and are referred to as periodic rectal motor activity (PRMA). The function of these non-propagating waves is not well delineated, but they may serve as a means for local mixing of luminal contents and may allow for adequate mucosal sampling [19–22].

Propagating pressure waves and contractions serve to propel the colonic contents in aborad and orad directions. Aborad pressure waves include propagating pressure waves that migrate aborad across ≥10 cm at a velocity of 0.5 cm/s and high amplitude propagated contractions (HAPC) of pressures ≥75 mmHg and that migrate aborad ≥15 cm. HAPCs occur approximately six times a day and serve to move stool *en masse* across the colon. Frequently, but not always, these occur prior to defecation. There are also retrograde waves that migrate orad ≥15 cm with a velocity of >0.5 cm/s [19, 21, 22].

Clear physiologic patterns of colonic motor activity are recognized. Phasic activity demonstrates diurnal variation with activity decreasing during sleep and increasing upon awakening. Phasic activity also increases within a few minutes after a meal and continues for up to 2.5 h depending on the nutrient composition and caloric content of the meal. High fat meals elicit more of a response than carbohydrate rich meals. At least 500 kcal needs to be ingested to predictably cause a colonic response to the meal. Finally, colonic instillation of bisacodyl or intravenous neostigmine induces HAPCs. Colonic tone can be measured with a barostat. In physiologic states, colonic tone increases in response to a meal [17, 21–23].

Altered colonic motility may be manifest as constipation. Patients with constipation can be evaluated with several modalities including radiopaque marker studies, radionuclide scintigraphy, magnetic resonance imaging, dynamic defecography, wireless motility capsule (smart pill®, Given Imaging) evaluation, and colonic manometry/barostat studies [17, 18, 22, 23]. While the details of these modalities are discussed in subsequent chapters, it is worth mentioning several common findings in patients with slow transit constipation. Patients with slow transit constipation have a reduced frequency of HAPCs. These patients also lack the normal phasic response that is elicited by the intake of a meal. The diurnal variation of colonic motor activity also may be abnormal in patients with slow transit constipation. Colonic bisacodyl administration also produces a blunted HAPC response in patients with slow transit constipation. A diminished increase in colonic tone following a meal has also been observed in slow transit constipation [21–24]. Loss and injury to the ICC has also been observed in patients with constipation [20]. Taken together, slow transit constipation may be associated with both myopathic and neuropathic etiologies.

Clinical Aspects of Colon Physiology

Ultimately, the main goal of understanding the concepts behind colonic physiology is to be able to translate these into effective therapy for the problems that plague our patients. Subsequent chapters in the text deal more specifically with these issues, but to illustrate this concept, we can consider the use of sacral neuromodulation (SNM). This is not a new therapy; however, its FDA approval for the treatment of fecal incontinence has brought it into the spotlight more recently. In addition to its efficacy for fecal incontinence and its complex interaction with the pelvic floor, European data has also shown its efficacy for the treatment of colonic motility disorders, specifically chronic constipation as well as low anterior resection syndrome. The postulated effectors for its success are based on the known principles of colonic motility

illustrated in this chapter. Dinning et al. performed an elegant study in which patients with slow-transit constipation were treated with SNM. A manometry catheter was positioned colonoscopically, with its tip fixed in the cecum. Electrodes were then placed in both the S2 and S3 foramina and stimulated. They found that stimulation to the S3 nerve root significantly increased pan-colonic antegrade propagating sequences (PS), while stimulation at S2 significantly increased retrograde PSs. During a 3-week trial 75% of patients reported increase frequency of bowel movements and decreased laxative use [25]. The true mechanism of SNM on the enteric nervous system is not known; however, it is hypothesized to affect autonomic innervation, largely through CNS-mediated effects.

The colorectum is a complex organ with multiple roles in human homeostasis. By increasing understanding of its anatomy and complex physiologic components, the colorectal surgeon can gain not only a better understanding of its normal role, but the etiology of derangement in pathophysiologic conditions, as well as an opportunity to develop new therapies based on its known functions. These examples are demonstrated with much greater detail throughout other sections of the text.

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3
Anal Physiology: The Physiology of Continence and Defecation

Vitaliy Poylin and Thomas E. Cataldo

Abbreviations

RAIR	Rectoanal inhibitory reflex
SNS	Sacral nerve stimulation
FI	Fecal incontinence
MR	Magnetic resonance

Key Concepts

- The innervation of the anal sphincter complex is a mixed sympathetic and parasympathetic crossed over system that provides redundant safeguards to continence.
- Normal continence and defecation require intact sensation and motor control and reflexes to sense, retain, and voluntarily expect the rectal contents at a socially appropriate time and place.
- The normal physiology of the anus can be disturbed in a variety of ways resulting in lack of control, inability to expel, or chronic pelvic pain.
- The process of childbirth can contribute significantly to alteration in anorectal anatomy and physiology resulting in a variety of disorders of defecation and/or incontinence.

Introduction

The physiology of the anus and its surrounding structures is in essence the physiology of continence and controlled defecation. This is a physiology of balance and continuous feedback and complex reflexes. Normal continence requires a balance between the pressure inside the rectum and the combined tone of the internal and external sphincters. Defecation and the controlled passage of gas or stool at socially appropriate circumstances required very fine sensation and ability to discern the rectal contents. Defecation requires the balance to tip in favor of the rectal pressure and contraction with simultaneous coordinated relaxation of the pelvic floor and internal and external sphincters. Disturbance in any part of this complex balance can result in incontinence either through reduced anal tone, excess rectal contraction, reduced sensation, or the inability to differentiate the consistency of the rectal contents. Alternatively, disorders tipping in the opposite direction may result in inability to properly or completely empty the rectum. Additionally, more proximal conditions resulting in chronic diarrhea or constipation may tip the balance. And forces even higher can contribute to the behavioral and psychosocial aspects of ordered and disordered function of the rectum and anal canal.

It is the patient and skilled practitioner who listens to what the patient can teach and tell about how and what they are doing combined with a good working knowledge of anorectal physiology that can effectively intervene in disorders of defecation.

Normal Anatomy and Physiology

For a detailed discussion on the anal anatomy, see Chap. 1. Briefly, the musculature of the anus is made up of three concentric cylindrical structures. The internal sphincter is derived as an extension of the involuntary circular smooth muscle of the rectum. The longitudinal muscle is derived from the outer longitudinal smooth muscle of the rectum, and ultimately does extend into the anus and turns medially through the internal sphincter to comprise the muscles of Treitz that support the internal hemorrhoids. Lastly, the external sphincter is derived from the voluntary striated muscle of the pelvic floor.

The internal sphincter begins as a condensation of the inner circular involuntary smooth muscle of the GI tract at the top of the surgical anal canal, as the top of the anorectal ring. It

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extends downward to just proximal to the end of the external sphincter in the non-retracted or effaced state. The length of the normal internal sphincter can vary from under 2 to over 4 cm. In the unstimulated state, the internal sphincter is chronically contracting and contributes approximately 50–75 % of the resting tone of the anus. It appears as a 2–3-mm hypoechoic band on transanal ultrasound imaging [1]. The internal sphincter may not represent a perfect cylinder in all patients. Proximal anterior defects have been demonstrated in nulliparous women [2]. Length and bulk of the sphincter can be reduced if deprived of innervation or hormones in postmenopausal women (progesterone).

The external sphincter is a cylinder of striated muscle that extends downward from the levator ani muscle to the distal anoderm. Like the internal sphincter, it exists in a chronically contracting state, but has the potential when stimulated under voluntary control, to more than double the tone of the anus above the resting state. It was initially considered to be divided into three separate segments, deep, superficial, and subcutaneous; this is no longer thought to be a meaningful distinction [3].

Between the internal and external sphincters is a layer of mixed smooth and striated muscle that is made up of an extension of the longitudinal outer muscle of the bowel and some striated extensions of the levator ani muscle. As it extends downward, some aspects of the muscle cross medially through the internal sphincter to contribute to the suspensory muscles that hold the hemorrhoid complex in place (Trietz's muscle). Distally, the conjoined muscle extends to the anoderm and through the external sphincter radially to form the corrugator cutis ani [1, 4, 5].

Innervation of the Anus and Pelvic Floor

The parasympathetic fibers to the rectum and anal canal emerge from the sacral foramina at the S2, 3, 4 levels. They join the sympathetic hypogastric nerves in the pelvic plexus. From there mixed postganglionic fibers extend to the lower rectum and anal canal. Thereby internal sphincter is innervated by L5–S4 mixed autonomic function in crossed fashion so that unilateral injury still results in preserved function. The external sphincter is similarly innervated from branches of S2–3 via the inferior rectal branch of the pudendal nerve and the perineal branch of S4. This nervous distribution also carries the nerves of sensation and contributes to the functional aspects of continence. The upper anal canal contains a high density of free and organized sensory nerve endings [1, 6, 7]. Organized nerve endings include Meisner's corpuscles (touch), Krause's bulbs (cold), Golgi-Mazzoni bodies (pressure), and genital corpuscles (friction).

Normal Continence

Rectal Capacity

Normal continence first requires a location to temporarily hold and assess the contents and expel them under control. The rectum therefore needs both a baseline capacity and the compliance to expand and the force to expel. The empty rectum is a low pressure vessel with the capacity to receive stool from the sigmoid. It must have the capacity to expand significantly to accommodate stool under pressure. Patients with diminished rectal capacity will suffer from fecal frequency, urgency and frequently may contribute to incontinence.

Pressure and Motility

Baseline pressure in the rectum is low, about 5 mmHg with frequent low amplitude contractions every 6–12 s. Occasional high pressure waves up to 100 mmHg have been demonstrated. The anal canal shows overlapping of resting tone with small oscillations of pressure and frequency of 15 cycles/min and cm H_2O. Pressure in the anal canal ranges 10–14 times that of the rectum. Motor activity is more frequent, and contractile waves are of higher amplitude in the rectum than in the sigmoid [6]. This reverse gradient provides a pressure barrier resisting forward motion of stool and may propel stool back into the sigmoid as part of delaying bowel movements when it is not convenient [7]. Slow waves are observed in the anal canal with increasing frequency distally. This gradient is thought to help maintain continence by propelling the contents back into the rectum and helps keep the canal empty.

Rectoanal Sensation and Sampling

The rectum does not itself have receptors for proprioception. The conscious sensation of the need to defecate lives in the levators and the anal canal, hence the preserved sensation in patients who have had complete proctectomies and anal anastomoses. Distention of the rectum triggers contraction of the external anal sphincter and significant internal anal sphincter contraction. As first described by Gowers in 1877 [8] the rectoanal inhibitory reflex (RAIR) is thought to allow the highly innervated sensitive epithelial lining of the upper anal canal to sample the contents of the distal rectum to determine its quality and consistency. This allows the patient to accurately discern flatus from stool, and liquid stool from firm. Alterations in this mechanism, either through reduced sensation, or impaired sampling can result in incontinence either through overflow or inability to

discern that defecation is occurring. Impaired anal sensation has been associated with childbirth, perineal descent, and mucosectomy [9–11].

Structural Considerations

In addition to the baseline resultant tone provided by the anal sphincter complex and the puborectalis sling, the entire structure is held closed by the angulation created by the puborectalis in its chronically contracted unstimulated state. This angle between the axis of the anus and the axis of the rectum is between 80° and 90° and is responsible for the majority of gross fecal continence. It may increase normally above 90 while sitting and will extend beyond 110° during normal defecation. In cases of dysfunctional defecation where the puborectalis does not sufficiently relax the angle can be enhanced by squatting and flexing the hips to an angle of less than 90°. The flap valve theory advocated by Parks suggests the anterior rectal mucosa constitutes a flap that lies over the upper end of the anal canal. Increased inter abdominal pressure not associated with defecation increased the angulation and closes flap more firmly over the upper anal canal. The flap is opened when the perineum descends and the anorectal angle is straightened. The anterior mucosal flap certainly seems to be a component of the issue when patients suffer from obstructed defecation and have evidence of internal rectal prolapse.

Role of Hemorrhoids in Normal Continence

It has also been postulated that the normal function of the hemorrhoids, in a non-pathologic state serve as an additional important component of normal continence. Stelzner referred to the hemorrhoids as the corpora cavernosum of the anus [12]. These vascular cushions have the ability to expand as needed to create a seal above the anus creating the fine tuning of continence. This concept is supported by the observation that after formal hemorrhoidectomy some patients experience minor alterations in continence.

Sensation and Innervation

Within the pelvis, the innervation of the proximal anal canal descends from the rectum. The rectum has a mixed sympathetic and parasympathetic innervation derived from the hypogastric nerves and the sacral parasympathetic nerves through the pelvic plexi. Extrapelvic innervation comes to the anus from the pudendal nerve derived from S2 to S4 via the inferior rectal nerve and ultimately spreads around the anus from both sides entering at lateral to slightly anterior positions. There is known to be significant crossover innervation around the anus as a complete disruption of either pudendal nerve does not result in asymmetric sphincter atrophy or fecal incontinence.

Sensory innervation within the rectum is sensitive only to stretch, resulting in vague sensation to visceral pelvic pain. Distal rectal stretch or distention can result in significant parasympathetic stimulation of the vagus nerve, thereby resulting in bradycardia and hypotension. The lack of pain-sensitive innervation proximal to a short distance from the dentate line is what allows some hemorrhoid treatments to be performed with relatively limited discomfort, e.g., elastic band ligation, injection sclerotherapy, and stapled hemorrhoidopexy. Somatic sensory innervation begins in the anal transitional zone proximal to the dentate line for a short variable distance 0.3–1.5 cm [13]. Within this zone, there is a dense collection of nerve endings for pain, touch, pressure, and temperature. As such they are theorized to be an integral part of the sampling aspect of the continence mechanism [14]. These fibers are derived from the pudendal branches, and complete anesthesia to this area can be provided by bilateral anal nerve blockade.

Normal Defecation

Normal defecation is a complicated mechanism that relies on a close interaction between the somatic and autonomic nervous system, which includes the conscious and unconscious control of both sensory input and muscle contraction. The process starts with stool arriving into the rectum and sampling as described above. If it is not an appropriate time for defecation, the anal sphincter will contract and rectum will start to distend [7]. This process continues with progressive distention of the rectum without a person's full awareness; patients are often unaware that they have stool in the vault during rectal exam. Conscious sampling, however, is also present during this process (one can differentiate between gas and stool and allow gas to pass, even with full rectum). As the rectum continues to expand, a person becomes aware (with continuous sampling) There is an urge defecate that usually lasts for a few seconds and can be controlled by further contraction of external anal sphincter (efferent nerve endings end in lumbosacral spine which is under higher control, that allows conscious suppression of the urge) [15, 16].

When it becomes socially appropriate to proceed, the defecation process again relies on both conscious and unconscious response. The process starts with contraction of abdominal musculature (Valsalva), which is also associated with contraction of the sigmoid colon to move stool forward. Pelvic floor musculature on the other hand relaxes, which is a combination of relaxation of puborectalis (releases sling around anorectal junction) and relaxation of remaining levator muscle. This allows the pelvic floor to descend slightly and straighten the anorectal angle. The rectum itself starts to contract and both internal and external sphincters relax. Even if the sphincters are not completely relaxed, at this point pressure in the rectum exceeds pressure in the anal canal and defecation will occur. This process can also be aided by assuming the squatting position, which increases

the intra-abdominal pressure and straightens the rectum further. If the conscious decision to defecate is made during sampling (rectum is contracting, internal sphincters already partially relaxed) allowing the external sphincters to relax, then defecation will occur [17–19]. Once begun a number of patterns can occur. There may be a single evacuation of the rectal contents accompanied by mass peristalsis of the left and sigmoid colon clearing the bowel in one continuous movement, or the passage of smaller volumes of stool individually over a short time requiring recurrent efforts and straining [20]. These two patterns and variations thereof are dictated by the habits of the patient and other factors including the overall consistency of the stool.

If a large volume of stool is delivered quickly to the rectum, normal rectal compliance and accommodation may be insufficient. In this case the patient with normal sensation and function will have a sense of acute urgency and can forestall defecation for 40–60 s with the use of voluntary contraction of the external sphincter to allow accommodation or move to a socially appropriate location to evacuate.

For obvious reasons, studying this process can be difficult, and thus our understanding of it relies on what is observed during testing (e.g., defecography—Video 3.1; and anal manometric studies) [2, 6], patients with neurologic deficits (specifically spinal injuries) [21] and animal studies. Animal studies revealed the presence of different, more sensitive mechanoreceptors in the rectum, when compared to the colon that are most responsive to tension and rapid distention [22–24]. These tension mechanoreceptors respond to both rectal distension and muscle contraction consistent with the observation that rectal filling sensation coincides with the period of raised rectal pressure during rectal distension [3–6].

Physiology of Tibial Nerve and Sacral Nerve Root Stimulation in Fecal Continence

For many years it has been recognized that chronic electrical stimulation of nerves entering the pelvis has had effects of visceral function and activity. Unilateral stimulation of the S3 or S4 nerve as it exits the foramen has been used for urinary incontinence for over 30 years; meanwhile benefits for fecal incontinence have been recognized as well. Most recently, sacral nerve stimulation has shown encouraging results for idiopathic constipation as well [25–27].

The exact mechanism of how sacral nerve stimulation creates its effect remains unclear. The physiological control of defecation relies on the coordinated sensory and motor efforts of the colon, rectum, and anus. Current opinion is that disordered defecation is secondary to several disturbances of anorectal and colonic physiology and not purely a sphincter disturbance in patients with FI or colonic transit failure in constipation. It is therefore likely that the therapeutic effects of SNS are due not only to peripheral motor stimulation of the anal sphincter complex in patients with FI as was initially proposed, but instead due to changes in the motor and/or sensory function of the combined functional anorectal unit. Such a hypothesis would explain the "paradox" of SNS effectiveness in both FI and chronic constipation, i.e., it is likely that SNS is effective in both conditions not due to paradoxical actions in each, but instead by improvement of common pathophysiologies. This hypothesis also explains why FI and disordered defecation so frequently coexist [28]. Similarly, intermittent stimulation of the posterior tibial nerve has a beneficial effect on fecal incontinence through a mechanism that is not fully understood [29].

In 2014, Carrington et al. performed an exhaustive review of the scientific literature regarding sacral and peripheral nerve stimulation for fecal incontinence and constipation [15]. To summarize their findings, SNS had no demonstrable effect of rectal compliance or motility. It did seem to reduce hypersensitivity in those with reduced capacity and hypersensitivity, while increasing sensitivity in those patients with reduced sensitivity. Additionally sacral nerve stimulation increases mucosal blood flow when on and returns to baseline when off. There are higher levels of the neuropeptide substance P identified in rectal biopsies of those undergoing stimulation, which reverses after it is discontinued. The exact importance or impact of these two phenomena has not been identified as yet. Forty studies have examined changes in anal sphincter function through the use of anorectal manometry. Direct comparison between studies is difficult, as equipment specifications, study protocol, and method of results reporting is extremely variable between centers. Fourteen studies reported a significant increase in voluntary anal squeeze, with eight of these also reporting an increase in resting pressure.

Spinal Cord Injuries and Defecation

The most interesting and informative studies in normal and abnormal defecation are provided by patients with spinal cord injuries. However, it is important to remember that this is a very heterogeneous group of patients with degrees of injury that can vary significantly from patient to patient [7]. High spinal cord injuries (above T7) interrupt higher control and sensation of the abdominal and pelvic floor musculature as well as colon in rectum [12, 29, 30]. This combination allows for lower tone in the colon and rectum. The decrease in propulsive ability of the colon, the decrease in tone resulting in distention and slower transit through the colon explains the constipation that often accompanies high spinal cord injuries. These patients are often unable to generate adequate intra-abdominal pressure or take squatting position to aid defecation [11, 13, 31]. At the same time, there is an unopposed stimulation of the lower neurons that increase contraction and spasticity of the pelvic floor and external anal sphincters.

Sensation is often also impaired which can eliminate the normal urge to defecate. Interestingly, this often does not affect mechanoreceptors and some patients will report vague sensation of pressure that is then interpreted as a need to defecate [31–33]. As a result, these patients often have chronic constipation caused by both diminished sensation and inability to move stool forward [12, 13]. This is combined with pelvic floor dysfunction and the inability to identify the urge to defecate and an inability to relax the pelvic floor. They often rely on a strict bowel program, which is a combination of laxatives, rectal stimulation and manual disimpaction [11–13]. Rectal stimulation can allow some patents to have decreased anal sphincter pressure. They can also experience fecal incontinence as a result of overflow and overfill of the rectum and well as damage to sphincters from manual disimpaction [12–14, 34].

Patients with low spinal cord injuries such as Cauda Equina Syndrome often have impaired afferent fibers that results in loss of tone in the internal and external sphincter muscle as well as impaired sensation. This can result in significant incontinence since any generation of intra-abdominal pressure may result in bowel movement [11–13].

Obstructed Defecation

Obstructed defecation is a poorly understood group of disorders resulted from an alteration in sensation, muscle relaxation or both. In many patients with these problems, the exact cause is multifactorial and/or the inciting event is not easily identifiable [35]. It is possible that an abnormality in the sensory mechanism is the primary insult in a number of patients [36]. Normal sensation is an integral part of normal defecation. It allows for appropriate reflexes, mostly importantly the anal sampling RAIR. Some causes of abnormal sensation can be fairly evident in patients such as those with significant proctitis (infectious or inflammatory) or those after anorectal injury/surgery. In the absence of above, the etiology is less clear. Dysfunction may be associated with conscious/subconscious inhibition of the need to defecate during childhood [15, 16, 37, 38]. According to this theory, repeated delays in defecation result in altered sensation that eventually leads to dyscoordination between the anorectal and pelvic floor musculature. As this process continues, even though patient may continue to experience “normal” urge to defecate, changes in sensation cause an increase in stimulation of lower (lumbosacral) neuronal loop; the relaxing effects of the upper parts of the nervous system are insufficient to overpower the abnormal stimulation. Once this occurs, and pelvic floor musculature such as puborectalis and sphincter complex fail to relax appropriately, increasingly higher intra-abdominal pressure is needed to overpower the rectal/anal pressure to evacuate [39]. This failure can be associated with pain and a feeling of incomplete evacuation.

Independent of what part of normal defecation was affected first, over time there is probably significant damage to the sensory pathways including receptors, efferent nerves and muscles. With time, this process will also start affecting the structural integrity of the pelvic floor. Obstructed defecation disorders include intussusception, rectocele, nonrelaxing puborectalis/levator muscle spasm, dyssynergic puborectalis, as well as enterocele and rectal prolapse. Although causes of enterocele and rectal prolapse may be complex, these disorders in their pure form are mechanical obstructions to defecation and thus beyond the scope of this chapter. Here we describe a few pathological conditions that are more directly affected abnormalities in sensory-muscular neurological loop.

Intussusception is mucosal descent causing blockage of the lower rectum/anal canal. It is possible that it is a primary process in some patients arising from redundancy of mucosa, possibly poor tone, and pelvic floor descent (either primary structural problems or as a result of childbirth and muscle/nerve damage in women). In most patients it is likely a secondary process resulting from increased pushing and decreased relaxation. Once developed, intussusception itself generates mechanical blockage to defecation and further attempts to generate more pressure to evacuate stool [17–19, 40].

Rectocele likely develops by a similar process. It is defined as greater than 2 cm of rectal wall out pouching or bowing anteriorly while straining. It can be accompanied by intussusception. Rectoceles are caused by abnormal relaxation of the pelvic floor/sphincter complex or structural defects in the rectal wall created during childbirth. As a result, when a patient attempts to evacuate, generated pressure delivers stool anteriorly towards the weakened portion of the wall that is not contracting appropriately. This generates a sensation of bulge and incomplete evacuation and can be at least in part relieved in women by pushing on the vagina in the initial stages of the disease (Figure 3-1**;** Video 3.2). However, a rectocele itself is a very common finding on the exam and only a small proportion of patients who have it will ever have symptoms. Most symptomatic patients likely have a combination of a weaker rectal wall as well as dyssynergy of the sphincters or puburectalis [15, 41].

Pelvic floor dyssynergy (pelvic outlet obstruction) results from a failure of the puborectalis and/or sphincter complex to relax. It can also be caused by an abnormal contraction during evacuation. As a result, when a patient tries to evacuate the anorectal angle may not increase or may even become sharper. A patient’s natural response is to generate higher pressures in which only further worsens the symptoms. Over time, these changes likely cause more damage to the musculature and nerves. Similar to the rest of the disorders in this group, rectal sensation is also impaired, but whether it is a result of long-term damage or from an inciting event is unclear [15, 16, 18].

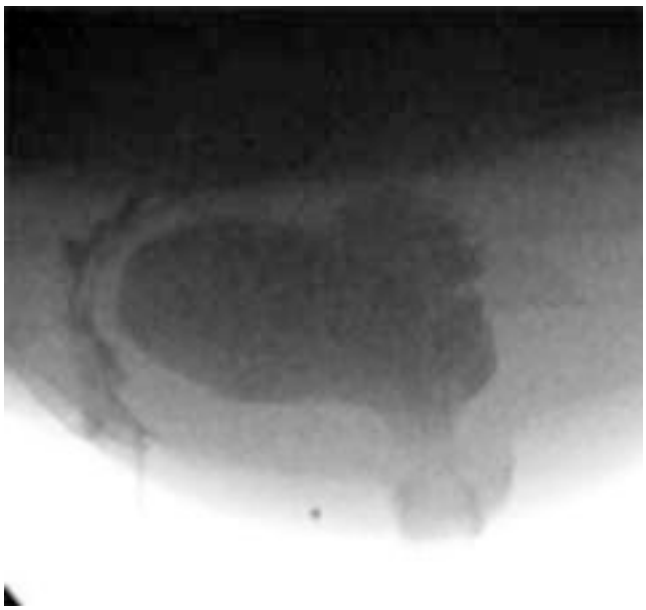

FIGURE 3-1. Defecography still image of a rectocele.

Functional Anorectal Pain

Most causes of anorectal pain can be routinely ascribed to such common conditions as anal fissures, hemorrhoidal disease, or inflammatory bowel diseases (see Chap. 11). There is a small group of disorders, however, that seem to be related to more functional, rather than structural problems [42].

Levator ani syndrome (levator spasm, puborectalis syndrome) is often described as dull pain, high in the rectum that is often made worse with sitting. By definition, it should last more than 20 min at the time and other causes are excluded [43]. Etiology of this condition is unclear. Interestingly, even though episodes may be triggered by difficult defecation (along with emotional stress among other things) it is not always associated with difficulty evacuating. Similar to other functional disorders, it is possible that alternations in sensation, and perhaps behaviors (deferring defecation, damage with hard stool) could contribute to the development and propagation of this problem. In addition, it is thought that prolonged muscle contraction may result in compression of vasculature, which then leads to relative ischemia and an increase in anaerobic consumptions. That in turn can cause activation of nociceptors in the muscle (bradykinin, Substance P), and further decrease in relaxation with spasm and pain [15, 16, 22].

Proctalgia fugax is a sudden severe anal pain, lasting seconds to minutes, that disappears completely. The etiology is unknown, but it seems to be related to stress. It is associated in some patients with a thickened internal sphincter muscle. Some studies suggest smooth muscle contraction is responsible for this pain [15, 16, 44].

Pathophysiology of Obstetric-Related Problems

One of the worrisome potential sequelae of pregnancy and delivery is fecal incontinence. It can develop as a result of direct disruption of the anal sphincter, muscle, connective tissue or pudendal nerve injury [45]. During pregnancy, there is direct pressure on the pelvic floor as well as hormonal changes. Progesterone, released during pregnancy, acts by suppressing contraction of smooth muscle and prevents premature uterine contraction. This leads to decreased gut motility (that can contribute to constipation) and diminished tonic contraction of anal sphincters [25, 46]. Androgen, progesterone, and estrogen receptors are found in squamous epithelium of the anal canal, indirectly supporting possible effects of this hormone on the sphincters [47]. In addition, progesterone causes ligamentous laxity [48]. When combined with increased intra-abdominal pressure, these changes contribute to stretching of the pelvic floor musculature, widening of the levator hiatus, and potentially pudendal nerve injury. The pudendal nerve can be affected during pregnancy by stretching as well as traction injury during delivery as described below [49]. Pudendal nerve injury can affect both external sphincters by de-innervating them and causing muscle atrophy as well as by affecting sensory components and altering RAIR. Evidence of neuropathy in pelvic floor musculature has been found after delivery as well as in idiopathic FI and constipation.

Labor further complicates issues of continence. Pushing during labor can significantly exacerbate the above problem [50]. It can be associated with further muscle stretching or even evulsion and pudendal nerve injury [25]. This explains why a longer second stage of labor (pushing) is associated with higher rates later in life. In addition, there is likely effects of traction injury (increased baby weight is associated with higher chances of immediate and long-term problems). Use of additional devices to aid labor such as forceps and vacuum is associated with increased incidence of FI [25, 51]. This is likely related to direct damage to the sphincters as well as traction injury. Tearing and episiotomy are additional risk factors for FI and related to direct damage to the sphincter complex. Cesarean section is associated with lower incidences of flatus and stool incontinence, but this difference is smaller when comparing emergent Cesarean sections and vaginal deliveries. Emergent cesarean are often initiated after failure of labor to progress following significant pushing [52]. Although many women experience immediate mild problems with incontinence to flatus or stool, most have enough reserves to compensate. Presence of symptoms after delivery is an additional risk factor for developing significant incontinence in the future when age further weakens already damages muscles and nerves.

Urogynecological Considerations and Pelvic Pain

With all its complexity, the pelvic floor is anatomically very small area. It includes pelvic musculature and their corresponding nerves responsible not only for maintenance of continence and normal defecation, but also normal urinary gynecologic function. Not surprisingly, although dysfunction in any single system is common, more than one system is frequently affected. For example, physiologic and muscular changes associated with pregnancy and labor which effects the posterior compartment often has similar effects on middle and anterior compartment structures as well. Uterine prolapse is more common in multiparous women, especially in complicated deliveries. Urinary problems including incontinence are also common [16, 25]. The mechanism for urinary issues is likely the same as in posterior compartment problems, which is a combination of hormonal effects as well as direct damage to the pelvic floor muscle, nerves, and sphincters. Widening of the levator hiatus has been shown to affect middle and anterior compartments as well as posterior one. This can result in uterine and bladder prolapse in addition to rectal prolapse, intussusception, and rectocele [21]. Pregnancy and delivery effects on anal sphincters can affect urinary sphincters as well. It is common for women presenting with urinary incontinence to report fecal incontinence as well [16, 25]. As a result, urogynecologists see and treat a number of patients with anorectal problems, especially since the treatments available are similar between specialties (e.g., pelvic floor physical therapy, sacral nerve stimulation). Pelvic floor prolapse problems, especially of the middle compartment, may contribute to obstructed defecation. For this reason care should be taken to obtain full history of pelvic floor problems. Otherwise one risks missing significant contributors to patients' symptoms and may compromise success of treatment.

Another common problem is pelvic pain, and women with these symptoms are often referred directly to gynecologists, although underlying cause could be levator spasm or pelvic floor dyssynergy [23]. These problems are also commonly treated by our urogynecology colleagues utilizing similar techniques including physical therapy and other pelvic floor relaxation techniques. Diagnostic techniques employed by urogynecologists to diagnose anterior pelvic problems are often the same (MR defecography and conventional cine defecography, anal manometry). As a result, when patients present with anorectal problems related to pelvic floor issues, one has to maintain vigilance in identifying related problems with anterior and middle compartment since they can affect overall symptom control as well as how these problems are ultimately addressed.

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4
Endoscopy

Kurt Davis and Michael A. Valente

Key Concepts

- The endoscopic examination is critical for patients with colorectal complaints and is a key component of the complete colorectal examination.
- The anoscopic examination is the best way to adequately evaluate the anoderm, dentate line and evaluate for internal and external hemorrhoids, and anal masses.
- Multiple bowel preparation regimens exist, but regardless of which prep is chosen, splitting the timing into the half the day prior to and half the day of the procedure results in a better prep.
- There is no ideal sedation medication, but the endoscopist must be familiar with the side effect profile of any medications being used and be prepared and comfortable with any reversal agents.
- Adjunctive maneuvers employed with endoscopy serve as the markers between seasoned experts and novices: these include abdominal pressure, adjusting position, torqueing, and dithering.
- PillCam endoscopy allows the clinician to evaluate the small bowel for occult gastrointestinal bleeding, insipient tumors, polyposis syndromes, or Crohn's disease.

Introduction

The endoscopic evaluation of the patient with colorectal complaints forms the keystone of the physical examination. It allows the physician to visually assess the entirety of the intestinal tract from the mouth to the anus and allows for the diagnosis, treatment, and monitoring of the effectiveness of any therapy. It is imperative for all physicians treating patients with colorectal diseases to be facile in the more common endoscopic diagnostic and therapeutic techniques.

The Complete Anorectal Examination

While performing any anorectal or endoscopic examination, an anxiety-free and modest environment must be created. Most patients will exhibit nervousness, and apprehension, which can cause anal or gluteal spasm that will preclude an accurate assessment. The examiner must reassure the patient and keep anxiety and embarrassment to a minimum. This can be accomplished by effective communication, keeping the patient covered as much as possible, keeping ancillary personnel in the room to a minimum and not rushing through the examination. Physicians should strive to actively communicate with the patient as the examination is progressing.

Before a discussion on endoscopic techniques, a thorough understanding of the initial steps of the anorectal examination is compulsory for success and patient well-being and satisfaction. Before any instrument is inserted, a focused history must be obtained coupled with a local examination. The local examination is an important precursor to any endoscopic examination and consists of: proper patient positioning, visual inspection, and manual palpation of the anorectal region followed by the digital rectal examination. Once this stepwise examination is complete, then inspection of the colon, rectum, and anus can commence.

Patient Position

There are two positions that may be used for effective anorectal examination. The choice of position may depend on several variables including available equipment, patient age and comorbid status, and physician preference. Regardless of the position chosen, both the patient and the examiner must be comfortable in order to carry out an effective anorectal and endoscopic evaluation.

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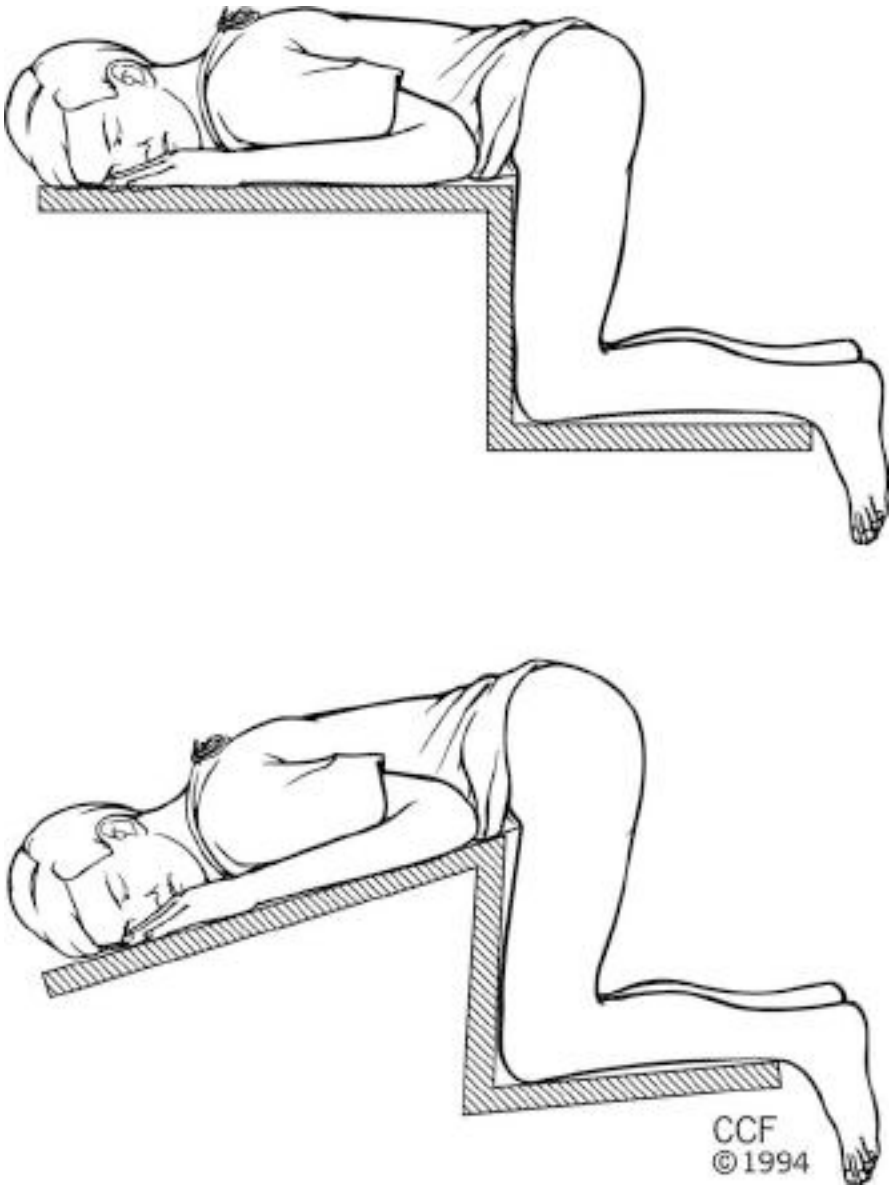

FIGURE 4-1. Prone jackknife position. Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography ©2015. All Rights Reserved.

Prone Jackknife

The prone jackknife position (knee-chest), performed with the aid of a specialized proctoscopic table is commonly employed and allows for excellent visualization of the entire anus and perianal and perineal region, as well as the sacrococcygeal region. The patient kneels on the padded portion of the table and leans forward with their trunk and arms extended forward (Figure 4-1). The table is angled forward gradually so that the patient's buttocks and perineum are superior, while the head and feet are inferior. This is a comfortable position for the examiner and also allows for easy insertion of the anoscope, proctoscope, or flexible sigmoidoscope. This position is well tolerated by most patients, but should be avoided in various situations, such as debilitated patients, recent abdominal surgery, cardiopulmonary issues, various arthritic/rheumatologic conditions, or late pregnancy.

Left Lateral

The left lateral recumbent (Sims') position is also widely used, especially if a specialty bed is not readily available (Figure 4-2). This position is very well tolerated and is well suited for elderly or debilitated patients. The patient lies on their left side and the thighs are flexed as to form a 90° angle with the trunk. It is imperative that the buttocks project slightly beyond the edge of the examining table. This position will allow for excellent visualization of the perianal and sacral regions, but the anterior perineum is often obscured and requires the retraction of the buttock by an assistant. Anoscopic or endoscopic evaluation is easily performed in this position.

Inspection and Palpation

Proper stepwise visual inspection of the perineum, anal canal, rectum, and vagina should precede any other examination.

FIGURE 4-2. Left lateral (Sims') position. Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography ©2015. All Rights Reserved.

Proper lighting is essential, and various light sources are commercially available, including overhead lights, gooseneck lamps, or headlamps. It should be noted that the "clockface" nomenclature is not recommended for localizing anorectal findings. This nomenclature is dependent upon the position of the patient, and hence different interpretations of the true location may differ from examiner to examiner. It is more proper to delineate anatomical location using the cardinal quadrants (i.e., left lateral, right anterior, right posterior). This is the practice most commonly employed by colorectal surgeons.

An overall assessment of the shape of the buttock and inspection of the lower sacrococcygeal area is undertaken. This is followed by the gentle spreading of the buttocks to gain proper exposure. A great deal of information can be gained from visualization. The physician should examine for and document any scarring, fecal soiling, purulence, blood or mucous drainage, excoriations, erythema, anal sphincter shape, perineal body bulk, hemorrhoidal disease, skin tags, overt signs of inflammatory bowel disease, external fistulous openings, rectal prolapse, neoplasm, and any evidence of previous anorectal surgery. Next, the patient is asked to strain (Valsalva maneuver) to help determine and assess for perineal descent, uterine, vaginal, or bladder prolapse, or rectal prolapse. It should be noted that the best position to evaluate rectal prolapse is in the sitting position on the toilet or commode after an enema has been administered. Gentle and directed palpation of the anorectal region also gives the examiner a great detail of information. Gently touching the anal verge will elicit the anocutaneous reflex (anal wink), which is indicative of an intact pudendal nerve. Additionally, gentle spreading of the anus will help elicit an anal fissure or ulceration. Palpation of the gluteal region can help identify an abscess, external opening of a fistulous tract, or possibly a mass.

Digital Rectal Examination

The digital rectal examination (DRE) is simple and is typically well tolerated and should be performed before all endoscopy of the rectum and colon. A well-performed DRE will provide information regarding the contents and potential pathology of the anal canal, distal rectum, and adjacent organs. The DRE may also permit an assessment of the neurological function of the muscles of fecal continence. While the medical school maxim of the only patient not receiving a DRE is the one that lacks an anus is obviously excessive—there are relative contraindications to performing this portion of the exam. These include painful lesions such as an anal fissure, thrombosed external hemorrhoids, grade IV internal hemorrhoids, and neutropenic patients. The keys to a successful DRE can be summarized by simple rules: adequate lubrication, gentleness, and attention to detail [1]. It is important to minimize pain during DRE as this may affect patient cooperation during endoscopy.

After proper communication with the patient, a well-lubricated index finger is placed across the anus to lubricate the general area. The fingertip is then gently inserted into the anal opening. Lubrication should be warmed if possible, and lidocaine jelly should also be available. If the patient's response is an involuntary spasm of the internal sphincter, the examiner should withdraw their fingertip and gently try again. Ask the patient to bear down as to pass a stool. This maneuver will cause relaxation of the entire sphincter complex and should facilitate an easy digital insertion [2]. The finger should be gradually and slowly advanced. The distal rectum and anal canal along with surrounding structures should be investigated in an organized and stepwise fashion. Resting anal tone followed by squeeze tone should be assessed. Assessment should be made of the entire circumference of the lumen by gently sweeping around the entire anus and distal rectum. Anteriorly in a male, the prostate should be palpated and assessed for nodularity, hypertrophy and firmness. In the female, anteriorly palpate for a rectocele. The cervix and uterus can also be palpated. Posteriorly, the presence of a presacral (retrorectal) mass may be palpated. Bimanual examination may be necessary when examining a female patient in order to adequately examine the rectovaginal septum and associated adnexal structures. Redundant rectal mucosa may be palpated as well as a stricture or narrowing. Induration or a fibrous cord, representing an internal fistulous opening, may also be felt on DRE. Exclusion of any masses should be carefully performed. The patient should be asked to perform a Valsalva maneuver to potentially bring any lesions of the upper rectum or the rectosigmoid into the examiners reach. If a mass is palpated, its size, position,

FIGURE 4-3. Various beveled anoscopes. From *top* to *bottom*: Large Hirschmann (short bevel); Buie-Hirschmann anoscope (long bevel); small (pediatric) Hirschmann anoscope.

characteristics (sessile, polypoid, ulcerated), mobility (mobile, tethered, fixed), and relationship to other structures (distance from the anal verge, distance for the anorectal ring) must be accurately recorded.

The levator ani/puborectalis muscles can also be assessed on DRE with evaluation of both the strength and function of these muscles, along with any tenderness on direct palpation, indicating a possible pelvic pain disorder. When a patient with good sphincter function is asked to squeeze these muscles, the examiner's finger will feel the muscle tighten and will have his finger pulled up into the rectum. Additionally, when the examiner pulls posteriorly on these muscles, the anal opening should gape and then return to normal, representing an intact reflex pathway to the thoracolumbar spinal cord.

Anoscopy/Proctoscopy

The anorectal examination in most cases should be followed with some component of an endoscopic investigation to complete the workup. This may include anoscopy, proctoscopy, or flexible endoscopy. Anoscopy and proctoscopy are typically performed in the clinic setting without sedation or mechanical bowel preparation and are tolerated quite well by the patient.

It should be noted that the term proctoscopy will be used as to describe the rigid scope implemented to evaluate the rectum and the distal sigmoid colon. Therefore, "rigid proctosigmoioscope" or "proctosigmoidoscopy" will be referred to as "rigid proctoscopy" or "proctoscopy." Sigmoidoscopy refers to the use of the flexible sigmoidoscope.

Anoscopy

Anoscopy is the examination of the anal canal and the distal rectum. Anoscopy offers the best way to adequately evaluate the anoderm, dentate line, internal and external hemorrhoids, papillae, fissures, anal masses, and distal rectal mucosa.

The anoscope is a relatively simple instrument consisting of an obturator, the scope itself, and a light source. There exist several variations in type, size, and length of anoscopes available. Additionally, commercially available anoscopes include slotted or beveled styles, reusable or disposable, and lighted or unlighted. The particular type of instrument and light source used are based on individual preference, expense, and prior training (Figure 4-3).

Regardless of the choice of instrument used, the examination is initiated only after a DRE has been performed (if a DRE is unable to be performed secondary to pain, spasm, or stenosis, an anoscopic exam should not be attempted). For most instances, cleansing of the anorectum with an enema is not warranted. The anoscope (with obturator in place) is liberally lubricated and gently and gradually advanced until the instrument is fully inserted. It is important to align the anoscope along the anterior–posterior axis of the anus. If unsuccessful due to patient intolerance, remove the scope, reapply lubrication and try again. After successful insertion, the obturator is removed and examination of the anorectum undertaken. The obturator should then be reinserted while the scope still in the anus, and the anoscope is gently rotated to examine a new area.

The prone jackknife position offers good visualization and ease of insertion as well does the lateral position, however, an assistant must retract the buttock if the lateral position is utilized. During the examination, the patient is asked to strain while the anoscope is withdrawn to visualize any prolapsing anorectal mucosa or hemorrhoidal tissue. During the anoscopic examination, hemorrhoids may be banded or sclerosing agents injected and biopsies of any suspicious lesions may be obtained. Complications are rare, but may include occasional bleeding from hemorrhoids or inadvertently tearing the anoderm.

Proctoscopy

Rigid proctoscopy is suitable to examine the rectum, and in some patients, the distal sigmoid colon may also be evaluated. Similar to the anoscope, the proctoscope consists of an obturator, the scope itself, and a light source. Illumination is supplied by a built-in light source and a lens is attached to the external orifice of the scope after the obturator is removed. The main difference between an anoscope is that a proctoscope needs to hold air so the rectum can be distended. This is achieved by having a bellows attached to the scope, which allows for insufflation of air to gain better visualization and negotiation of the scope proximally through the rectum. A suction device or cotton tipped swabs can be used to remove any endoluminal debris or fluid or to enhance visualization (Figure 4-4). Ideally, the patient should receive an enema preparation within 2 h of

FIGURE 4-4. Proctoscopy suction catheter and long cotton-tipped applicators for clearing small amounts of fecal debris. The cotton-tipped swaps are also used for manipulating the rectal and anal mucosa during anoscopy and proctoscopy.

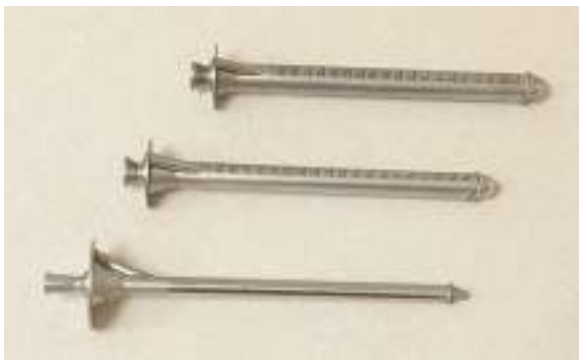

FIGURE 4-5. Proctoscopes. From *top* to *bottom*: large proctoscope, length 25 cm, diameter 19 mm; standard proctoscope, length 25 cm, diameter 15 mm; pediatric proctoscope, length 25 cm, diameter 11 mm.

the procedure in order to clear any stool, which may make passage of the scope and visualization difficult.

Proctoscopes are available in three sizes, all 25 cm in length. Different luminal diameters include 11, 15, and 19 mm (Figure 4-5). The largest scope is suited best for polypectomy or biopsies in which electrocoagulation may be needed. In most patients, the 15 mm × 25 cm scope is ideal for a general inspection. There is also a disposable plastic, self-lighted proctoscope which is available for use.

The procedure can be performed in either the prone jackknife or left lateral position as previously described. When properly performed, the patient feels little to no discomfort. Pain may occur with stretching of the rectosigmoid mesentery due to over insufflation of air or the scope hitting the rectal wall. An overzealous examiner trying to advance the scope too quickly or too proximal is the main cause of patient discomfort. Unfortunately, the art of using the rigid proctoscope has declined in recent years due to the ubiquity of flexible endoscopy. The proctoscope however, still has important indications, especially in the identification and precise localization of rectal lesions or in the evaluation of rectal bleeding. Contraindications are similar to anoscopy and include painful anorectal condition such as acute fissure, incarcerated hemorrhoids, recent anorectal surgery (<1 month), or anal stenosis.

After adequate lubrication, while the obturator is held in place with the right thumb, the instrument is gently inserted into the anal canal and advanced approximately 4–5 cm in the general direction of the umbilicus. The scope is then aimed toward the sacrum and advanced for an additional 4–5 cm. The obturator is then removed and the viewing lens is placed. Minimal air insufflation is used in order to open the bowel lumen and gently withdrawing and advancing the scope to straighten out angulations proximally aids in achieving successful navigation. It should be noted that the distal extent reached on proctoscopic examinations averages approximately 17–20 cm and very rarely can the scope be inserted to its full length [3]. If at any time the insertion becomes difficult or painful to the patient, the procedure should be terminated and the farthest extend reached should be recorded.

As the proctoscope is withdrawn from the farthest extent reached, careful examination is performed of the entire circumference of the rectal wall with minimal air insufflation and rotation of the scope. The valves of Houston are flattened out with the tip of the scope to reveal areas just proximal to the folds. If any lesions are found, accurate measurements and descriptions are necessary. These include: size of the lesion, the exact distance from the anal verge, appearance, and location on the bowel wall. Several different types of biopsy forceps are available (Figure 4-6) and biopsies can be done in the office setting with or without the use of electrocautery. Additionally, polyps or small lesions can be snared (Figure 4-7) or fulgurated. Proper suction, electrocautery and irrigation devices should be readily available in the examining room for these purposes (Figure 4-8).

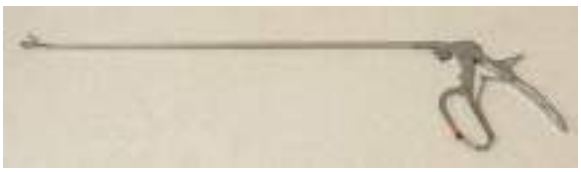

FIGURE 4-6. Turell angulated biopsy forceps. A curved upper jaw allows for 360° rotation. A variety of jaw sizes and types are available.

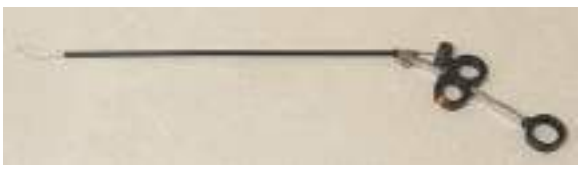

FIGURE 4-7. Rigid-wire (Frankfelt) snare. This snare allows for polypectomy or tumor debulking via the anoscope or proctoscope.

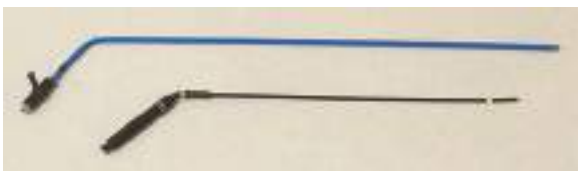

FIGURE 4-8. Suction catheter/electrocoagulation catheter. From *top* to *bottom*: an insulated catheter for combining suction and electrocautery, and an electrocoagulation catheter.

Serious complications during rigid proctoscopy are rare, with bleeding the most common, especially after biopsy or polypectomy. Perforation is a very rare occurrence and should not happen with proper technique. Before the introduction of flexible endoscopy, rigid proctoscopy was the standard technique to evaluate the distal sigmoid and rectum and large series of patients have shown minimal to no complications [4, 5]. Perforation of a normal rectum or sigmoid colon is a rare occurrence, but passing a scope or excess insufflation in a diseased or inflamed rectosigmoid may prove hazardous and caution must be undertaken in patients with inflammatory bowel disease, radiation proctitis, diverticulosis/diverticulitis, volvulus, or malignancy.

Anal and Rectal Ultrasound

Endoanal ultrasonography (EUS) is a highly reliable and reproducible imaging modality that provides information on the anatomy and function of pelvic floor structures, anorectal disease processes, and anorectal tumors. In experienced hands, EUS is accurate, with high sensitivity and specificity for detecting anal sphincter injuries. Advantages of EUS include the relatively inexpensive cost to perform and its widespread availability. One obvious disadvantage of EUS is that like all ultrasound examinations, it is an operator-dependent test, with varied published results for the same disease process.

Circumferential assessment of the anal canal and distal rectum is made possible by a 360° rotating transducer that is either a 7 or 10 megaHertz (MHz) probe for two-dimensional (2D) units or a 13 MHz probe for three-dimensional (3D) (Figure 4-9). In recent years, the use of 3D units has increased, with a similar sensitivity in detecting both external and internal sphincter defects, but it has been demonstrated that with the 3D units, intra-observer variation is decreased and thereby the diagnosis of pathology has been increased [6].

Prior to testing, patients receive an enema to clear the anorectum of any stool that may interfere with images due to artifact. Additionally, as with rigid proctoscopy above, EUS should not be performed on patients diagnosed with anal stenosis or fissure-in-ano, as this will undoubtedly render the test uncomfortable for the patient and difficult for the examiner to perform. EUS is most commonly performed with the patient in the left lateral recumbent position. After a gentle DRE, the well-lubricated ultrasound probe is inserted and slowly advanced and then withdrawn to view the entire area of the anal canal/rectum (in modern systems, a crystal moves up and down along the transducer to acquire images while the probe is held stationary).

The anal canal is divided into three levels on EUS: upper, middle, and lower based on anatomic landmarks. The upper anal canal is defined by the U-shaped puborectalis muscle; the middle canal has both EAS and IAS muscles visible (this is also where the IAS is at maximum width); and in the lower anal canal, only the most distal external sphincter fibers are visualized (Figures 4-10, 4-11, and 4-12). Highly reflective tissue on EUS reveals a hyperechoic (white) image, while poorly reflective tissues are hypoechoic (black). Thus, the smooth muscle-based IAS, which has higher water content, shows up black on EUS. In post-obstetrical sphincter injuries, the defect is usually located anteriorly and encompasses the EAS and may involve the IAS as well. In cases of postsurgical or posttraumatic injuries of the anal sphincters, defects can involve either or both muscles and may be unifocal or multifocal in nature (Figure 4-13). The accuracy of EUS compared to surgical findings has been reported to be as high as 90–100% by some authors and additionally, EUS has been used after operative sphincter repair to show the overlap of the muscles and to confirm a proper repair has been performed.

Flexible Endoscopy

Flexible Endoscopic Insertion Techniques

Due to the fact that no two colons are the same, the techniques described here are generalizations and guidelines to help navigate the flexible endoscope to its completion. The technique of performing an endoscopic examination, like any invasive procedure, is best learned under the watchful eye of a seasoned mentor, rather than reading a text; however, there are some points that can be generalized.

The keys to a comfortable and efficient endoscopic examination include a mastery of the insertion techniques described here to maintain a straight scope while keeping pain and trauma to the patient at a minimum. The skilled endoscopist must be able to use torque, tip deflection, dithering/jiggle, and push and pullback techniques as second nature in order to successfully achieve these goals. The techniques described here apply to both sigmoidoscopy and colonoscopy.

Torque

The twisting motion applied to the shaft of the scope by the endoscopist's right hand is called torque (Figure 4-14). Torque is an essential technique that allows for a stiffening of the scope and alters the direction in which the tip deflection controls work. Torque also has the ability to increase the scopes resistance to avoid troublesome loops. Torque can be to the right (clockwise) or left (counterclockwise) based on whichever direction seems to work best for the task at hand. Gentle torque is used while keeping the scope straight and a more forceful torque is used when removing or following a loop.

Tip Deflection

The tip of the endoscope should always be kept in the middle of the bowel lumen. The techniques of torque, pull/push, and

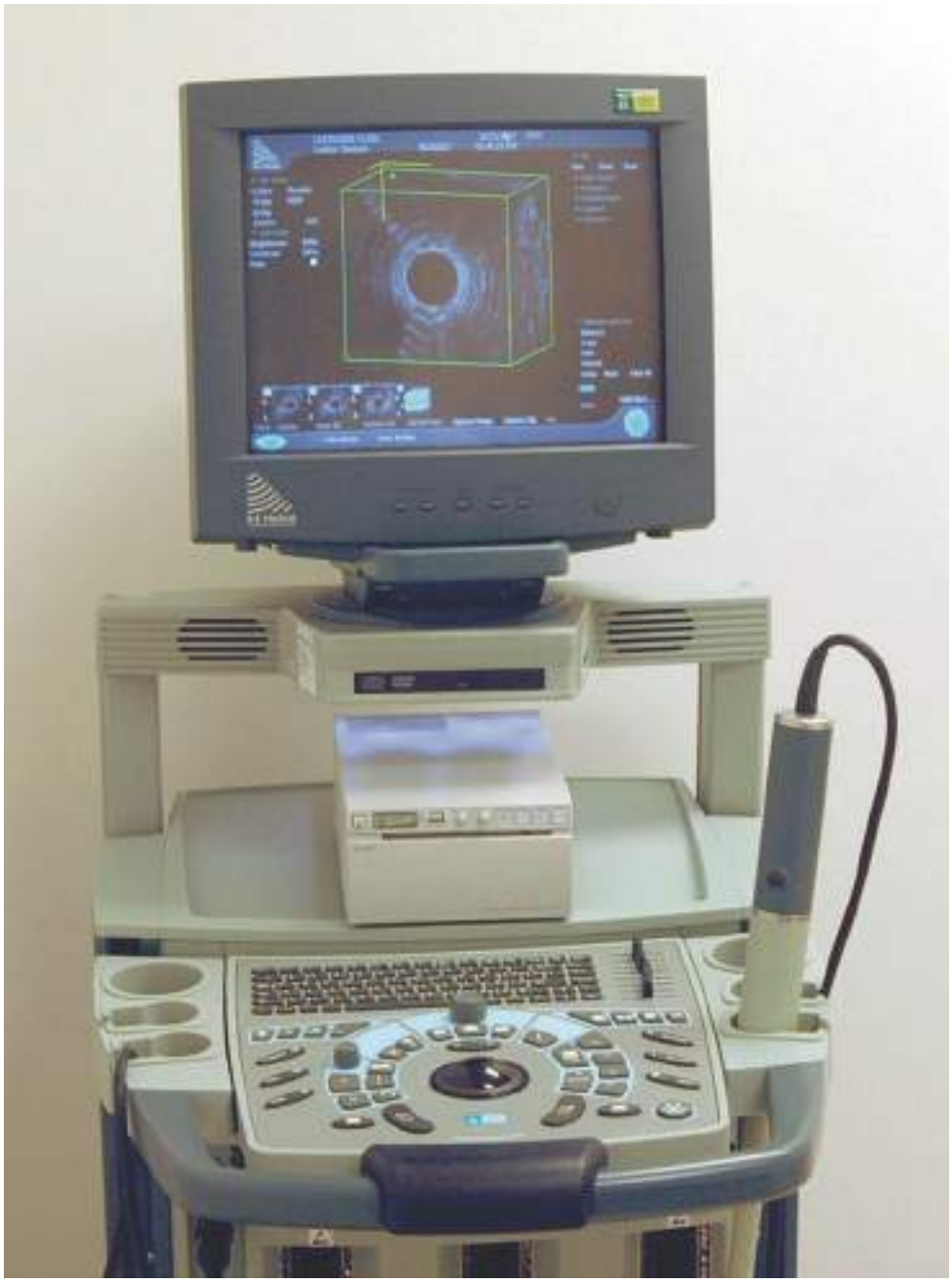

FIGURE 4-9. B-K Medical (Herlev, Denmark) three-dimensional anorectal ultrasound equipment.

dithering-jiggle will tend to move the tip in several directions. The endoscopist should bring the tip back by controlling both the outer and inner controls with their left hand. With practice, the endoscopist should be able to control and use both tip deflection control knobs in different directions with only the thumb of the left hand. The preference of locking one or both of the knobs is operator dependent. It should be noted, however, that the endoscopist should strive to keep their right hand on the shaft and their left hand on the tip deflection controls throughout the examination in order to maintain proper feel of the scope and to not miss opportunities for advancement and also to avoid "losing ground" by having the scope slide retrograde.

Dithering/Jiggle

The rapid up-and-down, side-to-side, and to-and-fro movements of the shaft of the scope are referred to as dithering or jiggle (Figure 4-15). This technique can be combined with rapid torqueing and rapid in-and-out movements of the scope. The object of this important maneuver is to pleat the colon onto the shaft of the endoscope in order to shorten the colon and to keep the scope straight. Every endoscopist should employ this technique throughout the entire insertion, even when scope advancement appears easy in a straight portion of the colon, especially the descending and transverse colon.

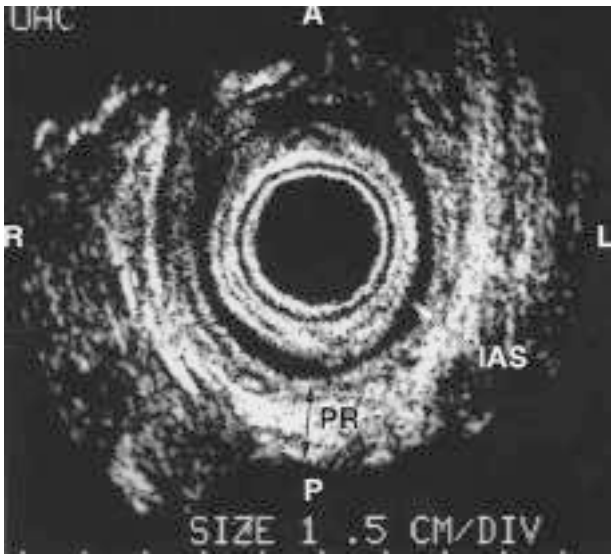

FIGURE 4-10. Two-dimensional endoanal ultrasound view of the U-shaped puborectalis muscle (PR). *IAS* internal anal sphincter.

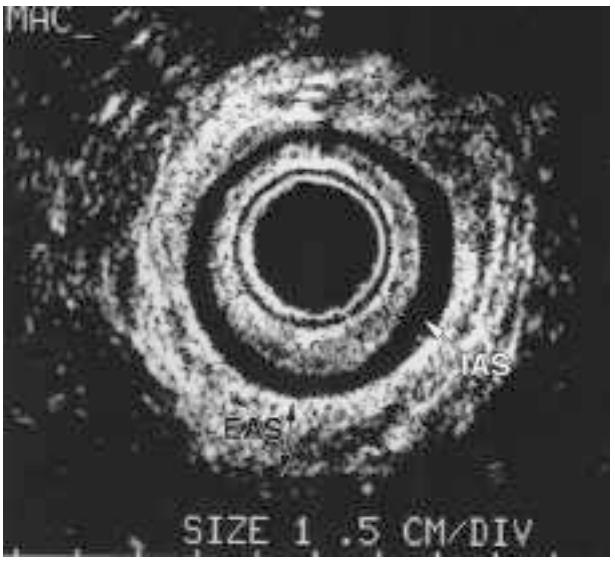

FIGURE 4-11. Two-dimensional ultrasound from the mid-anal canal. This ultrasound image represents normal, intact internal anal sphincter (IAS) (hypoechoic) and external anal sphincter (EAS), (hyperechoic).

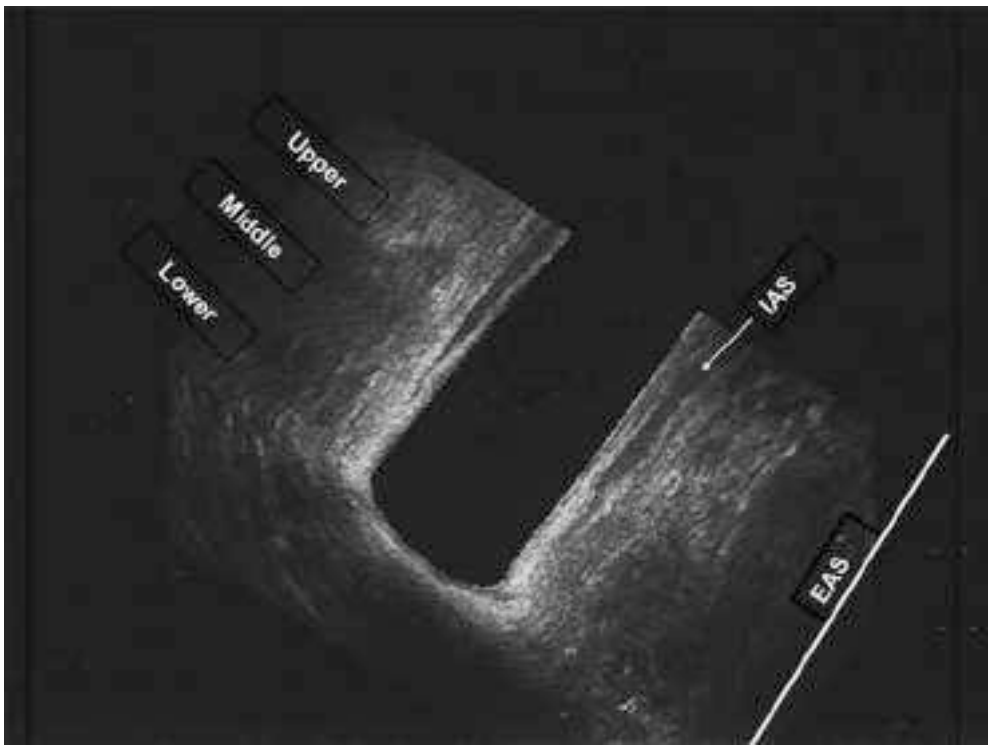

FIGURE 4-12. Three-dimensional coronal view of the upper, middle, and lower anal canal. *EAS* external anal sphincter, *IAS* internal anal sphincter.

Aspiration of Air and Breath Holding

As insufflation of air accumulates during the procedure, the colon becomes distended and elongates, thereby making the goal of reaching the cecum farther away and often causing discomfort to the patient. The judicious and cautious use of air is important during the examination, but thoughtful and calculated aspiration/suction of air is an important adjunct insertion technique. Aspiration of air can allow the scope to

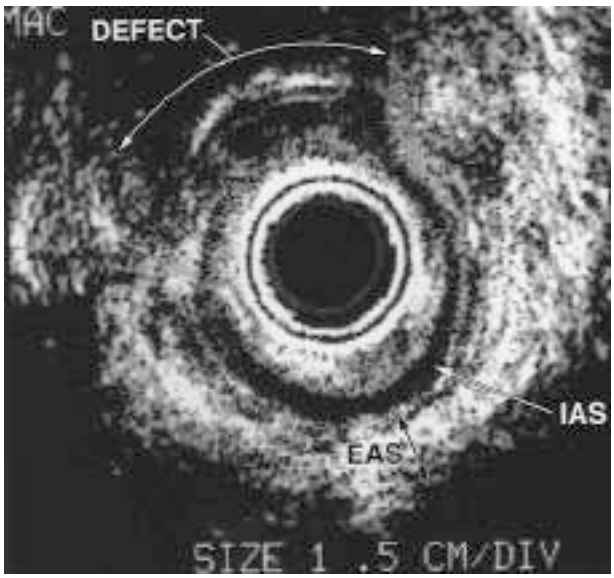

FIGURE 4-13. Anteriorly located defect of both the EAS and IAS in the mid anal canal.

FIGURE 4-14. Torque—a twisting motion of the endoscopist's right hand to the left (counterclockwise) or right (clockwise). Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography ©2015. All Rights Reserved.

advance the tip past a turn (especially at the hepatic flexure) without needed to push the scope forward and likely forming a loop. Once the tip of the scope is past the turn, advancement is much easier due to the straightness of the scope.

Another technique to help the scope around the flexure is the "breath-hold" maneuver. While negotiating difficult turns and bends (especially the hepatic and splenic flexure), have the patient take a deep breath in and hold it. This causes the diaphragm to drop and pushes the flexures over the scope and thereby allows the scope to pass [7]. Aspiration of air and breath holding can be used in conjunction along with precise abdominal pressure techniques.

FIGURE 4-15. Jiggle (Dithering)—rapid side-to-side, up-and-down, and to-and-fro movements of the endoscope in order to pleat or "accordion" the colon onto the scope's shaft. Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography ©2015. All Rights Reserved.

Slide-By

The technique of pushing blindly into a turn or bend with maximum tip deflection and without full visualization of the colon lumen to guide the scope along the curvature of the bowel wall to advance the scope past the turn is termed a slide-by technique. Slide-by is a controversial technique that should never be used by unsupervised trainees or novice endoscopists due to the potential dangers and complications that may occur, namely perforation. Slide-by should be terminated if there is any resistance to forward advancement or the mucosa becomes blanched at the tip of the scope. Slide-by can be very painful to the patient because it causes tension on the bowel mesentery and will need to be terminated if not tolerated by the patient. Once the slide-by is successful, the scope needs to be straightened and any loops need to be reduced. Modern endoscopes have a great deal of tip deflection and thus, slide-by is not as commonly employed as when endoscopy was in its infancy (Fig. 4.16).

Adjunctive Maneuvers for More Difficult Examinations

The adjunctive maneuvers employed with endoscopy often serve as the markers between seasoned experts and novices. There are several different maneuvers including abdominal pressure and other external manipulation provided by an assistant under the direct supervision of the endoscopist. In addition it is possible to adjust the position of the patient to either the supine or prone positions. There are also commercially produced overtubes, which are seldom required now with the advent of adjustable stiffness endoscopes. All of these adjunctive maneuvers are designed to reduce the loop formation of the endoscope or to prevent it from reforming

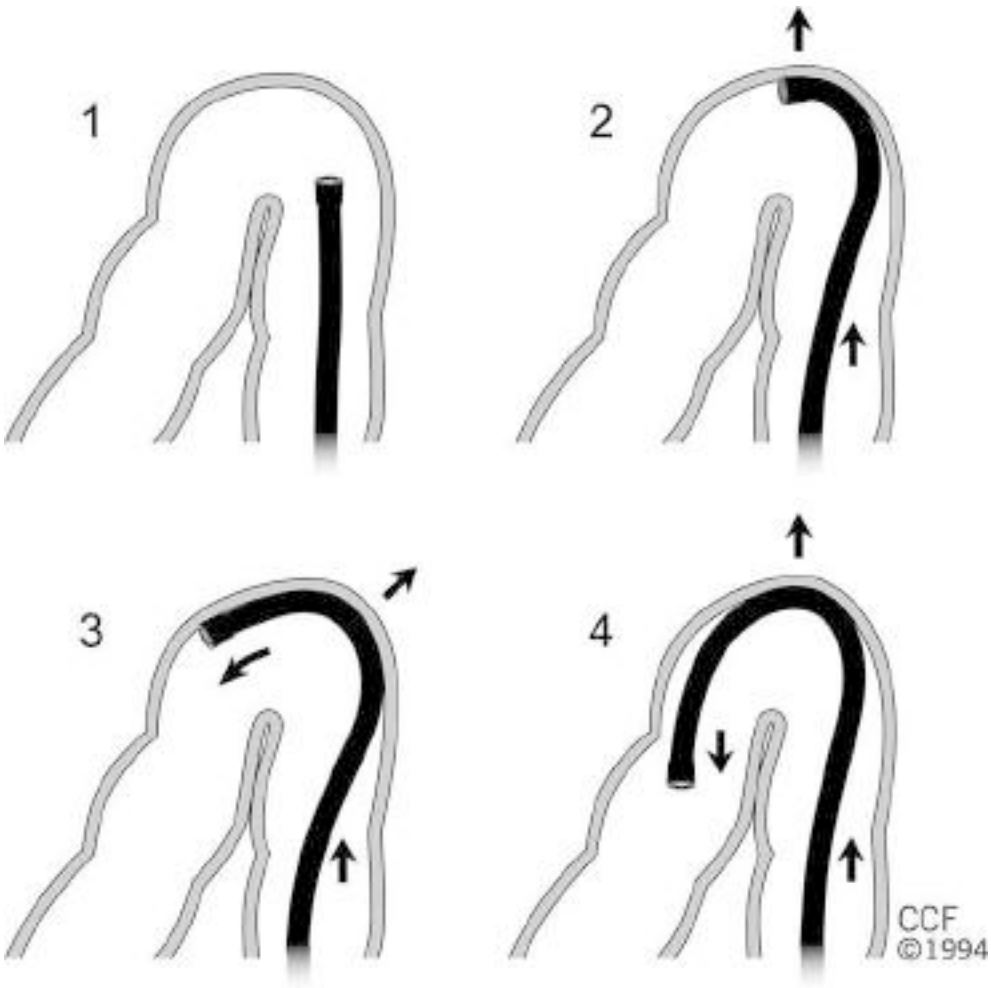

FIGURE 4-16. Slide-by technique. The colonoscope is blindly pushed around a bend, guided by the curve of the scope and the curvature of the bowel wall. Slide-by should be terminated with excessive patient pain or blanching of the mucosa occurs. This technique should be avoided in diseased bowel or in the presence of diverticuli. Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography ©2015. All Rights Reserved.

once it has been reduced. In one study evaluating the use of ancillary techniques, directed abdominal pressure was used in 56% of colonoscopies, while turning to the left and right was performed in 17% and 23% of exams respectively [7]. Like all techniques, however, they are best learned under the supervision of a seasoned endoscopist.

The most likely cause of a difficult examination is the formation of a loop, which makes further advancement of the scope impossible, painful, and potentially harmful. It should be remembered that when facing a difficult-to-negotiate area of the colon, a different technique must be employed to facilitate success. It is the authors' opinion that once a technique has failed twice, a new technique should be employed. The technique of withdrawing the scope all the back to the rectosigmoid and starting the procedure over is a valuable maneuver and again should not be overlooked. It may be necessary during a difficult examination to "take a few steps backwards in order to move forward."

Patient Position

While the procedure starts with the patient on their left side, transitioning to a supine position may ease the navigation of the sigmoid, sigmoid/descending, splenic flexure, and hepatic flexure. Alternatively, if the patient begins supine, turning to the left lateral will help achieve the same goal. While the patient is being moved with the assistance of the endoscopy team, the endoscopist should keep their eye on the screen and attempt to maintain the scope in the middle of the lumen, as it is common for the scope to lose its position during patient movement. Turning the patient to their right side is a technique that is especially useful when the examination has reached the ascending colon and it cannot be advanced into the cecum. Placing the patient into a prone position can also be performed, but this position is often difficult and cumbersome for the staff and the patient. Patient safety must be maintained during this maneuver. The authors

finds this technique useful very occasionally to help the scope navigate in more obese individuals, as the act of having their abdomen on the bed supplies abdominal pressure.

Abdominal Pressure

The technique of splinting certain redundant areas of the colon with external pressure via the abdominal wall may help reduction in loop formation. However, this technique is most effective when a known loop is present and the endoscopist can guide the staff to apply pressure in the correct location. The most common areas of looping are the sigmoid and transverse colon, but simply pressing on different areas of the abdomen will often clue the examiner where the problem exists. Initial attempts at "blind pressure" should be from superior and right of the umbilicus directed toward the left lower quadrant. This has the effect of stabilizing the sigmoid colon and giving counter-pressure to the scope. However, pressure may need to be applied to different areas of the abdomen in order to successfully reduce the loop. The scope should be in the middle of the lumen and as straight as possible before pressure is asserted. This technique should be performed gently and it should not cause the patient any discomfort.

Turning the Scope

During the navigation of a very difficult or acute turn, it may help to change the entire angle of approach of the scope. This is accomplished by torqueing the shaft 180°, while keeping the tip of the scope stabilized in the middle with the help of the deflection knobs (Figure 4-17).

Sigmoidoscopy

The use of the flexible sigmoidoscopy (FS) in the office setting has increased in popularity due to its many applications, ease of use and high yield of findings over conventional rigid proctoscopy. In approximately 50–85% of patients, the entire sigmoid colon can be evaluated and in some patients, the splenic flexure can be reached as well. The flexible sigmoidoscope is easier to handle and the technique is easier to learn than colonoscopy, but nonetheless, supervised training is compulsory. In terms of selective screening purposes, the flexible sigmoidoscope offers a three to sixfold increase in the yield of findings, especially neoplasms, in the rectum and sigmoid colon compared to rigid proctoscopy. It should be noted, however, that FS is not an adequate substitute to colonoscopy for detection of colonic polyps and neoplasms.

The flexible sigmoidoscope is available from various companies with minor variations between them. In general, the channel size ranges between 2.6 and 3.8 mm, the diameter of the scope ranges between 12 and 14 mm and the length varies from 60 to 71 cm (Figure 4-18). As with most instruments in a surgeon's armamentarium, the exact instrument selected is based on surgeon preference in regards to availability, cost and surgeon experience.

The indications for FS in the office setting are broad. FS is an excellent tool to evaluate the patient with bright red rectal bleeding as well as a myriad of other conditions such as in radiation proctitis, nonspecific proctitis, rectal ulcer, anorectal Crohn's disease, or suspected distal neoplasms. FS also

FIGURE 4-18. Flexible sigmoidoscope.

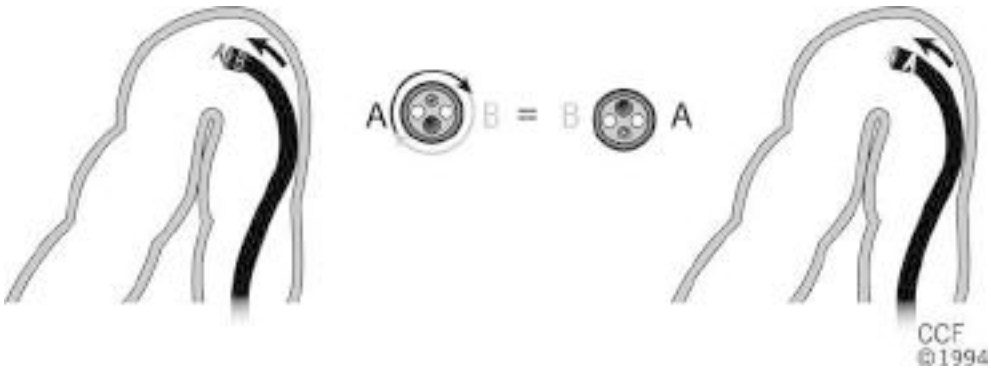

FIGURE 4-17. Turning the scope. This maneuver allows the examiner to change the angle of approach to a turn. Scope torque of 180° is accomplished while the deflection controls keep the tip centered in the lumen. Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography ©2015. All Rights Reserved.

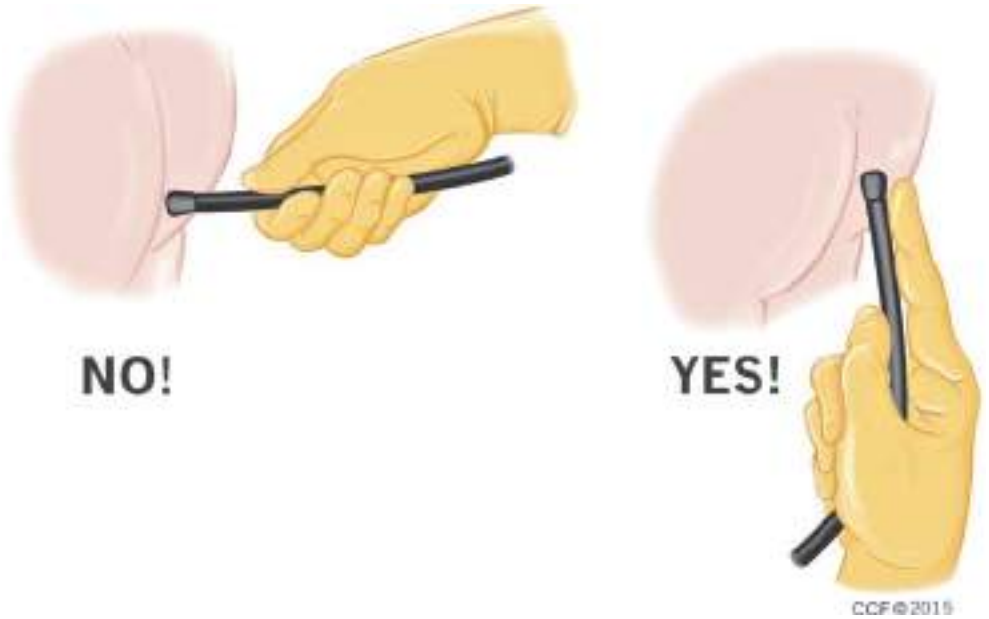

FIGURE 4-19. The flexible endoscope should be inserted "side first" for less painful passage through the anal canal. Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography ©2015. All Rights Reserved.

has utility in examining and acquiring cultures or biopsies of the distal colorectum in diarrheal states, ruling out *Clostridium difficile*, infectious and ischemic colitis. Radiographical abnormalities can be confirmed with the use FS as well as diagnosing or for the follow-up of inflammatory bowel disease. Additionally, postoperative evaluation of distal anastomoses can rapidly be performed, evaluating for stricture or recurrence of cancer as well as recurrences after local excision.

Patients are typically given one to two enemas prior to the procedure and generally do not require oral laxatives or dietary restrictions. The position that offers the easiest approach is the left lateral recumbent but the prone jackknife position can also be used. Sedation is not typically necessary in the vast majority of patients.

The well lubricated scope is inserted "side first" rather than "end on" which allows for the edge of the endoscope to act as a leading point and avoids pushing the blunt end "*en face*" against the anal sphincter with subsequent trauma and pain (Figure 4-19) [2]. After proper insertion of the scope, gentle air insufflation is achieved and the scope is advanced under direct visualization to approximately 10–12 cm. The instrument is then passed into the sigmoid colon by a combination of torqueing in either the clockwise or counterclockwise direction and short advancement and withdrawal (dithering). These maneuvers are used to advance the scope as far as the splenic flexure, if amendable. The endoscopist should use a combination of these techniques along with air insufflation, suction and irrigation to successfully advance the scope. After the scope has been advanced to its extent, careful and thoughtful withdrawal is achieved slowly, in order to evaluate the entire mucosal surface. Any lesions that are detected can be biopsied or have brush cytology performed to establish a diagnosis. Additionally, small polyps can be removed with cold or hot biopsy forceps. Larger polyp removal may be best suited during a subsequent colonoscopy when a full bowel preparation has been achieved. It is important to remember that FS is excellent at examining the proximal and mid rectum as well as the left and sigmoid colon, but is suboptimal for the most distal anorectal disorders, and therefore, another method such as anoscopy should be employed to visualize this area.

Complications of FS are uncommon but may be serious or life threatening when they do occur. Over distention of air will cause abdominal pain and patient discomfort or possibly perforation due to barotrauma. Perforation is most common at the distal sigmoid where it angulates from the relatively fixed rectum at the sacral promontory. It is critical for the endoscopist to be aware of any patient discomfort during the procedure, to use as little insufflation as necessary and abort the procedure if necessary. Electrocoagulation should be avoided or used very judiciously in biopsies or snare techniques unless the patient has received a full mechanical bowel preparation to reduce the risk of explosion due to the presence of hydrogen and methane gas present within the bowel lumen.

Colonoscopy

The colonoscopic examination is often at the center of the evaluation and treatment of many patients with intestinal complaints. A thorough colonoscopy allows the physician to completely evaluate the mucosa of the terminal ileum, colon,

and rectum as well as to obtain biopsies or photodocumentation of any abnormalities identified. The colonoscopy also remains at the forefront of the screening for colorectal carcinoma. The procedure also plays a central part of the clinical practice of most colon and rectal surgeons. Over 90% of colon and rectal surgeons reported performing colonoscopies as part of their regular practice, with these surgeons reporting an average of over 40 endoscopic procedures a month. Clearly the performance of colonoscopy plays a central role in the training and practice of colorectal surgeons across the world [8].

Indications and Contraindications

The specific indications for performing a colonoscopy are multiple and the endoscopic evaluation and management of these conditions is covered in the appropriate sections elsewhere in this text. There does exist some debate regarding the appropriateness of performing the procedure in varying clinical scenarios and an attempt to ensure the appropriateness of the procedure has been sought. In 2000, the American Society for Gastrointestinal Endoscopy and in 2008 the European Panel on the Appropriateness of Gastrointestinal Endoscopy was revised to EPAGE II [9]. Each published their respective appropriateness guidelines regarding when to perform a colonoscopy. The EPAGE II guidelines are intended to serve as a guide for referring physicians and is available to the clinician online at: http://www.epage.ch/, allowing the consulting physician to ensure the procedure is indicated prior to making the referral to an endoscopist. Despite the existence of these guidelines, they have not been widely accepted [10].

Using either of these two sets of guidelines, there are numerous publications demonstrating that many colonoscopies are indeed inappropriate. Using the ASGE guidelines there have been reports ranging from a 13% inappropriate procedure rate [11] to 18% [12]. These are even higher when the European criteria are utilized. Inappropriate procedure rates of 30% are reported [13], and these percentages have been confirmed in several multi-institutional studies [14, 15]. One reason for these high numbers is that an open access practice pattern is common among many physicians who perform endoscopy [16]. Indeed, these guidelines are designed primarily for the open access endoscopy scenario, where the endoscopist serves more as a technician: performing and interpreting the procedure for the physician ordering the procedure. These studies show that it is often surgeons that fall outside the ordering guidelines. Since colon and rectal surgeons seldom perform endoscopy in these open access systems, there are no studies evaluating the appropriateness of colonoscopies performed by these subspecialty surgeons.

The only absolute contraindication for performing a colonoscopy is in a patient who requires immediate operative intervention. All other contraindications are relative and are at the discretion of the endoscopist. Patients with active colitis or those with a recent intestinal anastomosis are at higher risk for complications but a careful endoscopic examination can be safely conducted in these patients [17]. As with any procedure being performed, the benefits must outweigh the risks.

Bowel Preparation

Unlike in elective colon surgery there is no controversy surrounding the necessity of mechanical bowel preparation prior to a colonoscopy. The bowel prep is of critical importance in order to be able to adequately examine the entire colon, with inadequate cleaning reported in up to 27% of patients [18]. It is often considered the most unpleasant part of the procedure on the part of the patient and a great deal of research has gone into making it more effective and the process more palatable for the patient. Despite this, the optimal regimen has yet to be determined [19]. While many practitioners add additional dietary restrictions such as protein restriction or a low residue diet for 2–3 days prior to the procedure but there are no studies that validate these practices.

There remain numerous options for bowel preparation prior to the procedure with three broad categories of agents in use: osmotic agents, polyethylene glycol (PEG) solutions and stimulants. The choice is somewhat practice-dependent, although more practitioners use PEG-based preparations in their practices than the osmotic agents. Osmotic agents such as Sodium Phosphate and Magnesium Citrate work by increasing the passage of extracellular fluid across the bowel wall. Following the FDA alert regarding renal damage associated with oral sodium phosphate with bowel cleansing prior to colonoscopy in 2008, its use declined precipitously in the USA [20, 21], yet it remains a viable option [22]. The potential side effects associated with its use include nephropathy and renal insufficiency resulting from the tubular deposition of phosphate [23]. These side effects are uncommon; yet, with many and potentially better options, most practitioners including the authors forgo using it in clinical practice. Stimulants such as Senna and Bisacodyl increase bowel wall smooth muscle activity, and are primarily used as adjuncts to one of the other preps rather than as a stand-alone prep [24].

There is also good evidence to suggest that regardless which agent is chosen, splitting the timing into the half-day prior to and half-day of the procedure results in an overall better cleansing [25]. The majority of patients seem willing to comply with this split preparation and this results in an improvement in the number of satisfactory bowel preparations [26]. At least one meta-analysis demonstrates that a 4-L split-dose PEG is superior to other preparation strategies [27]. It is also critical that the instructions that are given to the patient are understood. It is beneficial if the language is tailored to the individual and instructions should include commonly asked questions, as this will increase patient understanding and compliance with whichever agent(s) is chosen [28].

The reporting of the quality of the bowel prep is both an important part of documentation of the procedure as well as a standard of quality. An adequate bowel preparation should be achieved and documented in greater than 85% of procedures [29]. There are numerous scales for grading the adequacy of the bowel prep, yet none is proven superior. The Aronchick scale grades the overall quality on a scale of 5 (excellent) to 0 (inadequate) [30]. The Ottawa [31], Boston [32] and Chicago [33] scales grade the preparation quality in different anatomic areas of the colon adding them together to form a total score. These scores range up to 9 for the Boston, 14 for the Ottawa and 36 for the Chicago. The easiest and therefore the most commonly employed is the 4-point scale of excellent, good, fair, and poor. Regardless of which scale is chosen, they are all subjective and therefore subject to bias.

Special Considerations

The Difficult-to-Prep Patient

With the high number of patients with an inadequate bowel prep, as above, it is not uncommon to encounter patients with a prior history of a poor bowel prep presenting for a repeat evaluation. It is recommend that patients undergo early repeat colonoscopy when the bowel preparation quality is deemed inadequate, defined as the inability to detect polyps smaller than 5 mm [34]. Adenomas and high-risk lesions are frequently detected on repeat colonoscopy in these inadequate prep patients, suggesting that these lesions were likely missed at the time of the initial evaluation [35].

There are no prospective studies dealing with this patient population and the practices are individualized. Some practitioners either increase the amount of liquid diet by 1 day or add an osmotic or cathartic agent to the existing regimen. In addition antiemetics or anxiolytics may be added in an attempt to make the prep more palatable to the patient. It has also been demonstrated that patients tolerate a larger volume PEG prep solution [36]. In hospitalized patients it has also been demonstrated that the prep can be administered via a gastroscope the day prior to colonoscopy, improving patient tolerance and the subsequent quality of bowel preparation for colonoscopy [37]. Ultimately the clinician is left to their best clinical judgment.

The Patient Requiring Antibiotics

The data regarding the need for prophylactic antibiotics for patients undergoing a colonoscopy is lacking. While there are case reports of endocarditis following colonoscopy, the need for antibiotic prophylaxis for patients undergoing elective endoscopy is rare. Antibiotic prophylaxis against infective endocarditis is not routinely recommended for colonoscopy although there is some evidence suggesting that infective endocarditis due to *Streptococcus* and *Enterococcus* species may indeed warrant prophylaxis in these patients [38] Based upon current guidelines antibiotic prophylaxis is reserved for individuals with cardiac valvular disease at high risk of infective endocarditis. There has been a small but significant increase in the incidence of infective endocarditis since 2008, when the more restrictive guidelines regarding the lack of need for prophylaxis were issued [39], but the clinical significance remains unclear at this time [40, 41].

The ASGE guidelines published in 2003 and revised in 2008 (Table 4-1) divide the patients into high, moderate, and low risk based upon the cardiac risk factors [42]. However, even high-risk patients are not required to have antimicrobial prophylaxis prior to endoscopic procedures. In patients who fall into the high-risk category, a frank discussion with the patient's cardiologist or infectious disease specialist is warranted.

TABLE 4-1. Antibiotic prophylaxis for elective colonoscopy ± biopsy

Conditions	Patient risk	Antibiotics
Prosthetic heart valves	High-risk patients	Prophylaxis is optional
History of endocarditis		
Systemic-pulmonary shunt		
Complex cyanotic congenital heart disease		
Cardiac Transplant with valvulopathy		
Other congenital cardiac abnormalities	Moderate-risk patients	Prophylaxis is not recommended
Mitral valve prolapse with regurgitation		
Rheumatic heart disease		
Hypertrophic cardiomyopathy		
CABG	Low-risk patients	Prophylaxis is not recommended
Defibrillators		
Pacemakers		
Repaired septal defect or PDA		
Physiologic heart murmurs		
Mitral valve prolapse without regurgitation		
Prosthetic joints <6 months	Patients to consider prophylaxis	Consider prophylaxis
Peritoneal dialysis		
Vascular grafts	Insufficient data	Consider prophylaxis

The Anticoagulated Patient

The anticoagulated patient poses an even larger dilemma for the endoscopist. As the number of anticoagulation medications and the number of patients receiving these medications increase coupled with the rising number of colonoscopies performed, this clinical scenario is frequently encountered, and can be expected to increase. While a diagnostic colonoscopy itself poses little bleeding risk, the possibility of biopsies or polypectomy must be considered. It is imperative that the endoscopist weighs the risk of possible thrombotic events if any medication is withdrawn against those of bleeding. This must often be done prior to the procedure, when knowledge of any pathology or whether any biopsy or polypectomy does not exist.

According to the 2005 ASGE guidelines [43], a diagnostic colonoscopy or a colonoscopy with biopsy is considered a low-risk procedure for causing hemorrhage. A polypectomy however is considered to be a high-risk procedure and any anticoagulant medications should be adjusted according to the medication that is being taken (Table 4-2) [44–47]. These decisions will often need to be coordinated with the physician monitoring the anticoagulant, as it is often not within the purview of the endoscopist to evaluate the thrombotic risk. When to reinitiate anticoagulation is another difficult issue that must take into account what was performed at the time of the endoscopy, with the recommendation being to reinitiate the therapy as soon as hemostasis has been confirmed, which is obviously difficult [48]. The incidence of post-polypectomy hemorrhage peaks at 4–6 days and this risk extends to at least 14 days. In general, the morbidity of a thromboembolic event is greater than that of hemorrhage—therefore, resuming anticoagulation as soon as possible and treating hemorrhagic complications as they occur seems to be the most prudent management strategy.

Incomplete Colonoscopy

A complete colonoscopy examination to the cecum should be achieved in >95% for screening cases and is considered a major benchmark of quality. The slight decrease in colorectal cancer incidence over the past several decades is attributed in part to early detection and removal of colorectal polyps before they progress to invasive malignancy [49]. This decrease is attributed mostly to left sided lesions versus right sided lesions due to potential genetic factors, missed lesions, poor bowel preparation, and incomplete examinations [50]. Right-sided colon lesions tend to more flat and depressed which undoubtedly contributes to missing these lesions.

Rates of incomplete colonoscopy range from 5 to 25% and reasons are varied [49, 51]. Whatever the reason for incompletion, a secondary examination must be offered to the patient. The dilemma of what to do after an incomplete colonoscopy is best approached by delineating what was the specific reason for the incomplete exam.

TABLE 4-2. Management of anticoagulation medications for elective lower GI endoscopy

↑ Risk procedures			↓ Risk procedures
Polypectomy >1 cm			Diagnostic endoscopy
Endoscopic dilatation			Flexible sigmoidoscopy/colonoscopy ± biopsy
			Stent placement without dilation
Medications			
Medication	Risk	Medication instructions	Medication restart
Warfarin		Hold 3–5 days prior	
A-fib		Hold warfarin and start UFH or LMWH when INR ≤2.0	
A-fib w h/o embolic event		Hold warfarin and start UFH or LMWH when INR ≤2.0	
Mechanical valvular heart disease			
Low molecular weight heparin (LMWH)	↓	No medication adjustment necessary	
	↑	D/C 8 h prior to procedure	Restarting medication Individualized
Bridging LMWH: to replace Heparin Window D/C Warfarin 3–5 days prior to procedure		Consider 1 mg/kg q 12 h	D/C as above
Thienopyridines: clopidogrel/ticlopidine	↓	No change necessary	
	↑	D/C 7–10 days prior to procedure, consider continuing aspirin if on dual therapy	Restarting individualized
Dipridamole	↓	If no preexisting bleeding disorder, no change necessary	
	↑	Unknown	
GIIb/IIIa inhibitor		Medication not usually used in patients undergoing elective procedures. Consult with Prescribing Physician or Cardiology	

Patients who had an incomplete colonoscopy due to an unsatisfactory or poor prep must be re-educated on the preparation process, as above. A repeat colonoscopy in this situation is the most logical and effective approach [52, 53]. In patients whom the procedure was terminated secondary to tortuosity or pain, a repeat colonoscopy under alternate analgesia or a repeat colonoscopy with a more experienced endoscopist may be appropriate [49, 53]. Alternatively, CT colonoscopy (virtual colonoscopy) may also be performed with good success. It should be noted that any lesion >6 mm found on CT colonoscopy will require a standard colonoscopy as follow-up. As a final option, a double (air and ingested contrast) barium enema can be considered. Even though barium enema has been available for decades and is an accepted screening tool for colorectal carcinoma, a recent large population-based study showed a cancer miss rate of 22%, which makes this a very poor second test to either standard or CT colonoscopy [54].

In patients in whom the colonoscopy was incomplete secondary to stricture or an obstructing lesion, options include on-table colonoscopy at the time of resection, preoperative CT colonoscopy, or postoperative colonoscopy [49].

Procedure

The Endoscopy Suite

Unlike the flexible sigmoidoscopic examination that can be adequately performed in the office, a full colonoscopy typically requires a larger space with more equipment. The endoscopy suite should provide an adequate amount of space for the necessary endoscopic equipment and patient stretcher as well as allow adequate egress of staff and equipment. It is important that clear and unobstructed sight lines are maintained for all of the personnel in the endoscopy suite such that adequate visualization on the patient as well as any monitoring equipment is maintained at all times. It is dark in the endoscopy suite and the endoscopist is concentrating on the procedure therefore it is imperative to have a designated person, who's primary responsibility is for monitoring the patient throughout the procedure.

If sedation is to be used, as is most commonly performed in the USA, it is important that oxygen and routine EKG monitoring are performed. A consensus statement states that patients who are having their procedure performed under moderate or deep sedation "must have continuous monitoring before, during, and after the administration of sedatives." Monitoring may detect early signs of patient distress, such as changes in cardiovascular or pulmonary parameters prior to any clinically significant compromise. Standard monitoring of sedated patients undergoing GI endoscopic procedures includes recording the heart rate, blood pressure, respiratory rate, and oxygen saturation. Although electronic monitoring equipment often facilitates assessment of patient status, it does not replace a well-trained and vigilant assistant [55].

Instruments

As with flexible sigmoidoscopes above, there are numerous manufacturers of colonoscopes that typically vary from 130 to 168 cm in length. There are also pediatric colonoscopes that are smaller in diameter than the typical adult endoscope: 11.3 mm versus 12.8 mm. The basic colonoscope consists of a suction channel, an air/water channel, and fiber-optic bundles for light transmission, along with a biopsy port, which is connected into the suction channel (Figure 4-20a, b). Modern colonoscopes commonly possess variable stiffness controls that allow the endoscopist to vary the rigidity of the endoscope dependent on the clinical situation. It is hypothesized that this ability decreases the need for external over the tube stiffeners, and they have been proven to decrease procedure-related pain and the doses of sedative medications during colonoscopy [56].

Sedation

There are numerous studies evaluating the optimal method in which to sedate the patient for colonoscopy procedures and there is ample dogma employed as well. As with a bowel prep, there is no perfect sedation regimen but the endoscopist must be familiar with the side effect profile of medications being used and be prepared and comfortable with any reversal agents. While there is literature demonstrating that colonoscopy can be performed adequately and safely on the un-sedated patient, the practice in the USA is rare. In one study, less than half of the endoscopists polled practiced unsedated colonoscopy, listing a lack of patient acceptance as the most common reason for not offering it [57]. In an evaluation of Canadian gastroenterologists and colon and rectal surgeons, the endoscopists reported using sedation for more than 90% of colonoscopies they performed. The most common sedation regimen was a combination of midazolam and fentanyl [58]. While the combination of a narcotic with a benzodiazepine remains popular for providing colonoscopy sedation, several alternate medications have been evaluated.

Nitrous Oxide

Nitrous oxide is one medication that has been found effective in several studies to be effective for colonoscopic sedation. While some studies show that it is not an effective substitution for intravenous sedation and analgesics [59], there are several studies that show it to work well in that setting. In a review of seven randomized trials using nitrous oxide for colonoscopy, four showed that nitrous oxide is as good at controlling pain as conventional methods, while another showed that sedation was actually improved [60]. Despite this it is unlikely that Nitrous Oxide will become widely used in clinical practice.

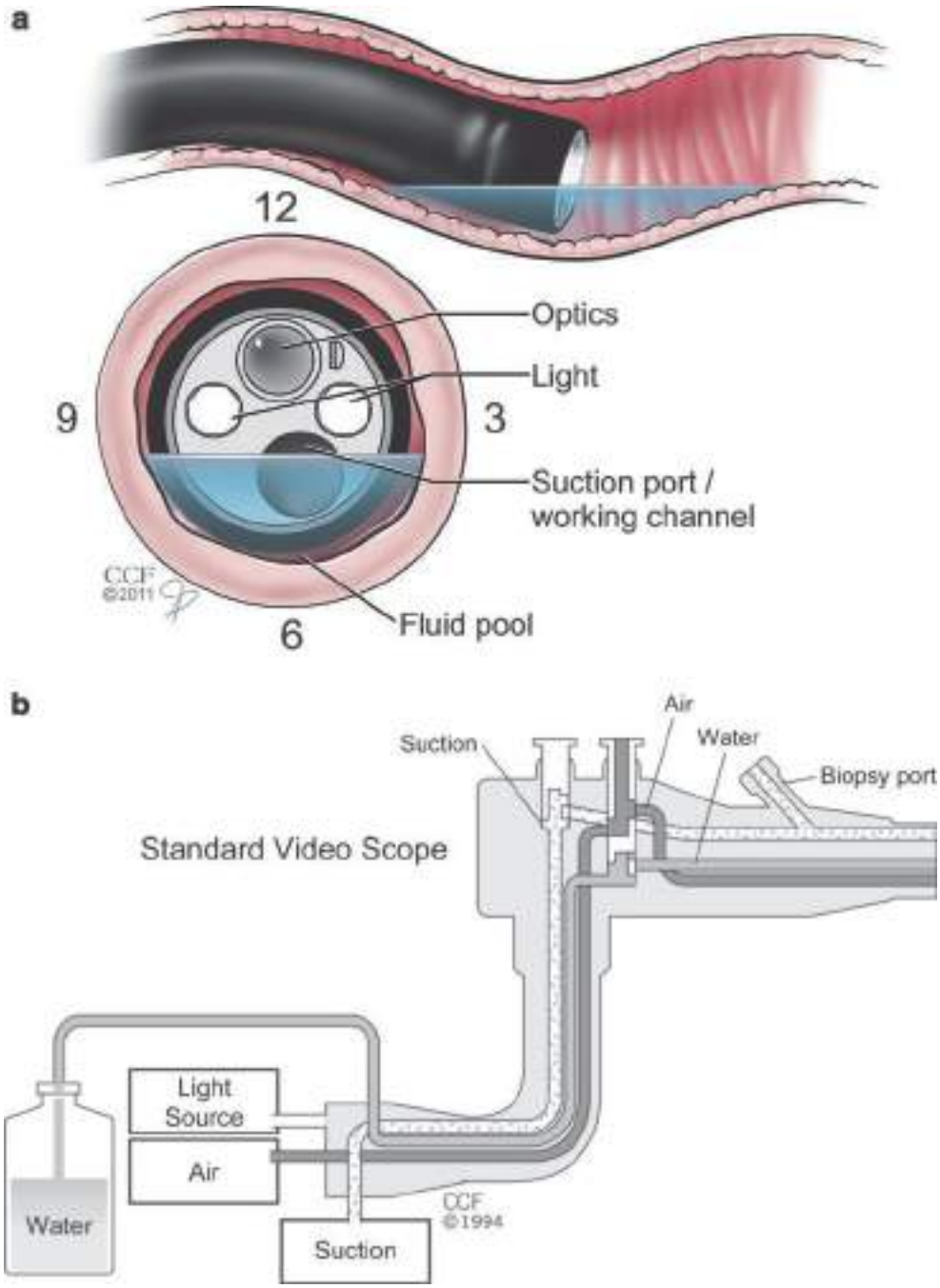

FIGURE 4-20. (**a**) End-on view of the endoscopic tip, showing suction/biopsy channel, air/water channel, lens, and light source. (**b**) Basic endoscope design. Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography ©2015. All Rights Reserved.

Ketamine

Ketamine is another medication that has demonstrated beneficial in colonoscopy. In one study, the addition of low-dose ketamine to a standard sedation regimen resulted in more rapid and better quality of sedation with stable hemodynamic status, and similar recovery times [61]. Due to a lack of familiarity with the medication and concerns regarding central nervous system alteration this medication is also unlikely to receive widespread use for endoscopic sedation.

Propofol

By far, the preponderance of the recent literature involving sedation for endoscopy involves the use of propofol, which has increased substantially among endoscopists [62]. In a Cochrane Review of the randomized controlled studies comparing propofol with standard sedation of a narcotic and benzodiazepine, the findings were that recovery and discharge times were shorter with the use of propofol. In addition, there was higher patient satisfaction with use of propofol. No difference in the procedure time, the cecal intubation rate

or the incidence of complications was noted [63]. A later meta-analysis confirmed these findings [64].

One criticism of the use of propofol is that an anesthesia provider is typically required to administer the agent—thereby increasing the cost associated with the procedure. It has been demonstrated that the medication can be delivered in a patient controlled setting [65] or by a nurse under the supervision of the endoscopist [66]. These methods are likely to remain in the minority, however, and the question remains unanswered in an era of cost containment whether the benefits listed above justify its use.

Colonoscopy Technique

Colonoscopy is the most challenging endoscopic examination, and appropriate training, practice, attention to detail, and patience is needed in order to successfully complete this examination. The act of negotiating a 5–6 ft flexible tube through a tortuous colon painlessly and efficiently while performing detailed surveillance and therapeutic maneuvers is a difficult task. This section will describe successful navigation to the full extent of the colonoscopy relying on the principles mentioned prior.

Anal Intubation

The well-lubricated colonoscope is inserted as previously described for sigmoidoscopy. The examiner must make sure that the scope is brought over to the patient straight without any twists or loops from the endoscopy tower.

The Rectum and Rectosigmoid

Once the endoscope is placed into the anus, it is advanced into the rectum while insufflating an appropriate amount of air to distend the rectum. The distensibility of the rectum is an easy way to evaluate rectal compliance based on how easily and how much the rectum distends. Negotiating through the rectum is usually not difficult, but if difficulty is encountered going through the three valves of Houston (Figure 4-21), torque can be employed to reach the rectosigmoid.

The rectosigmoid can pose extreme difficulty and is often one of the more challenging areas of the colonoscopy. There is often an acute angle at this junction from a redundant and floppy sigmoid colon. If the patient has undergone prior pelvic surgery, especially hysterectomy, the sigmoid may become fixed and adherent which makes negotiation of the turn difficult and often painful. In other patients (usually males) this turn is obtuse and very easy to advance. In situations where the turn is difficult, a combination of all the basic maneuvers discussed should be employed. The scope should be kept as straight as possible as a combination of short advancements—withdrawals with jiggle and a slight clockwise

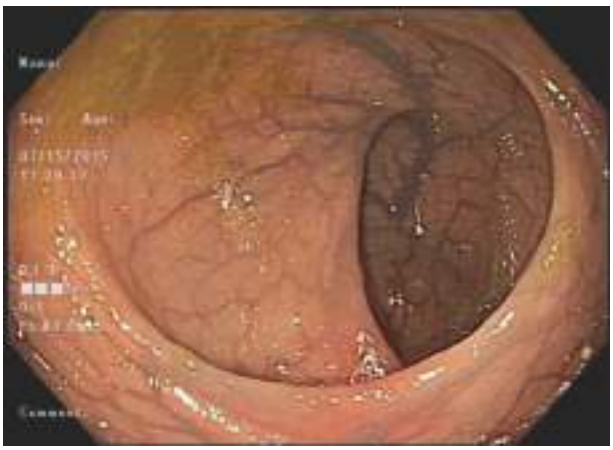

FIGURE 4-21. The first and second rectal valves of Houston. Note the large submucosal venous plexus.

torque (this torque may be considerable in certain individuals) should be employed to advance the scope into the sigmoid colon. This portion of the exam requires adequate patient sedation and relaxation. For the most acute angles, multiple small advancing steps toward getting the tip of the scope past the angle with tip deflection and torque are needed. Slide-by maneuvers should not be routinely performed.

Once the scope advances into the sigmoid, tip deflection and some torque will help reduce any loops. If this is not possible, the scope can be carefully inserted farther into the sigmoid with the loop still in place as long as this does not cause too much patient discomfort. Once the descending colon comes into view, any loops should be reduced with withdrawal and torqueing maneuvers. This may require a substantial torque with the right hand and usually the endoscopist can feel the scope reduce and any patient discomfort or pain will usually abate at this time. It should be noted that successful completion of the procedure is quite low if the rectosigmoid loop is not reduced [67].

Sigmoid Colon

The sigmoid colon is the most tortuous segment of the colon with associated high muscular tone, spasm, and a higher incidence of diverticulosis (Figure 4-22). The sigmoid colon is not fixed and can be very redundant and elongated. The sigmoid readily accepts the endoscope and a considerable length of scope can be inserted. All of these factors contribute to making this a difficult-to-navigate segment requiring insertion-pull back, jiggle, and a variable amount of torque (usually clockwise). These maneuvers will allow the sigmoid to "accordion" over the scope, which allows for efficient advancement and the prevention of loop formation.

Diverticula, when present, can be of various sizes and the larger ones can be dangerous as they can be mistaken for the true bowel lumen. Careful navigation around a diverticula

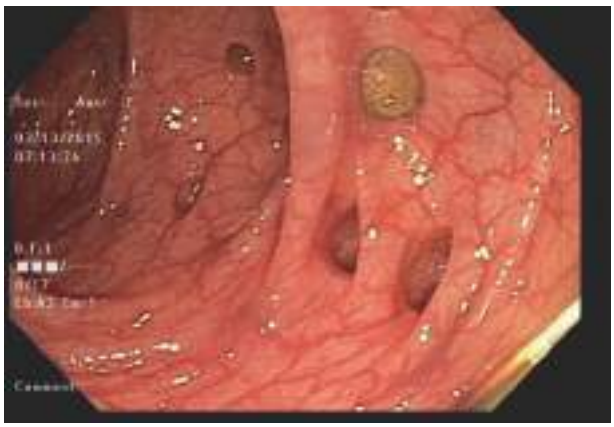

FIGURE 4-22. The sigmoid colon has variable degrees of tortuosity, spasm, diverticular disease, and muscular tone.

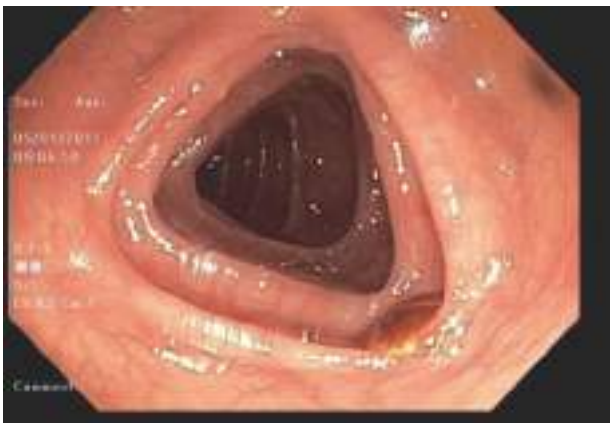

FIGURE 4-23. Transverse colon: note the common triangular appearance of the lumen.

laden sigmoid requires patience and the pull back techniques in order to gain a broader view of the colon. Perforation of a diverticulum can occur if too forceful or blind advancement (slide-by) is incorporated.

Sigmoid-Descending Junction

The junction of the sigmoid and descending colon can be difficult if a sigmoid loop is present or has only been partially reduced. Keeping the scope straight and gently advancing and withdrawing 1–2 cm at a time usually works, as opposed to pushing through the loop which will undoubtedly cause pain. One can also attempt to apply abdominal pressure at this point or turn the patient position to supine (or lateral) in attempts to advance into the descending colon.

Descending Colon

The descending colon is usually straighter and less muscular than the sigmoid colon. It should be noted that even though this segment of the colon is easier to advance, jiggle, torque, air suction, and push and pullback techniques should still be employed to pleat the colon over the scope.

Splenic Flexure

After advancing through the descending colon, the splenic flexure is the next obstacle. The splenic flexure is identified by the strong cardiac pulsations often seen and occasionally the blue shadow from the spleen itself. Often, this is a simple 90° turn that can be easily negotiated with some tip deflection and torque and other times, the splenic flexure may be a series of turns and twists in multiple planes. A difficult splenic flexure should be treated as already described using tip deflection, torque and push and pull techniques. Often, changing patient position or externally splinting the sigmoid with abdominal pressure can achieve flexure passage as well. It should be noted that the straighter the sigmoid colon is, the easier the splenic flexure will be. A sigmoid loop can form during this portion of the exam if forward push is used to get past the flexure.

Transverse Colon

The transverse colon is characterized by the triangular appearance formed by the taenia coli (Figure 4-23). If no proximal loop has been formed, the scope will advance readily through this segment. If a loop is formed in the splenic flexure or the sigmoid, application of abdominal pressure at the sigmoid coupled with a strong torque (left or right) will usually reduce the loop and allow for a one-to-one advancement rather than a paradoxical advance. It should be remembered that torque, jiggle, and push-pull should be employed even when this segment is straight.

One area of difficulty may be in the mid-transverse colon. The mid transverse colon may exhibit ptosis and descend down into the pelvis and could be fixed with adhesions, especially following pelvic surgery. Loops are commonly created during this part of the exam, and external pressure and changing the patient position to either right lateral or supine will help with advancement.

Hepatic Flexure

The hepatic flexure is often recognized by the large blue shadow from the liver (especially in thin patients) (Figure 4-24). As one advances through the transverse colon, the hepatic flexure comes into view, often with a variable amount of pooling liquid stool. If the flexure turn is very acute, the novice endoscopist often mistakes this “fools cecum” for the true one, believing that they are at the end of

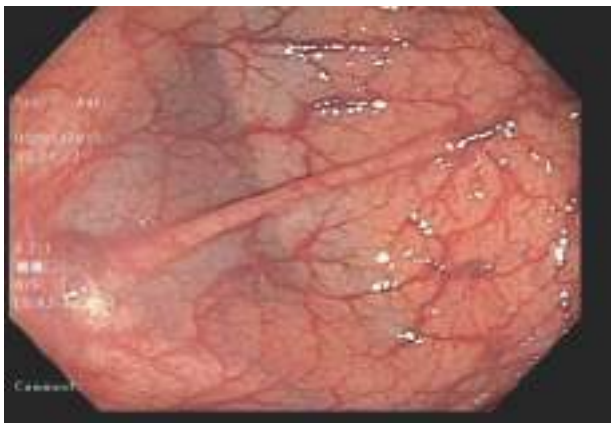

FIGURE 4-24. Hepatic flexure: note the *blue shadow* from the liver. There is usually a sharp turn which can be quite difficult to negotiate.

the colon. As with any other turn or flexure, if the scope is straight, advancement will be easier than if a loop is formed proximally. Often, one can gently push through a loop and get into the ascending colon and then reduce the loop. At other times, the examiner may find it useful to use air suction and abdominal pressure techniques to negotiate this turn. Another technique previously mentioned, involves having the patient take a deep breath of air to push the diaphragm down, and thus, the scope down into the ascending colon.

Ascending Colon and Ileocecal Valve

As the scope advances past the hepatic flexure into the ascending colon, prevention of a new loop is critical, as any proximal loop at this point will make further advancement of the scope extremely difficult. Pushing through a loop in the ascending colon is not as successful as it is on the left side of the colon since there are many bowel loops to accommodate before push pressure is transmitted to the end of the scope [67]. It can be very common to have the entire length of the scope inserted and there is still additional colon to traverse, due to inappropriate or minimal pleating techniques and the presence of loops. A change in patient position to either supine, right lateral, or prone coupled with the basic insertion techniques will prove to be extremely important in these situations and help advance the scope to the cecum.

The ileocecal valve is a fold at the base of the ascending colon that may appear as an obvious polypoid-like yellowish mass or can be totally hidden (Figure 4-25a, b). When the valve is not easily recognizable, the presence of gas, stool, or bile flowing from it is helpful to aid in its identification.

Cecum

The complete colonoscopic examination is ensured when the cecum has been reached. This blind sac is characterized by the "crow's foot" which is made up of the muscular arrangement of the colonic wall and the crescent or circular shaped appendicle orifice (Figure 4-26a, b). These landmarks are extremely important in quality assurance of a complete examination and photodocumentation is mandatory. Relying on trans-illumination of the scope through the abdominal wall in the right lower quadrant can be deceptive and is inadequate evidence of a complete examination. Careful and detailed examination of the entire cecum is important due to the fact that many cecal lesions, including serrated adenomas are flat or recessed and can be quite deceptive and easily missed with a casual examination.

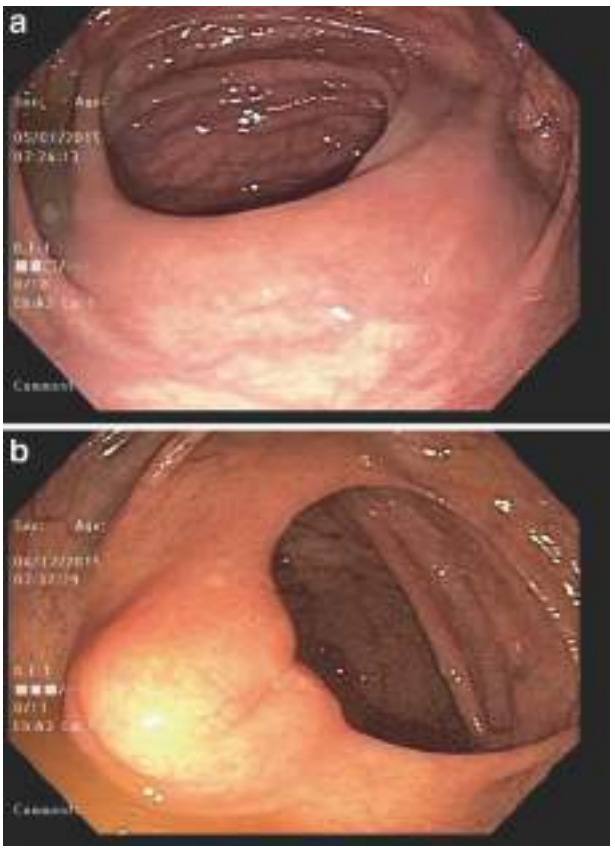

FIGURE 4-25. Different appearance of the ileocecal valve. (**a**) Flat and subtle. (**b**) Polypoid and obvious.

Ileocecal Valve Intubation

It is common for some endoscopists to routinely advance the endoscope into the terminal ileum. While it is considered a critical assessment when performing either an initial evaluation or follow-up for Crohn's disease, or in a search for obscure bleeding, it is unclear the precise role of routine visualization of the terminal ileum on colonoscopy. It is a skill, and the ability of the endoscopist to perform the maneuver improves with practice. The technique involves first removing any loops from the colonoscope, as significant looping of the instrument make entering the ileum much more technically challenging. The edge of the ileocecal valve is hooked

with the curved endoscope and the scope is then gently inserted into the ileum when the lumen is visualized (Figure 4-27). The intubation of the ileum confirms a complete colonoscopic evaluation and this confirmation can often be a frustrating endeavor for beginning endoscopist [68].

In an assessment of the ileal intubation learning curve, 50 procedures was the benchmark, but once learned could be accomplished in most patients in less than 1 min [69]. The addition of routine ileoscopy to screening colonoscopy has been demonstrated to detect asymptomatic small bowel carcinoid tumors and has led some to argue that this should be considered part of the endoscopic examination [70]. A large study at the Mayo Clinic involving over 6000 patients however did not validate this. Terminal ileum intubation showed gross abnormalities in only 1% of the patients, and pathologic abnormalities were identified for only 0.3% of the patients. These authors concluded that intubation of the terminal ileum should not be a required part of screening colonoscopy [71].

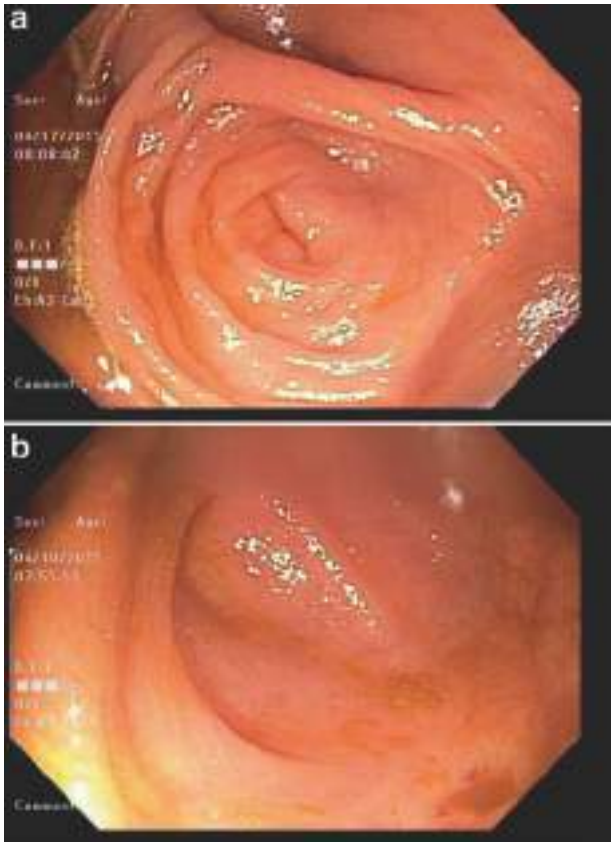

FIGURE 4-26. Reaching and proper identification of the cecum is compulsory for a complete examination. (**a**) Round appendiceal orifice with associated crow's foot. (**b**) Crescent shaped appendiceal orifice.

Terminal Ileum

If the endoscopist chooses to intubate the ileum, it is easily recognizable by its granular appearance and its increased motility (Figure 4-28). Quite often in younger patients, there will be innumerable lymphoid follicles that may resemble small polyps. The scope should be advanced as far as it is

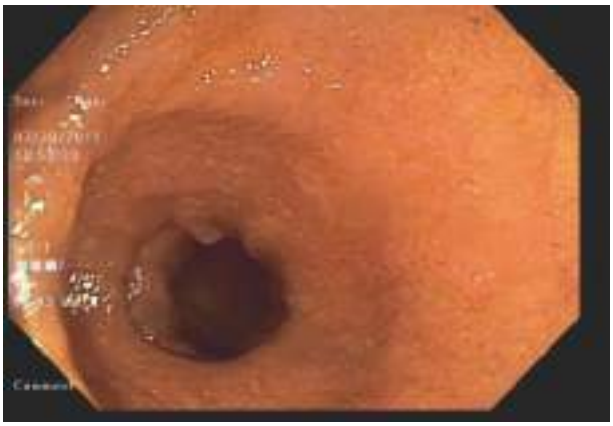

FIGURE 4-28. Terminal ileum: note the granular mucosa and the fine muscular folds.

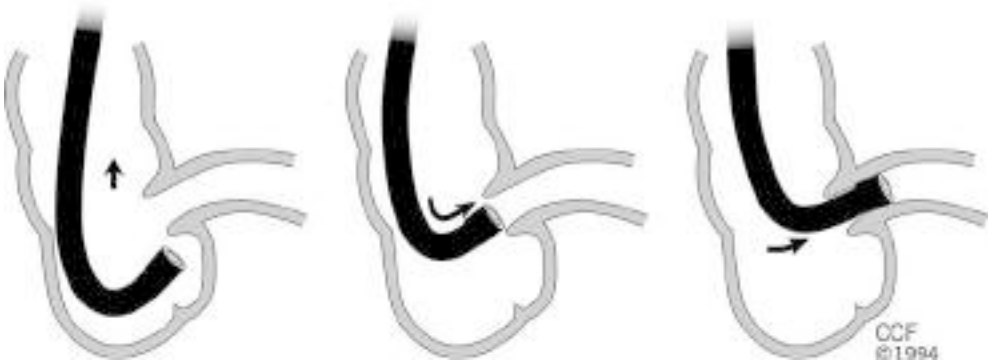

FIGURE 4-27. Intubation of the ileocecal valve: identification of the orifice, impacting the scope while giving air insufflation and then waiting for the bowel to relax before advancement into the terminal ileum. Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography ©2015. All Rights Reserved.

comfortable and appropriate biopsies taken when needed. One should try to keep air insufflation to a minimum during this portion of the examination.

Alternate Techniques

CO_2 Insufflation

Two alternatives to traditional air infusion colonoscopy are water-assisted colonoscopy and insufflation with Carbon Dioxide. Due to the fact that CO_2 is more rapidly expelled from the colon than air, the hypothesis is that due to this rapid diffusion, there will be decreased pain associated with CO_2 infusion compared to air. Some evaluations have been consistent with this [72] hypothesis, while others have not shared these findings [73]. Due to the paucity of literature documenting efficacy, the technique must be considered experimental at this point.

Water Insufflation

The second method shows more promise. It involves the infusion of water without air and subsequent suctioning either during the insertion or withdrawal of the endoscope [74]. It has been demonstrated in limited studies that the use of water-assisted colonoscopy has a positive effect on patients, predominantly with lower levels of pain during the procedure [75, 76]. In addition, one study demonstrated that water immersion colonoscopy prevented loop formation in the sigmoid colon [77]. In a meta-analysis of nine studies, warm water infusion was demonstrated to be less painful than standard air insufflation, while reducing the need for sedation or analgesia during the procedure. There is a higher incomplete colonoscopy rate with this technique, however, and the endoscopist must consider this if considering employing this technique [78]. Interestingly when the methods of water insufflation and CO_2 insufflation are compared to each other, there is no significant reduction in either moderate or severe pain with either technique, compared with patients receiving no sedation [79].

Chromocolonoscopy (Chromoendoscopy)

Chromocolonoscopy involves the use of dye with spray catheters to spray coat the colonic mucosa in an attempt to increase the visualization of the mucosa. The dye enhances delineation, thereby aiding the endoscopist in differentiating between small structures, especially small and flat neoplastic lesions that are hard to recognize with traditional endoscopy. There has been some demonstrated benefit with this technology in high-risk populations such as those with inflammatory bowel disease or those with known genetic disorders [80, 81], due to the difficulty in differentiating abnormal from normal mucosa in some of these patients. The technology has primarily demonstrated an increase in the yield of small polyps in the general population, however. Due to this lack of clinical significance in the population as a whole, there is a questioning of the necessity for widespread application of the technique [82].

High Definition/NBI Endoscopy

High definition endoscopes with wider angle viewing capability have the ability to increase the magnification and the visualization in endoscopy. High definition endoscopy has not proven superior in the ability to detect additional colon neoplasms, however [83]. Narrow Bandwidth Imaging (NBI) uses a filter to narrow the blue and green wave light and eliminates the red wavelength from standard white light. This leads to an accentuation of the microvasculature and improved visualization of pathology. The endoscopist is able to rapidly switch between white light and NBI views with the use of a foot pedal [84]. It has been noted in small studies that using NBI technology there is an increase in the number of adenomatous polyps detected [85]. In addition surface patterns differentiation between hyperplastic and adenomatous polyps is enhanced [86]. Due to this ability to better predict histology, NBI technology may play a role in the future resection and discarding of diminutive polyps, but it has not received widespread acceptance.

Full Spectrum Endoscopy

Full spectrum endoscopy uses three cameras, with the two additional cameras located adjacent to the scope's tip. This allows simultaneous viewing of all three cameras, which the endoscopist has from three adjacently located monitors. This colonoscopy platform has been demonstrated to be feasible, usable, and safe [87]. Despite the impressive visualization that is gained from the additional cameras, at this point, there is no proven benefit regarding increased adenoma detection, making it only a viable alternative to traditional endoscope technology [88].

Retroflexion

Many endoscopists routinely perform retroflexion, or the turning of the endoscope back upon itself in a U shape, in order to obtain a better view than with straight viewing. There is sparse data on either the benefits or the risks associated with the routine use of retroflexion of the endoscope in the rectum. There is one study that using the retroflexion technique with sigmoidoscopy increases adenoma detection [89]. Other studies cast some doubt on this. In one study of over 450 patients, in only 9 cases did the retroflex view identifiable pathology—predominantly hyperplastic polyps [90]. In another study of over 1500 patients, only 7 polyps were visualized solely by retroflexion. Six of these were hyperplastic and one was a

4 mm sessile tubular adenoma [91]. More concerning than a low yield is a higher rectal perforation rate reported associated with the technique [92]. The procedure can undoubtedly be performed safely, and some experts tout that it provides valuable information and photodocumentation of benign disease at the rectal outlet such as hemorrhoids [93]. It is unclear if the limited data is worth any added risk.

There is some data that retroflexion performed in the ascending colon, may offer benefit, however. One study evaluating routine retroflexion in the right colon showed that it could be safely achieved in the majority of patients undergoing screening colonoscopy [94]. In addition retroflexion identified additional polyps, predominantly adenomas, increasing the polyp yield as well as the adenoma detection rate in one study [95]. Due to the concerns regarding missed lesions in the right colon, retroflexion in patients with polyps identified on initial forward viewing should be considered.

Complications

While the performance of colonoscopy is very safe with several million procedures performed every year with no untoward events—it is an invasive procedure and complications are possible. These should be discussed with the patient frankly and documented prior to the procedure. The complications can be broadly grouped into those relating directly form the procedure such as bleeding and perforation and those relating to the sedation involved with the procedure—primarily cardiac and pulmonary complications. The exact incidence of complications varies widely in the literature, from 4.0 for 10,000 colonoscopies [96] to 17.8 per 1000 procedures [97]. The incidence varies somewhat depending on what exactly is considered a complication, and looking only at serious complications, defined as those resulting in hospital admission within 30 days of the procedure occur with a rate of 1 per 1000 [98–100] to 5.0 per 1000 exams [101, 102].

Sedation Complications

There are obviously risks associated with the administration of any medication, particularly sedative medications. The reason for the monitoring guidelines outlined above is to monitor for just these risks [103]. The primary concerns regarding the administration of sedation revolve around the cardiac and pulmonary complications associated with these medicines.

Vasovagal/Cardiac Arrhythmia

A vasovagal reaction is a slowing of the heart rate, often accompanied by a drop in blood pressure. This is believed to reflect the stimulation of the vagus nerve. It is common during colonoscopy and has been reported to occur in up to 16% of cases [104]. It is most likely not related to sedation, however, as the occurrence is unrelated to sedative medication administration and [105] it more likely results from the distension of the bowel or from a relative hypovolemic state resulting from the bowel prep. A vasovagal reaction is typically self-limited, but should be addressed by colonoscopic aspiration of air and/or reduction of loops. It typically requires no medical intervention other than monitoring and IV fluid administration. True cardiac arrhythmias are uncommon in association with colonoscopy. While there are reports of life threatening cardiac dysrhythmias during the procedure, these are primarily from case reports [106, 107]. Cardiac arrhythmias occur in approximately 2% of patients while undergoing endoscopic procedures [108] but the vast majority of these require no medical intervention [109].

The administration of sedative medications, particularly midazolam does cause transient hypotension in 20% of patients, with ST-segment depression in 7% of them [110]. It has also been noted in patients undergoing endoscopy that there is evidence of cardiac arrhythmias in 16%, with ischemic changes noted in 4% of those [108]. The clinical significance of these changes is unclear, however, as these are only electrocardiographic abnormalities. When comparing patients not having a colonoscopy, the incidence of myocardial infarction or stroke is similar to patients undergoing colonoscopy [111], implying that the procedure does not place the patient at increased risk for a cardiac event. In addition, it has been demonstrated that endoscopic procedures are safe and beneficial in patients after recent MI and should be performed if necessary in this patient population [112]. Colonoscopy in patients with a recent myocardial infarction is associated with a higher rate of minor, transient, and primarily cardiovascular complications compared with control patients but is infrequently associated with major complications [113].

Pulmonary

The incidence of pulmonary complications is even less common than for cardiac events, and any evidence of pulmonary issues following a colonoscopy should prompt the endoscopist to consider the abdomen as the ultimate source. The majority of patients that are undergoing colonoscopy are older and patients over 80 have not surprisingly demonstrated higher rates of pulmonary complications [111]. There are reports of aspiration following the administration of sedative medications for colonoscopy [114], but this is a very uncommon event. In addition, there are also numerous reports of pneumothorax or pneumomediastinum, following a colonoscopy [115]. These events are most commonly related to an intra-abdominal perforation, however, and should prompt a quick investigation for that possibility [116].

Procedural Complications

Procedural complications such as bleeding, perforation, and post-polypectomy syndrome serve as the other broad classification of complications. There are reports of unusual occurrences such as colonoscopes becoming incarcerated in either inguinal or ventral hernias [117, 118], but these are extremely uncommon events and serve primarily to warn the practitioner that there is always something else that can go wrong with any procedure. All endoscopists should be aware of the more common risks associated with the endoscopy and attempt to mitigate them.

Splenic Injury

The incidence of splenic injury in association with a colonoscopy is uncommon but is something that many endoscopists will encounter. A comprehensive literature search identified just over 100 patients worldwide with this complication [119]. It is likely that it is a much more common occurrence, however, as most of the cases in the literature are severe and the patients reported typically are managed with splenectomy [120]. There are likely many more cases that are not reported that are managed nonoperatively or even go unrecognized. It is believed that the etiology of this injury is from traction and subsequent tearing of the splenocolic ligament during the procedure, with subcapsular hematoma the most common injury pattern seen [121]. Splenic rupture at colonoscopy usually presents with abdominal pain developing within the first 24 h [122], although patients can present anywhere from a few hours to several days following the procedure [123]. Selection criteria for operative management may be extrapolated from those used for the management of traumatic splenic injury, but while there are reports of using splenic embolization [124], as mentioned above, the majority of patients in the literature have required splenectomy.

Perforation

A perforation of the colon during a colonoscopy can be a devastating complication that can result in serious morbidity or mortality. While it is uncommon, endoscopists will likely encounter it at some point in their career. The exact incidence of perforation is difficult to precisely define, but it is much less than 1/1000 procedures, with rates of 0.012% [125] to 0.016% reported in large studies [126]. It is believed to be more common when the procedure is performed in a diseased colon such as in inflammatory bowel disease patients, but a large study of IBD patients showed a low perforation rate of 0.16% [127]. In most series attempting to examine the etiology of the complication, the incidence is as common when a biopsy is performed as from a diagnostic endoscopy alone [99, 128, 129].

There are three mechanisms believed to be responsible for colonoscopic perforation. The first is believed to be a mechanical perforation resulting from direct trauma from the colonoscope itself [130]. The most common anatomic site for perforation is the sigmoid colon, occurring in up to [131] 74% in some series [132]. This would be consistent with direct trauma, as the sigmoid is the narrowest and most tortuous section of the colon. The second mechanism is believed to be a result of barotrauma from air insufflation, and the ascending colon or cecum, which would be the most susceptible to this mechanism, is the second most common location for a perforation. However, one series that examined specifically patients that had a cecal perforation found that cecal pathology such as inflammation or ulceration contributed to the perforation in most of these patients [133]. The final etiology of perforation is believed to be from therapeutic procedures such as polypectomy or the dilation of strictures.

The management depends not only on the condition of the patient, but on what the etiology of the perforation is felt to be. If the patient presents acutely and has peritonitis, the management is relatively clear and the patient warrants an emergent celiotomy. If the patient had a therapeutic endoscopy, and is clinically stable, then an attempt at nonoperative management is acceptable. The management with bowel rest and IV antibiotics has been demonstrated to be successful in 13/21 patients in one series of patients, all of whom had a perforation resulting from a therapeutic colonoscopy [134]. Perforations from a diagnostic colonoscopy are likely larger and are less successfully managed with nonoperative treatment [135]. The operative management of colonoscopic perforations has evolved as well. As in the trauma literature, if the patient requires surgical intervention, primary repair or resection with a primary anastomosis has proven to be an effective management strategy [132].

One emerging technology is the use of clips to manage a perforation that is either identified endoscopically or as prophylaxis when the endoscopist feels that the tissue has been thinned to the point that a perforation is likely. There are several case series reported in the literature with good results. A literature review of perforations managed with this technology show that if the clips were placed for a perforation during therapeutic colonoscopy it is successful in 69–93% of cases [136]. In one cohort of 27 patients with perforation from a therapeutic colonoscopy, the placement of clips resulted in successful nonoperative management in 25 of these patients [137]. In another review of 28 visible or suspected perforations, 13/19 evident and 8/9 suspected perforations underwent successful endoscopic closure with clips [138]. Clearly this technology has a place in the endoscopist's armamentarium, but should also be employed with surgical consultation, so that early decisions regarding operative management can be made.

Post-polypectomy Syndrome

Post-polypectomy syndrome is a spectrum of symptoms including abdominal pain, fever, leukocytosis, peritoneal tenderness, and guarding, following a colonoscopic polypectomy.

It is believed to be the result of an electrocoagulation injury to the colonic wall, thereby creating a transmural burn with localized peritoneal inflammation, but without evidence of perforation. It has carried several other monikers as well, including post-polypectomy coagulation syndrome and transmural burn syndrome. Typically patients present several days following a colonoscopy with fever, localized abdominal pain, and leukocytosis and may have localized peritoneal signs on physical examination. The majority of these patients do not require surgical treatment and are usually adequately managed with bowel rest, intravenous hydration, broad-spectrum parenteral antibiotics until symptoms resolution [139]. In one series, all patients were successfully managed medically without the need for surgery, with a median hospitalization of 5 days [140]. In an attempt to identify risk factors, one study found that polyp size greater than 2 cm and the presence of hypertension were the largest risk factors [141], but any patient who undergoes a polypectomy with cautery is at risk.

Bleeding

Bleeding following a polypectomy is the most common serious complication following a colonoscopy and patients should be given specific written instructions regarding the actions they should take if it should occur. It is estimated that significant bleeding, requiring a patient to seek medical care, occurs in over [142] 3% of all colonoscopic polypectomies, with significant bleeding in over 1% [143–146]. While bleeding can happen immediately when the polyp is removed, this is typically dealt with by the endoscopist at the time of the procedure [147]. Clinically significant hemorrhage typically manifests itself 4–6 days following the procedure when there is clot dissolution [145].

There have been several studies attempting to elucidate those patients at higher risk for this complication. A difficult colonoscopy with procedural bleeding is one group of patients at higher risk [148]. Hypertension has also been noted to be not only a risk for bleeding, but for increasing the interval between the polypectomy and hemorrhage [149] In addition, patients on anticoagulation medications are not surprisingly at higher risk, with 34% of patients in one series having been recently restarted on their anticoagulant medications [145]. While there is an increased risk with anticoagulants, surprisingly, this risk is not seen with aspirin, NSAIDS, or other antiplatelet medications [150]. The size of the polyps excised is the most consistent predictor of delayed hemorrhage after a polypectomy [151]. It is much more common with larger polyps. Polyps greater than 2.0 cm diameter were noted to experience bleeding 3.8% of the time, compared to 0.3% when the polyps removed were smaller than 2 cm in one study [148]. In addition to the absolute size, the risk is noted to increase by 13% for every 1 mm increase in polyp diameter. While polyp size correlates with bleeding, the type of polyp either sessile or pedunculated has not been demonstrated to be a risk factor [152]. The location of the polyp has, however, with polyps located in the right colon more susceptible to bleeding [153]. Microscopic examination of the vascular supply of resected polyps reveal that sessile and thick-stalked pedunculated polyps are supplied with more vessels than other polyps. Patients with polyps larger than 17 mm, pedunculated polyps with a stalk diameter >5 mm obviously place the patient at higher risk [154]. The endoscopist should obviously recognize those patients that are at highest risk for post-procedural bleeding and counsel them appropriately.

The initial management of a patient with post-polypectomy bleeding is identical to any other patient with intestinal bleeding. The patient should have coagulation parameters measured and resuscitation should be based upon hemodynamic parameters. There are no specific transfusion triggers with post-polypectomy bleeding, but advanced age is predictive of a patient receiving a transfusion [155]. Almost all patients can be managed with a repeat endoscopy and rarely are operative or other interventions necessary, although angiographic embolization has been demonstrated to be effective in the management of post-polypectomy bleeding [156]. The endoscopist should be familiar with advanced endoscopic hemostatic techniques for these procedures, or consult an experienced colleague.

As with the management of perforation above, endoscopic clipping has been demonstrated beneficial in patients at increased risk for post-polypectomy hemorrhage. In one evaluation of polyps 2 cm or larger, there was a significantly decreased rate of post-procedure bleeding when the site was prophylactically clipped [157]. In addition, clipping has been shown to be beneficial in anticoagulated patients with lesions larger than 1 cm who were able to undergo successful polypectomy without interrupting the anticoagulation or antiplatelet medications [158].

Infectious Complications

A word of caution should be made regarding the extremely rare infectious complications associated with endoscopy. Although it is uncommon, it is associated with sensationalistic press coverage when it does occur. The endoscopist should have a basic understanding of the process involved in the cleaning of the endoscopes and endoscopic equipment, as the majority of infectious complications result from breaches in cleaning procedures. In one survey of endoscopy centers, it was found that a significant number of centers did not conform to guidelines regarding the cleaning, processing and care of endoscopes [159]. A separate study found that several of the guidelines are inconsistent with one another, making it difficult to determine which guideline to follow [160]. *Salmonella*, *Pseudomonas*, and *Mycobacterium* species are the most commonly transmitted organisms associated with endoscopic equipment [161] and the ability of these bacteria to form biofilms on the inner channel surfaces is believed to contribute to their ability to survive the decon-

tamination process [162]. There have recently been reports of Carbapenem-resistant organisms associated with endoscopy as well [163]. The endoscopist should always be vigilant regarding the equipment used and ensure that proper protocols are in place and are being followed.

Training and the Use of Simulation

The training of medical personnel to safely and adequately perform colonoscopy is obviously critical. The criteria of what constitutes adequate training is controversial, however. Gastroenterologists perform the vast majority of colonoscopies and there are understandably differences in the manner in which different specialists, either gastroenterologists or surgeons educate and evaluate their trainees in performing procedures. Most of the literature on the topic involves gastroenterology fellows, and tends to focus on the number of procedures necessary in order to achieve competency. Surgical trainees obviously spend more time throughout their education learning procedural skills and it is doubtful that the two groups can be adequately compared regarding the speed or alacrity with which they learn procedures. It is unlikely that there will ever be a consensus on what constitutes adequate training. What is clear is that colonoscopy is a critical element in the treatment of the patient with colorectal disease and the colorectal surgeon must continue to be involved and have a voice in the education of the next generation of endoscopists.

The ability to perform a colonoscopy is undoubtedly a skill and as with any skill, the ability to perform it improves with repetition. It is a point of contention exactly how many of these repetitions a trainee must perform. In evaluating first year gastroenterology fellows, it was found that the ability to intubate the cecum successfully improved and reached the requisite standard of competence—defined as completing the task greater than 90% of the time and within 20 min after 150 procedures had been performed [164]. When comparing first and third year gastroenterology fellows, it was found that competence improved throughout training but an independent completion rate of 90% was not obtained until after 500 colonoscopies were performed [165]. As with the ability to technically perform the procedure, quality metrics improve with experience as well. In one study, the adenoma detection rate (ADR) increased by year of training [166]. Another study however showed that from the beginning of their education, trainees were able to provide high-quality investigations, again using ADR as the quality indicator benchmark [167]. In one of the few comparisons between gastroenterology and surgery trainees, there was a disparity in endoscopic performance between trainees favoring the gastroenterology trainees [168]. A different study showed that following the use of endoscopy simulation surgery residents were capable of performing colonoscopy equivalent to their gastroenterology counterparts using quality metrics as the benchmark [169].

Simulation

The practice of endoscopy lends itself well to simulation, yet it has not been fully embraced. While surgical simulation is difficult to portray, basic endoscopy skills are well illustrated. Due to the myriad of surgical procedures that are performed and the manner in which they are performed, it is difficult to incorporate surgical simulation into the educational curriculum. Endoscopy, lends itself much better to simulation. The improvement of trainees using simulation is most noticeable during the beginning of their endoscopic experience [170]. Following a 6-h colonoscopy simulation, trainees were noted to significantly outperform those who did not have the training but these advantages are negligible after approximately 30 procedures on patients [171].

Despite this reported advantage, the technology has not received widespread adoption in gastroenterology training. In a survey of active gastroenterology fellows, they noted that while half of the programs have endoscopic simulators, only 15% are required to use them prior to performing endoscopy on patients [172]. In a review of program directors, this was confirmed with 15% requiring their fellows to use simulation prior to clinical cases, with only one program having a minimum number of hours required in simulation training. The majority of the program directors felt that there is a need for endoscopic simulator training [173]. The reasons for a lack of embracing simulation are unclear. An attractive method to increase the quality of colonoscopy performance and to increase the skill levels of trainees without excessive numbers of procedures is the incorporation of endoscopy simulation into the curriculum of training programs that train endoscopists.

Documentation and Quality

Documentation

After completion of the procedure it is important to adequately document any findings as well as any adjunctive procedures that were performed at the time. It is imperative to photodocument any lesions or areas that were biopsied, as well as the endoscopists interpretation of these lesions. An attempt to place the location anatomically should be made, as the distance of the inserted colonoscopy can vary greatly depending upon looping and can vary depending on whether the measurement was taken on insertion or while the endoscope was being withdrawn. In addition, if any lesion was biopsied, or if a polyp was excised, the note should document whether the excision was complete or whether there was grossly abnormal tissue remaining.

A Multi-Society Task Force on Colorectal Cancer developed a consensus-based set of data points that reflected what should be included in any colonoscopy report (Table 4-3) [174].

TABLE 4-3. Recommended elements in standard colonoscopy report

Documentation of informed consent
Facility where endoscopy performed
Patient demographics and history
Age/sex
Receiving anticoagulation: if yes, document management plan
Need for antibiotic prophylaxis: if yes, document reason and management plan
Assessment of patient risk and comorbidity
ASA classification
Indication(s) for procedure
Procedure: technical description
Procedure date and time
Procedure performed with additional qualifiers (CPT codes, polypectomy, etc.)
Sedation: medications given and by the type of provider responsible
Level of sedation (conscious, deep, general anesthesia)
Extent of examination by anatomic segment: cecum, ascending colon, etc.
If cecum is not reached, provide reason
Method of documentation: i.e., photo of ileocecal valve and/or appendiceal orifice
Time of examination: scope was inserted, withdrawal started, when withdrawn from patient
Retroflexion in rectum (yes/no)
Bowel prep: type of preparation, quality, adequate or inadequate to detect polyps >5 mm
Technical performance: not technically difficult or examination difficult
Patient discomfort/looping/need for special maneuvers including turning patient
Type of instrument used: model and instrument number
Colonoscopic findings
Colonic masses or polyp(s)
Anatomic location: length/size (mm)
Descriptors: pedunculated/sessile/flat/obstructive (% of lumen reduced)/ulcerated
Biopsy obtained: hot/cold or snare/tattoo (if performed)
Fulguration or ablation with cautery
Completely removed (yes/no)/retrieved (yes/no)/sent to pathology (yes/no)
Mucosal abnormality
Suspected diagnosis: ulcerative colitis, Crohn's, ischemia, infection
Anatomic location/extent/pathology obtained (yes/no)
Other findings
Diverticulosis/arteriovenous malformations/hemorrhoids
Assessment
Follow-up plan
Immediate follow-up/further tests, referrals/medication changes
Follow-up appointments and recommendation for follow-up colonoscopy and tests
Documentation of communication directly to the patient and referring physician
Pathology
Pathology results reviewed, communicated with referring provider with recommendation for follow-up and communicated with patient

Adapted from Lieberman D, Nadel M et al. Standardized colonoscopy reporting and data system: report of the Quality Assurance Task Group of the National Colorectal Cancer Roundtable. Gastrointest Endosc 2007 May;65(6):757–66 (17)

There are numerous commercially available software programs that allow rapid and accurate documentation and these guidelines will look familiar to any provider who has utilized these systems. Unfortunately, the very ease of these programs and their check-box design allow trainees or busy professionals to perform documentation that is inadequate. In one study involving both community hospitals and academic centers several deficiencies in reporting were identified. For example, bowel preparation quality was reported in only 20%, but more concerning, the description of polyp appearance was present in only in 34% of notes [175]. In another study, photodocumentation was often missing and the size and morphology of polyps was present in only slightly more than 60% of cases [176]. Other studies show a consistent lack of documenting the quality of the bowel preparation, lack of documentation of the cecal landmarks as well as poor procedural interpretation [177, 178]. Clearly physicians who perform these procedures must not only ensure that the

procedure is done well and safely, but that it is properly documented and these findings are relayed to the patient and any other treating physicians.

Quality

There is increasing attention to quantifiable measures of quality in medicine, and colonoscopy lends itself well to metric analysis and therefore there has been a great deal of attention paid to these performance measures [179]. Almost 14 million colonoscopies are performed annually in the USA and there is understandably a great deal of attention paid to quality associated with the procedure. The five most frequently cited quality measures are cecal intubation rate, adherence to recommended screening and surveillance interval, adenoma detection rate, quality of bowel preparation, and colonoscopy withdrawal time [180]. While some of these elements are addressed elsewhere in this text, is imperative that surgeons remain involved in these discussions and the continuing quest for quality improvement for our profession and for our patients.

PillCam Endoscopy

The advent of PillCam endoscopy (PCE) has revolutionized the evaluation of the small intestine. It allows the clinician to evaluate this portion of the intestine that was previously relegated to inaccurate or uncomfortable studies such as small bowel radiographic series or enteroclysis. The procedure is most commonly used in patients with occult gastrointestinal bleeding or in the search for other small bowel pathology, such as insipient tumors, polyposis syndromes, or Crohn's disease [181]. It typically is performed after an upper and lower endoscopic examination has already been completed; however, it can complement the latter as well, as in at least one study 28% of abnormalities identified on PCE were within the area normally covered by an endoscopic exam [182]. The use of PillCam endoscopy is easy to perform and learn and is a natural adjunct in the endoscopists' armamentarium. Capsule endoscopy does not require a bowel preparation, but most patients are instructed to remain either NPO or on a clear liquid diet for 10–12 h prior to the procedure. The patient swallows the disposable capsule, which then transmits images wirelessly to a recorder, and the clinician can review the images at a time when it is convenient to spend the 15–60 min, on average, for image viewing and documentation [183].

PillCam endoscopy has been demonstrated to play a significant role in Crohn's disease, where the small intestine is difficult to visualize radiographically. While there are concerns for evaluating patients with stricturing Crohn's disease, as the capsule can be retained at the location of a stricture [184, 185], this is typically less of a concern for a surgeon contemplating operative management and can serve as a marker of stricture location enabling the procedure to be performed with minimally invasive techniques. PCE has resulted in medication changes in up to 60% of patients in some studies and [186] has proven superior to other imaging modalities in identifying obscure sources of intestinal bleeding and is beneficial in the localization of small bowel neoplasms [187, 188]. In addition, there is data that PCE may play a role in screening for colonic neoplasm, or in the evaluation of large intestinal inflammatory bowel disease. It is clear that the uses for this technology will only expand and physicians who treat intestinal disease will have to be familiar with the technology [189].

Summary

The endoscopic evaluation of the patient with colorectal complaints is essential in both the diagnosis and management of the patient. It allows the physician to visually assess the entirety of the intestinal tract and should not be thought of as a separate entity, but as an adjunct in the examination of the colorectal patient. These techniques should be familiar to the colorectal surgeon, and surgeons should continue to play a role in the testing, training, and advancement of endoscopic techniques and technology.

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5
Endoscopic Management of Polyps, Polypectomy, and Combined Endoscopic and Laparoscopic Surgery

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Key Concepts

- Colonoscopic polypectomy is the treatment of choice for diagnosing and removing most colon polyps.
- Operator variability influences the quality of colonoscopy for both detection and resection.
- Multiple questions remain about best practice techniques for colonoscopic polypectomy.
- EMR of colorectal lesions is safe and effective but results in piecemeal resection that may prevent accurate histological diagnosis. Colonoscopy surveillance is required to assess for and manage local recurrence of neoplasia.
- ESD is able to resect superficial lesions en bloc regardless of tumor size, location, and fibrosis. These advantages come at a cost of an increased risk of perforation, bleeding, and a longer procedure time as compared with EMR.
- Combined endo-laparoscopic surgery is an adjunct to endoscopic polypectomy that may help to avoid colectomy.

Introduction

It is estimated that 93,090 new cases of colon cancer will be diagnosed in the year 2015 with almost 50,000 estimated deaths due to colon cancer [1]. Although colon cancer is still the third most common cause of cancer related mortality in the USA, there has been a steady decline in the colorectal cancer incidence since the mid-1980s which is partially attributed to the introduction of colorectal cancer screening [2]. There has even been a more rapid decline in recent years (4% or greater per year from 2008 to 2011) which may be multifactorial but likely reflects the increased use of screening colonoscopy. Among adults aged 50–75 years, colonoscopy use increased from 19.1% in 2000 to 54.5% in 2013 [3]. Recently published data of the long-term follow-up from patients enrolled in the National Polyp Study provides evidence that colonoscopic removal of adenomatous polyps reduces colon cancer incidence and related mortality [4].

Colonoscopic polypectomy is the treatment of choice for diagnosing and removing most colon polyps. In the past decade, polypectomy technique, instrumentation, and evolution of endoscopy skills have improved polyp detection rates and the ability to remove polyps. Even so, large polyps or polyps in an anatomically difficult location can be challenging to remove endoscopically. Traditionally the most common recommendation for these patients has been to undergo a colon resection. Although the laparoscopic approach has reduced the morbidity of an abdominal operation, it still poses potential morbidities related to bowel resection. A combined approach using both laparoscopy and colonoscopy has more recently been described as an alternative to bowel resection in select patients with polyps that cannot be removed endoscopically. This chapter addresses endoscopic polypectomy—basic and advanced techniques and combined endoscopic endo-laparoscopic techniques.

Identification of Polyps

Although there is little dispute about the impact of colonoscopy, there remains marked variability in the quality of colonoscopy. Indicators of quality colonoscopy include cecal intubation, withdrawal time, and polyp detection rate [5]. The need for cecal intubation is based on the persistent finding that a substantial fraction of colorectal neoplasms are located in the proximal colon including the cecum. Low cecal intubation rates have been associated with higher rates of interval proximal colon cancers [6]. Colonoscopy studies in screening patients in the USA have reported cecal intubation rates of 97% or higher [7, 8]. As the detection of neoplastic lesions is the primary goal of most colonoscopic examinations, careful inspection of the mucosa is essential. In 2002,

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the US Multi-Society Task Force on Colorectal Cancer recommended a withdrawal time (defined as the time from cecal intubation to the time the colonoscope is withdrawn out of the anus) of at least 6 min as an indicator of quality colonoscopy [9]. In 2006, Barclay et al. found a correlation between longer withdrawal time and an increased rate in the detection of adenomas [10]. There have been variations in the adenoma detection rates (ADR) and for this reason, targets for ADR have been recommended. The American Society for Gastrointestinal Endoscopy (ASGE) and the American College of Gastroenterology (ACG) recommends a minimum target for overall ADR of at least 25% based on the observation that higher ADRs were associated with a reduced risk of both proximal and distal cancer [11, 12].

Criteria for Polypectomy

Polyps occur in all parts of the colon. It is the current practice, that when polyps are detected that they should be removed as any adenomatous tissue visualized should be assumed to carry some malignant potential [13, 14]. It is widely accepted that more than 95% of colorectal cancers arise from adenomatous polyps [15, 16]. This adenoma-carcinoma sequence is well described and is often an indolent process that takes many years. Polyps are characterized by their size and morphology (pedunculated or sessile), which are two important features that may predict underlying malignancy and should guide how polyps are managed. As defined by the US National Polyp Study, an advanced adenoma is one that is ≥ 1 cm in size or contains high grade dysplasia or appreciable villous tissue. When screening colonoscopy is performed in average-risk, asymptomatic individuals over the age of 50, the prevalence of advanced adenomas ranges from 6 to 9% [7]. It is accepted that removal of large adenomas is advisable to prevent progression to colorectal cancer. The malignant potential of adenomas < 0.5 cm is not as well studied. In order to determine the clinical significance of polyps <0.5 cm, a retrospective study from Vienna, 7590 adenomatous polyps from 4216 patients between 1978 and 1996 were analyzed. Size was the strongest predictor of advanced pathologic features. Advanced pathologic features were defined as high grade dysplasia or invasive cancer. The percentages of adenomas with advanced pathologic features were 3.4%, 13.5% and 38.5% for adenomas <0.5 cm, 0.5–1.0 cm and >1 cm respectively. Villous change, left sided location and age ≥60 were also associated with advanced pathologic features. No invasive cancer was found in any polyp ≤ 0.5 cm, but since 3.4% of these contained high-grade dysplasia, the authors recommended removal whenever possible [17]. Another study found that a small (≤0.5 cm) right sided polyp in a young patient (≤60 years of age) has only a 3.8% risk for containing advanced pathologic features whereas polyps in patients over age 60, in the presence of anemia, polyp size > 1 cm, or left sided location as single or combined parameters had a maximum predictive value of 75.4% for advanced adenomas [18].

There are several reasons why a polyp should not be removed during colonoscopy. If there are characteristics suspicious for malignancy and if its endoscopic appearance suggests penetration deeper than the submucosa, a polypectomy should not be performed. The characteristics of a polyp that may be indicative of malignancy are firmness or hardness, mucosal irregularity, vascular pattern on narrow band imaging, ulceration or central umbilication, large size, and if the polyp does not lift with submucosal injection [19, 20]. In these cases, one would consider biopsy of the polyp instead of removal. Large polyp size may be another reason to defer polypectomy. Large polyps in the cecum have a higher risk of perforation during resection, and therefore, one may consider doing a combined endo-laparoscopic approach. Finally, a polypectomy should not be performed if the risks outweigh the benefits. Examples of this would be any polyp in an asymptomatic patient whose life expectancy is less than 2 years (patients with terminal cancer), polyps discovered during unfavorable circumstances (patients undergoing workup for bleeding), patients with comorbidities or on medications that would make polypectomy too risky (anticoagulation) [19].

Polypectomy Techniques

Polypectomy is fundamental to the practice of colonoscopy. The principles of polypectomy are to remove all visibleadenomatous tissue. There are many different techniques that are used in creating a wide variability in practice. Reasons for variability likely reflect the lack of standardized polypectomy protocols, difference in training and experience, missizing of polyps, and concern regarding adverse events and time constraints [21].

Polypectomy is best performed with the polyp in the 5–7 o'clock position. Cold forceps biopsy is the simplest method of polypectomy. This is frequently used for diminutive lesions (polyps < 5 mm). In a survey of 187 gastroenterologists, forceps removal was the resection technique of choice for lesions 1–3 mm in size [22]. The technique for polypectomy using cold biopsy forceps is simple. The biopsy forceps is passed through the biopsy channel of the colonoscope and the jaws are positioned over the polyp. The polyp tissue is grasped and removed. The forceps is removed for tissue retrieval [23]. This technique requires minimal manipulation, uses no electrocautery, and has an insignificant risk of perforation [24]. Frequently however, more than one bite is needed to remove all polypoid tissue. In addition, after the initial bite, minor bleeding can obscure the field, increasing the risk of leaving residual polyp behind. Biopsy and histologic evaluation of polypectomy sites after what was considered a complete cold forceps polypectomy can show residual polypoid tissue in 29–38% of specimens [25–27]. In addition, if two bites are taken in one pass, the tissue obtained with the

first bite can become dislodged and get lost. Therefore, a single-bite polypectomy may be more efficient and decrease the risk of incomplete polypectomy. In comparing jumbo forceps (jaw volume 12.44 mm) to standard forceps (jaw volume 7.22 mm) in a randomized controlled trial, a trend toward a higher complete histologic eradiation was noted with the jumbo forceps but this did not reach statistical significance [28].

Another method of removing small polyps is with the application of electrocautery to the forceps during tissue removal. The application of thermal energy fulgurates the base of the polyp while the specimen is protected in the jaws of the forceps [29]. There are several drawbacks to this technique, which have caused it to fall out of favor. There may be architectural distortion from thermal energy resulting in impaired histologic evaluation of the specimen [30]. This technique has also been associated with an increased risk of delayed bleeding and perforation in the right colon [31, 32]. It has also been suggested that the use of hot biopsy forceps is unreliable in completely removing all adenomatous tissue with 17% of polypectomy sites revealing persistent viable polyp remnants [33]. National societies recommend avoidance of hot biopsy forceps for polyps >5 mm and those in the right colon [34, 35].

Snare polypectomy is the preferred method for polypectomy among clinical gastroenterologists [22]. Once the instrument is passed through the working channel of the scope, the snare is extended from a plastic sheath and then passed around the base of the polyp. Once it is in proper position, the snare is closed transecting the base of the polyp. Advancing the catheter tip or sheath to the base of the polyp will avoid the snare from slipping back over the head of the polyp [23]. Snare polypectomy can be done with a cold technique or combined with electrocautery. It has been suggested that cold snaring is the preferred technique for all small (<10 mm) and most diminutive polyps but this has not been well studied [36, 37]. The technique of cold snaring allows for a resection of a 1–2 mm margin of normal tissue around the polyp. Bleeding is typically minor and not significant [38]. Several randomized controlled trials have shown that the risk of bleeding is similar between cold and hot snare polypectomy in lesions up to 8 mm and use of the cold snare may actually shorten procedure times [38–40]. The application of electrocautery with snare polypectomy is more common for larger polyps (>7–8 mm) and pedunculated polyps [21, 22, 41]. As previously stated, the polyp should optimally be in the 5–7 o'clock position and if it is a pedunculated polyp, one may consider repositioning the patient so the base of the polyp is not in a dependent position to make post-polypectomy bleeding easier to control. When using electrocautery, the polyp should be tented toward the center of the lumen to stretch the submucosa away from the muscularis propria and serosa. The duration of energy delivery should be minimized to prevent injury to the wall of the colon. For pedunculated polyps, the snare should be closed at a third or halfway from the base of the polyp to ensure a sufficient stump to regrasp if there is immediate bleeding. Energy should be applied early and the snare should be closed slowly [23]. There are many different snare devices available and there are no trials to establish the advantage of one device over another. In a study looking at 147,174 subcentimeter polyps from the English Bowel Cancer Screening Program, pedunculated polyps were most commonly removed using hot snare (84.7%) although this technique was used somewhat less frequently in the right side of the colon than in the left side for all polyps sizes (69.6% vs. 88.3%, $p<0.001$). For non-pedunculated polyps, hot snare was also the most commonly used technique overall (29.2%) [21].

Endoscopic Mucosal Resection

Large polyps, those involving more than one third of the circumference of the colon or two haustral folds, or those with a flat or depressed morphology are more challenging to remove with the standard polypectomy technique. [42] Endoscopic mucosal resection (EMR) can assist in removal of these lesions that may otherwise require surgical intervention. EMR allows removal of superficial tumors of the gastrointestinal tract. This technique was originally described and popularized in Japan for the treatment of gastric and esophageal tumors. It was further described for removal of colorectal polyps that were not amenable to traditional endoscopic polypectomy techniques. Because the plane of resection of EMR is typically the middle to deep submucosal layer, compared with standard polypectomy, which normally provides resection at the mucosal layer, EMR offers the potential advantage of providing en bloc resection specimens for histopathologic analysis. Unfortunately however, EMR tends to result in piecemeal excision of polyps which can cause difficulty with histologic diagnosis, staging and evaluation of margins. In addition, in contrast to the stomach, the colon wall is much thinner which can lead to higher rates of complications, i.e., perforation. Indications for EMR include adenomas or small well differentiated carcinomas that are confined to the mucosa or with superficial invasion of the submucosa, polyps less than 1/3 the circumference of the lumen and flat or depressed polyps [42].

EMR is a modification of conventional snare polypectomy. A solution is injected into the submucosa beneath the lesion. This serves to elevate the mucosal layer that contains the lesion on a submucosal fluid cushion providing a safety zone for snare resection. Many different solutions have been used for injection including normal saline, hypertonic saline, 50% dextrose, glycerol solutions, hyaluronic acid, and diluted epinephrine solution. The ideal agent prolongs the "pillow effect" which decreases the risk of bleeding and perforation [42]. Once the lesion is raised, snare polypectomy is performed. For large lesions, piecemeal polypectomy is invariably required. The cap-assisted technique (EMRC) is

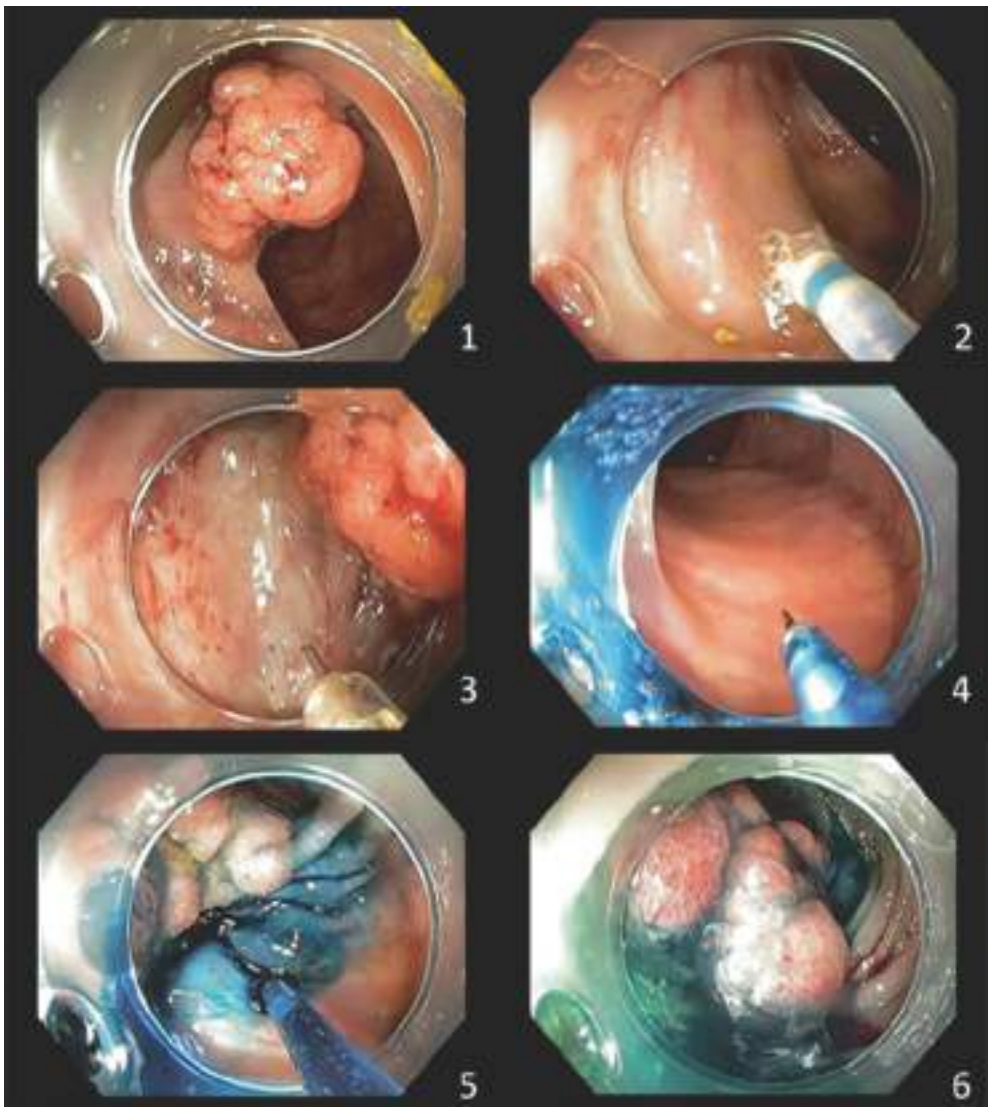

Figure 5-1. Illustration of piecemeal endoscopic mucosal resection. 1–6: mucosal lift by submucosal injection of indigo carmine.

another method used which involves a cap with a lip on the distal end. A snare is positioned around the lip of the cap and then the target mucosa is suctioned into the cap. Once the tissue is aspirated, the snare is then closed around the tissue (Figures 5-1 and 5-2). The benefits of this technique are reported better visualization and the possibility of resecting lesions in variable positions. The pressure of the cap on the wall of the colon allows flattening of the folds maximizing the view of interhaustral lesions. This technique is frequently performed in the stomach in Japan. EMRC is not as popular for colorectal polyps for fear of entrapping the muscularis propria into the snare, therefore increasing the risk of perforation [43].

EMR is limited by the difficulty in determining which lesions are likely to be confined to the mucosa. In a prospective, multicenter cohort, risk factors for submucosal invasion and failure of successful EMR were identified. In their experience, risk factors for submucosal invasion were Paris classification 0-IIa+c morphology, non-granular surface morphology, or Kudo pit pattern type V (Tables 5-1 and 5-2). The presence of multiple risks factors magnified the risk of submucosal invasion [44]. In this study, EMR was attempted on 464 patients and successful in 89% of patients. Risk factors for failure included a prior attempt at EMR (OR=3.8; 95% CI: 1.77–7.94), difficult position (OR=2.17; 95%CI: 1.14–4.12) and ileocecal valve involvement (OR=3.38; 95%CI: 1.20–9.52).

EMR is effective and practical with good outcomes (Table 5-3). When performed by experts, anywhere from 3 to 7% of patients are referred for surgical resection because of inability to remove the polyp endoscopically [45, 46]. Approximately 44% of lesions are removed en bloc and the remaining are removed piecemeal [45]. Complication rates

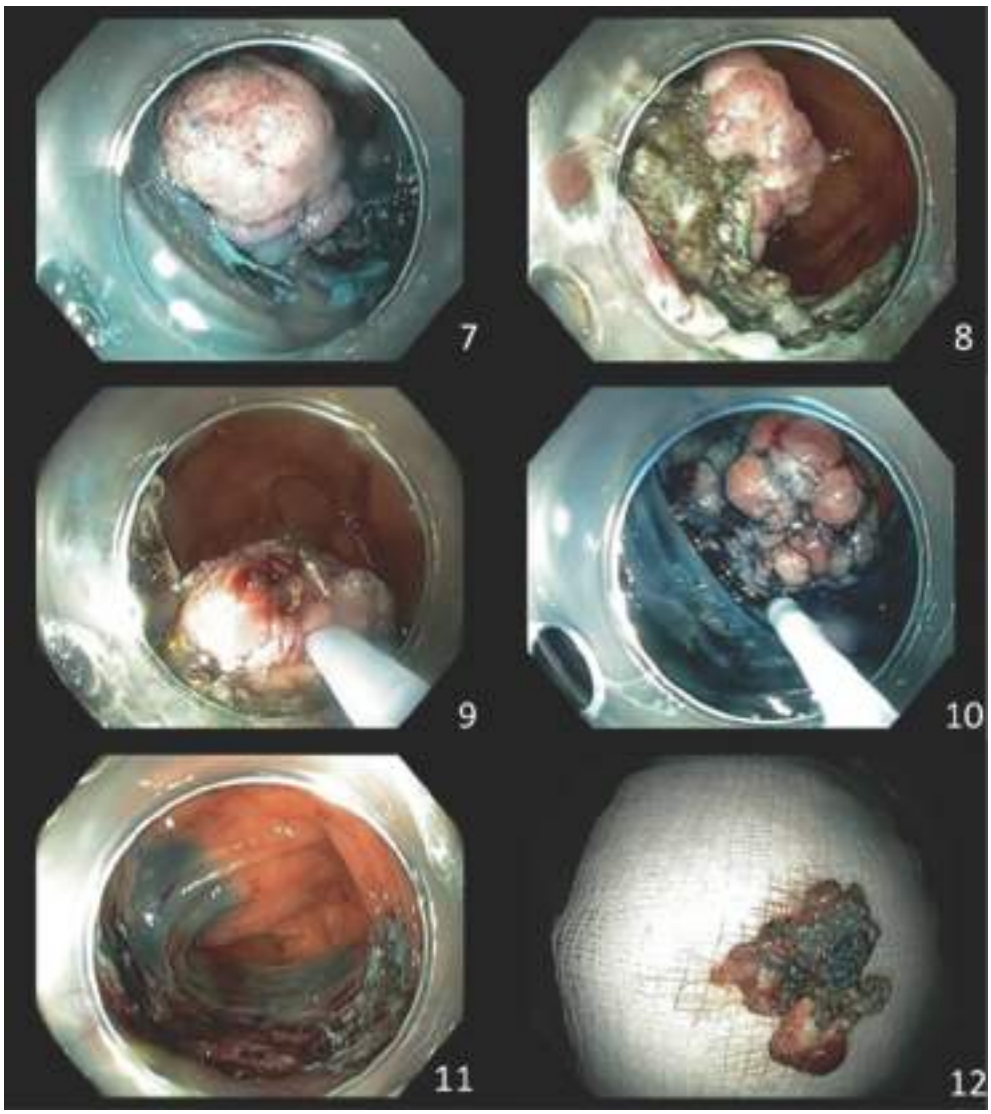

FIGURE 5-2. Illustration of piecemeal endoscopic mucosal resection. 7–10: Piecemeal hot snare polypectomy. 11: intact muscularis. 12: Removed specimen.

TABLE 5-1. Paris classification

Pedunculated	Ip
Subpedunculated	Isp
Sessile, higher than height of closed forceps (2.5 mm)	Is
Slightly elevated, below height of closed forceps (2.5 mm)	IIa
Completely flat lesion, does not protrude above mucosal surface	IIb
Slightly depressed, lower than mucosa but depth < 1.2 mm	IIc
Excavated/ulcerated, deep ulcer below mucosa below 1.2 mm	III

TABLE 5-2. Kudo pit pattern

Pit pattern type	Characteristics
I	Round pits
II	Stellar or papillary pits
III S	Small tubular or round pits (smaller than type I pits)
III L	Large tubular or round pits (larger than type I pits)
IV	Branch-like or gyrus-like pits
V	Irregular or non-structured pits (absence of pit pattern)

are low. Intraprocedural bleeding occurs in about 8% of patients, post-procedural bleeding in 0–1%, and perforation 1–2% [45, 46]. Local recurrence after EMR is variable and reported in up to 27% of cases [47]. In a multicenter, prospective study of 1000 consecutive patients treated with EMR where the lesion was thought to have been completely treated, early recurrent/residual adenoma (4 months following EMR) was present in 16% and late recurrent/residual adenoma (16 months following EMR) was uncommon (4%). On multivariate analysis, risk factors for recurrence were

Table 5-3. Endoscopic mucosal resection

Author	Year	Polyps	Polyp size (cm)	Macroscopic classification	Operating time (min)	En bloc resection (%)	LOS (day)	Leakage/ fistula (%)	Postoperative bleeding (%)	Cancer (%)	Depth	Recurrence (%)
Gomez	2014	131	3.3	NA	NA	27	NA	3	2.3	7.6	Unknown	17
Maguire	2014	269	2.8	NA	NA	0	NA	1.3	3	16	Tis: 6.3%; T1: 9.3%	24
Knabe	2013	252	>2.0	Paris	NA	12	NA	1.6	1.6	3.2	Unknown	22
Buchner	2012	315	2.3	Paris	NA	54	<1	0.4	7.2	4.4	Unknown	27
Conio	2004	139	2.0	NA	NA	0	NA	0	0	12.2	Tis: 6; T1: 3; T2: 1	21.9
Stergiou	2002	68	>3.0	Sessile/pedunculated	NA	38	NA	0	4	10	Unknown	29

LOS length of stay, *Tis* carcinoma in situ, *NA* not available

lesion size >4 cm, use of argon plasma coagulation to ablate adenomatous tissue and intraprocedural bleeding. The recurrent adenoma was usually unifocal and diminutive, and was managed endoscopically in 93% of cases [45]. Further reported risk factors for recurrence include granular appearance of the lesion and distal rectal lesions. Incomplete resection and resections with deep positive margins should be considered for surgery [48].

Endoscopic Submucosal Dissection

The technique of endoscopic submucosal dissection (ESD) developed for en bloc resection for large and ulcerative lesions in the stomach has been widely accepted in Japan for the treatment of early gastric cancer [49]. Compared with EMR, ESD has the advantage of definitively permitting an en bloc and therefore histologically complete resection. With this technique, one is able to resect superficial lesions regardless of tumor size, location, and fibrosis [50–52]. These advantages come at the cost of an increased risk of perforation, bleeding, and a longer procedure time as compared with EMR. [53]

As the major difference between surgical resection and endoscopic resection is the absence of lymph node dissection, endoscopic resection should only be considered in lesions that have an insignificant risk of lymph node metastasis. The risk of lymphatic disease is largely based on a tumor's depth of invasion, and hence, a large part of the evaluation is determining this. Therefore, the use of ESD for colorectal lesions has been limited to patients who have undergone accurate preoperative diagnosis. This technique is indicated when an en bloc resection cannot be done with EMR. It is also indicated for polyps with intramucosal to shallow submucosal invasion as well as lesions with submucosal fibrosis that cannot be lifted with submucosal injection during conventional EMR. It may also be indicated in sporadic localized tumors in conditions of chronic inflammation such as ulcerative colitis or local residual or recurrent early carcinomas after endoscopic resection [54]. Experience with ESD outside of Japan is still limited. In a consensus statement by a panel of experts, the goals of ESD remain: treating mucosal cancer, achieving an R0 resection, meeting quality standards, ensuring the procedure is performed by endoscopists trained in this technique and under institutional review board approval [55].

The technique of ESD is similar to EMR in that it involves a single channel scope and submucosal injection. The border of the lesion may first be marked out by injecting indigo carmine or using indigo carmine dye spray. A variety of solutions have been used for submucosal injection but the most common are normal saline, glycerol or hyaluronic acid. Normal saline is safe and widely available but the lift that it creates is of short duration, which may come at a disadvantage. For safety in the thin walls of the colon, longer lasting solutions such as glycerol or hyaluronic acid are needed [56]. The optimal injection solution should achieve and maintain the necessary submucosal lifting height and duration, not influence the histological evaluation, not have tissue toxicity and be easily prepared and administrated [57]. Once the lesion is lifted, specialized endoscopic knives help to dissect out the lesion (Figure 5-3). There are a variety of knives available but the two traditional types of needle knives and insulted tip knives. Both types of knives are used in combination with electrocautery to dissect and separate the mucosal and submucosal layers. Bleeding is common during ESD, and therefore, management of bleeding is important for the procedure to be successful. Hemostasis is maintained using either monopolar or bipolar coagulation forceps, which can increase the risk of perforation or hemoclips, which can obstruct the plane of dissection [56].

Similar to new techniques elsewhere, ESD has a high learning curve. Compared with gastric lesions, ESD in the colon and rectum is more difficult due to anatomic features (thin wall, peristalsis, folds) and the position of the endoscopic is less stable especially outside of the rectum. Probst and colleagues divided their experience with ESD into three periods and demonstrated a clear learning curve over time with resection rates increasing and procedure times decreasing as expected. They suggest a learning curve of 25–50 cases [58]. Others have suggested 40 procedures are necessary to acquire skill in avoiding perforation and 80 cases to be proficient in resecting large colorectal lesions [59]. Successful en bloc resection may be as low as 60% in initial cases but increases up to 88–97% with experience [58–60]. Similarly, R0 resection rate improves with experience and is reported as high as 96% [58]. Procedural complications are higher than with EMR and consist of bleeding in 1.5–7.9% and perforation in up to 10.7% of cases (Table 5-4) [58, 60, 61]. Frequently, complications are successfully treated with endoscopic clipping. Follow up and surveillance after ESD should be case dependent. The aim of surveillance is to detect residual disease or recurrent disease early. The follow up plan should be based on whether resection was en bloc or piecemeal, the pathology of the lesion, risk factors for multiple lesions and underlying disease [54].

Combined Endo-Laparoscopic Surgery (CELS)

As previously discussed, large polyps or polyps within or behind a haustral fold can be very challenging to remove endoscopically. Although EMR and ESD are performed for

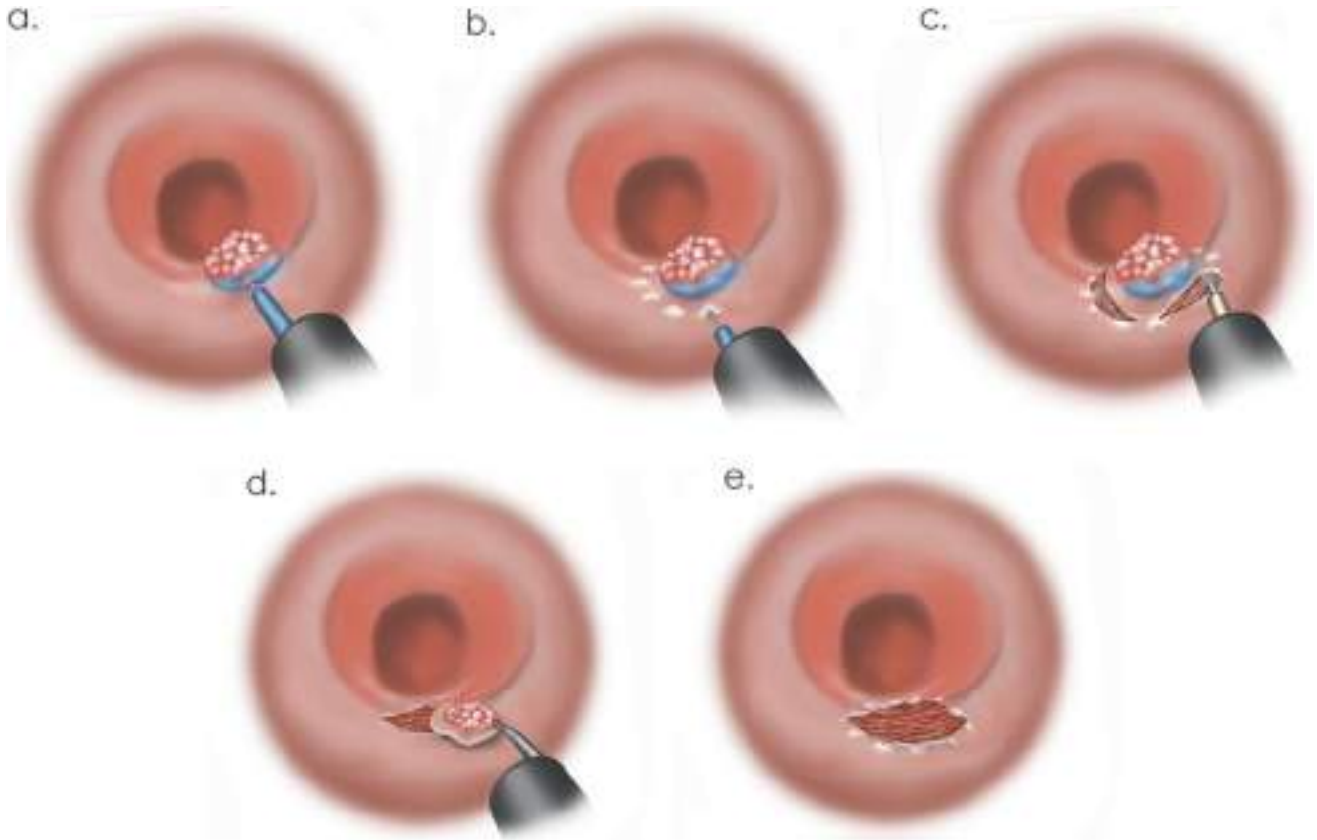

FIGURE 5-3. Steps of endoscopic submucosal dissection. (**a**) submucosal injection. (**b**) marking of the resection margin. (**c**) submucosal dissection using a needle knife. (**d**) extraction of specimen. (**e**) intact muscularis.

these polyps, these techniques are not widely available and require a high level of technical skill. Traditionally, the most common recommendation for these patients has been segmental colectomy—an oncologic resection. Although the laparoscopic approach can minimize the morbidity associated with colectomy, only a minority of the colon resections performed in the USA are being done laparoscopically [62]. Furthermore, even if a minimally invasive approach is used, it still entails a major abdominal operation with associated morbidities. Combined endo-laparoscopic surgery (CELS) has been described as an alternative to bowel resection in select patients.

Laparoscopic assisted polypectomy was first described in 1993 as a means to avoid bowel resection [63]. Larger retrospective studies have since been published indicating that the technique is safe and effective [64–69]. There are several ways in which laparoscopic assistance during colonoscopic polypectomy can be helpful: (1) the underlying colon can be invaginated to assist in snaring of a flat polyp, (2) laparoscopic mobilization of flexures and angulated colon can provide better access and exposure, and (3) full-thickness injury to the colon can be detected and repaired laparoscopically. Simultaneous performance of laparoscopy and colonoscopy can often present technical challenges. Insufflation using room air during colonoscopy can significantly obscure the laparoscopic view and compromise exposure. A technique of laparoscopically clamping the terminal ileum to minimize bowel distention has been described, but colonic distension is still a major impediment with this method [63, 64]. The use of carbon dioxide (CO_2) for insufflation during

TABLE 5-4. Endoscopic submucosal dissection

Author	Year	Polyps	Polyp size (cm)	Macroscopic classification	Operating time (min)	En bloc resection	LOS (day)	Perforation (%)	Postoperative bleeding (%)	R0 resection rate (%)	Cancer (%)	Depth	Recurrence (%)
Saito	2014	900	3.7	Paris	60	91	NA	2.7	1.7	87	74	Unknown	NA
Toyonaga	2014	468	3	NA	60	99	NA	1.5	1.5	NA	66	Tis: 49%; T1: 17%; T2: 0.4%	NA
Lee	2013	874	2.7	sessile/pedunculated	54	97	3.5	5.3	0.5	91.2	43	Tis: 28%; T1: 15%; T2: 0.2%	0.4
Yoshida	2013	530	3.1	protruding/superficial	93	91	NA	4.1	2.3	NA	54	Tis: 41%; T1: 12%	NA
Nakamura	2014	300	3.0	LST/ non-LST	90	91.7	5	1.7	5	91	99	M-SM-s: 92%; SM-d: 7%	NA

LOS length of stay, *NA* not available, *Tis* carcinoma in situ, *M-SM-s* mucosal or shallow submucosal invasion <1000 mcm from the muscularis mucosae, *SM-d* >1000 mcm of submucosal invasion

TABLE 5-5. Combined endo-laparoscopic surgery

Author	Year	Patients	Polyps	Polyp size, (cm)	Frozen section	Operating time (min)	Intraoperative complications (%)	Postoperative complications,%	Mortality (%)	LOS (days)	Tis (%)	Submucosal cancer (%)	Successful endoscopic resection (%)	Conversion to open surgery (%)	Prognosis (m = months)
Goh	2014	30	30	1.4	–	105 (75–125)	0	13.3	0	2.0	HGD 26.7	6.7	73	0	no recurrence at 20m
SW Lee	2013	75	75	3 (1–7)	if needed	145 (50–249)	0	9.2	0	1	HGD 9.3	6.7	74	3	10% recurrence at 65m
Wood	2011	13	16	3 (2–5)	all	NA	0	15	0	2	7.7		77	0	NA
Grunhagen	2011	11	12	2 (0.6–4.5)	–	45 (15–80)	0	18.1	0	1	9	0	82	0	no recurrences at 11m
Cruz	2011	25	25	2.4 (1–4)	–	92.7 (60–145)	0	8	0	1.5	8	4	76	0	NA
Agrawal	2010	19	19	0.6–6	all	35.3–37	0	5.6	0	0–14	5.3		58	NA	no recurrences at 3m
Wilhelm	2009	146	154	NA	–	100 (40–272)	1	25	0.7	8	11		73	5	Local recurrence of adenoma 0.9% at 35m
Franklin	2009	176	251	3.7 (2–6)	all	96.5	0	10	0	1.1	10.2		91	0	no recurrences at 65m

NA not available, *HGD* high grade dysplasia, *Tis* carcinoma in situ, *LOS* length of stay

colonoscopy has been shown to be safe and can remedy this issue. CO_2 gas is absorbed approximately 150-times faster than room air so there is minimal unwanted distention of the colon providing excellent simultaneous endoscopic and laparoscopic visualization [70].

Consideration for CELS starts by reviewing the initial procedure report and photographs looking for any concerning signs of malignancy, such as ulceration and hypervascularity. Presence of high-grade dysplasia is concerning for malignancy but is not necessarily a contraindication to performing CELS. In our practice, prior to obtaining laparoscopic access to the abdomen, colonoscopy is performed and at that point, decision is made whether the polyp is resectable using colonoscopy alone or if laparoscopic assistance is needed (Video 5.1). If laparoscopic assistance is needed, then abdominal access is performed. The exact location of the polyp is determined by visualizing the tattoo mark and manipulating the polyp laparoscopically while visualizing the polyp endoscopically. For laterally and retroperitoneally located polyps, the colon needs to be mobilized. Polyps located on the mesenteric side may be difficulty to visualize and laparoscopically repair in case of perforation. Once the polyp is identified intraluminally, using laparoscopic manipulation, the base of the polyp is exposed. The lesion can then be elevated further with submucosal injection. Malignancy is suspected with specific morphology (ulceration, central umbilication, or a vascular pattern on narrow-band imaging) or if the polyp does not lift up with injection. If there is no suspicion of malignancy, polypectomy is performed using snare and electrocautery. The wall of the colon can be invaginated laparoscopically to aid in optimal snaring of the polyp. While polypectomy is performed, the serosal aspect of the colon can be monitored for thermal related changes. If a full-thickness burn of perforation is even suspected, repair can be done intracorporeally. An air leak test can also be performed using insufflation with the colonoscope. If the polyp feels firm on palpation or seems in any way suspicious for malignancy after excision, an intraoperative frozen section can be performed. In select patients with cecal or right colon polyps, if the polyp is located on the anti-mesenteric side of the colon, a colonoscopic assisted laparoscopic wall excision can be performed using a laparoscopic stapler. When the stapler is placed across the bowel wall, colonoscopy can be used to monitor the margins of excision and the ileocecal valve when in the cecum.

Several published studies have similarly addressed this combined technique, considering it a safe and effective method to avoid colectomy and remove difficult polyps in many cases (Table 5-5). A large study describing a 10-year experience with the technique of combined laparoscopic endoscopic resection reported results on 146 patients with 156 lesions. The authors performed four separate techniques combining endoscopy and laparoscopy but only eight patients (5.4%) had laparoscopic-assisted endoscopic resection. Most of the patients (76.7%) underwent either an endoscopic-assisted transluminal resection, which was done through a colotomy. In addition, the mean length of stay was 8 days, which is long compared with other studies. This may have been due to the nature of the resections. There was also a 25% complication rate, which may have contributed to the prolonged length of stay. Although there was only a 0.9% local recurrence rate, with a follow up of 2.9 years [65]. One of the largest studies to date was reported by Franklin and Portillo describing the technique of laparoscopic-monitored colonoscopic polypectomy in 176 patients with excision of 251 polyps. The procedure was performed successfully in all but four patients (97.8%). This study was an update of two previous publications from their group in 2000 and 2007. In their practice, all specimens were sent for frozen section and ultimately, 18 (10.2%) patients required colectomy for cancer [71].

Overall, technical success rates for CELS are consistently reported between 74 and 97%. Postoperative complications are typically minor and less than 5%. Recurrence rates are low, reported in 10–15% and can typically be approached endoscopically or with CELS [65, 69, 70].

Conclusion

Polypectomy is fundamental to the practice of colonoscopy. A range of techniques is available and the choice of technique should be tailored to the size, site, and morphology of the polyp. There is a wide variation in practice. Advanced endoscopic techniques such as EMR, ESD, and combined endolaparoscopic techniques provide options for patients with benign polyps not amenable to traditional endoscopic removal that would have otherwise undergone colon resection. Although polyp removal using these advanced techniques may be an effective alternative in select patients, they require both experience and expertise to become an available option in a surgeon's armamentarium [66, 70, 71].

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6
Preoperative Assessment of Colorectal Patients

Jennifer S. Davids and Justin A. Maykel

Key Concepts

- A thorough history and physical exam performed by the surgeon is the single best preoperative "test."
- Complex surgical patients with multiple comorbidities need careful preoperative assessment in order to minimize risk of perioperative complications.
- Preoperative laboratory studies should be ordered on a selective basis, as "routine" preoperative labs on otherwise asymptomatic, healthy patients have low diagnostic yield.
- Depending on patient's risk factors, a preoperative cardiac risk assessment should be made and appropriate testing obtained. Cardiac medications should be continued, although beta blockers should not be initiated in the preoperative setting. Cardiac interventions should be performed for standard indications, independent of the need for abdominal surgery.
- Smoking cessation should be strongly encouraged prior to elective surgery.
- The surgeon should carefully review the patient's medication list, paying particular attention to anticoagulants, immunosuppressants, and chemotherapy agents.

Evaluation of the Routine Colorectal Patient

In Office by Surgeon

The in-office surgical consultation, including a detailed history and physical exam performed by the surgeon, is the single most important part of the preoperative evaluation. This also includes a thorough review of the patient's medical record, which often will uncover additional relevant medical and surgical history, as well as medications. Particularly for complex patients with known cardiopulmonary disease or other major comorbidities (as well as patients with surgical diseases involving multidisciplinary care teams such as inflammatory bowel disease (IBD) and rectal cancer), it is essential to obtain the names, phone numbers, and e-mail addresses of the patients' specialists for further communication and coordination of care. Many patients shuttle between different hospital systems and despite advances in information technologies, fluid communication between specialists remains challenging. The task of coordinating these patients' preoperative care can be enormously time-consuming for the busy surgeon; however, it is incredibly important to communicate and exchange vital information prior to elective surgery, in order to minimize risk of perioperative complications.

Major Abdominal Surgery

It goes without saying that the surgeon should personally perform a detailed history and physical examination of every patient undergoing elective abdominal surgery. The history should make sure to include a detailed list of active medications, including blood thinners and over-the-counter drugs or topical agents. The history should include complementary or alternative medicine practices and substances. Personal and/or family history of clotting or bleeding disorders (or bleeding complications from prior surgery) should be obtained. Additionally, the surgeon should ask about activity level, in order to estimate exercise capacity. Poor baseline exercise capacity has been shown to correlate with increased risk of perioperative cardiac complications [1]. Can the patient walk up a flight of stairs, do heavy housework, or walk up a hill? "Yes" to these questions indicates that the patient can perform at least four METs (metabolic equivalents) and if otherwise healthy, the patient does not need a preoperative cardiac workup [2].

Anorectal Surgery

Anorectal surgical procedures are considered low acuity and do not trigger the major physiologic changes associated with major abdominal surgery. Accordingly it is not necessary to obtain any additional preoperative workup for healthy patients undergoing

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elective anorectal procedures. This includes patients who are over 50 years old, with comorbidities such as hypertension, hyperlipidemia, and diabetes that are well-compensated and properly managed by their PCP or specialists.

Preoperative Testing

Laboratory Studies

Multiple studies have demonstrated that routine preoperative labs are very low-yield in identifying abnormalities that require a change in management in healthy, asymptomatic patients. A selective approach to preoperative laboratory studies should be taken, based on the evidence outlined in this section. A landmark retrospective study of 2000 patients undergoing elective surgery demonstrated that approximately 60% of all preoperative laboratory studies were not indicated, and only 0.2% of these non-indicated tests (which occurred in ten patients) revealed abnormalities that could potentially result in a change in management [3]. Further analysis of these ten individual patient charts was performed and it was determined that no further actions were taken in any instance. When laboratory tests are indicated, lab values from the 4 month timeframe prior to surgery may be used, unless there has been a change in clinical status (uptodate.com, preoperative evaluation of the healthy patient).

Hemoglobin is recommended for all patients age 65 or older who are undergoing abdominal surgery. Younger patients should be tested if there is potential for major blood loss, or if the history is suggestive of anemia. *White blood cell count* as a screening test is of limited utility, but is certainly relevant in cases where recent infection has been treated or in the setting of immunosuppression. *Platelet counts* should be checked if the patient will undergo spinal or epidural anesthesia. *Coagulation studies and bleeding time* are not needed in patients with no personal or family history of bleeding disorders. Further, abnormal prothrombin time and bleeding time have not been shown in large studies to correlate with increased risk of intraoperative or postoperative bleeding complications [4, 5]. Pre-transfusion testing consisting of *ABO and Rh typing* ("type and screen") should be performed preoperatively in all patients undergoing major abdominal surgery, including bowel resection. This is particularly important for patients who have a significant transfusion history, who may have multiple alloantibodies.

Serum *creatinine* should be checked in patients 50 years or older, as elevated creatinine is an independent predictor of increased postoperative cardiac complications [6], as well as mortality [7] in elective noncardiac surgery. Further, some anesthetics require dose adjustments for patients with impaired renal function, so this information is vital to our anesthesia colleagues. Routine *electrolytes* are not required unless the patient has a history of prior electrolyte abnormalities, chronic kidney disease, or diuretic use. Routine blood **glucose** measurements are not indicated in nondiabetic patients, as the incidence of asymptomatic hyperglycemia is low [8]. The same logic also applies to *liver function tests*, which also should not be routinely ordered in a healthy, asymptomatic patient [4]. Routine *urinalysis* does not need to be performed in healthy, asymptomatic patients, and should be only performed on a more selective basis, in patients with history of frequent urinary tract infections or other relevant urinary symptoms. In most instances, asymptomatic patients with positive urinalyses may be treated empirically for urinary tract infection, and may proceed with elective abdominal surgery as scheduled. Most studies of the utility of preoperative urinalysis are from the orthopedic surgery literature, and they do not demonstrate a correlation between preoperative positive urinalysis or bacteriuria and postoperative infectious complications [9].

Pregnancy tests should be performed on all women of childbearing age, if the results would alter management [10]. While serum human chorionic gonadotropin (HCG) assays are the most sensitive in detecting very early pregnancy, most urine pregnancy tests are positive within a week of a missed period, and can be processed quickly in the preoperative setting.

Electrocardiogram

Electrocardiograms (ECGs) are quick, noninvasive, and inexpensive; consequently, they are overutilized in the routine preoperative workup of most patients. In asymptomatic patients undergoing low-risk surgery, ECG is unlikely to identify abnormalities that result in a change in management. Further, the incidence of abnormal ECGs is very low in patients under 45 years old. According to the ACC/AHA guidelines, preoperative ECG should be performed on patients with known heart disease, peripheral arterial disease, or cerebrovascular disease [11].

Chest X-Ray

The American College of Physicians recommends obtaining chest X-ray (CXR) for patients with known cardiopulmonary disease, as well as all patients 50 years or older who require major abdominal surgery [12]. The American Heart Association also recommends CXR (posterior–anterior and lateral views) on obese patients with BMI $\geq$ 40 [13]. Despite these recommendations, CXR are low yield in identifying clinically significant abnormalities that alter management [14].

Patients with Specific Comorbidities

Assessment of Cardiac Risk

The overall risk of perioperative cardiac events is low in patients undergoing elective noncardiac surgery; however, it is essential to identify patients who may be at increased risk, in order to optimize them preoperatively and thereby minimize their potential for adverse perioperative cardiac events. A large study of over 8000 high-risk patients undergoing noncardiac

surgery demonstrated that postoperative myocardial infarction is associated with high 30-day mortality (11.6%), and the majority (65%) was not associated with ischemic symptoms [15]. It is therefore important to ensure that these risks are identified preoperatively and patients are optimized, as these adverse events can range from subtle to fatal.

Initial Workup

The most common postoperative cardiac events include myocardial infarction, heart failure, arrhythmia, and cardiac arrest. The first step is to obtain a detailed history and physical during the office consultation. Patients should be asked whether they can climb two flights of stairs, and/or walk four city blocks (noting that some may have orthopedic issues limiting these tasks) [16]. They should also be asked about the following symptoms: palpitations, chest pain, syncope, dyspnea, orthopnea. Not only is history of cardiac disease important (including valvular or ischemic heart disease, cardiomyopathy, and arrhythmia), but history of diabetes, renal impairment, peripheral artery disease, and cerebrovascular disease is also highly relevant in assessing risk due to their association with coronary artery disease.

There are several validated models that can be used by the clinician to predict risk of perioperative cardiac adverse events. The simplest of these models is the Revised Goldman Cardiac Risk Index (RCRI) (Table 6-1) [6]. Other user-friendly models include the American College of Surgeons' National Surgical Quality Improvement Program (ACS-NSQIP) risk calculator, which requires more input variables, but also will provide quantification of other, noncardiac risks [17]. The calculator is online, and accessible at http://riskcalculator.facs.org.

Who Needs Additional Testing?

The extent of preoperative workup is based on the patient's estimated risk according to these models. Patients with less than 1% risk of perioperative death from cardiac disease do not require additional workup. Patients whose risk is 1% or more are likely to have a known history of recent myocardial infarction, unstable angina, heart failure, valvular disease, or arrhythmias. These patients should be evaluated preoperatively by their cardiologist, as the decisions regarding which additional testing to pursue, if any, is rarely simple. The American College of Cardiology/American Heart Association (ACC/AHA) guidelines suggest that functional performance status is an important indicator of whether additional testing is necessary in higher risk patients [11]. Further testing may include echocardiography, stress test (exercise or pharmacologic), 24-h ambulatory monitoring and cardiac catheterization. Generally, additional testing is not usually performed beyond what is ordinarily needed if the patient were not undergoing surgery, as this has not been shown to improve perioperative outcomes in noncardiac, nonvascular surgery.

Preoperative "Optimization"

Once the preoperative cardiac assessment has been completed and risk estimated, the primary care physician or cardiologist may institute treatment that optimally limits the risk of a perioperative cardiac adverse event. While long-standing beta-blockers should be continued, beta-blockers should NOT be initiated in the preoperative setting. While there may be a benefit with regard to non fatal MI, multiple studies and meta-analyses have documented a significantly increased risk of non fatal stroke and mortality when beta-blockers are started as soon as 24 h before surgery [18, 19]. Antihypertensive medications can be adjusted to avoid perioperative hypotension, targeting a systolic blood pressure of 116–130 mmHg and heart rate of 60–70 beats per minute [18, 20]. When diagnosed, new dysrhythmias can be controlled with antiarrhythmic agents. Decompensated heart failure increases perioperative risk and this risk may be mitigated by treatment with ACE inhibitors, aldosterone antagonists, and digoxin for at least 1 week preoperatively [21]. While cardiac catheterization should be reserved for patients with high-risk features on noninvasive testing (including

Table 6-1. Revised Goldman Cardiac Risk Index (RCRI) [6]

Six Independent Predictors of Major Cardiac Complications [1, 85]
• High-risk type of surgery (examples include vascular surgery and any open intraperitoneal or intrathoracic procedures)
• History of ischemic heart disease (history of myocardial infarction (MI) or a positive exercise test, current complaint of chest pain considered to be secondary to myocardial ischemia, use of nitrate therapy, or ECG with pathological Q waves; do not count prior coronary revascularization procedure unless one of the other criteria for ischemic heart disease is present)
• History of heat failure (HF)
• History of cerebrovascular disease
• Diabetes mellitus requiring treatment with insulin
• Preoperative serum creatinine <2.0 mg/dL (177 μmol/L)
Rate of cardiac death, nonfatal myocardial infarction, and nonfatal cardiac arrest according to the number of predictors [2]
• No risk factors—0.4% (95% CI: 0.1–0.8)
• One risk factor—1.0% (95% CI: 0.5–1-4)
• Two risk factors—2.4% (95% CI: 1.3–3.5)
• Three or more risk factors—5.4% (95% CI: 2.8–7.9)

reversible large anterior wall defect, multiple reversible defects, ischemia occurring at a low heart rate, extensive stress-induced wall motion abnormalities, transient ischemic dilatation) the role for percutaneous coronary intervention (PCI) or operative revascularization remains controversial. While the discussion is beyond the scope of this chapter, revascularization should be reserved for those patients who meet criteria for cardiac intervention regardless of the need for non cardiac surgery and the timing should be chosen based on the indication for and urgency associated with the colorectal resection.

Coronary Stent Management

For patients with either a bare-metal stent (BMS) or drug-eluting stent (DES), the current recommendation is to continue dual antiplatelet therapy (aspirin plus an oral antiplatelet agent such as clopidogrel) for at least 12 months. For patients who need to undergo nonemergent noncardiac surgery, the recommendation is to complete at least 1 month dual antiplatelet therapy preoperatively for BMS, and at least 6 months for DES [22, 23].

These recommendations are based on existing data that quantifies risk of postoperative coronary and cerebrovascular thrombotic events in this patient population. The RECO study is a prospective multicenter observational cohort study of 1134 consecutive patients with coronary stents undergoing noncardiac surgery from 2007 to 2009. The goal of the study was to quantify risk of adverse cardiac and cerebrovascular events (MACCEs) and major bleeding, and to risk stratify patients according to preoperative characteristics. Of the study group, 54.9% had bare-metal stents (BMS) only, and 32.4% had drug-eluting stents (DES) (± BMS); in 12.7% the stent type was unknown. Overall, there was a 10.9% rate of MACCEs, and a 9.5% rate of hemorrhagic complications. Multivariable logistic regression was used to determine preoperative characteristics that were risk factors for MACCEs, which included the following: complete cessation of oral antiplatelet agent >5 days preoperatively, preoperative hemoglobin <10 g/dl, creatinine clearance <30 ml/min, and emergency or high-risk surgery. Risk factors for major bleeding included hemoglobin <10 g/dl, creatinine clearance 30–60 ml/min, duration from stent implantation to surgery <3 months, and high-risk surgery. This study highlights the importance of delaying elective surgery >3 months after stent placement if possible, as well as the need to maintain oral antiplatelet agents through the perioperative period in order to minimize risk for major adverse cardiac and cerebrovascular events.

Not infrequently colon and rectal surgeons are presented with patients who require urgent abdominal surgery, who also have recently implanted DES. A common scenario is the patient who has a lower gastrointestinal bleed while on oral antiplatelet therapy after DES implantation, who is found on colonoscopy to have a bleeding colon cancer. Patients on oral antiplatelet agents for recently implanted drug-eluting coronary stents can be safely "bridged" with IV infusions of shorter-acting antiplatelet agents. A pilot study of 30 patients with recently implanted DES (median 4 months; range 1–12 months) undergoing major (ten had abdominal surgery) or eye surgery had clopidogrel withheld 5 days preoperatively and were bridged with tirofiban (started 24 h later, discontinued 4 h preoperatively and restarted 2 h postoperatively until clopidogrel is resumed) [24]. Fourteen of the patients (47%) were maintained on aspirin throughout the perioperative course. There were no adverse cardiac events during the index hospitalization, and 28 patients (93%) did not experience significant postoperative bleeding. One of the two patients had an anastomotic bleed after partial colectomy that occurred 4 days after restarting clopidogrel; this was controlled with endoscopic clip placement. This study demonstrates the importance of careful coordination with the inpatient cardiologist in order to optimize outcomes for these complex patients who require urgent abdominal surgery while on antiplatelet therapy for a recently placed coronary stent.

AICD/Management

For nonemergent procedures, it is essential that these high-risk and complex cardiac patients are evaluated by a cardiologist, preferably the patient's own electrophysiologist. The importance of communication between the cardiologist and anesthesiologist cannot be overstated; above all, it is the obligation of the colon and rectal surgeon to ensure that this occurs. Patients with automatic implantable cardioverter-defibrillators (AICD) often have underlying ischemic heart disease, which should not be overlooked during the preoperative assessment. It is important for the anesthesiologist to find out from the cardiologist whether the patient is pacemaker-dependent, which means that the patient has atrial, ventricular, or both chambers paced 100% of the time. For patients who are not pacemaker-dependent, the anesthesiologist should place a magnet over the device, which will prevent inappropriate delivery of shocks [2]. For patients who are pacemaker-dependent, the device may need to be reprogrammed intraoperatively. All AICD patients should have an external defibrillator and transcutaneous pacer immediately available, and the pads should be affixed to the patient at the start of the case. In emergent settings, in which a formal cardiology consultation is not feasible, a 12-lead EKG can be used to determine pacemaker-dependence.

It is important for the surgeon to understand that AICD activity can be affected by monopolar cautery, causing electromagnetic interference [2]. This can result in delivery of inappropriate shocks to the patient, or inadequate pacing. Intent to use monopolar cautery should be clearly communicated to the anesthesia team prior to the case. Use of bipolar whenever possible can help decrease risk of electromagnetic interference but is not feasible for most colorectal procedures.

Assessment of Pulmonary Risk

COPD

Patients with chronic obstructive pulmonary disorder (COPD) are at high risk of perioperative pulmonary complications. Preoperative optimization of pulmonary function is the best way to minimize risk. These patients should be evaluated by their primary care physician, or pulmonologist, if they see a specialist. Bronchodilators should be continued perioperatively. Glucocorticoid use must be balanced against potential for increased risk of surgical complications such as anastomotic leak (see below section on steroids); tapering down or off is advantageous if at all possible, and should be discussed with the specialist. A randomized controlled trial of 48 high-risk pulmonary patients demonstrated significant decrease in postoperative pulmonary complications, 60% versus 22% ($p<.01$), in the group receiving aggressive pulmonary care, which included bronchodilators, antibiotics, chest physical therapy, nebulizers, and smoking cessation, compared to a group who did not receive these therapies [25].

Obstructive Sleep Apnea (OSA)

Obstructive sleep apnea (OSA) is the most common sleep disorder, and is characterized by upper airway obstruction, causing apneic episodes. Rates of OSA are on the rise, partially due to increased incidence of obesity, a major risk factor. A study of almost 1000 patients revealed that 60% of surgical patients with moderate-to-severe OSA are undiagnosed by the anesthetist, and 92% were undiagnosed by the surgeon [26]. OSA is important to recognize preoperatively, as it is a risk factor for perioperative cardiopulmonary complications, and is associated with unplanned ICU admission [27]. One reason why OSA is under diagnosed is that it can present with a wide range of symptoms, beyond the more classically described loud snoring, daytime sleepiness, and witnessed apnea by a sleep partner. Other symptoms include morning headaches, poor concentration, altered mood, vivid or disturbing dreams, restless sleep, GERD, and nocturia [28].

Patients undergoing major abdominal surgery should be screened for OSA, particularly those with high BMI and multiple comorbidities. There are several simple and efficient clinical screening tools available, including the STOP-Bang questionnaire (Table 6-2) [29]. Patients with high scores who are undergoing major abdominal surgery should be referred to a pulmonologist for a formal workup. A randomized controlled trial of 177 patients with documented OSA demonstrated that patients who used auto-titrated continuous positive airway pressure (APAP) perioperatively ($N=87$) had significantly decreased rates of hypoxia and apnea compared to the untreated group ($N=90$); the APAP group had three events/hour postoperatively, decreased from their preoperative baseline of 30 events/hour ($P<0.001$), and the control group had 31.9 events/hour, increased from preoperative baseline of 30.4 events/hour ($P=0.302$). Importantly, the investigators noted compliance rates (defined as wearing the device nightly) of only 45%, which was most commonly attributed to generalized discomfort, nausea, or vomiting [30]. Patients with a known diagnosis of OSA should provide the anesthesiologist with documentation of their sleep study results and recent pulmonary consultations, and should bring their CPAP machine to the hospital for perioperative use.

Diabetes

Diabetic patients represent a complex subset of surgical patients, who often have long-term complications of their disease (neuropathy, visual impairment), as well as other

TABLE 6-2. STOP-bang questionnaire [29, 84]

○ Yes	○ No	*Snoring*? Do you *Snore Loudly* (loud enough to be heard through closed doors or your bed-partner elbows you for snoring at night)?
○ Yes	○ No	*Tired*? Do you often feel *Tired, Fatigued, or Sleepy* during the daytime (such as falling asleep during driving)?
○ Yes	○ No	*Observed*? Has anyone *Observed* you *Stop Breathing* or *Choking/Gasping* during your sleep?
○ Yes	○ No	*Pressure*? Do you have or are being treated for *High Blood Pressure*
○ Yes	○ No	*Body Mass Index more than 35 kg/m2?*
○ Yes	○ No	*Age older than 50 years old?*
○ Yes	○ No	*Neck size large? (Measured around Adams apple)* For male, is your shirt collar 17 in. or larger? For female, is your shirt collar 16 in. or larger?
○ Yes	○ No	*Gender = Male?*
*Scoring criteria**:		
Low risk of OSA: Yes to 0–2 questions		
Intermediate risk of OSA: Yes to 3–4 questions		
High risk of OSA: Yes to 5–8 questions		

OSA obstructive sleep apnea

related comorbidities, such as chronic renal insufficiency and cardiovascular disease [6, 31]. The initial office consultation with the surgeon should include a detailed history, focusing on the type and duration of diabetes, symptoms, how glucose is monitored at home, baseline glucose range, glycated hemoglobin (A1C) levels, related symptoms, as well as the contact information of their primary care physician and/or endocrinologist. Diabetic patients undergoing major abdominal surgery should have the following as part of their preoperative workup: ECG, CXR, serum creatinine, serum glucose, and an AIC level (within 4–6 weeks preoperatively). In particular, elevated A1C levels have been shown in cardiac surgery to be associated with increased risk of surgical complications, including infections, myocardial infarction, and death [32]. Close perioperative involvement of the anesthesiologist is also critical, as some patients undergoing major operations will require preoperative intravenous insulin infusion to attain euglycemia prior to initiation of surgery [33].

Obesity

More than one-thirds of adults in the USA are obese, which is defined as having body-mass index (BMI) of 30 or more. One in 20 adults is considered super-obese (BMI of 40 or more) [34]. BMI is considered a screening tool to identify obesity, and is calculated as the patient's weight (in kilograms) divided by square of the height (in meters). An online BMI calculator is available at on the CDC website (http://www.cdc.gov/healthyweight/assessing/bmi/adult_BMI/english_bmi_calculator/bmi_calculator.html).

Despite the fact that the obese patient creates substantial technical challenges for the surgeon, they do not have significantly greater risk of perioperative mortality. A prospective multicenter study of over 100,000 patients undergoing nonbariatric surgery demonstrated that overweight and obese patients actually had a statistically significantly lower postoperative mortality, compared to nonobese patients (overweight patients: OR 0.85, 95% CI 0.75–0.99; moderately obese OR 0.73, CI 0.57–0.94). This unexpected result was termed the "obesity paradox" and can potentially be explained by increased nutritional stores, as well as the chronic inflammatory state of obesity that may prime these patients for the inflammatory surge of surgery [35].

In terms of postoperative morbidity, obese patients undergoing nonbariatric abdominal surgery have been shown to have increased risk of perioperative venous thromboembolism and superficial site infection. A prospective study of over 6000 patients found that the risk of superficial site infection after open abdominal surgery was 4% for obese versus 3% for nonobese patients, $P = 0.03$ [36].

Obese patients pose significant intraoperative challenges, some of which can be mitigated with appropriate preoperative planning. For example, if a stoma may be needed, a visit from the enterostomal therapist is extremely important, as marking on the thinner upper abdomen will be helpful. It is especially important to ensure that these patients are able to reach the stoma so they can care for it independently. Both laparoscopic and open surgery is technically demanding in obese patients; however, if feasible, laparoscopic surgery has the advantage to the patient of smaller incisions and improved visualization for the surgeon. Avoiding lower midline and Pfannenstiel incisions is helpful in minimizing superficial site infections and other wound-related complications in the obese patient with a large pannus. Clear communication with the operating room staff prior to the case is essential, to ensure availability of long instruments, deep retractors, appropriate beds and equipment such as blood pressure cuffs and large pneumatic compression boots.

Malnutrition

Colorectal surgeons are commonly faced with challenging patients who are malnourished due to advanced malignancies or inflammatory bowel disease that result in intestinal blockages, intestinal fistulas, poor absorptive capacity, and large volume losses from the GI tract. Nutritional risk tends to be a reflection of the patient's overall health, and in oncology has correlated with the Eastern Cooperative Oncology Group score and the presence of anorexia or fatigue [37]. Such nutritional risk is associated with increased postoperative complications, longer length of stay, and higher mortality following elective surgery [38, 39], and is particularly pronounced in patient with colorectal cancer [40]. Incidence remains under recognized and malnutrition continues to negatively impact postoperative recovery and patient outcomes, as well as mortality [41]. Although logistically challenging, nutritional support can be delivered in the preoperative or postoperative setting and can be administered via the enteral and parenteral routes. Most studies are limited by heterogeneous patient populations, variable study designs, different feeding protocols that often result in parenteral overfeeding, and outdated methodologies. When delivered appropriately, the malnourished colorectal patient realizes several benefits from perioperative nutritional support including fewer postoperative complications, shorter hospital length of stay, and lower mortality [42].

The evaluation of the potentially malnourished patient begins with the history and physical examination. Most patients will complain of some degree of intolerance of oral intake as a result of poor appetite, nausea, abdominal bloating, abdominal pain, and weakness. Patients will relate a recent weight loss, typically over a 1–3 month time period. On physical examination, the patient appears thin, pale, and weak with muscle wasting and loose skin. These variables can be objectified using grading systems such as the relatively intuitive Subjective Global Assessment (SGA) to classify patients as well nourished, moderately malnourished, or severely malnourished [43]. The SGA utilizes five features of the history (weight loss over 6 months, dietary intake

change, gastrointestinal symptoms, functional capacity, and the impact of disease on nutritional requirements) and four features of the clinical exam (loss of subcutaneous fat, muscle wasting, ankle edema, sacral edema, ascites) to elicit a SGA rank based on subjective weighting.

Serum albumin level has been considered the "classic" test reflecting overall nutritional status, with serum concentration of <3.0 g/dL defining the "malnourished state." However, in real practice its utility and reliability is limited as levels fluctuate for many reasons, including production alterations in the catabolic or anabolic states, external losses, or redistribution between the various fluid compartments of the body [44]. Other short turnover proteins such as prealbumin, transferrin, and retinol binding protein have similar limitations as nutritional markers as a result of variable half-lives and response to dietary intake and renal/liver dysfunction, although all of these proteins can be useful when followed as trends over time.

Inflammatory bowel disease, intestinal obstruction, large tumors, fistulizing diseases, and patients with diarrhea are often unable to sustain themselves orally due to a poor appetite or resultant abdominal bloating and pain. This limits the ability to intervene preoperatively, particularly when considering utilizing the enteral route. Options include oral nutritional supplements (standard or immunonutrition) or feeding via nasoenteric feeding tubes. Total parenteral nutrition (TPN) can be uses as long as central intravenous access is obtained, an appropriate formula is prescribed (1.5 g per kilogram and 25 kcal per kilogram) and tight glycemic control is maintained (serum blood sugars <150 g/dL). Unfortunately, the use of preoperative nutrition has not been well studied in the malnourished GI surgery patient populations. A recent Cochrane review [45] highlights this paucity of evidence and the reality that many of the studies are outdated, with only two trials evaluating the administration of enteral nutrition (years 1992 and 2009) including only 120 participants and a high risk of bias. Neither study showed any difference in primary outcomes. The three studies that evaluated preoperative parenteral nutrition (years 1982, 1988, and 1992) showed a significant reduction in postoperative complications, predominantly in malnourished patients.

Solid Organ Transplant Recipients

The introduction of novel, more effective immunosuppression regimens has resulted in improved long-term survival after solid organ transplant. Over 150,000 patients in the USA are living with functional kidney transplants, and this number is on the rise. It is increasingly common for surgeons to encounter transplant patients in their practice, in both the elective and emergency settings. The vast majority of these patients are maintained on chronic immunosuppressive regimens. These agents are generally continued throughout the perioperative and early postoperative period in order to minimize risk of rejection. It is therefore essential that surgeons familiarize themselves with the more commonly used immunosuppressive agents and their potential to impact perioperative outcomes. Communication with the transplant team of physicians is necessary prior to elective surgery.

The newer immunosuppressive agents, sirolimus and everolimus, which belong to the drug class known as inhibitors of the mammalian target of rapamycin (mTOR), have been shown to negatively impact healing of surgical wounds. mTOR is a cytoplasmic kinase that is essential for cell growth and proliferation [46]. Inhibition of lymphocyte proliferation despite stimulation results in immunosuppression. This same mechanism is also responsible for inhibition of the wound healing process. In a prospective trial of 123 patients randomized to receive either sirolimus or tacrolimus on postoperative day 4 after kidney transplant, Dean et al. found a significantly higher rate of wound-related complications (including superficial site infection and incisional hernias) in the sirolimus cohort, compared those receiving tacrolimus (47% vs. 8%, $P<0.0001$) [47]. This data has prompted clinicians to replace mTOR inhibitors with tacrolimus for 6 weeks prior to elective surgery.

Substance Abuse

All surgical patients should be asked about their use of tobacco, alcohol, and street drugs. A large database study from 2002 determined that 7.6% of Americans had a substance abuse disorder within the prior year (95% CI 6.6–8.6%) [48]. The surgeon must also recognize narcotic dependency and use of prescription opioids that are not medically indicated. It is important for surgeons to make patients feel comfortable in answering these questions honestly and accurately. It is never safe to simply assume that a particular patient does not fit the expected profile of an "alcoholic" or "drug addict." Substance abuse has been shown to affect the elderly [49], as well as highly functional individuals with families and careers [50]. It is therefore critical to screen *all* patients preoperatively in order to minimize perioperative risk.

Alcohol

Alcoholism has been shown to be associated with a number of different perioperative complications, in a dose-dependent manner. Large studies have demonstrated that alcoholism is associated with surgical site and other infections, cardiopulmonary complications, and also correlates with longer hospital stay, increased rates of ICU stay, and increased rates of reoperation [51, 52]. The AUDIT-C questionnaire is a validated screening tool that can be used by the clinician to identify patients at high risk for perioperative complications (Table 6-3) [53]. A randomized controlled trial of 41 patients with alcoholism (defined as consumption >60 g ethanol per day) undergoing elective colorectal surgery demonstrated that abstinence 1 month preoperatively was associated with fewer cardiac complications, including myocardial ischemia

Table 6-3. AUDIT—C questionnaire

Question # 1: How often did you have a drink containing alcohol in the past year?	
Never	(0 points)
Monthly or less	(1 point)
Two to four times a month	(2 points)
Two to three times per week	(3 points)
Four or more times a week	(4 points)
Question # 2: How many drinks did you have on a typical day when you were drinking in the past year?	
1 or 2	(0 points)
3 or 4	(1 point)
5 or 6	(2 points)
7 to 9	(3 points)
10 or more	(4 points)
Question # 3: How often did you have six or more drinks on one occasion in the past year?	
Never	(0 points)
Less than monthly	(1 point)
Monthly	(2 points)
Weekly	(3 points)
Daily or almost daily	(4 points)

The AUDIT-C score on a scale of 0–12 (scores of 0 reflect no alcohol use). In men, a score of 4 or more is considered positive; in women, a score of 3 or more is considered positive

(23% vs. 85%, $P<0.05$) and arrhythmias (33% vs. 86%, $P<0.05$), as well as overall decreased complication rate (31% vs. 74%, $P=0.02$) [54]. It is unknown what the optimal alcohol-free interval is prior to elective surgery, in terms of maximizing risk reduction, although the trial investigators recommend 3–8 weeks, highlighting the importance of intensive counseling and monitoring of these patients during this interval [55].

Tobacco

Smoking has been shown in multiple studies to increase perioperative pulmonary risk, as well as risk of wound infections, neurologic complications, and ICU admission [56]. The best way to minimize this risk is to encourage patients to quit smoking prior to elective surgery. Previously it was felt that smoking cessation less than 8 weeks preoperatively was associated with a paradoxical increase in pulmonary complications, possibly due to a compensatory increase in secretions. This has now been disproven in multiple large studies. A large trial of 522 smokers undergoing gastric cancer surgery compared risk of postoperative pulmonary complications between three groups: (1) active smokers or those who quit less than 2 weeks prior to surgery, (2) those who quit 4–8 weeks prior, and (3) those who quit 8 or more weeks prior to surgery. The odds ratio for postoperative pulmonary complications were 2.92 for group 1 (95% CI 1.45–5.90), 0.98 for group 2 (0.28–3.45), and 1.42 for group 3 (0.66–3.05) [57]. Therefore, the recommendation is to encourage smoking cessation, regardless of the timing of surgery, although ideally surgery can be planned for at least 4 weeks from the "quit date."

Opioids

There are many different types of patients with chronic opioid dependence, including: abusers of street drugs such as heroin; abusers of prescription-only opioids; patients with prior history of opioid abuse, maintained on long-acting agents such as methadone; and patients on long-term narcotics prescribed for a chronic medical condition. Overall, prescription opioid use is on the rise in the USA and therefore this is being encountered by the surgeon with increasing frequency [58]. For all patients on narcotics, the surgeon should always ask preoperatively what the indication is, how long they have been taking it, side-effects (such as constipation), if there is a plan to wean off the drug, as well as who has been prescribing it. The patient's responses should be corroborated with the prescribing physician and/or medical record. Regardless of whether it is warranted for an underlying condition, opioid dependency will result in increased narcotic requirements perioperatively. Whenever possible, it is helpful to involve the acute pain management service preoperatively, in anticipation of these issues, in order to provide the best perioperative pain management. Non-narcotic adjunct therapies can be considered, including thoracic epidural catheters, transversus abdominus plane (TAP) blocks, as well as drugs such as ketorolac (Toradol), acetaminophen and gabapentin (Neurontin). Preoperatively, a clear plan should be made with the patient and the clinician who has been prescribing chronic opioids regarding postoperative pain management following hospital discharge, particularly who will be prescribing, and for how long. This is instrumental in avoiding concerns in the outpatient setting with overprescribing and relapse.

Other Illicit Drugs

All patients undergoing elective surgery should be screened for the use of illicit drugs— not just "street drugs," but also other prescription-only drugs, such as benzodiazepines, that are not medically indicated. For patients requiring elective surgery, intensive efforts should be made to encourage cessation prior to planned surgery. This requires clear communication with the patient's primary care physician and/or psychiatrist. Discussion of individual drugs is beyond the scope of this chapter; however, additional information is well-summarized in this 2014 reference from the anesthesia literature [59].

Medications

In the era of polypharmacy, it is essential for the colorectal surgeon to carefully assess the patient's current medication list. Novel anticoagulants, chemotherapy, and immunosuppressants may be disguised by long, difficult to pronounce names. It is therefore critical for surgeons to be familiar with these newer agents. In many instances, patients are maintained indefinitely on medications that may pose significant perioperative risk. Discussing these situations preoperatively with the prescribing physician is essential, as the need for surgery may provide the necessary impetus to discontinue chronic medications that are no longer necessary or applicable.

Anticoagulation

In recent years, several novel oral anticoagulants have become commercially available and are widely used in patients with atrial fibrillation or history of stroke, as well as in patients with coronary or endovascular stents. When determining how to manage anticoagulation perioperatively, risk of bleeding must be balanced against the risk of thromboembolic complications. Additionally, it should be determined whether "bridging" with a short-acting anticoagulant is necessary. Although there are evidence-based guidelines, these decisions should be made on a case-by-case basis, and should closely involve the patient's cardiologist and/or hematologist. The patient should be educated upfront about the potential risks involved and to recognize that the ability to restart the medication postoperatively relates to the extent of surgery and associated bleeding risk.

Clopidogrel (Plavix) is a member of the platelet receptor PY12 blocker drug class, and is used in patients with history of myocardial infarction or stroke, as well as recent coronary or peripheral vascular stent placement. For most patients, the maintenance dose is 75 mg orally per day. If the decision has been made to discontinue clopidogrel prior to elective surgery, it should be discontinued 5–7 days preoperatively [23]. Clopidogrel should be restarted as soon as possible after surgery. A more extensive discussion of clopidogrel earlier in the chapter—refer to the section on "Coronary Stent Management."

Warfarin (Coumadin) is an inhibitor of vitamin-K-dependent clotting factor synthesis (factors II, VII, IX, and X). The half-life of warfarin is 36–42 h. Therapeutic dose range is measured by the prothrombin time (PT), which is generally maintained at a goal of INR (international normalized ratio) 2.0–3.0 for most conditions. Patients with cardiac valves may be maintained at higher doses, with a goal INR 2.5–3.5. For elective surgery, warfarin should be discontinued 5 days preoperatively. Most abdominal surgery is safe to perform when INR is $\leq$1.4 [60]. Ideally, INR should be checked the day prior to surgery, if possible. For urgent surgery (within 1–2 days), warfarin can be reversed with vitamin K (2.5–5 mg oral or intravenous). For emergency surgery, warfarin can be rapidly reversed with fresh frozen plasma (FFP), which contains the necessary clotting factors [61]. Provided that there was adequate hemostasis during surgery, warfarin may be restarted (at the preoperative dose) as early as 12–24 h postoperatively, although the timing depends on indication for anticoagulation (for example short term thromboembolic risk is higher with a mechanical mitral valve compared to atrial fibrillation).

Heparin binds to and inactivates antithrombin III and has a half-life of 45 min. Unfractionated heparin is administered as an IV infusion, using a weight-based nomogram to titrate the dose [62, 63]. Compared to low molecular weight heparin, unfractionated heparin is less costly, is easier and faster to reverse, and is preferable in patients with renal insufficiency (the dose is not affected by creatinine clearance). Unfractionated heparin should be held 6 h prior to surgery. *Enoxaparin (Lovenox)* is a low molecular weight heparin that has comparable efficacy to unfractionated heparin, but has many advantages. It is easier to use, is administered as a subcutaneous injection (and therefore can be given in the outpatient setting) and does not require monitoring. Its half-life is 3–5 h. It can be given at prophylactic dose for venous thromboembolism, as well as therapeutic, weight-based dose. In preparation for surgery, if twice-daily dosing is used, the evening dose should be held on the night prior to surgery; if once daily dosing is being used, a half-dose should be given the morning prior to surgery [60]. Other low molecular weight heparin products available in the USA include dalteparin (Fragmin) and tinzaparin (Innohep). Patients on any heparin derivative need to be monitored for heparin-induced thrombocytopenia (HIT), although this risk is less significant with low molecular weight heparin. Heparin products can be reversed with protamine sulfate.

Apixaban (Eliquis) is an oral factor Xa inhibitor that is commonly used in patients with atrial fibrillation, as well as for both prophylaxis and treatment of venous thromboembolism. Additionally, apixaban has been used as postoperative DVT prophylaxis after hip surgery [64]. The major advantage of apixaban over coumadin is that drug levels do not need to be checked routinely (although the drug does prolong PT/PTT/INR). The drug is dosed twice daily, is unaffected by dietary intake, and can be crushed and administered via nasogastric tube. The dose must be decreased for Cr $\geq$ 1.5,

as well as for age >80 and body weight ≤60 kg. The drug is generally well-tolerated with a favorable side-effect profile. Apixaban should be discontinued a minimum of 48 h prior to abdominal or anorectal surgery, although depending on the indication for anticoagulation, it would be acceptable to discontinue it 24 h preoperatively for anorectal surgery, if necessary from a risk standpoint. There is a boxed warning regarding the use of neuraxial anesthesia and risk of spinal or epidural hematoma (which could result in temporary or permanent paralysis), as the optimal interval from drug discontinuation to intervention is not well-defined. Therefore we recommend not using this drug for perioperative anticoagulation if an epidural catheter or spinal anesthesia is planned. Although not routinely used to assess drug levels, anti-Factor 10a (Anti-FXa) levels can help guide management. There are currently no specific reversal agents for this drug.

Aspirin impairs platelet function primarily by downstream effects of irreversibly inhibiting cyclooxygenase-1 (COX-1). Its antiplatelet effects start as soon as 30 min after ingestion, and last throughout the platelet life span, which ranges from 8 to 10 days.

Despite the fact that there is no clear consensus among surgeons regarding perioperative aspirin use in noncardiac surgery, the risk of aspirin on postoperative bleeding is actually well studied in the literature. Perioperative continuation of low-dose (81 mg) aspirin in low-risk patients (for primary prevention of thrombotic cardiovascular events) undergoing abdominal surgery has not been shown in randomized controlled trials to be associated with an increase in major postoperative bleeding complications [65] . Other larger randomized controlled studies have demonstrated comparable results in patients at higher risk for adverse cardiovascular thromboembolic events, who are on chronic low-dose aspirin for secondary prevention of myocardial infarction or stroke. The STRATAGEM trial randomized 291 patients undergoing elective intermediate- or high-risk noncardiac surgery (of which 20% was abdominal surgery) to receive low-dose (75 mg) aspirin versus placebo starting 10 days preoperatively; these patients were all on long-term aspirin or another antiplatelet agent for secondary prevention of cardiovascular thromboembolic events [66]. Although the study was underpowered due to difficulty with recruitment, the investigators found no statistically significant difference in the rate of major bleeding complications within 30 days postoperatively between the aspirin and placebo groups, 6.2% versus 5.5%, respectively; $P=0.81$. Importantly, they also found no difference in the rate of cardiovascular thrombotic events, 3.4% versus 2.7%, $P=0.75$. Surprisingly, very few studies specifically evaluate the perioperative risk of high-dose (325 mg) aspirin; many of the larger studies on antiplatelet agents do not even take the aspirin dose into account [67]. A retrospective analysis of 1017 patients undergoing elective pancreatic resection compared patients on aspirin (55 patients on 325 mg aspirin, 234 patients on 81 mg aspirin) to no-aspirin ($n=728$), and found no significant difference in rate of blood transfusion within 30 days postoperatively between groups (29% versus 26% $P=.37$) [68]. The higher dose aspirin group was too small to stratify risk according to aspirin dose.

In our practice, we do not discontinue low-dose "baby" aspirin perioperatively for anorectal or abdominal cases, regardless of the indication for its use. For patients on high-dose (325 mg) aspirin, the decision is more individualized and requires input of the patient's cardiologist and/or vascular surgeon. If the decision is made to discontinue aspirin preoperatively, it should be held for 7 days prior to surgery.

Immunosuppressive Agents

Corticosteroids have been shown to impair wound healing in both animal models as well as clinical studies. In animal models, corticosteroids have been shown to alter multiple independent signaling pathways, impairing all three phases of wound healing: inflammatory, proliferative, and remodeling. Clinical studies have also demonstrated a higher rate of anastomotic complications in patients on chronic steroids [69]. A prospective study performed in the 1980s specifically evaluated the risk of steroids in Crohn's patients, and demonstrated in multivariate analysis that corticosteroids were associated with an increased overall postoperative complication rate in Crohn's patients undergoing surgery involving bowel anastomosis (15.4% vs. 6.7%; $p=.03$) [70]. One of the largest studies looking at anastomotic leak in colorectal patients included 250 left sided resections with anastomosis. The overall anastomotic leak rate was 7.5%. When patients were administered corticosteroids, either perioperatively or long term, the multivariate model concluded that corticosteroid use increased the risk for AL by more than seven times (OR, 7.52; standard error, 4.47; $P=0.001$; 95% CI, 2.35–24.08 [71]. A meta-analysis evaluating the risk of corticosteroids on colorectal anastomotic integrity is included 9564 patients from 12 studies demonstrated an overall leak rate of 6.77% (95% CI 5.48–9.06) compared to 3.26% (95% CI 2.94–3.58) in the non-corticosteroid group [72]. In addition, corticosteroids impact wound healing and are a risk factor for the development of superficial and deep surgical site infections and have even been shown to impact postoperative mortality [73]. Ultimately, this understanding allows the surgeon to better counsel the patient regarding possible postoperative complications, wean steroids during the preoperative period when possible, and make decisions in the operating room (such as the decision to create diverting stoma and wounds closure) to optimize patient outcomes.

Immunomodulators, including azathioprine and 6-mercaptopurine, are used in both Crohn's disease and ulcerative colitis to maintain steroid-induced remission. These drugs often take 3–4 months until clinical benefit is apparent, and have infrequent but serious side-effects such as leucopenia, liver function abnormalities, pancreatitis, and lymphoma.

A retrospective study of 417 operations involving bowel anastomoses for Crohn's disease demonstrated no difference in the rate of anastomotic complications for patients on immunomodulators (10% vs. 14%; $p=0.263$) [74]. Similar to the studies above, they also found that in multivariate analysis, corticosteroids (preoperative prednisolone 20 mg or more) was a predictor of anastomotic complication (OR 0.355, 95% CI 0.167–0.756; $p=0.007$). Accordingly these medications are often continued until surgery.

Biologic agents include infliximab (Remicade), a chimeric monoclonal antibody that targets tumor necrosis factor, a pro-inflammatory cytokine that has been shown to be elevated in inflamed tissue of IBD patients. Biologics including infliximab have been demonstrated to induce remission and control symptoms in patients with moderate-to-severe Crohn's and ulcerative colitis. With more widespread use of biologic agents such in other inflammatory conditions such as rheumatoid arthritis and psoriasis, surgeons are seeing a larger percentage of patients on these agents perioperatively. Krane et al. performed a retrospective analysis of 518 patients with IBD undergoing elective laparoscopic bowel resection, of which 142 patients were on preoperative infliximab [75]. There was no difference in the rate of anastomotic leak, which was overall low in both groups (2.1% with infliximab versus 1.3% without; $p=0.81$). A significantly higher percentage of the patients on infliximab were also on steroids, 73.9% vs. 58.8%, $p=0.006$, and still this did not impact anastomotic leak rate. Overall the existing literature is limited and controversial but biologic agents are thought to impact wound healing and most surgeons prefer to hold these agents for 4–6 weeks if possible prior to major abdominal surgery [76].

Chemotherapy

Through a myriad of mechanisms, the final common pathway of cytotoxic chemotherapy is induction of cell death. Ideally this effect is minimized in nontumor cells, including healing anastomoses. Large studies have attempted to evaluate the overall effect of neoadjuvant and adjuvant chemotherapy on the rate of anastomotic leak, and there have been conflicting results. In a recent single-center study of 797 patients with a single anastomosis, Lucan et al. determined in multivariate analysis that preoperative chemotherapy was one of the strongest independent risk factors for anastomotic leak, with an odds ratio of 2.85 (95% CI 1.21–6.73, $P=0.017$) [77]. Morse et al. performed a similar study of 682 patients with intestinal anastomoses over a 5 year period, and determined in bivariate analysis that chemotherapy (administered within 6 weeks of the operation) was not a risk factor for anastomotic leak.

Bevacizumab (Avastin) is a humanized monoclonal antibody, which targets vascular endothelial growth factor A (VEGF-A), and is thought to work in solid tumors by restricting neoangiogenesis, which is necessary for tumor growth. It is the first of the antiangiogenic drugs to be approved for first-line treatment of metastatic colorectal cancer, and is also used for other solid tumors including breast, kidney, ovarian, and lung cancer. Bevacizumab is associated with increased incidence of postoperative complications, including impaired wound healing and anastomotic leak. Consequently, phase II and III studies of bevacizumab for colorectal cancer excluded patients who underwent major surgery within the previous 28 days [78–80]. Yoshioka et al. retrospectively evaluated 78 patients with resectable advanced or metastatic colorectal cancer who received neoadjuvant bevacizumab prior to surgical resection (this included 46 rectal resections and 4 colectomies) [81]. Overall median interval from last bevacizumab dose to surgery was 9 weeks; anastomotic leaks occurred in six patients, four of which required re-laparotomy. The mean interval from surgery to diagnosis of anastomotic leak was 15.8 days (range 4–34 days). Although the authors did not document mean in-hospital length of stay, presumably most of the leaks occurred after discharge. In multivariate analysis, primary colorectal anastomosis was the only independent predictive risk factor for major postoperative complications (OR 8.285; $P=0.013$). Interestingly, the interval from last bevacizumab dose to surgery was not an independent risk factor for postoperative complications. Bevacizumab has also been associated with late anastomotic complications [82]. Unsurprisingly, other newer antiangiogenic drugs have also been implicated in the development of anastomotic leak, including pazopanib and aflibercept in small series and case reports [83]. As with most chemotherapy agents, these agents are held for 6 weeks before major surgery, when possible.

Conclusion

The preoperative assessment of colorectal surgery patients should be comprehensive and often requires involvement of physicians from multiple specialties. The assessment of cardiopulmonary risk has been well studied and tends to be the focus of most surgeons. Attention to other organ systems as well as comorbidities such as substance abuse, malnutrition, and obesity deserve specific attention. Medications including anticoagulation and immunosuppressive agents are commonly encountered and their optimal management (or cessation) demands a balance between the treatment of conditions and the risk of bleeding and wound healing. With a thorough preoperative patient evaluation, patient outcomes can be optimized, by minimizing the risk of perioperative complications.

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7
Optimizing Outcomes with Enhanced Recovery

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Key Concepts

- Enhanced recovery pathways (ERPs) include measures for preoperative management, intraoperative care, postoperative recovery, and pathway quality evaluation.
- ERP improves the quality of patient care by establishing standardized care paths based on evidence-based literature and current practice guidelines.
- A modified frailty index (MFI) allows for preoperative risk stratification and identifies patients that will require extra healthcare resources.
- A combination of oral antibiotics administered during the preoperative phase combined with intravenous antibiotics administered within 1 h of surgery appears to be the most efficacious strategy to decrease SSI.
- Measurement of ERP compliance is necessary to make sure the individual stated pathway items are being accomplished.

Introduction

Among the goals of a successful surgical practice, delivering high-quality patient-centered care while maintaining a low procedure-specific morbidity and readmission rate is of paramount importance. Facilitating a patient's recovery and assisting them to return to their usual activities safely, but also as soon as possible, should be viewed as part of these goals [1]. Accomplishing these goals benefits not only patients, but by decreasing length of hospital stay (LOS) and costs associated with diagnosis and treatments of complications, they also help to improve the efficiency with which healthcare is provided [2–5].

In the era of bundled payment, "pay for performance," and ongoing cuts in healthcare reimbursement, decreasing hospital operating expenses may contribute to increasing or at least maintaining hospitals' financial viability [6]. Cost-analysis data demonstrating that a specific healthcare system is able to deliver comparable patient care at a lower cost may also influence insurance preference to established contracts with a specific healthcare system over another.

Minimally invasive techniques have had a major impact on postoperative recovery, contributing to a reduction in LOS and cost [6]. In many subspecialties, these techniques have now substituted open operations and become the standard of care. However, optimizing patient recovery goes far beyond a particular technical approach. It requires a multidisciplinary approach that includes not only surgeons, anesthesiologists, and nurses, among others but also the patient himself. Enhanced recovery protocols (ERPs) start at the surgeon's office by engaging the patients in this process, managing expectations, and converting them from a passive recipient of care into an active member of this recovery team. Standardization of perioperative care measures combined with minimally invasive colorectal surgery has decreased, in our hands, LOS to an average of 2.6 days, without a significant impact on readmission rate [7–12].

What Is an ERP?

Traditionally, pre-, intra-, and postoperative management had varied depending on individuals' practice preferences of the various members of the healthcare team involved. This approach creates significant variability throughout the healthcare process, since surgeons, anesthesiologists, hospitalists, and ancillary support to name some managed patients based on past experiences, usually gained during residency or school training. This variability increases complications and healthcare cost as patients are not necessarily managed according to current recommendations [2, 4, 5, 10–33].

In an effort to reduce postoperative complication rates and decrease or contain healthcare costs, the concept of creating specific evidence-based protocols or pathways where the various components of pre-, intra-, and postoperative care are outlined and could, therefore, be followed by all the

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members that participate in any given healthcare episode was developed [2, 3, 10, 16, 17, 23].

Initially called fast-track pathways, these care paths are now most commonly called enhanced recovery pathways (ERPs), which refer to the multimodality patients' care approach where patients' orders are clearly established based on evidence-based literature and current practice guidelines. These orders are then routinely followed, minimizing variability among providers with the goals of decreasing morbidity and mortality rates and increasing quality of care as a result. The decrease in healthcare resource utilization achieved as a result of decreased complications, and LOS contribute to decrease costs [10, 15, 21, 23, 25]. As patients progress through a healthcare intervention, specialty-specific order sets clearly outline patients' management at any given point in time, from the preoperative encounter until care is completed, generally at the time of hospital discharge.

The direct consequences of the application of specialty-specific pathways are well documented and include a reduction in morbidity, mortality, and length of hospital stay (LOS). This reduction in LOS is seen both after open and laparoscopic operations when compared to patients that are managed outside a pathway. An even greater reduction in LOS is seen when open versus laparoscopic colorectal procedures coupled to a perioperative pathway are compared. This difference persists even when readmission rates are included into the overall LOS for any given patient [7, 10, 12, 16–18, 21, 22, 27, 30–32, 34–42].

Components of an ERP

From a practical standpoint, ERP can be divided in four parts: (a) preoperative management, (b) intraoperative care, (c) postoperative recovery, and (d) quality pathway evaluation measures.

Each part includes a series of measures or steps as follows:

(a) *Preoperative management*: (1) preoperative evaluation (i.e., frailty score and pre-habilitation); (2) fasting prior to surgery, mechanical bowel preparation, and preoperative antibiotics usage; (3) patient education; and (4) analgesia (*for practical purposes*, *as it overlaps with pre-*, *intra-, and postoperative management*, *analgesia is addressed as a whole in the intraoperative section*).

(b) *Intraoperative care*: (1) minimally invasive colorectal surgery when possible, (2) standardized intraoperative fluid resuscitation, (3) analgesia, and (4) venous thromboembolism prophylaxis (VTE).

(c) *Postoperative recovery*: (1) analgesia; (2) intravenous fluid management; (3) early oral feeding and ambulation; (4) prevention of postoperative nausea and vomiting (PONV) and postoperative ileus (POI), role of nasogastric tube and motility agents; (5) venous thromboembolism prophylaxis (VTE); and (6) discharge planning, follow-up, and coordination of care.

(d) *Quality pathway evaluation measures*: (1) electronic order sets creation and updates to comply with best practice parameter guidelines and evidence-based literature, (2) implementation and monitoring of pathway application, and (3) quality improvement measures.

Enhanced Recovery Pathways (ERPs) After Surgery: Challenging "Traditional" Patients' Care Management

Traditionally, postoperative care varies depending on surgeon's preferences and his understanding of patients' clinical condition. In general, perioperative management practices learned during training tend to be maintained once in practice despite evidence that would suggest that new available pathways may help decrease postoperative complications, length of stay, and the associated healthcare cost. Furthermore, compliance with ERP application has been associated with improved outcomes, decreased LOS, and cost reduction [19, 43].

Multiple factors may impact the application of new models of care. Limited time to interact with patients both in the preoperative setting and during the inpatient stay leads to a feeling of lack of control when attempting to implement changes. As surgeons adjust to the demands of current practice styles, and the implementation of electronic medical records, providing coverage to multiple hospitals and to increase productivity, modifying patient care patterns learned through personal experience during training in favor of new care pathways described on medical literature, but without any clinical experience is difficult [44–46].

However, as teaching hospitals expose trainees to these new models of care, a new generation of surgeons is entering the working force with the knowledge and experience to implement and lead these changes.

Electronic medical records, with the capability of creating order sets, also play an important role in eliminating variability in patients' management as they provide a blue print that is easily reproduced from patient to patient.

Successful implementation of these new models of care depends not only on the surgeon; on the contrary, they required significant institutional support as multiple teams across the healthcare spectrum are necessary in order to improve patients' care and reduce costs [47, 48]. As pathways are developed and implemented, full potential can be achieved with active participation from anesthesiologists, nursing staff, physical therapists, and ostomy teams. This increase in resource utilization may contribute to a perception of increased cost and healthcare expenditure and lead to a lack of support from hospitals' administration. Although there is an initial increase in cost, the increased healthcare expenditure is offset through a reduction in patients' morbidity and length of hospital stay [49–51].

Table 7-1. Quality measures between patients managed within and outside an established enhanced recovery pathway (ERP)

Author	Within ERP	Outside ERP	Morbidity (ERP vs. non-ERP)	LOS (days) (ERP vs. non-ERP)	Readmission rates (ERPs vs. non-ERP)
Bradshaw et al. [155]	36	36	8% vs. 11%	4.9 vs. 6	3% vs. 3%
Basse et al. [157]	130	130	25% vs. 55%	3.3 vs. 10	21% vs. 12%
Anderson et al. [158]	14	11	28% vs. 45%	3.9 vs. 6.9[a]	0% vs. 0%
Raue et al. [156]	23	29	17% vs. 24%	4 vs. 7	4 % vs. 7 %
Delaney et al. [15]	33	31	22% vs. 30%	5.2 vs. 5.8[a]	9.7% vs. 18.2%
Gatt et al. [159]	19	20	47% vs. 75%	6.6 vs. 9[a]	5.3% vs. 20%
Khoo et al. [59]	35	35	25% vs. 51%	5 vs. 7[a]	9% vs. 3%
Serclova et al. [160]	52	51	21% vs. 48%	7.4 vs. 10.4[a]	0% vs. 0%
Muller et al. 2009 [161]	75	76	21% vs. 49%	6.7 vs. 10.3[a]	3.9% vs. 2.6%
LAFA 2011 laparoscopic [153]	100	109	34% vs. 37%	5 vs. 6	6% vs. 6.4%
LAFA 2011 open [154]	93	98	43% vs. 41%	6 vs. 7	7.4 % vs. 7.1 %

[a]Mean length of stay (LOS)
Data obtained and combined into current table from Wind et al. [153], Vlug et al. [154], and Adamina et al. [1]

The concept of "team" is key to the success of these changes in patients care practices, as surgeons alone without the appropriate supportive environment may encounter difficulties in improving patient experience. Monitoring adherence to a given pathway allows for quality control measures to be periodically evaluated, ensuring participation of the various teams involved and allows for modifications to the pathway to be implemented as necessary [52–54].

At the end, incorporating an enhanced recovery pathway (ERP) into a practice or hospital system should lead to improve patient care, decreased morbidity and mortality, reduced length of hospital stay (LOS) and healthcare cost, while maintaining or even decreasing readmission rates (Table 7-1) [1].

Where Does the Pathway Start?

The answer to this question needs to be considered both from the surgeon and from an institutional viewpoint.

From a surgeons' perspective, in its simplest form, an ERP starts with a surgeon implementing a specialty-specific order set. As the use of ERP is applicable to most specialties across the board and affects hospitals' expenditure and therefore profit margins, more advanced setups require the participation of multiple teams (surgery, anesthesia, nursing, etc.) [55].

As specialty-specific ERPs are created, institutional support facilitates their introduction and use. Creation of specialty-/department-specific committees allows for input from these teams to be incorporated into the ERP. There is no point in modifying preoperative fasting time to 2 h for liquids, to cite an example, if the individual anesthesiologist will not accept and be willing to anesthetize a patient due to his own practice preferences, despite the fact that guidelines indicate that such practice is safe [56–58]. Multiple examples like this one can be described, and consensus is necessary among healthcare providers and ancillary teams as the institution moves forward in the development of these pathways. Teams usually involved include, but are not limited to, surgeons, nursing staff, physical therapist, information technology personnel, residents, respiratory therapist, and ostomy team members. The configuration of these committees may vary, as pathways have been successfully implemented across multiple specialties and specialty-specific needs are targeted [59].

Preoperative Management

Preoperative Evaluation: Frailty Score and Pre-habilitation

Several patient factors can negatively affect the outcome after elective colorectal surgery. Among them, nutritional status has been directly associated with outcomes and should be viewed as part of the preoperative assessment of patients within an ERP program [60]. Several tools can be used to evaluate nutritional status. The subjective global assessment (SGA) tool allows patients to be stratified in well, moderate, and severe malnutrition (SGA-A, SGA-B, and SGA-C, respectively). Postoperative complications after colorectal surgery, as well as LOS, have both increased as patients' nutritional status worsens. Morbidity increases from 11% for SGA-A to 31% and 41% for SGA-B and SGA-C. Length of stay increases as well, with hospital days increasing from 4 to 5 and 7, respectively, for SGA-A, SGA-B, and SGA-C [61]. Prolonged preoperative nutrition, either enteral (whenever use of the gastrointestinal tract is possible) or parenteral, may improve nutrition within 2–3 weeks and decrease complications. Therefore, preoperative nutritional assessment and optimization should be part of an ERP, as both morbidity and LOS improve when appropriate steps are implemented [62, 63].

Frailty, defined as a decrease in physiologic reserve and multisystem impairment independently of the normal aging process, where patients show a combination of decreased muscle mass and functionality, signs of chronic inflammation, and altered metabolism, is also a marker of increased postoperative morbidity and mortality as well as prolonged LOS [64, 65].

A modified frailty index (MFI) allows for preoperative risk stratification and may allow to identify patients that will require extra healthcare resources early on and to plan in accordance. Eleven variables are considered, and some of them can be optimized preoperatively, such as chronic obstructive pulmonary disease or congestive heart failure [66]. Published data has demonstrated a correlation with LOS, and utilization of MFI may allow surgeons to identify patients early on that may require additional healthcare resource utilization. Data suggest that approximately 61% of patients with a MFI of 1 or less had a LOS between 1 and 3 days, while more than 50% of patients with a MFI of 3 or more are hospitalized between 4 and 8 days [61].

Preoperative optimization is recommended when possible, and certain measures such as stopping alcohol or smoking 4 weeks prior to surgery are associated with improved outcomes [60, 61, 64]. Pre-habilitation, a term that refers to a structured process, aims to improve patients' capacity to respond to surgical stress, and decreased postoperative complications are currently an area of research within ERP protocols. Although creation of a structured program that combines preoperative exercise training, nutritional support, and optimization of chronic disease processes appears as a logical progression of preoperative management, there is not sufficient data at this time to support the allocation of resources to the creation of such programs. They represent, however, an avenue for active research with potential to positively impact patients' outcomes and could be considered at the time of creation of an ERP.

Fasting Prior to Surgery, Mechanical Bowel Preparation, and Preoperative Antibiotics Usage

Classic preoperative management teaching had focus on limitation of oral intake prior to surgery, the role of mechanical bowel preparation, and antibiotics usage [60].

Traditionally, patients are asked to fast from midnight onwards prior to surgery. Published literature has evaluated the role of carbohydrate loading prior to elective surgery. Solid intake is then limited to 6 h prior to surgery and carbohydrate-rich fluids to 2 h. It appears to be of some benefit in terms of decreasing postoperative insulin resistance, LOS, and patient satisfaction (i.e., decreased in thirst); however, the level of evidence is low, and further studies are required to determine how it may affect patient recovery. Some literature suggests that preoperative carbohydrate loading improves PONV and decreases loss of muscle mass. However, further studies are needed, as patient benefits may not be superior when preoperative oral glucose is compared to intravenous glucose infusion during surgery. Independent of potential benefits, reducing fasting times and the usage of preoperative carbohydrate drinks up to 2 h prior to surgery is safe as there is no increased risk of anesthesia complications [67–70].

Mechanical bowel preparation prior to colorectal surgery has also been a topic of debate, with a large body of literature showing that there is no difference in outcomes whether mechanical preparation is used or not [71–74]. A Cochrane review that included 5805 patients demonstrated no difference in wound infection, anastomotic leakage, intra-abdominal infectious complications, or need for reoperation independently of whether a mechanical bowel preparation was used or not [75]. However, colonic manipulation during laparoscopic surgery is easier when a mechanical bowel preparation is used. Jung et al. randomized 1343 patients to mechanical bowel preparation versus no preparation and found similar results. This study, published in 2007, evaluated patients enrolled between 1999 and 2005 [76]. Recently, long-term follow-up data from this study found a change in cancer-specific survival when a mechanical bowel preparation was used. The 10-year cancer-specific survival was 84.1% versus 78% for patient who underwent mechanical bowel preparation versus those who did not [77]. However, Van't Sant et al. reviewed data from 382 patients (median follow-up 7.6 years) and found no difference in survival among groups (bowel preparation vs. none) [78]. Although further studies are now needed in order to evaluate the relationship of mechanical bowel preparation and long-term specific survival, as the authors themselves point out, surgeons should consider reviewing their current practices, as mechanical bowel preparation may not change early postoperative outcomes, but it may impact long-term survival.

It is our practice to use mechanical bowel preparation when a patient will be diverted, for left colon and rectal resections, when an intracorporeal anastomosis is planned, and in those cases that may require an intraoperative colonoscopy. As a result of the data mentioned above, mechanical bowel preparation for right colectomies is being used by part of our team.

The third component of the preoperative management includes the usage of antibiotics prior to surgery. Adequate coverage should include both aerobic and anaerobic flora. Meta-analyses have shown that there is a decrease in surgical wound infection (SSI) when antibiotics usage is compared to placebo. A risk reduction of at least 75% has been found with a decrease in wound infection from 40% to 14–6% [79–82]. As surgeons currently administer antibiotics routinely within 1 h of the surgical starting time as part of compliance with Surgical Care Improvement Project guidelines (SCIP), the decision-making process currently centers in what the ideal regimen is. The ideal regimen should not only control SSI

but also consider cost and adverse effects of a selected regimen. A combination of oral antibiotics administered during the preoperative phase (usually while the patient undergoes mechanical bowel preparation) combined with intravenous antibiotics administered within 1 h of surgery appears to be the most efficacious strategy to decrease SSI (6.5%). Continuation of antibiotics beyond 24 h after elective surgery offers no benefit, and it is not recommended under current guidelines [79, 83]. It is our practice to give antibiotics the day prior to surgery during the bowel preparation, followed by one dose in the operating room. Re-dosing varies depending on the antibiotic used half live and the length of the case.

Patient Education

From a surgeon-patient interaction perspective, an ERP starts in the first office visit. The concept of early hospital discharge is not new. The first reports are from the 1990s. Although successful implementation was demonstrated back then, they also showed that managing patients' expectations is important, as a significant number of patients felt they were discharged home too early despite meeting discharge criteria, based mainly in their perception of inpatient postoperative recovery times.

Patient education is a key component of an ERP. The concept or view of patients being passive recipients of care should be changed. Patients should be actively engaged in the recovery process and understand that they play a significant role in decreasing complications. A motivated patient, with clear goals to meet in mind, is more likely to comply with perioperative tasks such as ambulating, incentive spirometry usage, and reduction of narcotics intake to name a few [1, 3, 60].

These goals and expectations can be discussed during the preoperative encounter and reinforced by written educational material, preoperative meeting with the ostomy team when necessary, and encouraging the patient to communicate their questions or concerns as needed. Easy patient accessibility to the care team, in many cases through a nurse practitioner or a medical assistant, plays an important role in the development of the patient-physician-healthcare team relationship. From a patient's perspective, being discharged home in postoperative day 2 or 3 after a major abdominal surgery may be perceived as a daunting scenario. Easy accessibility to the healthcare team through healthcare extenders helps develop trust in the system and contributes to improve patient satisfaction. Institutional support plays an important role in this process, as resources need to be available to incorporate, for example, nurse practitioner into the teams. However, having someone available within the team to address patients' questions once discharged, either through phone or email communication, can contribute to decrease readmission rates and should be seen as part of the efforts to improve care and patient satisfaction.

Intraoperative Pathway

Minimally Invasive Colorectal Surgery

Current data shows that only 50–70% of colorectal resections in the United States are performed in a minimally invasive fashion. The national average LOS after colorectal surgery reported by Medicare is approximately 9 days; a substantial variability in the quality of care that has been delivered can be seen when LOS of 2–3 days is common after laparoscopic colorectal resections [1, 6, 14, 18, 23, 30, 42, 84]. From an economic point of view, the average cost per inpatient day in the United States varies between $1625 and $2025 (2010 data). This difference in LOS represents gross savings of approximately $9750 per patient per hospital stay.

Minimally invasive colorectal surgery combined with enhanced recovery protocols has shown to decrease LOS to an average as low as 2.6 days, with some patients being safely discharged home within 24 h. At the same time, early hospital discharge has been associated to readmission rates comparable to patients being managed outside an ERP [4, 7–10, 12, 38, 40, 41, 85].

ERP can be successfully applied for patients undergoing open colorectal procedures, with data supporting a decrease in morbidity and LOS compared to non-pathway patients. However, LOS is invariably longer when compared to patients undergoing a minimally invasive procedure. Therefore, procedures performed open, laparoscopic, and in an emergent basis should be managed within the established ERP, with minimally invasive surgery preferred over open when possible [5, 8, 10–12, 17, 24, 26, 31, 38, 40, 41, 43, 86, 87].

Intraoperative Fluid Administration

Fluid administration during surgery is an area of ongoing debate. As fluid homeostasis is affected by changes in several hormones during the postoperative period, the amount of fluid given during the surgery itself varies significantly based on individual practices. Historically, fluid resuscitation tends to overestimate requirements which translate into early postoperative weight gain secondary to fluid retention and third spacing [55]. Studies using restrictive fluid resuscitation strategies have shown a decrease in cardiopulmonary complications and LOS without an adverse effect in anastomotic leakage or surgical-specific complications. However, the data is not clear regarding the optimal strategy, as different studies had used different regimens, with variations in the type of fluid used (colloid vs. crystalloid) and the option of increasing fluid administration based on intraoperative clinical parameter interpretation by the individual anesthesiologist [88]. These situations make comparison difficult; therefore, there are no clear guidelines as to what the ideal regimen is. By measuring intraoperative "real-time" volume status using transesophageal Doppler to determine stroke

volume and vasopressor medication once normovolemia is achieved, a LOS as low as 2.7 days has been reported, with a subgroup of patients being discharged home within 23 h [55]. This approach, described as a goal-directed therapy, as patients' fluid resuscitation is tailored based on individual needs, has shown similar results to data published by Delaney et al., who has reported a similar LOS without the need of additional intraoperative equipment (i.e., transesophageal Doppler probe) and the need of anesthesiologists with that particular skill set. Both these factors may increase cost without a clear change in outcomes in elective cases or in patients with minimal comorbidities [88–97]. These results are further validated by Senagore et al., who randomized patients undergoing a minimally invasive procedure within an ERP pathway and compared standard versus goal-directed fluid resuscitation. The standard group has a shorter LOS (64.9 h vs. 75.5 h, respectively) [98].

Currently, intraoperative restrictive fluid administration appears to be superior to traditional intraoperative fluid resuscitation protocols, and a standardized anesthesia protocol should be established as part of an ERP. However, further studies are necessary to determine the role of goal-directed therapy, independent of whether intraoperative transesophageal Doppler monitoring or finger-probe monitoring is used, as there may be a subset of patients that could benefit from this technology [55].

Analgesia

From our standpoint, pain control starts prior to surgery, continues during the procedure and the hospital stay, and adequately maintains based on specific patients' needs after discharge. Pain management is described in this part of the chapter; however, the ERP should address pre-, intra-, and postoperative pain control.

Adequate pain control is of paramount importance after surgery, as patients are more likely to ambulate and resume some routine daily activities sooner when postoperative pain is well managed. The opposite is also true, as patients with inadequate pain control are most likely to remain in bed, to avoid deep breathing and actively engaging in their recovery, as they perceive pain as a limiting factor to what they can do. At the same time, it is considered a patient's right and patients' satisfaction can be negatively affected when pain management is not adequate. It is not only indicative of poor patient management in most cases, but it may also affect hospital reimbursement as patients' satisfaction becomes tied to it [55, 60].

There is no ideal pain regimen, as analgesia requirements vary from patient to patient and type of analgesic used is influenced by patients' history of chronic narcotics usage, liver and kidney function's profiles, and age to name some. Ideally, the selected analgesia regimen will control patients' pain while minimizing the development of adverse effects, such as PONV, POI hypotension, or kidney injury, among others.

Blocking nociceptor activation prior to a painful stimulus, a term described as "preemptive" analgesia, has been extensively discussed in the medical literature. However, high-quality data to support its usage is scarce. Preemptive analgesia includes multiple interventions, from oral analgesic administration starting the day prior to surgery to placement of epidural catheters or spinal analgesia prior to the beginning of the procedure or local infiltration of the surgical sites in the case of laparoscopy. Data supporting these different strategies varies; however, simple measures such as preoperative intake of oral medication should be considered as part of an ERP. Nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen or diclofenac are usually incorporated into the ERP and administered starting 24 h prior or the day of surgery [99–101]. Gabapentin, a central acting agent, can also be started in the preoperative stage, and it is part of the ERP protocol used by the authors. Data regarding the use of short- and long-acting anxiolytic medication has been reported; however, these drugs are currently not recommended by the ERAS society [60, 102–106].

Intraoperatively, local infiltration of the surgical port sites has not shown to decrease postoperative pain requirements. Liposomal bupivacaine may be used; however, there is yet no evidence to support its use. On the contrary, peripheral nerve blocks such as a transverse abdominis muscle pain (TAP) block have shown to decrease postoperative opioid usage. It is a technically simple, low-cost procedure that can easily be performed under laparoscopic or ultrasound guidance [107–109].

Postoperative analgesia has also been subject to extensive debate. The use of epidural analgesia versus a combination of intravenous opioids delivered using patient controlled analgesia (PCA) equipment and scheduled intravenous NSAIDs such as ketorolac and/or paracetamol appears to be similar in controlling pain in most cases. Although the use of epidural catheters may improve pain scores initially, overall pain control, LOS, and patient satisfaction appear to favor the latter [33, 110–115].

The combination of an opioid PCA and intravenous ketorolac or acetaminophen in the initial postoperative phase (postoperative day zero or 1) followed by a combination of these medications by mouth as soon as patients start oral intake is favored by the author and is part of the standard ERP protocol and the electronic order sets.

A combination of epidural analgesia administered and intravenous opioids and NSAIDs is an alternative that should be considered in chronic opioids users. Epidurals analgesia may be limited to the administration of a local anesthetic or to a combination of a local anesthetic and opioids. Although there is extensive data regarding the use of thoracic epidural analgesia documenting its safety, it is an invasive procedure with associated complications such as pruritus, urinary retention, and postoperative hypotension. Postoperative hypotension secondary to an inhibition of the sympathetic tone is of particular importance when using an epidural catheter. In these cases, patients may benefit from

a decrease in the amount of medication being delivered rather than from the administration of intravenous fluids boluses [115, 116].

A one-time intrathecal administration of an opioid and local anesthetic (0.5% bupivacaine) followed by a combination of a narcotics PCA and NSAIDs appears to be superior than both of the abovementioned options; however, it is an invasive procedure, and further data is required to determine its real impact on LOS [116]. It is not currently part of our standard ERP.

Venous Thromboembolism Prophylaxis (VTE)

Venous thromboembolism prophylaxis is currently part of the SCIP guidelines and commonly built in as part of the mandatory electronic admission order sets. SCIP guidelines require starting of prophylaxis within 24 h of surgery. This allows for variability in the usage of the medication, as surgeons may opt to administer it prior to the surgical procedure itself or within the 24 h period. Data supporting the use of either unfractionated heparin versus low molecular weight heparin shows very little difference between these prophylactic agents. However, data regarding the length of prophylaxis after surgery is still controversial [60, 117]. A Cochrane meta-analysis that included four randomized trials demonstrated a reduction in VTE from 1.7 to 0.2% when prophylaxis was maintained for 4 weeks [118]. However, a database review of more than 52,000 patients found that the prevalence of postoperative symptomatic VTE after only inpatient prophylaxis was 0.67% [119, 120]. A recently published randomized controlled trial of 1 versus 4 weeks of pharmacological VTE prophylaxis specifically after colorectal laparoscopic surgery showed that VTE occurred in 9.7% versus 0.9%, respectively [121]. Symptoms of VTE were present in only two and one patient respectively. No episodes of pulmonary embolism occurred in either group. Guidelines indicated that prophylaxis should be continued for 4 weeks, especially in oncologic patients [60].

In our practice, patients with limited mobility, being discharged to a skill nursing facility, morbid obese, with advanced malignancies, with coagulation disorders, or with prior history of VTE or PE, are usually discharged on a 4-week course.

Postoperative Recovery

Analgesia

Pain control should continue during the inpatient stay as well as after discharge. Pain management strategies have been described earlier in the chapter. From an outpatient pain management standpoint, a gradual decrease in medication usage is expected. Medication (both opioids and NSAIDs) should be prescribed, keeping this in mind and considering the potential for abuse associated with narcotics usage. The amount of narcotics usage in the United States is significantly higher when compared to the rest of the world, and efforts are being implemented at a government level to monitor opioids usage. A fine line is required to maintain adequate pain control and patients' satisfaction while preventing abuse.

It is our practice to start a combination of acetaminophen and NSAIDs the day after surgery unless a specific contraindication exists. These medications are scheduled, while opioids are used for breakthrough pain control. Opioid PCA is usually discontinued in postoperative day 1 after a laparoscopic resection.

Intravenous Fluid Management

ERP have demonstrated the safety of initiating early oral intake, thus being able to decrease intravenous fluid requirements. At the same time, published data indicated that restricting intravenous fluids to less than <2 l/day versus >3 l/day are associated with increase gastric emptying, faster recovery of gastrointestinal function, and overall decrease morbidity and LOS [55]. It is our practice to limit or stop intravenous fluids within 24–48 h of surgery.

Early Oral Feeding, Ambulation, and Role of Nasogastric Tube

A large body of literature has shown that early introduction of oral intake within 24 h of surgery is safely tolerated in 70–90% of patients. Even though a Cochrane review and a meta-analysis fail to show a reduction in LOS when early feeding is introduced, numerous single institution reports over the last 10 years or more have reported average LOS of just over 2 days, and restarting oral intake within the first day of surgery has been an integral part of their ERPs [122]. Although early feeding increases the risk of vomiting [123], the risk of aspiration pneumonia remains the same whether feeding is started early on or after return of bowel function (absolute risk of 0–6.3% vs. 0–7.1%, respectively) [122–126]. Early feeding has also been associated with a decrease in insulin resistance, hyperglycemia, and wound infection.

Encouraging and facilitating early ambulation through the aid of ancillary staff while the patient is still in the hospital is key to achieve the goal of a short LOS. Early ambulation helps decrease muscle waste and helps prevent a reduction in gastrointestinal motility associated with an increased time in bed [125, 126].

Prevention of Postoperative Nausea and Vomiting (PONV) and Postoperative Ileus (POI): Role of Nasogastric Tube and Motility Agents

ERP routinely includes medications that try to decrease PONV and prevent the development of POI. Several classes of antiemetics are available, and each class has been shown to be superior to placebo in the management of PONV. A combination of two or more drugs decreases even further the incidence of PONV [127–133].

A single dose of intravenous dexamethasone during surgery combined with ondansetron (serotonergic 5-HT3 receptor antagonists) appears to be the most adequate strategy to prevent PONV. Ondansetron is continued during the postoperative period at a dose of 4 mg every 6–8 h as needed. Studies have demonstrated a decreased incidence in PONV with ondansetron compared to metoclopramide. For patients at increased risk of developing PONV, a combination of a transdermal scopolamine patch and ondansetron can be used with studies suggesting increased efficacy when compared to ondansetron alone [131, 132].

Postoperative ileus (POI) refers to a transient impairment in gastrointestinal motility that prevents oral intake. Various definitions of POI have been proposed. Classically, it has been described as a delay to restart oral intake for more than 3 days after laparoscopic surgery or to more than 5 days after open procedures. Senagore et al. proposed an alternative classification by describing POI as any situation that requires a return to "nil per os" or the insertion of a nasogastric tube (NG). He further defines ileus as primary or secondary based on whether it is associated (secondary) or not to any other complication (i.e., anastomotic leakage) [9, 128, 129].

Primary POI causes not only patient discomfort and delays hospital discharge; it is a significant cause of healthcare expenditure, accounting for approximately $750 million per year [55, 132].

Alvimopan, a peripheral-acting mu-opioid receptor antagonist, has been shown to decrease the time required for return of gastrointestinal function and decrease POI and LOS after open and laparoscopic colorectal surgery. However, its role after laparoscopic colorectal surgery and an established ERP is less clear; Delaney et al. described a reduction in POI from 4 to 12% when comparing two matched laparoscopic colectomy groups when alvimopan was used. However, LOS (3.6 vs. 3.7 days) and hospital readmission rates (4% vs. 4.2%) were the same in both groups [134–141].

Oral magnesium oxide was described to facilitate return of bowel function after colonic surgery and as part of an ERP protocol. However, the data available is small and have not been validated in further studies.

Bisacodyl, either orally or as a suppository, facilitates return of bowel function; however, LOS is unchanged, and the amount of data available is limited [142, 143].

Chewing sugarless gum postoperatively has also been associated with a decreased time to return of bowel function and decreased LOS. The level of evidence is very robust, and its associated cost and reported adverse effects (i.e., bloating) are minimal [144–147].

Nasogastric tube decompression has been shown to have no role as a preemptive measure to prevent PONV or POI. Furthermore, it delays return of bowel function and hospital discharge. Therapeutic NG decompression still has a role in the treatment of POI; however, its usage is required in less than 10% of patients [148–150].

Venous Thromboembolism Prophylaxis (VTE)

VTE prophylaxis should be initiated within 24 h per SCIP guidelines. This topic has been addressed earlier on the chapter while discussing intraoperative management; however, addressing VTE prophylaxis is mandatory during the postoperative period under current practice parameters.

Discharge Planning, Follow-Up, and Coordination of Care

Discharge planning, follow-up, and coordination of care with other healthcare teams (i.e., predischarge appointments coordination with the different healthcare provider such as oncology, as needed) should be initiated early on during hospital stay. This process is facilitated by the electronic medical records system and electronic orders/appointments scheduling. Incorporation of ancillary support staff such as nurse practitioners, stoma therapists, social workers, and physical therapists as members of the ERP team allows for active education, planning, early identification of patients that may need home care or to be discharged to physical rehabilitation or extended care facilities, and decreased unnecessary hospital stay secondary to poor planning or administrative delays such as insurance approval [2, 9, 15, 21, 29, 31, 151, 152].

Quality Pathway Evaluation Measures

Electronic Order Set Creation and Updates to Comply with Best Practice Parameters Guidelines and Evidence-Based Literature

Creation of specialty-specific order sets requires the participation of the various members that contribute on a daily basis to patient care and application of the ERP. This includes surgeons, anesthesiologists, information technology personnel, nurses, ostomy/wound care team members, physical therapist, residents, and social workers to name a few. Data

have shown that the initial cost of implementing an ERP is offset by the reduction in morbidity and LOS achieved with the subsequent pathway implementation. Regular meetings are required to ensure that the ERP and the associated order sets remain in compliance with changes in practice parameters, evidence-based guidelines, and government and insurance policies [1, 43, 60].

Implementation and Monitoring of Pathway Application

Compliance and application of the numerous components of an ERP have been shown to vary within members of any given colorectal group. Changes in members of the ERP can impact the way ERPs are implemented, and morbidity and LOS may change accordingly. Mobile Internet-based applications currently exist and are being used in high-volume centers to monitor in real-time ERP compliance and to identify variables that can affect its application, such as individual surgeon's preferences or a lack of support personnel. As information technology progresses and variables that affect patient care are identified, an opportunity for further improvement of ERP may occur. There is no data at the present time to evaluate its effect in overall patients' experience, quality of care, and healthcare cost [153–156].

Quality Improvement Measures

Since the beginning of the century and secondary to high morbidity and mortality rates and a constant increase in healthcare cost, numerous programs have been developed to try to standardize care. With the objective of improving quality by decreasing variability among healthcare providers and contain cost, programs such as SCIP and National Surgical Quality Improvement Program (NSQIP) were developed. Over time, regional initiatives supported by private funding also developed as the opportunity to change individuals' practice styles toward an evidence-based, and best practice guidance model was seen as a way to achieve those goals.

Compliance with SCIP measures is becoming part of everyday practice. However, some of the standardized measures have failed to significantly improve quality. Internal practice monitoring and benchmarking them to national standards, as long as confounding variables can be included (i.e., tertiary center patients' complexity and postoperative morbidity), may allow physicians and hospitals to modify practice parameters and improve outcomes [1, 36–38, 45, 48, 64]. An easy-to-apply metric to evaluate for quality in colorectal surgery was described by the senior author of this chapter. The HARM score takes into consideration hospital stay, readmission, and mortality rates. The score is calculated by giving each patient discharge a value from 1 to 10. As the hospital mean HARM score increases from <2, to 2–3, to 3–4 and more than 4, an increase in complication rates after elective colorectal surgery is seen, changing from 15.2% to 18.2%, to 24.0%, and to 35.6%, respectively. This metric provides surgeons a low-cost tool to compare quality and may allow for identification of true outlier performers [152].

Conclusion

The combination of ERPs and minimally invasive colorectal techniques has demonstrated a reduction in morbidity and mortality and overall length of hospital stay and is associated with a low readmission rate. This multimodal approach, based on interdisciplinary work, contributes to the standardization of patients' care and, as a result, contributes to increase quality of care. Its implementation through specialty-specific order sets covers the whole episode of care, from preoperative management until completion of care is achieved. Continuous pathway monitoring allows for updates in the order sets to be made to adjust to changes in best practice parameters and pathway compliance. Overall, the decrease in complications associated with the implementation of an ERP and minimally invasive colorectal surgery achieves the goals of improving quality of patients' care while simultaneously reducing healthcare-related cost when compared to patients managed outside a specific pathway [1–3, 6–9, 13–16, 18, 21, 35–38, 45, 47, 48, 62, 64, 84, 86].

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8
Postoperative Complications

Andrew Russ and Gregory D. Kennedy

Key Concepts

- Thorough preoperative evaluation including assessment of social situation, cognitive status, and comorbidities contribute to safe postoperative recovery.
- Laparoscopic approach to colorectal surgery is associated with a decreased risk for postoperative complications.
- Risk for mortality after major postoperative complications is a reflection of surgeon as well as the system in which the surgeon operates.
- Meticulous operative technique with particular attention to hemostasis will lead to improved postoperative outcomes.
- Postoperative management with an enhanced recovery after surgery protocol leads to decreased postoperative complications.
- Bowel preparation with oral antibiotics correlates with a decreased risk of superficial surgical site infection.

Introduction

Postoperative complications are common in colorectal surgery with an incidence as high as 40 % depending upon the study. Many studies have been reported which characterize the complications and their frequency. The overarching goal of this chapter is to highlight some of this literature in an attempt to give the reader a broad overview of some of the issues surrounding postoperative complications.

Preoperative Considerations and Prediction of Postoperative Complications

Given the frequency of postoperative complications and their implications on quality of life, much current work focuses on prevention of complications. To that end, many authors have used the database that has come out of the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) to characterize postoperative complications [1–6]. Perhaps one of the most significant developments is that of the ACS NSQIP surgical risk calculator [7, 8]. This tool uses procedure-specific information to provide an accurate prediction both of risk for various complications as well as hospital length of stay. Importantly, the ACS NSQIP calculator provides risk stratification that allows the patient to see their risk in the context of other more average-risk patients. Figure. 8-1a, b is an example of a report obtained from the ACS NSQIP risk calculator. These types of tools allow surgeons to not only anticipate various complications but to guide patient counseling on expected outcomes. This type of informed consent allows surgeons to consider the outcomes that are most important to patients so they can make decisions that align with their goals of life [9, 10].

While this risk calculator seems to accurately predict postoperative complications [8], risk prediction is dependent upon the accuracy of the data entered into the model. Furthermore, factors exist that impact the outcomes that cannot be measured by any specific model. For example, Dr. Senagore's group investigated the accuracy of the ACS NSQIP risk calculator in predicting outcomes in a high-volume minimally invasive colorectal surgery practice [11]. The authors of this study found that the risk calculator generally overestimated the rate of complications [11]. The authors proposed that the discrepancy in the observed to expected rate of complications was related to the inability of the calculator to account for surgeon-specific experience, volume, and prior outcomes. However, the authors did not report how well the results of the calculator correlated with the actual patient outcomes on a per-patient basis, which is a major limitation to their conclusions. Nonetheless, it is clear that any prediction calculator developed will always be able to be improved with more accurate data input.

Patient comorbidity clearly impacts risk for postoperative complications [1]. The NSQIP risk calculator, as well

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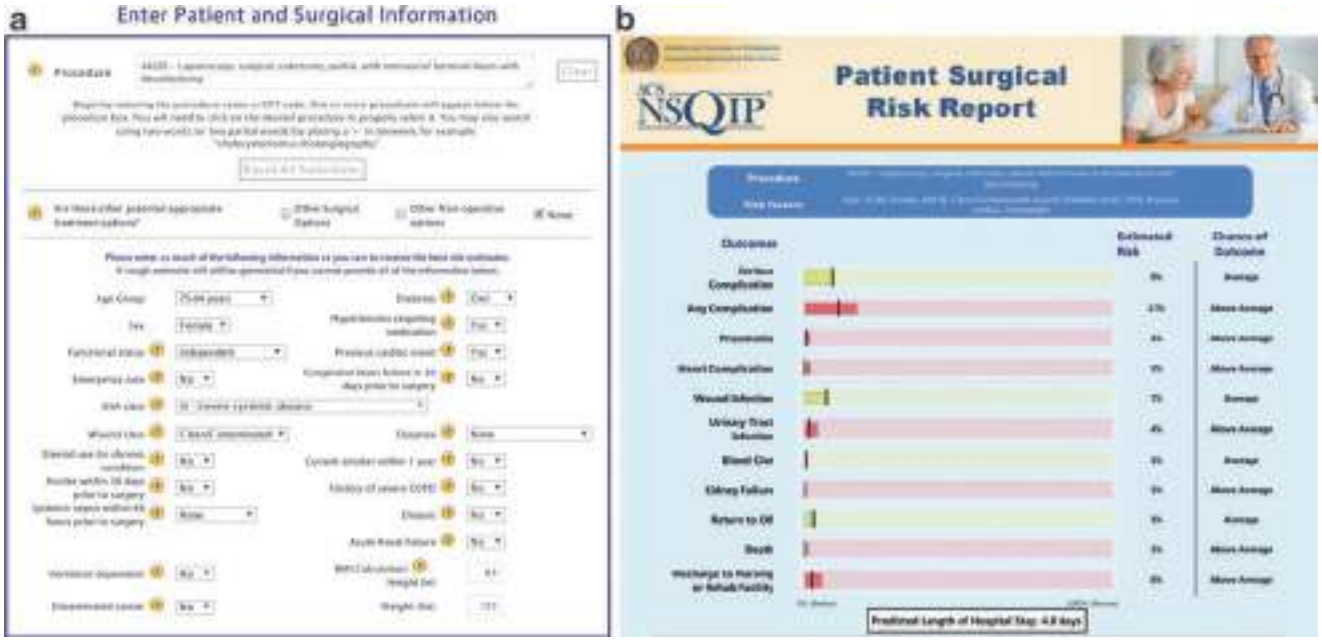

FIGURE 8-1. A sample of the American College of Surgeons risk calculator is shown. The calculator was found at http://riskcalculator.facs.org/ and details of a made-up patient were inserted according to the instructions. (**a**) In this example, a 77-year-old female patient will undergo a laparoscopic right hemicolectomy. Her made-up comorbidities were inserted and the risk calculator was run. (**b**) Results of the risk calculation were obtained and shown here. This sample patient was found to be of average risk for serious complication and slightly higher than average risk for any complication. Risks for specific complications are shown. © American College of Surgeons, used with permission.

as many other investigators, has clearly shown the impact of these comorbidities on risk for postoperative complications. However, as patients with surgical problems age, surgeons must be able to address issues that are specific to the older adult population. In particular, it is important to begin to understand how frailty, cognitive impairment, and social support impact patient outcomes. These variables are largely neglected by any current predictive nomogram, but it is clear that these factors contribute to postoperative outcomes. For example, cognitive impairment has been shown to correlate with discharge to a higher level of care in the older adult population [12]. In this study, 41 % of patients with a score ≤14 on the mini-mental status examination (MMSE) were discharged to a higher-level care facility compared to only 11 % of patients who scored >14 (OR 4.76, CI 1.72–13.17, $P=0.003$) [12]. These findings indicate that preoperative cognitive impairment is an important predictor of discharge destination. Others have also found that preoperative cognitive impairment correlated with a higher risk for postoperative complications (42 % rate of complications in the impaired group compared to 24 % in the intact group, $P=0.011$) [13]. Cognitive impairment also correlated with longer length of stay and higher 6-month mortality. Taken together, the data indicate that cognitive impairment should be considered an important predictor of outcome when dealing with the older adult population.

Another commonly forgotten consideration in the high-risk older adult population is frailty. Frailty is a syndrome characterized by age-related declines in functional reserves across an array of physiologic systems. The syndrome is highly prevalent in older adults and confers a high risk for falls, disability, hospitalization, and institutionalization. Despite the prevalence of this syndrome in older adults and the wide recognition of the importance of frailty on postoperative outcomes, it has not been well defined in the literature until recently. Many different strategies have been used to measure frailty [14]. Perhaps the best measurement is termed the frailty phenotype that is characterized by unintentional weight loss, decreased energy, and decrease in activity and strength [15]. It is clear that frailty directly impacts postoperative outcomes in the older adult population [16, 17]. In fact, given all of the issues associated with surgical care of the older adult patient, the American College of Surgeons assembled a task force of experts to put together a best practice guideline for the optimal preoperative assessment of this group of patients [18].

Finally, as a patient is assessed in clinic for an operation, another important factor likely to impact the recovery course is the social structure of the patient. Many authors have investigated how social structure impacts postoperative recovery and results have been mixed [19]. In general, it is thought that social structure contributes to postoperative recovery either in alleviating anxiety, pain, or response to

pain [20, 21]. One group from Michigan recently examined the concept of social connectedness as it relates to postoperative recovery [22]. They found that patients with more social connectedness, as measured by number of friends and family as well as by interaction within the network, experienced less subjective pain and less perceived unpleasantness from the pain as compared to patients who had less social connectedness [22]. While it is clear that a patient's social structure is related to their perception of the recovery, it is not understood if connectedness contributes to recovery after suffering a major complication or if the concept of connectedness contributes to a patient's underlying risk for suffering a postoperative complication. It is likely that social connectedness does contribute to risk, as patients who are alone may have poor overall health and malnutrition [23].

As we consider the future, we must begin to consider how to properly counsel patients prior to surgical intervention. Quality measures, including outcomes related to safety, effectiveness, and patient centeredness, are already included in many facets of clinical practice such as credentialing and reimbursement. Therefore, it is imperative that all surgeons embrace these measures, become more comfortable with the details, and strive to improve outcomes. Risk stratification systems such as the ACS NSQIP risk calculator will be important in preoperative assessment. How these assessments will be used to change management and outcomes remains to be determined. Future work will focus on enhancing the scoring systems as well as understanding how a surgeon can modify the approach to improve surgical outcomes.

Intraoperative Factors that Contribute to Postoperative Outcomes

Operative Approach and Postoperative Impact

Laparoscopy for colon surgery was first reported in a small case series in the early 1990s [24]. Shortly after these reports, Dr. Wexner and his group published results from their earliest prospective studies, which found no difference in outcomes between open and laparoscopic-assisted colectomy [25, 26]. These studies began the debate on the role of laparoscopy in the treatment of colorectal diseases. Multiple subsequent publications have highlighted the benefit of a laparoscopic approach to colorectal surgery. Nonetheless, it is interesting to note that in many circles this debate continues in spite of the multiple published studies highlighting the benefits of a laparoscopic approach to colorectal surgery. However, it is important to consider those endpoints that are affected by surgical approach in order to fully appreciate the benefit of laparoscopy in improving outcomes.

Postoperative bowel obstruction is a common complication of many abdominal and pelvic surgical procedures. Given the unpredictable timing and potentially quite delayed presentation of postoperative bowel obstruction, it is difficult to know the exact incidence of this complication. A landmark paper published in 1999 by Beck et al. used the Health Care Financing Administration dataset from 1993 to address this question. They found that between 12.4 and 17 % of Medicare beneficiaries undergoing either pelvic or abdominal operations suffered a bowel obstruction sometime within 2 years of the primary operation [27]. Importantly, this study found the incidence of bowel obstruction to be quite a bit higher than previous reports. Since this paper, others have found the incidence of bowel obstruction due to adhesive disease to be less than 3 % and to be dependent upon the cavity in which the operation was performed [28]. For example, in one study, an operation on the lower GI tract carried a higher risk for bowel obstruction than did an operation on the abdominal wall only (3.8 % versus 0.5 %) [28]. The evidence regarding the impact of laparoscopy on the development of postoperative bowel obstruction is somewhat mixed [28, 29]. A retrospective study of nearly 300 patients undergoing restorative proctocolectomy at a single institution found no difference in incidence of postoperative small bowel obstruction between open and laparoscopic approaches [30]. In summary, the use of laparoscopy may decrease adhesion formation, which likely will result in lower rates of adhesive postoperative bowel obstruction.

The impact of laparoscopy on other complications and outcomes is more clear. The prospective randomized controlled trial reported by the Clinical Outcomes of Surgical Therapy Study Group found that perioperative recovery was faster in subjects randomized to laparoscopy compared to those undergoing open procedures, as reflected by a shorter hospital length of stay [31]. Rates of intraoperative complications, 30-day mortality, complications at discharge and at 60 days, hospital readmission, and reoperation were similar between groups [31]. Similarly, results from the MRC CLASICC trial demonstrated shorter length of stay for patients treated with a laparoscopic approach, with no difference in 30-day or 3-month complications [32]. While these randomized controlled trials failed to show differences in some short-term outcomes between operative approaches, it should be noted that they were not designed to detect these differences. Furthermore, randomized controlled trials are inherently biased and nonrepresentative of the daily practice of medicine and surgery, which highlights the importance of observational and comparative effectiveness studies [33].

A review of the literature reveals several comparative effectiveness studies looking at the issue of laparoscopic versus open approach to colon surgery. In general, all have found that minimally invasive techniques are correlated with improved short-term outcomes. Specifically, these studies report at least a 50 % reduction in superficial surgical site infections, a 50 % reduction in deep wound infection, and a significant reduction in postoperative length of stay in patients who have a laparoscopic operation [5, 34–42]. However, these studies have generally reported similar mortality associated with the two approaches, suggesting that

while surgical approach may decrease some types of postoperative complications, other outcomes such as mortality are more complex and multifactorial. In fact, when examining the so-called "failure to rescue" phenomenon first published by Silber in 1992 [43], it is clear that the surgeon, surgical volume, and the system in which the surgeon operates contribute to the rate of postoperative mortality following major complications [44–46].

In summary, operative approach clearly relates to the development of postoperative complications. The exact mechanism of protection provided by the minimally invasive approach is unknown and is not reflected in every outcome. Therefore, future research should address the complication phenotype, and surgeons should strive to reduce variability in operative approach.

Luminal Organ Injuries and Postoperative Impact

In 2003, the Agency for Healthcare Research and Quality (AHRQ) proposed a set of patient safety indicators (PSIs) intended to reflect the quality of care delivered in hospitals. Several PSIs are included in the current CMS pay for performance plan, directly affecting reimbursement. These PSIs are presumed to be preventable by provider or system changes and include iatrogenic events such as accidental puncture or laceration (APL) during a procedure. Accidental puncture or laceration is defined as an accidental perforation of a blood vessel, nerve, or organ occurring during a procedure [47]. When applying this definition to over two million Veterans Health Administration admissions, 7023 were flagged for APL. These included serosal tears, enterotomy, and injury to the ureter, bladder, spleen, and blood vessels. Of true APLs, 27 % were minor injuries such as small serosal tears with no clinically significant impact [48]. The clinical significance of serosal tears is also found to be minimal in other large-volume studies [49]. In fact, further evidence from the Cleveland Clinic group found that accidental puncture laceration was more correlated with complexity of the operation and largely had no impact on postoperative recovery [49]. Since the rate of APL is publicly available and used in pay for performance models, it is important that we fully understand the limitations of this PSI. These data suggest that the utility of APL is limited and better measures of safety are necessary if we are to compare organizations in a fair and non-biased fashion.

Vascular Injury and Failure of Hemostatic Devices

Blood loss has been shown in many studies to correlate with outcomes across various different types of operations [50–52]. Using the NSQIP PUF database, Greenblatt et al. found intraoperative blood transfusion to be significantly associated with postoperative complications in patients undergoing surgery for rectal cancer [53]. These results are consistent with those found in the single-institution study published by Gu and others examining outcomes in patients undergoing ileal pouch-anal anastomosis [50]. Halabi et al. demonstrated a dose-dependent effect of blood transfusion, with worse outcomes in patients receiving more than 3 or more units of blood compared to those receiving only 1–2 units of blood [54]. All of these data together indicate that careful attention to hemostasis is not only consistent with good operative technique but also contributes to decreased postoperative morbidity.

The exact incidence of major vascular injury during colorectal surgery is unclear. However, examination of the surgical literature indicates that major vascular injury is relatively rare. For example, in a series of 404 patients undergoing retroperitoneal laparoscopic nephrectomy, Meraney and colleagues reported seven patients who had major vascular injuries. Conversion to open or repair of the injury through the extraction site was necessary in three of the seven patients. Overall postoperative complication rate in the group sustaining an injury was 25 % [55]. Others have examined the rate of trocar injuries to the vasculature at the time of laparoscopy [56, 57]. One series examined the number of trocar injuries reported to the FDA through the Center of Devices and Radiological Health [56]. In this study, the authors found 408 cases of vascular injury reported to the FDA as a result of trocar insertion. It is impossible to know the actual incidence from this study without a denominator; however, they did note that 26 of the 408 patients died as a result of the injury for a mortality rate of around 6 % [56]. The actual incidence of trocar injury was reported by Larobina and Nottle in a case series report as well as a literature review [57]. Here they found no major vascular injuries in their case series of 5900 patients and a rate of 0.04 % in a literature review which included over 760,000 patients [57]. They concluded that vascular injuries at the time of trocar insertion are rare and can be eliminated by an open, Hasson access technique [57].

While it is difficult to know the exact impact of vascular injuries and blood loss on postoperative outcomes, there is enough data to warrant meticulous attention to hemostasis. There are a myriad of minimally invasive and open instruments available for hemostasis during colorectal procedures. These devices can be used for adhesiolysis, dividing embryological attachments, ligating mesentery, and even ligating named vascular pedicles. The technology continues to evolve at a rapid pace. A recent Cochrane review looked at various commercially available instruments used for laparoscopic colectomy. It evaluated six separate randomized controlled trials including a total of 446 patients [58]. These trials evaluated laparoscopic staplers and clips, as well as electrothermal bipolar vessel sealers (EBVS), monopolar electrocautery scissors (MES), and ultrasonic coagulating shears (UCS) [58]. This review found significantly less blood loss in studies using UCS compared to MES. Overall, hemostatic control was found to be improved in UCS and EBVS over

MES. No definite conclusion on the cost difference between these three instruments was made in this review. This review also found that laparoscopic staples/clips used for pedicle ligation in colectomy were associated with more failures in vessel ligation and cost more when compared to EBVS [58]. Additionally, a randomized clinical trial comparing the cost and effectiveness of bipolar sealers versus clip and vascular staples for laparoscopic colorectal resection found that bipolar sealers reduced both the time spent and the cost of disposable instruments for achieving vascular control [59]. Another prospective randomized trial by Marcello and colleagues found increased failure rates in cases where vascular staplers and clips were used for pedicle ligation [60]. However, the amount of blood loss associated with device failure was higher in those using EBVS for pedicle ligation [60].

The choice of ideal device remains largely up to surgeon preference. There are now multiple instruments capable of 7 mm vessel sealing with various other capabilities. Based on the current available literature, electrothermal bipolar vessel sealing allows for faster operating times, less blood loss, and less sealing failure [58]. However, sealing failure with an energy device often leads to more blood loss than sealing failure with the use of clips and vascular staplers [60]. It is our practice to take vascular pedicles with an electrothermal bipolar vessel sealing device. For device failure or inadequate seal, we favor the use of clips or alternatively an endo-loop, as blindly sealing vessels in a crimson field is often fraught with complication. In the setting of a known atherosclerotic vessel, the application of a vascular stapler should be considered.

Urologic Injuries and Their Management

Ureteral Injury

One of the most dreaded complications related to colorectal surgery is ureteral injury, which thankfully remains an exceedingly rare occurrence. Iatrogenic ureteral injury has a documented incidence of 0.3–1.5 % in most studies. A retrospective analysis of over two million colorectal surgical procedures found an incidence of 0.28 %; however, a significantly higher incidence was found in the latter time period of this analysis, suggesting a trend toward increasing rate of this complication [61]. Risk factors for ureteral injury in this study included the presence of rectal cancer, adhesions, metastatic cancer, weight loss/malnutrition, and teaching hospitals. A study by Palaniappa et al. examined their series of over 5000 patients undergoing colectomy for various indications [62]. They found a significantly higher rate of ureteral injury associated with laparoscopic colectomy compared to open (0.66 % versus 0.15 %, $P<0.05$) [62]. They also found that female sex, increased operative blood loss, and reoperation conferred an increased risk of iatrogenic injury [62]. Ureteral injuries were associated with higher morbidity and mortality, longer length of stay, and higher hospital charges by over $30,000 [61]. It does appear that experience and working through the learning curve lead to a decrease in these types of iatrogenic injuries [63].

Preoperative or intraoperative ureteral catheterization is sometimes used to aid in identification of the ureters and subsequent injury. Most data suggest that placement of ureteral stents neither reduces the incidence of injury nor ensures intraoperative identification of injury [64]. In an NSQIP analysis, there was an increasing trend of ureteral stent use over time from 1.1 to 4.4 % from 2005 to 2011 [65]. Independent predictors of stent utilization included diverticular disease, LAR and APR, recent radiation therapy, and more recent year of operation [65]. After adjustment for baseline patient and operative characteristics, there were no statistically significant differences in any primary or secondary endpoints, including overall renal complications. There was, however, a statistically significant increase in length of stay associated with stent utilization, which was also observed by Halabi and colleagues [61, 65].

Early identification of injury is paramount in minimizing morbidity and preserving renal function. Diagnosis of a suspected injury can be confirmed with an on-table intravenous pyelogram (IVP), retrograde injection of methylene blue, intravenous administration of methylene blue or indigo carmine, or ureteral catheter contrast administration. Injuries can be classified as a laceration, ligation, devascularization, or energy related. Transection and laceration are repaired based on location of injury. General principles include use of absorbable suture (to prevent stone formation), tension-free spatulated anastomosis over an indwelling stent, and placement of a closed suction drain. For those injuries in the proximal one-third (2 % of injuries), repair depends on length of the damaged segment. Simple spatulated ureteroureterostomy (UU) is the preferred method of repair. For additional mobilization, a nephropexy can be performed with fixation to the psoas tendon. Bowel interposition can be utilized for long-segment damage. Additionally, a psoas hitch or Boari flap can be used to reach the upper ureter; however, these procedures are more commonly used for injuries of the middle or distal third. Injuries to the middle third account for 7 % of ureteral injuries, and the preferred method of repair is via ureteroureterostomy for short-segment injury. A psoas hitch or Boari flap should be used if a tension-free anastomosis is not possible, with the Boari flap preferred for injuries spanning longer and more proximal distances. Lastly, a transureteroureterostomy (TUU) can be performed with anastomosis to the contralateral uninjured ureter. Injuries to the distal one-third of the ureter are preferentially repaired with ureteroneocystostomy. A Foley catheter should be left in place for 7–14 days with stent removal 4–6 weeks after surgery [64].

Bladder Injury

Bladder injury also presents a significant management challenge for the colorectal surgeon. These injuries can present in a delayed fashion or at the time of initial surgery. Risk factors

include previous operations, radiation treatment, malignant infiltration, chronic infection, and inflammatory conditions. Radiographic diagnosis can be obtained with CT cystogram or fluoroscopic cystogram. Untoward complications of missed bladder injury can include development of a colovesical or enterovesical fistula. Abdominopelvic CT scan with oral and rectal contrast may be performed for accurate diagnosis [64].

Primary repair (cystorrhaphy) with placement of closed suction drains is the preferred approach when injury is immediately recognized. Small extraperitoneal injuries can be effectively treated with 7–14 days of Foley catheter decompression. Larger or intraperitoneal bladder injuries require operative repair. For injuries to the ventral bladder, dome, or posterior bladder away from ureteral orifices, the bladder can be repaired primarily with two-layer mucosal and seromuscular closure using absorbable suture. A third layer, in the fashion of Lembert, can be added for high-risk cases. Permanent suture must be avoided to prevent the long-term development of bladder stones. For injuries involving the posterior bladder or trigone, near the ureteral orifices, inspection for ureteral injury is mandatory via mobilization of the space of Retzius and subsequent anterior cystotomy, allowing for full exposure of the trigone and interior of the bladder. Indigo carmine can then be administered intravenously to aid in identification of ureteral orifices. Posterior repair is then performed through this anterior cystotomy [66]. Delayed diagnosis of urine leak from the bladder is often managed with percutaneous drainage of a urinoma and continued Foley catheter decompression. Finally, it is always prudent to at least consider consultation with specialized services when faced with difficult scenarios and specific complications. This allows for the obvious support with the repair as well as additional advice in difficult scenarios.

Urethral Injury

Perhaps the least frequent intraoperative urologic injury involves those to the urethra. The most common urethral injury during colon and rectal surgery is related to traumatic Foley catheter placement. The exact rate of this injury in the colorectal patient population is difficult to ascertain. Kashefi and others prospectively studied men in their institution over 1 year and found the rate to be 3.2/1000 catheter insertions [67]. After the implementation of an educational program teaching the inserter to investigate for the presence of risk factors such as benign prostatic hypertrophy, the incidence decreased to 0.7/1000 catheter insertions [67]. Direct injuries also occur during extirpative surgery. Many of these patients have a history of radiation therapy and are prone to fistula formation. Intraoperatively, retrograde injection of methylene blue-tinted saline can aid in diagnosis. The most common presentation of a urethral injury is postoperatively by virtue of fistula formation. Cystoscopy, retrograde urethrogram, exam under anesthesia, and CT scan with both oral and rectal contrast help to delineate the location of injury, which has significant impact on reparative options [64].

Primary repair at the time of injury in two layers with absorbable suture is of course the preferred method. In the setting of poor tissue or neoadjuvant radiation, utilization of an omental flap or local tissue flap can reduce the risk of postoperative fistula formation. In the case of extensive urethral loss recognized at the time of surgery, local tissue flaps may be used to aid in reconstruction. If repair is not feasible, a suprapubic catheter should be placed and repair can be performed after several months [64].

Injuries recognized postoperatively with resultant fistula formation must be staged according to location, size, and history of radiation treatment. Spontaneous closure of rectourethral fistula is extremely rare [68]:

Stage 1—low (<4 cm from anal verge, nonirradiated)
Stage 2—high (>4 cm from anal verge, nonirradiated)
Stage 3—small (<2 cm diameter, irradiated)
Stage 4—large (>2 cm diameter, irradiated)
Stage 5—large (ischial decubitus fistula)

Principles of repair include transection and closure of fistulas and placement of interposed local or regional tissue flaps or grafts [69]. Fecal diversion is recommended for stages 3 through 5, usually in advance. Reparative choices depend on local tissue integrity and staging. A suprapubic catheter is recommended in addition to a Foley catheter for adequate decompression and drainage [70]. Transanal advancement flap alone can be performed for stage 1 fistulas or in combination with other techniques for higher-stage fistulas [71]. Perineal approaches and transanal or transsphincteric approaches have also been described [72, 73]. Other operative approaches include harvest and interposition of regional myofascial flaps [74, 75]. Muscle interposition repairs can be used alone or in combination with abdominoperineal pull-through with resection of the fistula and hand-sewn colo-anal anastomosis [76].

Postoperative Management Decisions that Contribute to Postoperative Complications

IV Fluid Management

There is little doubt that the administration of intravenous fluids contributes to postoperative complications. In a study published by Lobo et al., 20 patients were randomly allocated to either standard fluid management or a restricted fluid protocol [77]. Patients randomized to a restricted protocol had earlier return of bowel function as measured using radioscintigraphic studies, as well as shorter length of stay and lower rates of complications [77]. While this was a small study, other larger trials examining fluid restriction as part of an enhanced recovery after surgery (ERAS) pathway have clearly shown that fluid restriction is an essential component of these protocols [78–81]. In a meta-analysis of randomized

controlled trials, Adamina et al. found that length of stay was reduced by an average of 2.5 days and postoperative morbidity was 50 % lower in patients managed on an ERAS protocol compared to those receiving standard postoperative care [80]. The authors of this study estimated that one complication was avoided for every 4.5 patients managed on the ERAS protocol [80]. Of course, outside of an ERAS protocol, the management of fluids should be tailored to each individual patient [82]. In support of this principle, a trial of liberal fluid management versus fluid restriction in patients not being managed in an ERAS fashion was published by Mackay and others [83]. In this study, fluid restriction had no impact on early return of bowel function [83]. In contrast, patients in the restricted arm had a slight increase in their postoperative levels of serum BUN and creatinine, which did not reach statistical significance. In general, the data indicate that fluid restriction is a critical part of an ERAS protocol and that patients have improved outcomes when managed on these types of regimented pathways.

Wound Management

While there are no clear guidelines for the postoperative management of wounds, there are some general recommendations that may lead to lower rates of postoperative superficial surgical site infections (SSIs). Dressings are considered a standard of care in the management of surgical wounds, but there has been no standardization [84]. A recent Cochrane review on the topic of wound dressings and their effect on wound infection was published by Dumville and colleagues [84]. In this manuscript, the authors identified 20 randomized controlled trials, all of which had significant methodological problems. Despite the limitations of the studies, the authors performed a thorough review and found no evidence that one type of wound dressing decreased incidence of SSI over any other type [84]. In short, dressing selection should be left up to the operating surgeon and should probably reflect cost and convenience. Table 8-1 lists features of an ideal wound dressing [84].

Some have recently been interested in using new technology to manage wounds. For example, the utility of a negative pressure wound dressing on primarily closed wounds for the prevention of wound infections has been examined [85–87]. In general, the work with negative pressure units is filled with bias, and the role for this technology for the prevention of wound infections remains to be seen.

The etiology of a wound infection is largely unknown. While contamination at the time of surgery contributes to risk for infection, it has been thought that a wound hematoma or seroma may be the inciting event that leads to the postoperative infection in those cases where contamination did not occur. In an attempt to eliminate this fluid collection from the wound, Towfigh and others randomized 76 patients with high-risk wounds to either daily wound probing or standard wound management [88]. Patients treated with daily wound probing had lower rates of SSI (3 % versus 19 %) and shorter postoperative stay by 2 days [88]. While these results were promising, they have unfortunately never been reproduced or expanded to a larger population in general or colorectal surgery. In summary, there is no good evidence that any one wound management strategy is better than another. The choice of management strategies should be based on institutional experience and buy-in of the surgeons involved and should ultimately be incorporated into an institutional SSI reduction bundle which packages all care around the episode of surgery in order to reduce wound infection risk [89–93].

Table 8-1 Features of an ideal wound dressing

1. The ability of the dressing to absorb and contain exudate without leakage or strike-through
2. Lack of particulate contaminants left in the wound by the dressing
3. Thermal insulation
4. Impermeability to water and bacteria
5. Suitability of the dressing for use with different skin closures (sutures, staples)
6. Avoidance of wound trauma on dressing removal
7. Frequency with which the dressing needs to be changed
8. Provision of pain relief
9. Cosmesis and comfort
10. Effect on formation of scar tissue

Bladder Management

Urinary tract infection (UTI) and catheter-associated UTI (CAUTI) are frequently encountered postoperative complications related to colorectal surgery procedures. A study from the NSQIP PUF found the rate of UTI after colorectal resection to be 4.1 % compared to 1.8 % after other general surgery operations [94]. The authors concluded that the actual rate of UTI in colorectal surgery patients is higher than expected by predictive models. Factors that correlated with an increased risk for developing a postoperative UTI included female sex; ASA class >2; procedure of a total colectomy, proctocolectomy, or APR; functional status of partially or totally dependent; and age greater than 75 [94]. Other significant factors such as presence of indwelling catheter, number of catheter days, and incidence of postoperative urinary retention are known to strongly associate with risk for UTI but are unfortunately not included in the NSQIP database. Therefore, while NSQIP database studies indicate that colorectal procedures are high risk, they offer little insight into the modifiable source of this risk.

In 2008, the Centers for Medicare and Medicaid Services (CMS) implemented a policy whereby they would reduce payment for hospitalizations that included a preventable complication [95–97]. Effective for discharges beginning October 1, 2014, CMS instituted a 1 % payment reduction for those hospitals whose ranking falls in the bottom quartile of conditions acquired during the hospital stay [97]. Included

among these hospital-acquired conditions is the surveillance measure of catheter-associated urinary tract infection (CAUTI). Best practices and care bundles have been widely published in attempts to decrease the rates of CAUTI [98, 99]. While CMS has emphasized CAUTI, many in the hospital-acquired infection community point to the limitations of these surveillance definitions. For example, it is clear that a CAUTI is often not relevant to the care of the patient diagnosed after an unindicated urinalysis has revealed the presence of asymptomatic bacteriuria [100, 101]. However, the unintended negative consequences of such a urinalysis cannot be ignored [100, 101]. The unnecessary antibiotic use that often results from this type of test result leads to increased risk exposure to the patient and increased antibiotic pressure on the patient's microbial environment and ultimately contributes to the selection of multidrug-resistant organisms.

Given all of these implications of CAUTI, it makes sense that surgeons pay attention to these measures and contribute our efforts to the improvement of patient safety and reduction of hospital-acquired conditions. The question facing surgeons is how to effectively do this while still managing the patient according to a standard of care. For example, if all catheters are discontinued upon completion of an operation, we will certainly reduce the rate of CAUTI in our patient population. However, Kwaan et al. have found that early removal of the urinary catheter increases rates of urinary retention in patients undergoing pelvic surgery [102]. These high rates of urinary retention lead to increased catheter reinsertion, which likely contributes to an increased rate of urinary tract infection in patients who suffer postoperative urinary retention (POUR) [103]. However, a randomized controlled trial of early catheter removal in patients with an epidural was performed by Coyle and colleagues [104]. Here the authors found no difference in rates of POUR in epidural patients who had their catheter removed on postoperative day number 2 compared to those patients who had their catheters removed after the epidural was removed [104]. The conclusions drawn from these studies must be tempered given the clear limitations of both data and study design. Therefore, before a policy of early catheter removal can be instituted for all patients undergoing colorectal surgery, we must better understand the problem of POUR and implement effective methods to deal with this complex problem.

Pain Management

Perioperative pain is a potent trigger for the stress response that can activate the autonomic nervous system and may contribute to adverse postoperative outcomes. While there is very little evidence that poor pain control itself contributes to worse postoperative outcomes, one study found that hospitals with low patient satisfaction scores related to pain control had higher rates of postoperative mortality compared to similar hospitals [105]. Others have found that poor postoperative pain control after thoracotomy was associated with the development of chronic long-term pain [106]. While it is not clear if poor pain control contributes to those complications colorectal surgeons commonly worry about (anastomotic leak, wound infection, etc.), Lynch and colleagues did find a correlation between high postoperative pain scores and the development of postoperative delirium [107]. In addition, high pain is often treated with high doses of opioids, which increases risk for respiratory depression and other complications related to oversedation [108]. Irrespective of the lack of high-quality data showing a clear relationship between poor pain control and postoperative complications, very few surgeons will argue against the principle of good pain control in order to ensure humane, high-quality postoperative care of all patients.

Because of the many obvious negative implications of poor pain control, many studies have assessed the best route of analgesic delivery. Specifically, many studies have examined intravenous versus epidural delivery of pain medications and have, in general, found that epidural delivery results in improved postoperative pain control [109–113]. Randomized controlled trials of laparoscopic versus open colectomy have found pain scores to be generally decreased in patients undergoing laparoscopic colectomy [114]. Therefore, as laparoscopy becomes more widespread in colorectal surgery, the use of postoperative epidural must be reexamined. In fact, a meta-analysis recently published found that although pain control was improved by the use of an epidural in patients undergoing laparoscopic colectomy, there was no difference in return of bowel function and no impact on length of stay [115]. Other studies have found no real differences between epidural and patient-controlled intravenously delivered analgesia [115–118]. Enhanced recovery after surgery protocols have largely adopted non-opioid-based pain regimens, and more work is focusing on local blocks, such as the transversus abdominis plane (TAP) block, to enhance pain control [119, 120]. Further studies are needed to identify the ideal pain control regimen for patients undergoing laparoscopic and open colorectal surgery. Regardless, it is clear that adequate pain control improves the overall patient experience.

Impact of Hospital Structure on Postoperative Complications

Academic Medical Center

The impact of resident training on patient outcome has long been debated in both the academic and lay press. In fact, Kiran et al. found a correlation between increased rates of complications and resident involvement in patient care [121]. While these results must be interpreted in the light of the limitations within the NSQIP participant use file, they do suggest that resident participation may be potentially detrimental to patient care. However, they also found that resident participation was associated with a lower rate of failure to rescue, indicating that even though patients treated at an academic

medical center may have a slightly higher rate of complications, they have a lower mortality rate as a result of these complications [121]. This is likely related to resident hospital presence at all hours allowing rapidity of assessment and implementation of rescue measures. Others have similarly queried the NSQIP dataset from various years and similarly found that resident participation increases rates of postoperative complications [122–124]. While the NSQIP database controls for many factors of patient morbidity that increase risk for postoperative complications, there are many limitations of the dataset that must be considered prior to drawing hard and fast conclusions. First, missing data fields is a common problem of this database, which limits risk stratification. In addition, there is no control for the attending surgeon's gestalt assessment of risk, which also contributes to operative approach and ultimately to the operation performed.

While the above studies have examined the question of resident impact on outcomes from the binary, yes-no perspective, others have examined this question from the seasonal perspective. In particular, Englesbe et al. examined the rate of complications according to the time of year using the NSQIP dataset [125]. They found that patients treated later in the academic year had lower rates of mortality and morbidity [125]. While these results are intriguing, they still fail to control for confounding variables including differences in the environment that may contribute to complications. In fact, one study of over one million patients undergoing coronary artery bypass grafting examined outcomes by time of year in both academic and nonacademic medical centers [126]. The authors of this study found that rates of complications were higher in the first part of the year, independent of teaching status. However, they found that the rate of mortality following complication, or failure to rescue, was higher in patients treated at nonacademic medical centers. They concluded that a seasonal variation to complications and mortality exists in medical centers and cannot be explained by the presence of trainees alone [126]. In summary, it is not entirely clear that trainee presence is independently associated with postoperative complications. Furthermore, mortality rates after major complications seem to be lower in hospitals that have training programs. These findings suggest that more studies are necessary to clearly define the relationship between resident training and patient outcomes, as well as the source of the seasonal variability in postoperative morbidity and mortality.

Surgical Volume and Postoperative Complications

Much has been written on the effect of surgical volume on complications. On the surface, these papers seem to be largely self-serving works that conclude low-volume surgeons have higher rates of mortality and complications, which would necessitate referral to higher-volume surgeons. While this may be true on some level, a more critical evaluation of the literature reveals that there is a very complex interplay between the volume of the surgeon and the volume of the institution. This interplay can be seen quite nicely in two papers written by Dr. Birkemeyer and colleagues [127, 128]. In these papers, he first described a relationship between hospital volume and postoperative mortality for specific complicated operations—pancreatectomy, esophagectomy, etc. [128]. In general, they found that the rate of mortality after all resections, including proctectomy, decreased as the volume of the procedure increased at the hospital. The group then expanded this work and looked at the impact of provider volume on these mortality rates [127]. They found that provider volume could mitigate some of the effect of the institutional volume for some operations. However, not all of the effect on mortality could be explained by provider volume. The end result is a complex relationship between provider and institutional volume, suggesting that the system in which a patient undergoes an operation contributes to outcomes. This type of work has been demonstrated multiple times using many different datasets over the years [129–136]. While most of this work has indicated that higher volume is associated with improved outcomes, little work has been accomplished in understanding the mechanism behind this complex observation. Specifically, it would be interesting to truly understand the impact of the hospital system on outcomes. In recent work, Ghaferi et al. examined the features of hospital systems that correlate with low rates of mortality after major complications [44]. In this study from the Nationwide Inpatient Sample database, the authors found that teaching hospitals with more than 200 beds, increased nurse-to-patient ratio, and with a high level of technology had lower rates of failure to rescue [44]. While the results were not completely surprising, this study lays the groundwork for future investigations into how systems of care directly impact patient outcomes.

Prevention and Management of Specific Complications

Wound Complications

Wound complications and, specifically, surgical site infections (SSIs) are among the most common source of nosocomial morbidity for patients undergoing surgical procedures. SSIs are associated with increased hospital length of stay, increased risk of mortality, and decreased health-related quality of life [137, 138]. This risk is significantly increased in those patients undergoing colorectal surgery [139]. This of course is related to the clean-contaminated nature of many colorectal procedures and exteriorization of the bowel. Wound infections are commonly thought of as occurring in the superficial tissues, deep tissues, or organ space. The bulk of this discussion will focus on the prevention and treatment of superficial surgical site infection. However, all principles are applicable to deep surgical site infections and many are also applicable to organ-space infections.

It has been estimated that an SSI adds between $10,000 and $25,000 to the care of a patient depending on extent of infection [140, 141]. Given the implications of SSI on both patient outcomes and healthcare costs, much effort has been directed toward the prevention of these complications. Preoperative, perioperative, and postoperative interventions have been implemented in an attempt to decrease the rates of wound infections in all patients.

Preoperative Considerations

There are a myriad of patient-specific factors that predispose to an increased risk of perioperative complications. The number of people classified as overweight [body mass index (BMI) = 25 to <30 kg/m^2] or obese (BMI ≥ 30 kg/m^2) is at pandemic proportions. The prevalence of obesity is increasing and significantly influences overall survival of the general population. The most recent data from the United States show that 40 % of adult men and 30 % of women fall within the overweight category [142]. Elevated BMI has been a validated risk factor for SSIs, with some reporting SSI rate as high as 60 % among obese patients [143–148]. However, BMI does not account for all risks associated with wound infection. In an attempt to better quantify the impact of BMI on both medical and surgical complications, there has been recent interest in the role of waist circumference (WC) and waist-to-hip ratio (WHR) on the development of cardiovascular events, as well as specifically the relationship between these measurements and perioperative outcomes of colorectal surgery. Waist circumference is thought to better reflect abdominal adiposity, including the subcutaneous fat layer, and intra-abdominal visceral adiposity. The INTERHEART study found that increased WC and WHR was predictive of myocardial infarction. To evaluate the effect of WC and WHR on surgical complications, a prospective, multicenter, international study of 1349 patients undergoing elective colorectal surgery was performed. Increased WHR was identified as an independent predictor of intraoperative complications, conversion, medical complications, and re-interventions, whereas increased BMI was a risk factor only for abdominal wall complications [149].

Another well-established risk factor for SSI is administration of allogeneic blood transfusion [139, 150, 151]. It is hypothesized that the underlying mechanism is related to transfusion-induced immunosuppression [150]. In addition to the deleterious effect that transfusion may have on disease-free survival in colorectal cancer patients, reduction in SSI risk is another compelling reason to use blood judiciously in colorectal surgery patients [152].

Perioperative Interventions

The role of mechanical bowel preparation in the prevention of SSIs has been extensively studied and debated. The data are conflicting, and oftentimes the arguments for or against bowel preparation relate more to personal preference than to evidence. That being said, much has been written on this topic. For example, there have been three recent meta-analyses of RCTs evaluating the need for mechanical bowel prep prior to surgery. One study evaluating nine RCTs demonstrated a significant increase in the percentage of anastomotic leak in prepared patients (6.2 % versus 3.2 % [OR 2.03]) [153]. An update of this analysis failed to detect significant differences in anastomotic leakage or SSI between those patients receiving and not receiving bowel preps [154]. A second meta-analysis similarly found no difference in anastomotic leakage rates; however, analysis of secondary outcomes yielded a significant difference in SSI, favoring no MBP [155]. Despite these results, the majority of colorectal surgeons still favor the use of mechanical bowel prep. Reasons for this include improved handling of a prepared colon and reduction of stool burden proximal to a fresh anastomosis. Interestingly, recently, a large retrospective review of nearly 10,000 patients did not find any difference in SSI between those with and without MBP. However, the use of oral antibiotics alone was associated with a 67 % decrease in SSI, and oral antibiotics plus mechanical bowel prep were associated with a 57 % decrease in SSI. Additionally, hospitals with higher rates of oral antibiotics had lower SSI rates [156].

Skin preparation has also been extensively examined in relation to wound infection risk. Various skin prep techniques and products are available for colorectal procedures, but clear evidence supporting one over another is lacking. In one randomized controlled trial, the use of chlorhexidine-alcohol rather than povidone-iodine was shown to significantly reduce both superficial surgical site infections and deep incisional infections but had no demonstrable effect on organ-space infections [157]. Another group performed a sequential implementation study in which different skin preparation agents were serially used over the course of a defined time period [158]. The authors of this study found the lowest rates of SSI in the time frame that used iodine povacrylex in isopropyl alcohol, which subsequently led to institutional adoption of this skin prep agent [158]. This is a perfect example of classic quality improvement work characterized by the FOCUS-PDCA process (Figure 8-2) [159–161]. This quality improvement model facilitates concrete steps toward a defined goal and ultimately implementation of change to enhance patient care. However, it is important to note that quality improvement is an iterative process. As implied in Figure 8-2, the FOCUS-PDCA process is a cycle that repeats itself. This cycle allows us to always search for a better "best practice."

Another relatively straightforward intervention at the time of operation that may prevent superficial SSI is the use of a wound protector. While there are conflicting data regarding the utility of these devices in preventing wound infections in abdominal surgery, a recent randomized study of 130 consecutive patients undergoing elective, open, colorectal surgery found that the use of a wound protector was significantly

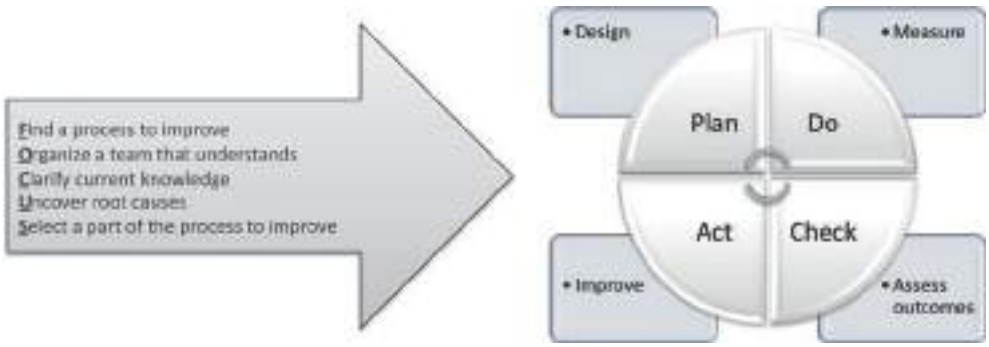

FIGURE 8-2. FOCUS-PDCA cycle is shown. The key to a successful quality improvement process is the continuous assessment and process improvement implied by the cycle.

associated with reduced incidence of incisional SSI [162]. A recent meta-analysis supported these results, concluding that the use of a dual-ring wound protector is associated with decreased risk for SSI [163].

In addition to interventions aimed directly at reducing microbial burden, treatments that improve oxygen delivery to the wound have also been examined in the context of SSI prevention. Murray et al. [164] performed a review of level 1 evidence looking at non-pharmacologic modalities for decreasing the incidence of SSI. These include easily implemented, cost-effective interventions with a low-risk profile such as administration of supranormal oxygen, active rewarming strategies, and adjustment in wound closure techniques. Several prospective randomized trials have attempted to define the impact of supranormal levels of oxygen during anesthesia on SSI [165–168]. A meta-analysis of such trials demonstrated a significant decrease in SSI with the use of 80 % FIO2 in the perioperative setting, favoring the use of perioperative hyperoxia. In contrast, a recent multicenter study [PROXI] that randomized patients to receive 80 % FIO2 intraoperatively and 2 h postoperatively versus 30 % FIO2 in a similar fashion found no difference in outcomes [168]. Of note, none of these studies reported any adverse events attributable to the administration of supranormal levels of oxygen [164]. Another readily available intervention that has been shown to reduce SSI in colorectal surgery patients involves the application of an active warming strategy perioperatively [169, 170].

Multiple reports have demonstrated the utility of closing the midline wound with a suture length-to-wound length ratio of at least 4 [171]. This technique mandates taking either >10 mm fascial bites at greater intervals than previously recommended or alternatively smaller bites of the fascial edge (5–8 mm) in closer intervals. These techniques were compared in a randomized controlled trial which demonstrated a significant increase in SSI and incisional hernia when utilizing the former approach [172]. Specific to colorectal surgery, ileostomy closure poses a unique challenge with regard to infection. In this setting, purse-string closure of ileostomy wounds has been significantly associated with reduced SSI rate in a meta-analysis of three RCTs [173, 174].

In summary, multiple low-risk perioperative interventions can be taken that likely improve short-term outcomes. This phase of care should not be neglected when implementing a bundle of care designed to decrease risk for surgical site infection. Such a bundle might include bowel preparation with oral antibiotics, skin preparation with a chlorhexidine-based agent, hyperoxygenation, active warming, and meticulous closure with careful attention to tension and hemostasis, all of which together may contribute to improved outcomes.

Management of Superficial Surgical Site Infection

Given the enormity of the problem of surgical site infections, it is clear that the best management strategy is one of prevention. Regardless of the interventions taken to prevent these hospital-acquired infections, it seems that the most efficient method involves standardizing the practice to include a bundle of care that is included for every operation. Dr. Cima and others have recently published their experience on a surgical site infection reduction bundle at their institution in Rochester, MN. They have found a reduction of surgical site infections from 9.8 % pre-bundle to 4.0 % after the bundle implementation [92]. Monitoring of compliance with the care bundle is also critically important. As shown by Waits et al., compliance with all parts of a bundle correlates with a lower risk of wound infection (2.5 % in those hospitals with 100 % compliance compared to 17.5 % in those hospitals that were the most noncompliant) [175]. We have similarly implemented a surgical site infection reduction bundle in our hospital and have seen our rate of SSI as monitored by NSQIP to drop into the “as expected” range with the most recent site report showing our rate of SSI in colorectal surgery to be in the second decile (data not shown). The adoption of bundled care ensures all members of the surgical team are focused on the safety of the patient and gives the team a template from which to work.

Despite all attempts to prevent surgical site infections in colorectal surgery, the average institution will continue to see rates of infections near 10 %. Therefore, understanding

the principles of treatment is critical. For an uncomplicated superficial surgical site infection, the standard treatment is drainage of the infection and local wound care without the routine use of antibiotics [176–178]. If patients exhibit signs and symptoms of shock, one must suspect the presence of a deeper infection. This type of infection may involve the deeper layers of the wound (muscle and fascia) or may even involve the organ space. Aggressive interventional therapy is often required to adequately treat a deep surgical site infection and organ-space infections may require reoperation as well. It is critical that the surgeon stay intimately involved in all aspects of the patient's care and also remain vigilant as the best treatment of these infections is often through early identification and infection control.

Cardiovascular and Respiratory Complications

Additional postoperative complications befall those undergoing colorectal surgery. These include cardiovascular complications, which as mentioned have an increased incidence in those patients with an elevated BMI, as well as more recently found, elevated waist-to-hip ratio. In the previously mentioned study of 1349 patients, which identified elevated waist-to-hip ratio (WHR) as a predictor for postoperative complications, the incidences of stroke, deep venous thrombosis, myocardial infarction, congestive heart failure, and pulmonary embolism were all less than 1 %. All complications, to include cardiovascular and respiratory complications, as well as sepsis and septic shock, were previously shown to be decreased in those patients undergoing laparoscopic colorectal procedures compared to those patients undergoing similar procedures in an open fashion [34, 179].

Postoperative venous thromboembolism carries a current prevalence of 1.4–2.4 % in colorectal surgery patients and is one of the most important potentially preventable conditions leading to increases in morbidity, mortality, hospitalization length, and hospital charges [180–182]. A recent study of 116,029 patients utilizing the ACS NSQIP database analyzed the incidence, risk factors, and 30-day outcomes of VTE in patients undergoing colorectal procedures [183]. Risk-adjusted analysis for preoperative factors associated with DVT included age greater than 70, African American race, ASA score >2, hypoalbuminemia, disseminated cancer, steroid use, and obesity. Additionally, open colorectal procedures had a higher risk of postoperative DVT compared to laparoscopic procedures, as did emergently admitted patients, ulcerative colitis on pathology, and anesthesia length greater than 150 min. Similarly, with regard to PE, risk-adjusted analysis found that age greater than 70, emergency admission, open surgery, hypoalbuminemia, steroid use, and obesity all conferred a significantly increased risk of postoperative PE. Additionally, as expected, mortality risk is significantly increased among those patients diagnosed with PE. This analysis also found that the majority of VTE and PE events occurred during the first week after surgery; however, interestingly, they also found that 34.6 % and 29.3 % of patients diagnosed with VTE and PE, respectively, were diagnosed after discharge [183].

These data underscore the importance of VTE and PE prophylaxis in the perioperative setting and also suggest a possible role for anticoagulating after discharge. It is our practice to administer 5000 units of unfractionated heparin (UFH) prior to skin incision and to immediately implement additional prophylaxis to include UFH or LWMH, on postoperative day 1, provided there are no contraindications. We do not routinely anticoagulate after discharge; however, this practice should be considered as we evaluate the most recent literature. Specifically, a recent randomized prospective analysis evaluating 1-week versus 4-week prophylaxis in patients undergoing laparoscopic colorectal surgery for colorectal cancer found a significant reduction in rates of VTE among those undergoing 4-week prophylaxis with LMWH with similar rates of bleeding between the two groups [184].

Mortality and Failure to Rescue

While postoperative mortality is uncommon after elective colorectal surgery [34, 35], it would be remiss to not address this particular outcome as the patient population ages and becomes higher risk. Fortunately, even in the oldest patient populations undergoing elective colectomy for colon cancer, the rate of mortality is at most 4 % in hospitals participating in the NSQIP program [185]. Given this relatively low rate of postoperative mortality, it is worth considering what leads to death after surgery. In general, mortality after elective surgery does not occur in isolation but rather follows another major complication. In fact, the Agency for Healthcare Research and Quality (AHRQ) has defined death rate among surgical inpatients with serious treatable complications as a patient safety indicator in order to track this metric across institutions. Failure to rescue is defined as death per 1000 surgical discharges among patients aged 18–89 with serious treatable complications such as deep vein thrombosis/pulmonary embolism, pneumonia, sepsis, shock/cardiac arrest, or gastrointestinal hemorrhage/acute ulcer [186]. Failure to rescue is considered a measure of the system of care in which a patient is treated and was discussed previously in relation to the impact of resident involvement on postoperative outcomes at academic medical centers. Sheetz and colleagues examined failure to rescue rates across the state of Michigan using the Michigan Surgical Quality Collaborative [187]. Failure to rescue rates varied by hospital even when controlling for differences in patient characteristics, and rates of complications were highest in the hospitals with the highest mortality [187]. These results suggest that failure to rescue is

more related to the system of care than to the patient population. Ghaferi et al. similarly found that systems-related factors such as number of hospital beds, teaching status, nurse-to-patient ratio, and high technology utilization correlated with low failure to rescue rates [44]. More research is necessary to further delineate both risk and mitigating factors for failure to rescue after major complications.

Long-Term Complications

Many colorectal surgery interventions result in long-term physiological changes for patients. Effective management and patient counseling require a thorough understanding of potential long-term complications and their natural history.

Genitourinary Complications

Bladder dysfunction following colorectal surgery is most commonly related to extirpative procedures in the region of the autonomic pelvic plexus. Abdominoperineal resection and low anterior resection have incidences of postoperative bladder dysfunction of nearly 50 % and 15–25 %, respectively [188]. The most common sequel of autonomic nerve damage during colorectal surgery is parasympathetic detrusor denervation, resulting in impaired contractility of the bladder. A majority of patients will regain the ability to empty the bladder; however, this can take up to 6 months. In the interim, the bladder is managed with clean intermittent catheterization. If careful bladder care is neglected, deleterious effects such as hydronephrosis, urinary reflux, pyelonephritis, and declining renal function may ensue [189]. The use of urodynamics allows for objective measurements to identify those patients at risk, and treatment must be highly individualized [189].

Fertility Complications

Female patients undergoing pelvic procedures should be engaged in a thoughtful discussion preoperatively of the potential risk for fertility problems. A meta-analysis found a postoperative infertility rate of 48 % after restorative proctocolectomy for ulcerative colitis, compared to 15 % preoperatively [190]. Additionally, a systematic literature review was undertaken to evaluate the impact of restorative proctocolectomy on sexual function, urinary function, fertility, pregnancy, and delivery in patients with ulcerative colitis. Infertility rates of 12 % before surgery and 26 % after surgery were reported among 945 patients in seven studies [191]. However, some authors contend that this is more likely related to the disease process itself, rather than the type of surgery performed. A cross-sectional study of FAP patients found no association between fertility problems and type of surgery but did report an increased risk of fertility difficulty in women undergoing surgical procedures earlier in life [192].

Bowel Dysfunction

Pelvic surgery that includes restoration of bowel continuity is not only technically complicated but introduces new physiology to the life of the patients. For example, low anterior resection syndrome includes a variety of symptoms, including fecal incontinence, urgency, frequent bowel movements, and clustering of bowel movements [193]. When undergoing a procedure for rectal cancer, it is often assumed that restorative and sphincter-sparing techniques afford patients a quality of life, which is superior to that of a permanent stoma, with equivalent oncological outcome. This has been challenged by recent inquiries comparing patients' quality of life postoperatively following low anterior resection and abdominoperineal resection for rectal cancer. Certain prospective studies found better cognitive and social function, as well as less symptomatology with respect to pain, sleep disturbance, diarrhea, and constipation in those undergoing abdominoperineal resection. Those undergoing low anterior resection reported better sexual function; however, 72 % reported some degree of fecal incontinence [194]. A recent Cochrane review further calls into question that the quality of life (QoL) with a permanent stoma is inferior to the QoL of those with restored bowel continuity. This review did not find evidence that the QoL after anterior resection is superior to that of patients who had undergone abdominoperineal resection or Hartmann's procedure [195]. This lack of significance led some authors to surmise that this was in direct relation to bowel function postoperatively. Indeed, 50–90 % of patients undergoing sphincter-sparing low anterior resection have some degree of bowel dysfunction postoperatively [196, 197]. Using a validated LARS score [198], Juul et al. found that the quality of life after rectal cancer surgery is closely associated with the severity of the low anterior resection syndrome [193].

The etiology of the symptoms constituting LAR syndrome is unknown; however, it is often manifest by some degree of fecal or gas incontinence, clustering of bowel movements, frequency, and urgency. The severity of symptoms also seems to correlate with tumor height more than 5 cm, total mesorectal excision, and patient treatment with radiotherapy [199]. In fact, Marijnen et al. found that short-term preoperative radiotherapy led to significantly slower recovery from defecation problems, a negative effect on sexual functioning in males and females, as well as more ejaculation disorders and erectile functioning in males, when compared to those patients who did not undergo preoperative radiotherapy [200]. This did not, however, affect health-related quality of life in their study. Interestingly, when patients who underwent low anterior resection versus abdominoperineal resection were compared, those who underwent APR scored better

on physical and psychologic dimensions of quality of life [200]. An additional randomized controlled trial found that a short course of preoperative radiotherapy increased male sexual dysfunction, as well as an increased level of fecal incontinence [201]. Taken together, the risk of bowel dysfunction after surgery can be directly attributed to difficulties with symptoms related to the low anterior resection syndrome. While previous reports have assumed that the quality of life with restorative and sphincter-sparing procedures is greater than the quality of life with a permanent stoma, this is not always the case. When evaluating a patient with rectal cancer, specifically one who qualifies for neoadjuvant treatment, an earnest conversation must be had regarding postoperative functional outcomes.

Impact of Postoperative Complications on Oncologic Outcomes

It is clear that postoperative complications carry implications for short-term quality of life and negatively impact the cost of care. In addition, there is evidence that postoperative complications impact long-term oncologic outcomes [202, 203]. While the exact mechanism of the impact on long-term survival is unclear, it seems likely that postoperative complications result in either delay in receiving or complete omission of chemotherapy in patients with clear indications for systemic treatment. Hendren and colleagues used the SEER-Medicare database from 1993 to 2005 to examine risk for chemotherapy omission [203]. Patients who suffered postoperative complications were more likely to have chemotherapy omitted, but this was unable to be correlated with long-term survival [203]. Tevis and colleagues looked at this question in patients undergoing surgery for rectal cancer [202]. In this cohort, patients with postoperative complications had worse long-term survival than did those with no complications. Postoperative complications independently correlated with decreased overall survival even in patients who received chemotherapy, suggesting that in addition to omission of chemotherapy, complications may otherwise lead to poor long-term survival [202]. While no single study has definitively answered the question, most have found similar negative correlations between postoperative complications and long-term survival, suggesting that there is a relationship between the two. Further work is required to fully understand this relationship.

Conclusion

Postoperative complications after colorectal surgery are common. While we should strive to make postoperative complications, so-called never events, given the imprecise and uncontrollable nature of our profession, it is unlikely that we will achieve such a status. Therefore, we must have a good understanding of the issues related to these complications and be able to work through the implications of these complications. Research to better understand risk factors and preoperative risk mitigation may continue to lead to improved outcomes. How risk modulation can be achieved with surgical approach and intraoperative management must also be examined if we want to continue to improve outcomes. While quality improvement efforts are difficult and not always rewarding, it is clear that continued focus on preventing postoperative complications is beneficial not only to the patient's short-term health and quality of life but will also deliver downstream benefits such as improved long-term physiologic and oncologic outcomes. Finally, it is self-evident that improvements in short-term outcomes will have a positive impact on the healthcare delivery system by decreasing costs associated with postoperative complications.

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9
Anastomotic Construction

Steven R. Hunt and Matthew L. Silviera

Key Concepts

- Benign effluent from a peri-anastomotic drain does not rule out anastomotic leak or abscess.
- It is safe practice to leave the mesenteric defect open after constructing an ileocolic anastomosis.
- Fecal diversion reduces septic complications in patients with coloanal anastomoses.
- Diverting loop ileostomy and loop colostomy have similar complication rates.
- Leak testing should be performed on anastomoses to the rectum.

Introduction

The purpose of this chapter is to review the various anastomotic techniques for abdominal and pelvic anastomoses. There are many unique and innovative ways to create anastomoses; however, this chapter will focus on the most common techniques and the problems associated with their construction. It is difficult to overemphasize the importance of judgment and technique in preventing anastomotic complications while still preserving function. Various clinical situations and differing anatomy make it important to be familiar with multiple approaches to the same type of anastomosis. Knowledge of these various techniques is of paramount importance in achieving good outcomes. No matter how well planned the creation of an anastomosis is, problems will arise during execution, and the ability to salvage an anastomosis is a skill every colorectal surgeon must master.

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General Principles of Anastomoses

Surgical Staplers

Rudimentary surgical staplers first appeared in the early 1900s, but stapling devices improved dramatically in the 1970s with preloaded disposable cartridges of multiple staggered staple lines. Titanium staples have replaced stainless steel and are found in a variety of staple heights that are bent into a "B" configuration in order to match tissue thickness. Surgical staplers can be divided into two major groups: linear and circular. The simplest linear stapler (TA or thoracoabdominal) applies two rows of staples in a staggered configuration but requires manual transection of the bowel. The linear cutting stapler (GIA or gastrointestinal anastomosis) applies four rows of staggered staples and cuts between the middle two rows of staples, allowing for the division of bowel and the creation of anastomoses. Circular staplers (e.g., EEA or end-to-end anastomosis) have a detachable anvil. Once the anvil and head are coupled together, two circular rows of staggered staples are applied as a circular blade cuts out the interior tissue, allowing communication of the two lumens. EEA staplers come in a variety of diameters, with 25–31 mm staplers being the most common in colorectal surgery [1].

Hand-Sewn Anastomoses

Gastrointestinal anastomoses have been performed by various hand-sewn techniques for many years. Single-layer and double-layer anastomoses have been studied extensively, and a lone randomized controlled trial and three comparative studies have shown no difference in anastomotic leak rates between the two techniques [2–6]. Interrupted and continuous suture techniques have similarly been studied; however, there is not a high level of evidence to support one over the other [6]. With regard to suture material, clinical studies have failed to show benefit of one material over another.

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Anastomoses are frequently constructed with absorbable monofilament suture and absorbable braided suture. Two experimental studies comparing both suture materials showed similar anastomotic burst pressure and histologic characteristics [7, 8]. Given the lack of clear support in the literature for one hand-sewn anastomotic technique, it is the authors' preference to construct hand-sewn anastomoses with a single continuous layer of 3-0 PDS, as the monofilament slides easily through the bowel wall and the anastomosis is quick and easy to construct.

Compression Anastomoses

A compression anastomosis is created when two ends of bowel are held together for a period of time by physical forces during which anastomotic healing takes place. Several days later, the compressed tissue necroses and the device separates and is passed from the body. The anastomosis is held together by the adhesions that form between the tissues adjacent to the area of necrosis. This obviates the need for foreign material (suture/staples) in the anastomosis, which can lead to inflammation, foreign body reaction, and stricture. The idea of compression anastomoses was first reported back in the 1800s but then reemerged in the 1980s with the development of two commercially available products. In the United States, the biofragmentable anastomotic ring (BAR) was developed and studied extensively. Numerous publications, including randomized controlled trials, reported that the BAR was safe and effective [9–14]. Despite the encouraging clinical data that was accumulating, several reports of intraoperative problems with the BAR emerged, and the device never gained widespread acceptance.

A recent advance on this approach utilizes a smart metal (nitinol) that is a temperature-dependent, shape-memory alloy. Two compression rings are mounted on an instrument that is very similar to a conventional EEA stapler (ColonRing). When engaged, the rings are compressed together by nitinol springs, and with the aid of a circular blade, a compression anastomosis is created. Over time, simultaneous healing and necrosis take place, and ultimately the rings detach and pass transanally [15].

Recently a prospective multicenter study of 266 patients who had colorectal compression anastomoses with the nitinol ColonRing was published. The overall anastomotic leak rate was 5.3 % after low anterior resection, with septic complications occurring in 8.3 % [16]. Additionally, a multicenter data registry of 1180 patients was published with an overall leak rate of 3.2 % in all left-sided anastomoses [17]. This data is encouraging, but we are still awaiting a prospective randomized trial comparing the ColonRing to conventional stapled or hand-sewn colorectal anastomoses. At present, it has once again been taken off the market and is not available in the United States.

Tension

One of the tenants of anastomotic creation is that it must be tension-free. With small bowel and ileocolic anastomoses, tension is usually not a problem owing to the mobility of the small bowel. On the other hand, tension can be a significant problem with the pelvic colorectal anastomosis. In order to gain adequate length of the descending colon so that it may reach down into the pelvis, three maneuvers may be employed: (1) high ligation of the IMA, (2) ligation of the IMV at the inferior border of the pancreas, and (3) complete mobilization of the splenic flexure with division of the distal transverse colon mesentery back to the middle colic vessels. Complete mobilization of the splenic flexure is much more than simply dividing the peritoneal attachments at the flexure, and the technical considerations will be discussed in greater detail later in this chapter. It may be tempting to omit complete mobilization of the splenic flexure for an upper colorectal anastomosis, but it is the authors' recommendation to routinely mobilize the splenic flexure after high ligation of both the IMA and IMV in order to consistently create a tension-free colorectal anastomosis.

Blood Supply

Ensuring adequate blood supply to the proximal and distal ends of the bowel that will be anastomosed is of paramount importance. The first step is to confirm that the bowel looks viable and healthy, but this is not entirely sufficient. Sharply cutting an epiploicae at the level of the planned anastomosis and confirming bright red bleeding is reassuring. Additionally, the bowel can be opened sharply (rather than with cautery) to confirm bleeding from the bowel wall. The marginal artery is responsible for proximal colon perfusion for a left-sided anastomosis. We routinely isolate the marginal artery between clamps and "flash" the artery to confirm pulsatile bleeding. Brisk, bright red, pulsatile bleeding nearly guarantees excellent perfusion to the examined colon. Very dark or even black blood from the marginal artery often indicates a problem with the venous outflow and requires a change in the level of the planned anastomosis. Likewise, complete lack of bleeding shows that there is clearly inadequate perfusion to the colon. Both ends of the spectrum are fairly easy to interpret, but it is the gray zone of sluggish bleeding from the marginal artery that is troublesome and should prompt further scrutiny of the blood supply.

A new method of intraoperative perfusion assessment has been developed that uses near-infrared indocyanine green (ICG)-induced fluorescence angiography. The mesentery of the bowel, including the marginal artery, is divided, and the patient is given an intravenous push of ICG. The appropriate platform is used to excite the ICG with near-infrared light to visualize bowel perfusion (Video 9.1). The laparoscopic

platform can also be advanced transanally with the aid of a special proctoscope to endoscopically assess mucosal tissue perfusion of the colorectal anastomosis (Video 9.2). Currently, all perfusion assessments performed with this technology are subjective, and no purely objective measure of bowel perfusion exists.

Jafari et al. have published the results of the PILLAR II trial that was a prospective, multicenter, clinical trial that studied the utility of fluorescence angiography on colorectal anastomoses [18]. Nearly 140 patients were analyzed, with the mean level of anastomosis 10 cm from the anal verge. The overall anastomotic leak rate was 1.4 %. Additionally, 8 % of patients had a change in their anastomotic plan due to findings from the perfusion assessment, and none of those patients had an anastomotic leak. The encouraging low leak rate in the PILLAR II trial has paved the way for the current PILLAR III trial, which is a prospective RCT comparing fluorescence angiography to standard of care. This trial will attempt to determine if perfusion assessment with ICG reduces the rate of anastomotic leak.

Prophylactic Drainage

The prophylactic use of drains to avoid anastomotic complications is quite controversial. Drain usage among surgeons is variable. Some surgeons routinely drain anastomoses, others use drains only as dictated by circumstances, and there are others that eschew the practice of drainage. Multiple studies have been conducted with varying results. In general, two types of drains are used to drain anastomoses. The first is an open, or passive, drain. These drains are made of synthetic material and act to provide a route of egress for fluids. The second type is a closed suction drain, consisting of a soft, hollow tube that is placed under negative pressure to actively evacuate fluids. Advocates of drainage maintain that drains will prevent the accumulation of fluid or blood around the anastomosis, permit early detection of a leak, mitigate the consequences of a leak, and provide a "window into the abdomen."

Critics assert that drains provide the surgeon with a false sense of security, that they may cause a leak secondary to negative pressure, or that they may provide an avenue for the introduction of infection. Some detractors feel that drains may cause pain that leads to decreased ambulation, poor inspiratory effort, and associated complications.

The largest meta-analysis of prophylactic drainage includes a heterogenous group of studies with regard to the type of drain used and the location of the anastomoses [19]. In this evaluation of more than 1000 patients in six randomized controlled trials, no difference was seen between the routine drainage group and the group that did not have prophylactic drains. This analysis evaluated clinical anastomotic leak, radiographic anastomotic leak, wound infection, reoperation, and mortality—revealing no difference between the two groups. Many patients included in these studies had open/passive drainage. These studies also included both intraperitoneal and extraperitoneal anastomoses.

A smaller meta-analysis showed no difference in drain-related complications between routine drainage and non-drainage regimens [20]. Interestingly, of the 20 patients with drains that developed anastomotic leaks, only 1 patient (5 %) had any evidence of enteric contents in the drain effluent. This finding certainly disputes the "window into the abdomen" theory and lends credence to the argument that drains may provide surgeons with a false sense of security.

The largest randomized controlled trial of closed suction drainage involved 494 patients that had both intraperitoneal and extraperitoneal colonic anastomoses [21]. There was no difference between the drainage and non-drainage group in anastomotic leak rate, reoperation, mortality, or other abdominal complications.

A more recent systematic review of observational studies looking strictly at extraperitoneal colorectal anastomoses showed that there was a difference in the rate of anastomotic leakage favoring the drained group [22].

While there is scant data to support routine prophylactic drainage, there is no evidence that drains cause adverse events. The decision to drain anastomoses should be left to the discretion of the surgeon. Importantly, if drains are used, benign-appearing effluent in the drain does not rule out an anastomotic leak or abscess. Sound clinical judgment should still prevail when a leak is suspected.

Treatment of Mesenteric Defects

Prior to the popularization of laparoscopic colon resections, routine closure of the mesenteric defect was considered essential to avoid internal herniation leading to obstruction or strangulation. As laparoscopic colectomy propagated, the necessity of closing these defects was questioned. It proved difficult to perform the closure through the small extraction excision, and laparoscopic closure of the defect was cumbersome.

Proponents of leaving the defect open contend that closure of the mesentery creates a risk for bleeding, mesenteric hematoma, and compromise of the anastomosis. While the catastrophic consequences of an open mesenteric defect have been discussed in case reports, studies that have looked at this question specifically have shown that it is safe, and perhaps even prudent, to leave the defect open after creating an ileocolic anastomosis [23, 24].

With ileorectal and ileal pouch anal anastomoses, there is the risk of axial torsion of the small bowel around the free edge of the mesentery. Because this can have devastating consequences if a significant amount of small bowel herniates under this mesenteric edge, some surgeons choose to close this defect by securing the free edge of the small bowel mesentery to the preaortic retroperitoneal fascia. There is no evidence to support this practice.

Diversion

For an in-depth discussion on diversion, see Chap. 55. Briefly, fecal diversion has a role in protecting distal anastomoses that are at high risk for leakage. Commonly, diverting stomas are used to protect low pelvic anastomoses. Any anastomosis within 5 cm of anal verge should be considered for diversion as these anastomoses have a five- to sixfold increase in the rate of clinical anastomotic leakage compared to more proximal anastomoses [25, 26].

Defunctioning stomas can also be used to divert more proximal anastomoses at risk for leakage. These include selected anastomoses in the setting of malnutrition, immunocompromised patients, irradiated tissue, soilage, inflamed tissue, and to protect anastomoses that have been technically difficult to perform. Diversion in these settings should be used judiciously, as proximal diversion itself is not a license to create an anastomosis regardless of the clinical situation. An end ostomy and an interval return to the operating room is the safe option when the integrity of an anastomosis is jeopardized.

While the true value of a diverting stoma is difficult to quantify, it is clear that diversion mitigates the consequences of anastomotic leaks. Given the relatively low rate of anastomotic leaks, the majority of diverting stomas are created unnecessarily. The difficulty lies in predicting which patients are most likely to leak. Diverting stomas and the procedure to reverse them have their own attendant morbidity [27, 28]. In many patients, the diverting stoma is never able to be reversed [29, 30].

A recent analysis of patients included in the National Surgical Quality Improvement Project (NSQIP) examined the use of diverting stomas in patients having a low anterior resection with either a colorectal anastomosis or a coloanal anastomosis [31]. Comparing patients who had a defunctioning stoma to those that did not, they found no difference in sepsis, septic shock, or wound complications after creation of a colorectal anastomosis. In patients with coloanal anastomoses, there was a significant difference favoring diversion for septic complications, reoperation, and length of stay. They also found a significant increase in the incidence of acute renal failure in patients who were diverted.

In theory, proximal diversion decreases the load of contamination in an anastomotic leak and may allow the body to seal off a leak—diminishing clinical consequences. Multiple studies demonstrate that diverted anastomoses have a decreased rate of fecal peritonitis, sepsis, and reoperation [32–36].

The method of diversion is often dependent on the clinical situation. Both loop colostomies (Figure 9-1) and loop ileostomies have advantages and disadvantages. Ileostomies are associated with peristomal dermatitis, pouching difficulties, dehydration, and acute renal failure. Diverting colostomies are more prone to prolapse. Additionally, loop colostomies can be difficult to close through a peristomal incision, and the blood flow through the pre-anastomotic marginal blood vessels can be compromised at the time of loop colostomy closure.

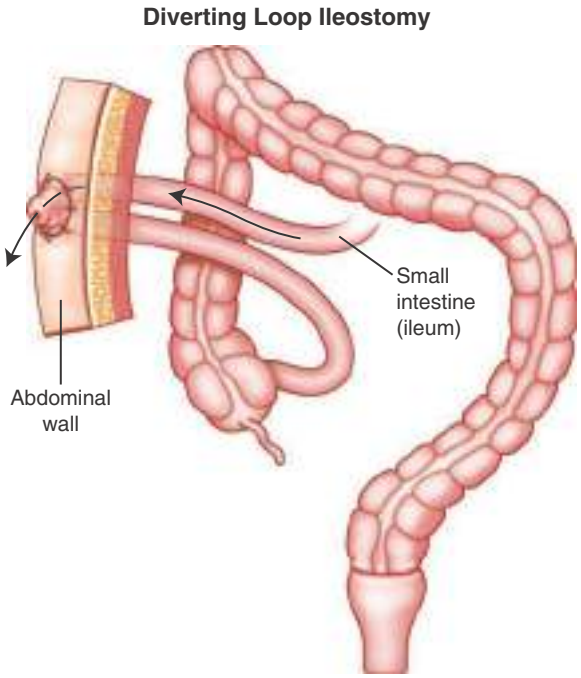

FIGURE 9-1. Diverting loop ileostomy.

A meta-analysis of randomized controlled trials comparing diverting loop colostomies to loop ileostomies shows no difference between the two groups in complications related to the stoma or in time to ostomy closure [37].

High-Risk Anastomoses

There are certain clinical situations in which clinical judgment precludes the creation of an anastomosis, even with proximal diversion. Such situations include severe malnutrition, significant immunosuppression, gross or long-standing fecal contamination, massively dilated bowel, and the risk of developing hemodynamic instability in the postoperative period. In these situations, even the best technical anastomoses may fail due to factors beyond the surgeon's control. Rather than risk anastomotic failure in these cases, an end ostomy that will allow for future restoration of continuity should be performed.

Abdominal Anastomoses

Small Bowel Anastomoses

Small bowel anastomoses are frequently performed during ileostomy closures, as part of complex adhesiolysis, or during resections for Crohn's disease or small bowel neoplasms. Both stapled and hand-sewn techniques can be used to complete the anastomosis. In creating a stapled side-to-side (functional end-to-end) anastomosis, the bowel should be divided proximally and distally with a linear stapler, taking

care to make sure that the staple line is oriented along the axis from the mesentery to the antimesenteric border of the bowel. Additionally, the staple line should be beveled from the mesenteric side away from the specimen. These subtle but simple steps ensure that the mural blood flow to the anastomosis will not be compromised. After the bowel has been divided, the antimesenteric corners of the transverse staple line are removed, and the limbs of the GIA stapler are introduced. As the stapler is closed, the mesentery of each limb of bowel should be pulled laterally to ensure that the stapler is fired on the antimesenteric border of the bowel. The anastomosis is completed by closing the common enterotomy either with a stapler (GIA or TA) or a hand-sewn technique.

Cost can be contained by eliminating two loads of the GIA stapler by creating the anastomosis without dividing the bowel proximal and distal to the resection. Instead, the mesentery to the intended points of transection is divided, and enterotomies are created on the antimesenteric bowel wall proximal and distal to the specimen. The GIA stapler is introduced through these openings and fired along the antimesenteric border. The common enterotomy is closed, and the specimen resected with a single firing of a linear stapler. Alternatively, the bowel can be divided proximal and distal to the specimen with electrocautery, and the GIA stapler can be used to create the anastomosis along the antimesenteric border. The common enterotomy can then be closed with another linear stapler or hand sewn.

During loop ileostomy closure, it can be difficult to adequately mobilize both the proximal and distal limbs of the ileum through the peristomal incision in order to allow for a stapled side-to-side anastomosis. Rather than blindly sweeping down adhesions with your finger and potentially deserosalizing bowel, a hand-sewn anastomosis can be performed. This can be accomplished by resecting the ileostomy and performing a hand-sewn end-to-end anastomosis (one layer, interrupted or continuous) or by unfolding the Brooke ileostomy and simply closing the enterostomy transversely with sutures [38]. A meta-analysis by Leung et al. failed to show any differences between surgical techniques for ileostomy reversal; however, there was a trend toward less postoperative bowel obstruction with stapled small bowel anastomoses [39].

Ileocolic Anastomoses

Ileocolic anastomoses are frequently created after an ileocolic resection for Crohn's disease or a right hemicolectomy for cancer. A recent Cochrane review looked at seven RCTs comprising 1125 patients comparing the techniques of stapled side-to-side anastomoses with hand-sewn anastomoses [40]. The overall leak rate was significantly lower for stapled anastomoses (2.5 %) compared with hand-sewn anastomoses (6 %). In a subgroup of 825 cancer patients, stapled anastomoses remained superior with a significantly lower leak rate (1.3 %) compared to hand-sewn anastomoses (6.7 %). There were no differences for any other reported outcomes nor were there any differences for the noncancer subgroup that included Crohn's disease.

When contemplating an anastomosis for Crohn's disease, one must take several variables into consideration, including the physiologic and nutritional state of the patient, general condition of the bowel, and presence of additional active disease and peritoneal contamination. Additionally, the chronic use of high-dose immunosuppression may portend an increased risk of anastomotic leak. In some instances, an end ileostomy or even a primary anastomosis protected with a loop ileostomy may be a safe option for the malnourished, immunocompromised Crohn's disease patient. If considering a protective loop stoma, one must be cognizant of how proximal the stoma would be to determine if a persistently high-output stoma is likely. If an ileocolic anastomosis is going to be created, there is no absolute consensus as to the optimal technique for Crohn's disease; however, stapled anastomoses are generally expeditious and easy to construct.

When creating a stapled side-to-side (functional end-to-end) anastomosis, up to four linear stapler firings may be needed to construct the anastomosis. The typical ileocolic anastomosis is created by dividing the small bowel and colon with a GIA at the proximal and distal resection margins, followed by a stapled side-to-side anastomosis along the antimesenteric border of the bowel, and finally the stapled closure of the common enterotomy. Cost can be contained and overlapping staple lines avoided by creating a "Barcelona" anastomosis (Figure 9-2a–d). In this technique, after the mesentery of the bowel has been divided up to the points of proximal and distal resection, two enterotomies are created on the antimesenteric border of the bowel. The limbs of a GIA stapler are advanced into these openings and fired along the antimesenteric border of the bowel. The common enterotomy is then closed and the specimen transected with a second firing of a linear stapler.

Another technique for an ileocolic anastomosis is the stapled end-to-side technique in which an EEA stapler (25–29 mm) is used (Figure 9-3a–d). This has been shown to be a safe and effective anastomotic technique [41]. The terminal ileum is divided, a purse-string suture is placed, and the EEA anvil is secured in the end of the ileum. A colotomy is created within the specimen, and the EEA stapler is advanced through the colotomy in an antegrade fashion to the antimesenteric border of the colon several centimeters distal to the intended margin of transection. The spike is brought out through the antimesenteric wall of the colon, and the anvil within the ileum is connected. The stapler is then closed and fired. The colon is divided with a linear stapler a few centimeters proximal to the EEA anastomosis to ensure that the anastomosis and blind end of the colon are well perfused.

Laparoscopic ileocolic resections and right hemicolectomies are being performed with more frequency. Classically, the colonic mobilization and vascular pedicle ligation are performed laparoscopically. The specimen is resected and

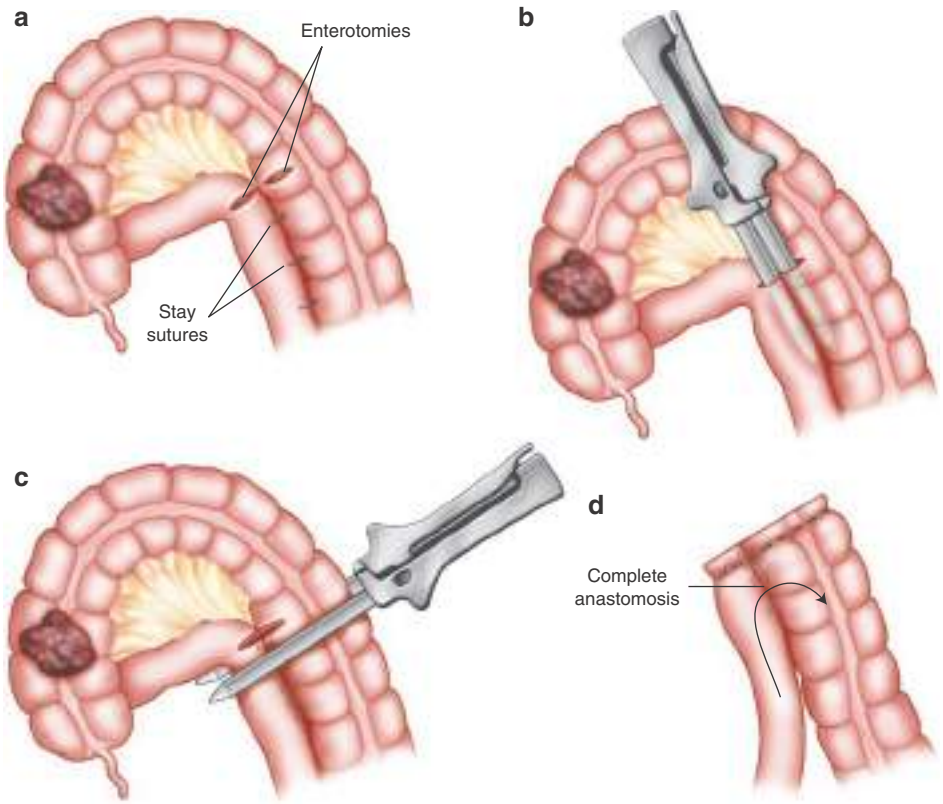

FIGURE 9-2. Barcelona anastomosis. (**a**) Stay sutures are placed and two antimesenteric enterotomies are made. (**b**) A linear stapler is used to construct the common wall. (**c**) An additional firing of the linear stapler is used to complete the anastomosis and resect the specimen. (**d**) Completed anastomosis.

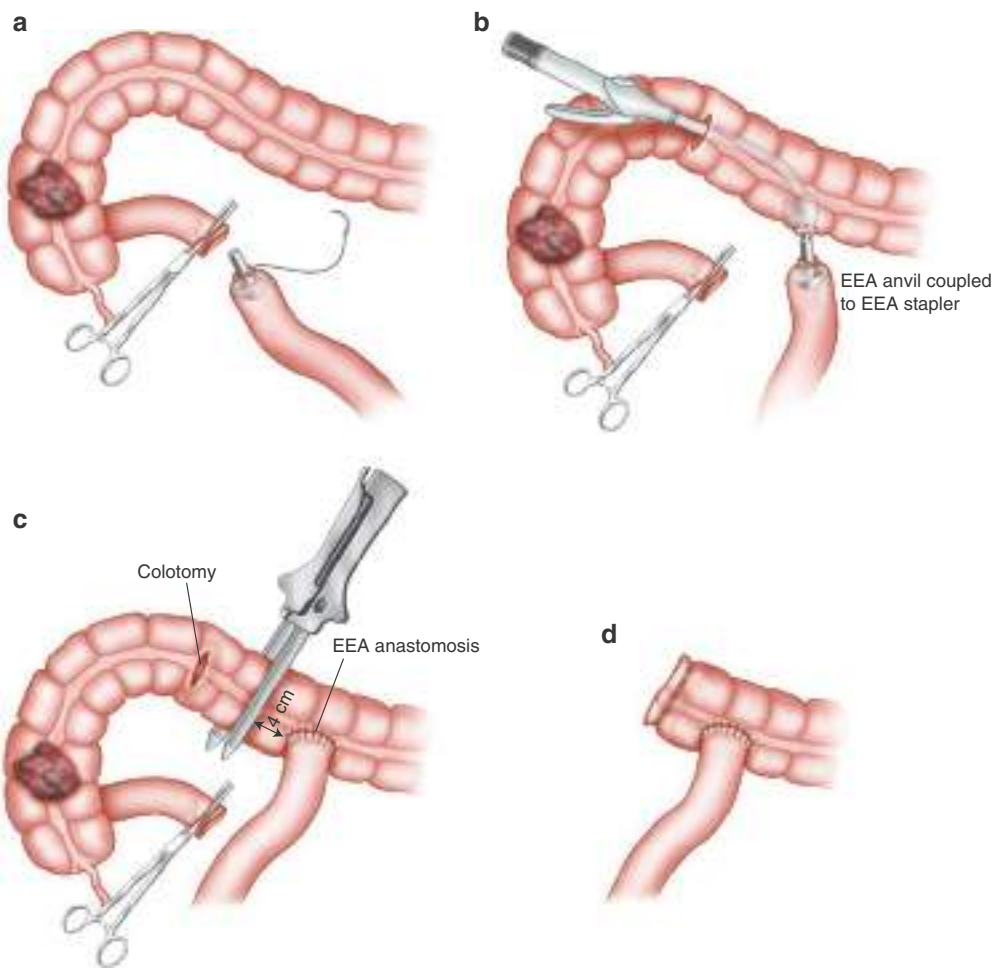

FIGURE 9-3. End-to-side ileocolic anastomosis. (**a**) An EEA anvil is placed into the end of small bowel through a purse string after dividing the bowel. (**b**) A colotomy is made, and the EEA stapler is passed and coupled the spike to the EEA anvil. (**c**) Following the EEA anastomosis, a linear stapler is used to close the colon defect. (**d**) Completed anastomosis.

anastomosis created extracorporeally through a small periumbilical incision. In recent years, totally laparoscopic right hemicolectomy with intracorporeal anastomosis has gained popularity. Advocates of this technique maintain that there is less bowel manipulation and less traction on the bowel mesentery, which may translate into faster return of bowel function. Additionally, the extraction site can be moved to a location associated with decreased risk of hernia, such as a small Pfannenstiel incision. The most common technique for performing an intracorporeal anastomosis is to create a stapled side-to-side (functional end-to-end) anastomosis using laparoscopic linear staplers. The resultant common enterotomy can then be stapled or sewn closed. Intracorporeal anastomosis may be particularly beneficial in obese patients because they often have thick, foreshortened mesenteries that make extracorporealization particularly difficult and often result in extended extraction site incisions. A meta-analysis of nonrandomized comparative studies looking at intracorporeal anastomosis vs. extracorporeal anastomosis for laparoscopic right hemicolectomies shows no difference in the rate of anastomotic leak, with a trend toward decreased short-term morbidity in the intracorporeal anastomotic group [42]. Given that these are comparative studies and no randomized trials exist, it appears that the intracorporeal anastomosis is safe, but further studies are needed to determine if there is a true benefit [43].

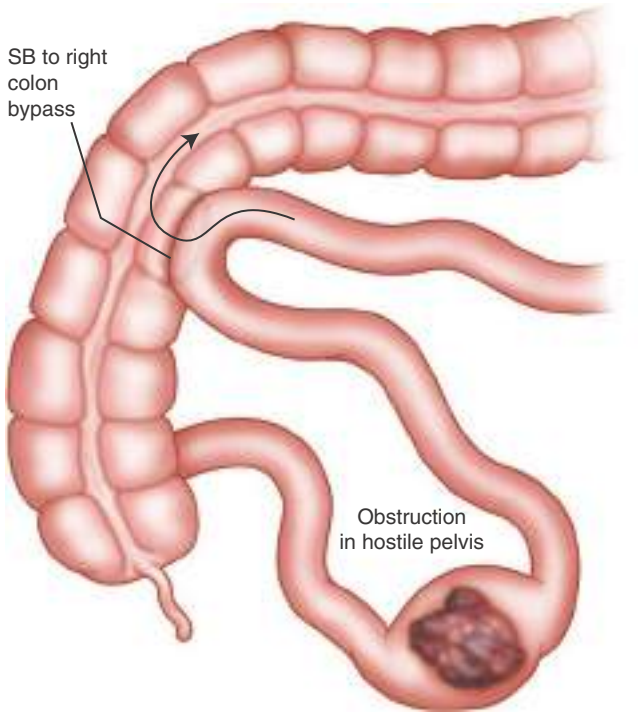

FIGURE 9-4. Intestinal bypass.

Intestinal Bypass

Deep pelvic small bowel obstructions that result from unresectable malignancies or severe radiation damage may be difficult or dangerous to approach surgically. In these situations, options include decompressing gastric tubes, proximal diversion, or intestinal bypass. If the obstructed loop of bowel can be isolated, a simple bypass from the obstructed limb to bowel distal to the obstruction can be performed in either a hand-sewn or side-to-side stapled fashion (Figure 9-4). For distal ileal obstructions, the ascending colon is frequently used as the distal limb of the bypass. If the colon is to be used, mobilization of the ascending colon and hepatic flexure is often necessary to allow the colon to lay alongside the obstructed limb without creating tension on the bypass anastomosis.

When contemplating an intestinal bypass, one must also consider the potential for obstruction of the bowel distal to the bypass. Many of these patients will already have an end colostomy, so bulky pelvic disease or dense pelvic adhesions should not result in an obstruction distal to the bypass. If the patient is in GI continuity, a preoperative contrast enema can assess the distal colon and rectum. One should have a low threshold for creating an ileostomy in a patient who is in GI continuity with bulky pelvic disease. Simply performing an intestinal bypass in this situation may be further complicated by a future distal obstruction in the pelvis.

Pelvic Anastomoses

Basic Principles of Pelvic Anastomoses

Creating an anastomosis in the pelvis can be extremely challenging. Studies have documented that low pelvic anastomoses have a higher rate of leakage than more proximal anastomoses [44, 45]. The increased leak rate highlights the challenges of operating in the pelvis. The space is limited by the unyielding bony structures, making visualization difficult. There are multiple structures within the pelvis that can interfere with or become incorporated into the anastomosis. Tension is a concern with all anastomoses but significantly more so in the pelvis, where anatomic factors can make it a significant challenge to create a tension-free anastomosis. When a low anterior resection is performed, the reservoir function of the rectum is lost proportionally to the length of rectum resected, and anastomotic misadventures can have major consequences on a patient's future quality of life.

Adequate visualization during dissection and creation of the anastomosis is extremely important. It is important to have optimal lighting—accomplished through the use of a headlamp, lighted pelvic retractor, or careful placement of external lights. Because of limited sight lines, it is often not possible for more than one person to visualize pelvic structures simultaneously.

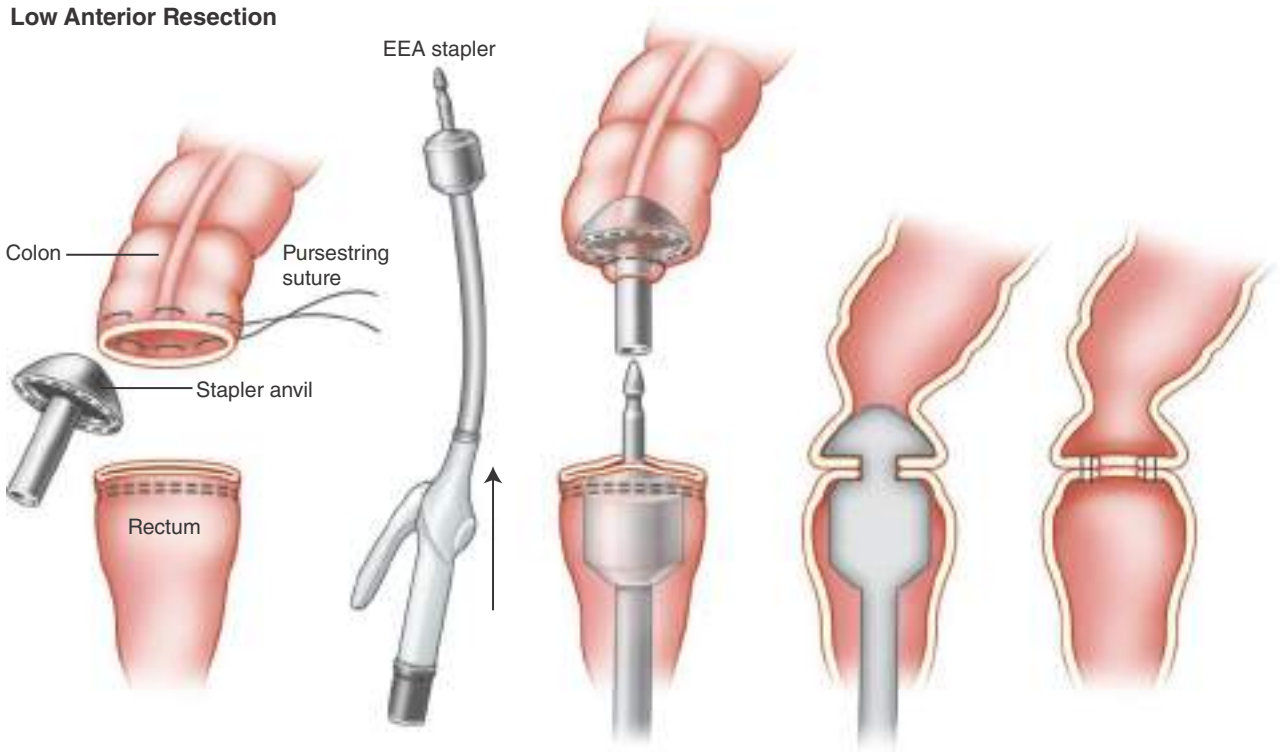

FIGURE 9-5. Stapled colorectal anastomosis. Following a low anterior resection, the EEA stapler is used to construct an end-to-end anastomosis.

When creating a pelvic anastomosis, extraneous structures can be incorporated in the anastomosis. The structure with the greatest consequences of inclusion is the vagina. This should be at the forefront of the surgeon's mind in every female patient. One must be diligent in ensuring that the vagina is out of harm's way during the dissection, rectal division, and anastomotic construction. For anastomoses in the mid- and upper rectum, the surgeon must ensure that the vagina is dissected away from the rectum for several centimeters below the site of the intended anastomosis. Additionally, for stapled anastomoses, the vagina must be visualized and confirmed to be free from the EEA staple line.

In the lower pelvis and especially with coloanal anastomoses, perfect visualization can be difficult to attain. In these situations, it is necessary to use other means to verify that the vagina has not been included in the anastomosis. One of the simplest methods to improve visualization deep in the pelvis is to ask an assistant to break from the sterile field and apply cephalad pressure to the perineum with a fist. If the vagina cannot be visualized after the stapler has been closed, the vaginal wall should be palpated to confirm its independence from the staple line. When performing hand-sewn anastomoses, careful bites should be taken anteriorly to avoid the vaginal wall. As with more proximal anastomoses, the vagina needs to be dissected off of the rectum and anal canal well below the level of intended anastomosis.

Rather than struggle to perform the maneuvers necessary to gain adequate colonic length to reduce anastomotic tension, it can be tempting to use the floppy sigmoid colon as the proximal end of the anastomosis. There are several reasons why the descending colon should be used preferentially to the sigmoid colon when creating the colorectal anastomosis. In a resection for cancer, the inferior mesenteric artery should be divided at its origin for an adequate lymphadenectomy. This high ligation, coupled with the loss of collateral flow from the distal middle rectal vessels, frequently makes the blood supply to the sigmoid colon insufficient. This scant blood flow to the anastomosis puts it at risk for leak or stricture. Additionally, the sigmoid colon's thick muscular wall and diverticulosis make this segment a poor substrate to use in creating what is already a precarious anastomosis. In general, it is better to invest the effort to adequately mobilize the colon to create length for a descending to rectal anastomosis.

Stapled Colorectal Anastomoses

With wide availability of circular EEA staplers, the stapled colorectal anastomosis has gained favor among surgeons (Figure 9-5). Both single-stapled and double-stapled techniques will be described.

In both these techniques, the stapler anvil is secured in the proximal colon with a purse string. The purse-string suture should be placed with small but full-thickness bites of the colon wall, so that there is not a bunching of tissue around the anvil post when the purse string is tied. It is important to ensure that there is not a significant burden of mesenteric or epiploic fat on the stapler anvil. All that is required is to incise the peritoneum overlying any fat that would be incorporated in the staple line. This simple maneuver will allow any extraneous fat to be compressed out of the anastomosis as the stapler is closed, without denuding or devascularizing the colon wall that will be part of the anastomotic staple line.

When the specimen has been removed, preparations should be made prior to creating the anastomosis. Ensure that the pre-anastomotic colon courses to the left of the ligament of Treitz and falls easily into the pelvis. The mesentery of the colon should be straight with no twists. If it appears that the anastomosis will be under *any* tension, further lengthening maneuvers should be performed. These will be described later.

Reevaluate the colon for blood flow—making sure that the colon appears pink and healthy. Confirm that there are no areas of demarcation and that the colon is not hyperemic. The colon must also be scrutinized for signs of venous stasis—mottling or small congested veins containing dark, almost black, blood. If there is any question as to the viability of the pre-anastomotic colon, the anastomosis should not proceed until these concerns have been addressed satisfactorily. A simple method of evaluating blood flow is to sharply incise an epiploic appendage adjacent to the anvil. While rarely pulsatile, bright red bleeding from this incision should be comforting. If there is only dark blood from this incision or any other signs that the blood flow to the anastomosis is compromised, a more proximal site should be chosen to create the anastomosis.

Once matters relating to blood supply and tension have been satisfied, the EEA stapler is gently introduced through the anal canal and remaining rectum by an assistant who is outside of the sterile field. Communication between the surgeon and the assistant is essential. In women, the assistant must confirm that the stapler is not placed in the vagina. As this portion of the procedure is often done with less than optimal visualization of the perineum, the assistant can confirm the rectal location of the stapler by placing a finger in the vagina after the stapler has been introduced. Ideally, the stapler should be advanced all the way to the transverse rectal staple line when creating a double-stapled anastomosis. The abdominal operator must confirm that the stapler is indeed at the end of the rectal stump prior to advancing the stapler spike. If there is any intervening tissue including valves or other gathered rectal tissue, the edges of the stapler will not be well defined at the pouch apex, and the stapler must be repositioned. When navigation of the stapler through the rectum proves difficult, it may be necessary for the abdominal operator to advance the stapler with one hand out of the sterile field and the other hand guiding the device through the rectal pouch.

Once the stapler is in the appropriate position, the spike is advanced slowly under close scrutiny of the abdominal operator. The stapler spike should be delivered near the midpoint of the transverse staple line. After the stapler spike has been fully deployed, the apex of the rectal pouch must be well seated on the stapler. The anvil is secured to the spike and the stapler is closed under direct visualization, taking care to confirm that extraneous tissue is not included. After the stapler has been closed, the abdominal operator must verify that the colonic mesentery is not twisted. This requires following the mesenteric edge all the way back to the middle colic vessels. In laparoscopic procedures where this visualization can be difficult, this might require reestablishment of pneumoperitoneum if necessary. Following this, the abdominal operator directs the assistant to fire the stapler. The stapler is then opened, twisted in order to dislodge from the tissue of the anastomosis, and removed. Any difficulty removing the stapler should generate concern, as this can be a sign of anastomotic failure. The integrity of the anastomosis should then be assessed by one of the various methods discussed later in this chapter.

The single-stapled technique differs from the double-stapled technique in that there is no transverse staple line on the rectal pouch. Instead, the rectum is divided sharply, and a purse string is also placed around the open rectal stump. The stapler is introduced and passed all the way to the proximal end of the rectum. The spike is then introduced through the purse string, and the purse string is tied around the spike. The stapled EEA anastomosis is then created in a similar fashion to the double-stapled anastomosis. While this technique avoids intersecting staple lines, it does leave the rectal stump open briefly, potentially allowing for spillage of stool or even intraluminal tumor cells into the abdominal cavity. For this reason, the single-stapled anastomosis is often used only as a salvage technique.

Rarely, advancing the EEA stapler to the apex of the rectal stump can prove to be extremely difficult, even with bimanual introduction. Excessive force should not be used to advance the stapler. Instead, further circumferential mobilization of the rectum in the mesorectal fascial plane will often eliminate the kinks or folds that inhibit stapler introduction. If this fails, the anastomosis can be created in an end-to-side fashion on the anterior wall of the rectum, several centimeters below the transverse staple line. Should this option be selected, there must be an adequate distance between the upper edge of the circular staple line and the transverse staple line in order to avoid ischemia of the tissue bridge separating the two staple lines. Another option is to attempt to use a smaller caliber stapler, but this requires removal and replacement of the anvil in the pre-anastomotic colon.

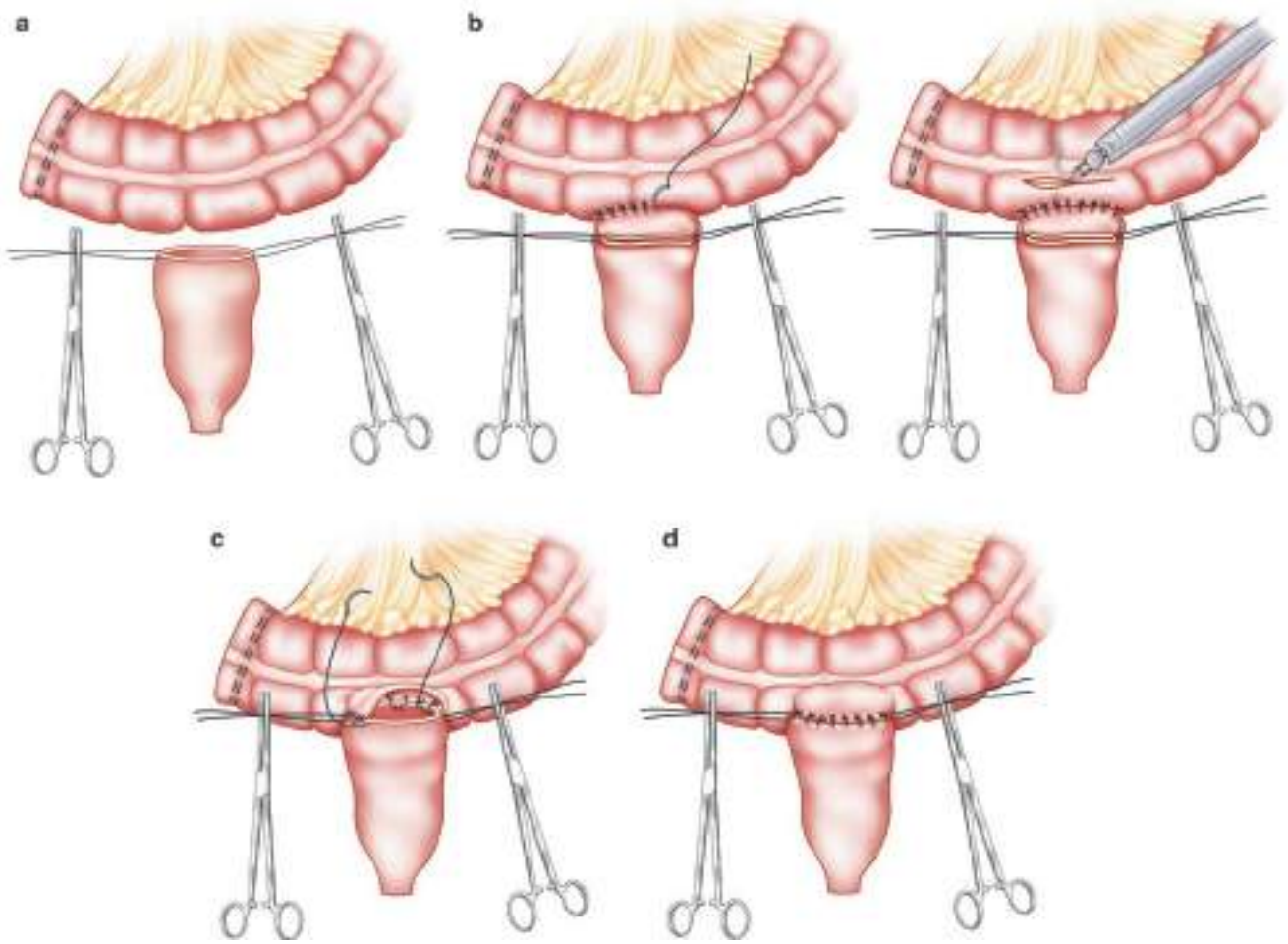

FIGURE 9-6. Hand-sewn colorectal anastomosis. (**a**) The distal end of the colon is closed, and stay sutures are placed on the rectum. (**b**) A posterior layer of sutures are placed (*left*) and a colotomy is made (*right*) to match the size of the opening on the rectal stump. (**c**) The anastomosis is constructed using two continuous running sutures. (**d**) The anterior suture line is oversewn with interrupted sutures.

Hand-Sewn Colorectal Anastomosis

In the upper and mid-rectum, it is possible to create a hand-sewn colorectal anastomosis (Figure 9-6a–d). The evidence suggests that hand-sewn and stapled colorectal anastomoses are equivalent in leak rate. Indeed, the hand-sewn colorectal anastomosis may have a slightly lower rate of stricture [46]. The choice to perform a hand-sewn or stapled anastomosis should be dictated by surgeon preference, patient habitus, clinical circumstances, anatomic accessibility, availability of staplers, and cost. Soilage or spillage of malignant cells is a theoretical problem with this technique, but this has never been borne out scientifically.

If a hand-sewn anastomosis is selected, there is no proven advantage of double-layer over single-layer anastomosis. We will describe a two-layer colorectal anastomosis, but the techniques to create a single-layer anastomosis are similar.

The fatty mesentery of the colon and rectum makes a hand-sewn end-to-end anastomosis difficult to perform. Additionally, there is often a substantial size difference between the proximal bowel and the rectal lumen. For these reasons, a side-to-end colon to rectal anastomosis, as described by Baker, is more practical and allows for better visualization while creating the anastomosis [47]. The distal end of the colon is stapled or sewn closed. The anastomosis will be created several centimeters proximal to this closure on the antimesenteric wall of the colon. In order to set up the anastomosis, two stay sutures should be placed on opposite sides of the anastomosis in order to align the two structures. A posterior layer of interrupted Lembert sutures is placed first. After the posterior row has been placed, a longitudinal antimesenteric colotomy is created to closely approximate the size of the rectal lumen. Two simple running sutures of absorbable monofilament suture are then started at the midpoint of the posterior wall and advanced in opposite directions to create the posterior inner layer. As the sutures proceed onto the anterior aspect of the anastomosis, a Connell suture can be used to create the anterior inner layer closure. The anterior suture line is then oversewn with interrupted Lembert sutures. While other methods exist, this technique is simple and ensures that the mucosa is inverted.

Ileorectal Anastomosis

The ileorectal anastomosis after an abdominal colectomy is performed in the same fashion and following the same precautions as the colorectal anastomosis. Often, the small caliber of the ileum will not accommodate the use of the larger EEA stapler, and a smaller 25 mm stapler diameter is required. Due to the risk of an axial volvulus under the free edge of the small bowel mesentery, some surgeons approximate the free ileal mesenteric edge to the retroperitoneum in the midline.

Ultralow Colorectal and Coloanal Anastomoses

The techniques involved in creating the low anastomoses in the pelvis remain the same as the upper rectal anastomoses. However, in addition to the technical challenges inherent in creating a low anastomosis, the surgeon must be mindful of the functional consequences of resecting the majority of the rectal reservoir. "Anterior resection syndrome" refers to the symptoms of frequency, urgency, stool fragmentation, incontinence, and evacuatory difficulties (see Chap. 56). This syndrome occurs to varying degrees in the majority of patients with low colorectal or coloanal anastomosis [48, 49]. Preoperative radiation and the distance of the anastomosis from the anal verge are risk factors for these symptoms [50]. This syndrome may require patients to take antimotility agents or wear pads or diapers. In the most extreme cases, patients become homebound or request a colostomy.

Neorectal Reservoirs

Many hypothesized that the functional consequences of a low anastomosis could be attributed to the loss of reservoir with straight colorectal or coloanal anastomosis [51]. The colon is less distensible than the native rectum, and it was thought that this low capacitance was responsible for the symptoms. Using techniques developed for restorative proctocolectomy, Lazorthes and Parc both proposed the creation of a colonic reservoir in order to decrease the functional consequences of a low anastomosis [52, 53]. These early studies showed improvement of bowel function in patients with colonic J-pouches.

Over the ensuing years, multiple studies confirmed these findings, demonstrating that the colonic J-pouch was superior to the straight coloanal anastomosis in terms of frequency, incontinence, and quality of life [44, 54–59]. While most studies evaluated function in the first 1–2 years after surgery, the studies evaluating longer-term results show that these functional advantages are durable out to 5 years [60–62]. The superiority of the colonic J-pouch over the straight coloanal anastomosis was also supported by a Cochrane systematic analysis [63].

While almost all defecatory problems improved with a J-pouch reservoir compared to a straight coloanal anastomosis, many patients in the early series reported significant constipation and evacuatory difficulties [53, 64]. The original descriptions of neorectal reservoirs were large, 10–12 cm colonic J-pouches. Some authors theorized that the emptying difficulties were related to large pouch size. Several trials evaluating smaller (5–6 cm) colonic pouches found them to be superior to larger pouches [64, 65].

The creation of the colonic J-pouch first requires confirmation that the colon is adequately mobilized and that the intended apex of the pouch will reach the cuff without tension (Figure 9-7a–c). An antimesenteric colotomy is then created 5–6 cm from the divided end of the colon. A linear cutting stapler is inserted through this colotomy, with one limb of the stapler inserted into the blind end and the other limb delivered up to the proximal limb of the colon. As the stapler is closed, the mesentery of the two limbs is rotated laterally to ensure that the staple line will be centered on the antimesenteric colon. Once the mesentery is oriented and the stapler closed, the pouch is created by firing the stapler. If a stapled anastomosis is to be created, a purse-string suture is then placed around the apical colotomy, and the anvil is secured in the pouch. The anastomosis is then created similarly to other colorectal anastomoses.

Anastomotic leak is a feared complication of low pelvic anastomoses and creates a significant fibrotic reaction in the pelvis that can have disastrous consequences on defecatory function [66]. Some evidence suggests that there may be fewer anastomotic complications with a colonic J-pouch. Doppler flow studies demonstrate that the pouch apex has improved blood flow compared to the colon used for the straight colorectal anastomosis [67]. Indeed, some studies showed a significant decrease in the anastomotic leak rate for the colonic J-pouch when compared to a straight coloanal anastomosis [44, 45].

While colonic reservoirs have benefits for low rectal and coloanal anastomosis, reservoirs anastomosed more than 5–6 cm above the anal verge may actually create problems emptying. It is recommended that a straight colorectal anastomosis be created for mid-rectal and more proximal anastomoses [45, 68, 69].

Occasionally, clinical circumstances make the creation of a colonic J-pouch difficult. Patients with a small pelvis, fatty mesentery, extensive diverticulosis, mucosectomy, or insufficient colonic length are not good candidates for J-pouch creation. Studies have shown that these technical factors preclude J-pouch creation in at least one-quarter of patients [70, 71]. In these situations, a transverse coloplasty offers another option.

Z'graggen was the first to describe the transverse coloplasty as an alternative to the colonic J-pouch, proposing that this technique may provide the functional benefits of the J-pouch reservoir while avoiding the evacuatory difficulties [72]. The coloplasty is created by making an 8 cm longitudinal

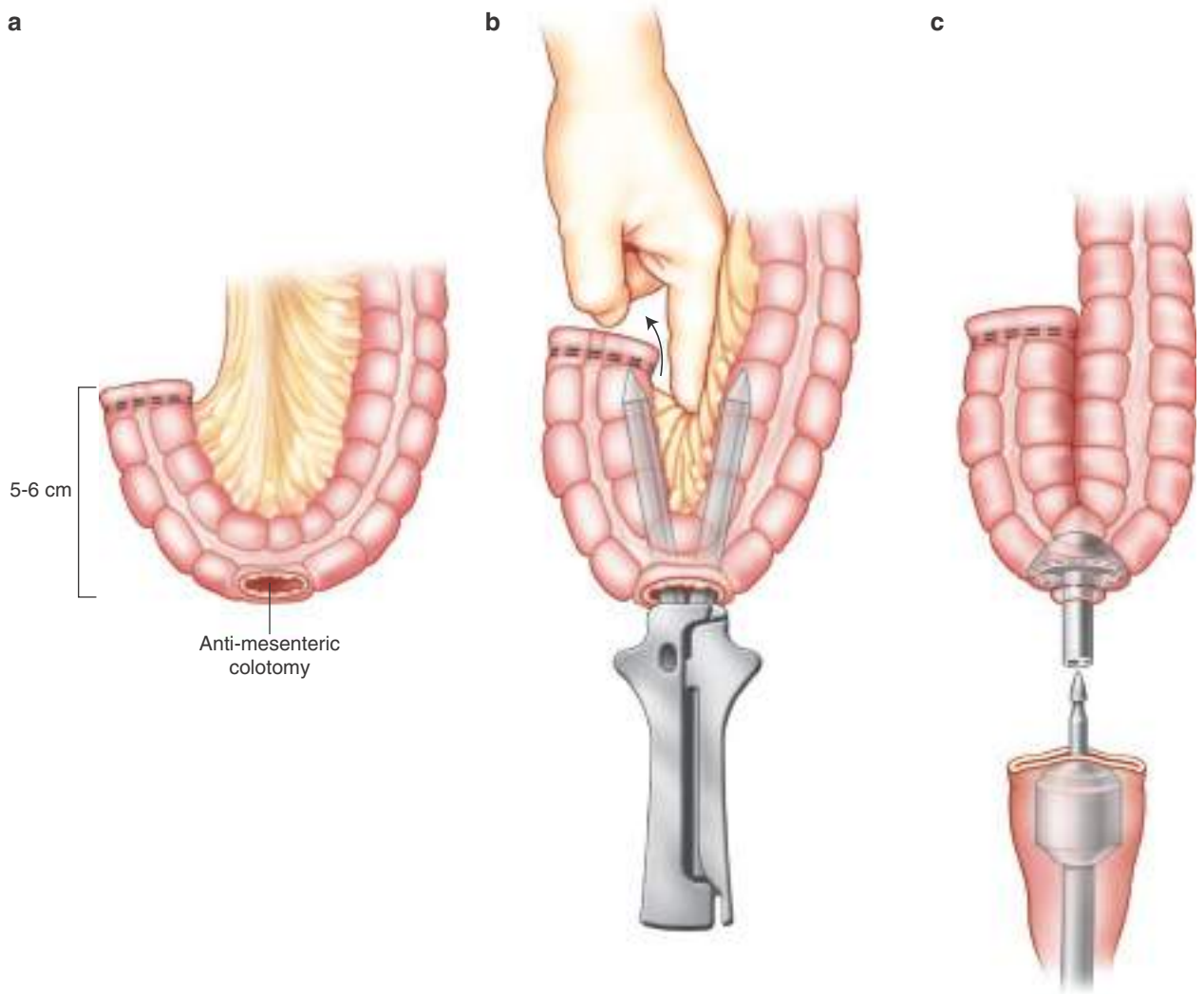

FIGURE 9-7. Colonic J-pouch. (**a**) A 5–6 cm colonic J-pouch is formed, and a colotomy is made on the antimesenteric portion of the bowel wall. (**b**) The pouch is formed using a linear stapler with 1–2 loads ensuring the colon mesentery is pulled out of the staple line. (**c**) The colorectal anastomosis is constructed using an EEA stapler.

incision in the antimesenteric colon between the tenia coli (Figure 9-8a–d). The incision is created after the purse string and anvil have been placed in the colon, with the distal end of the incision approximately 4 cm proximal to the stapler anvil. Stay sutures are placed on each side of the midpoint of the colotomy to provide lateral traction. The colotomy is then closed transversely, in the fashion of a Heineke-Mikulicz strictureplasty, creating the reservoir. Early studies comparing this technique to the colonic J-pouch found no difference between these two techniques in terms of bowel function, continence, or quality of life, but these studies were small single-center trials [70, 73, 74].

In a large, multicenter randomized controlled trial, Fazio et al. compared the colonic J-pouch to the transverse coloplasty [71]. Taking into account the fact that a significant percentage of patients have technical circumstances that do not allow for J-pouch creation, the authors then compared the transverse coloplasty to the straight coloanal anastomosis for patients in whom a J-pouch was not possible. After the resection was performed, the surgeon made the determination if a colonic J-pouch was possible. If so, patients were randomized to colonic J-pouch or coloplasty. If a pouch was not feasible, patients were randomized to transverse coloplasty or straight coloanal anastomosis. At 2 years, the colonic J-pouch proved superior to the transverse coloplasty in frequency, clustering, soilage, and continence. Although the sample sizes were smaller, the transverse coloplasty showed no improvement in any functional assessment compared to the straight coloanal anastomosis.

Huber et al. proposed the side-to-end anastomosis as an alternative to the colonic J-pouch for coloanal anastomoses [75] (Figure 9-9a, b). These techniques were compared in a randomized controlled trial of 100 patients [76]. The trial showed that the two techniques had similar frequency, continence, and functional scores at 1 year. At 2 years, the groups remained similar in bowel function, but neorectal volumes

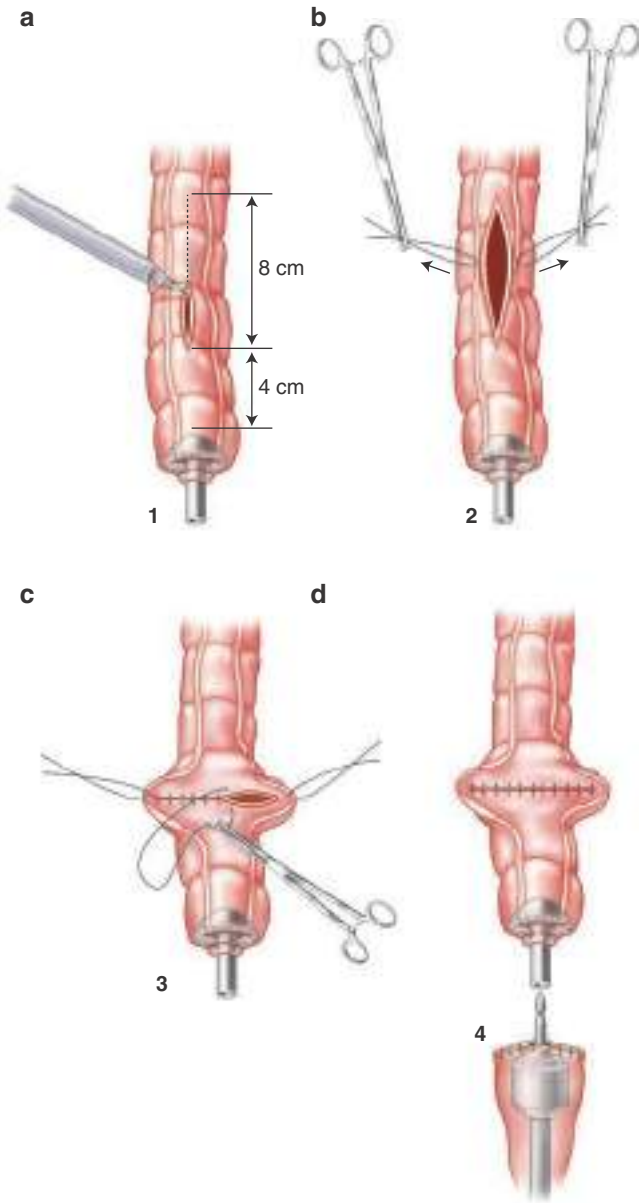

FIGURE 9-8. Transverse coloplasty. (**a**) An 8 cm linear colostomy is made 4 cm from the distal end of the colon. (**b**) The anvil is placed in the end, and stay sutures are placed at the midpoint on each side of the colotomy. (**c**) The longitudinal colotomy is closed in a transverse fashion. (**d**) An end-to-end anastomosis is performed.

were 40 % higher in the colonic J-pouch group compared to the side-to-end anastomosis [77]. A systematic review comparing the side-to-end anastomosis to the colonic J-pouch was also performed [63]. With admittedly small numbers, the analysis did not show any difference in function between these two techniques.

The physiologic basis for the improved function of neorectal reservoirs is not completely understood. Early proponents of the colonic J-pouch touted the increased volume reservoir, but some have questioned the neorectal "reservoir" theory [78, 79]. Ho et al. were the first to question the reservoir theory based on a small randomized controlled trial. In this study, they compared an 8 cm colonic J-pouch to straight coloanal anastomosis by functional results and anorectal physiology. While the function of the J-pouch was again proven superior, the physiology testing showed that the neorectal capacity was similar for both groups.

In a subsequent study comparing straight coloanal anastomosis to a 5 cm J-pouch, Furst et al. reached the same conclusion—functional improvements with the colonic J-pouch are not the result of an increased reservoir capacitance. These authors suggested that the pouch works by decreasing forward propulsive motility in the J-segment.

Based on these findings, Ho et al. developed a nuclear medicine study using radioactive isotopes designed to mix differentially with either solid or liquid stools [80]. They then conducted a small randomized controlled trial comparing the colonic J-pouch to the straight coloanal anastomosis. As before, while they found better functional results with the J-pouch, the maximal tolerable volumes were similar between the two groups. On scintigraphy, they found that solid stool transport through the colon was the same for both techniques. Interestingly, they found that the J-pouch had significantly better retention of liquid stools in the distal colon above the pouch. While they could not directly prove a link between the retention of liquid stool and decreased motility through the J-pouch segment, their findings support this theory. The better retention of liquid stool certainly explains the superior functional outcomes associated with the colonic J-pouch and may explain why other "reservoir" techniques have not proven as advantageous.

In summary, for low colorectal or coloanal anastomoses, the colonic J-pouch may give the best functional results, but the long-term durability of this benefit is unclear. When the J-pouch is not feasible, the transverse coloplasty or the straight coloanal anastomosis appears to offer similar functional results. The role of the side-to-end coloanal anastomosis is still undefined.

Hand-Sewn Coloanal Anastomosis

The double-stapled coloanal anastomosis is simple and can be created more rapidly than the hand-sewn anastomosis, making stapling the preferred method to create the coloanal anastomosis for most surgeons. There are, however, many circumstances in which a hand-sewn coloanal anastomosis is the only option to avoid an ostomy. Such situations include mucosectomies, failure of the transverse rectal staple line, and tumors that require a combined transabdominal and transanal approach to achieve an adequate margin. Knowledge and expertise in creating a hand-sewn coloanal anastomosis are requisite for any surgeon who performs proctectomies, as it is sometimes difficult to predict when these skills will be called into action.

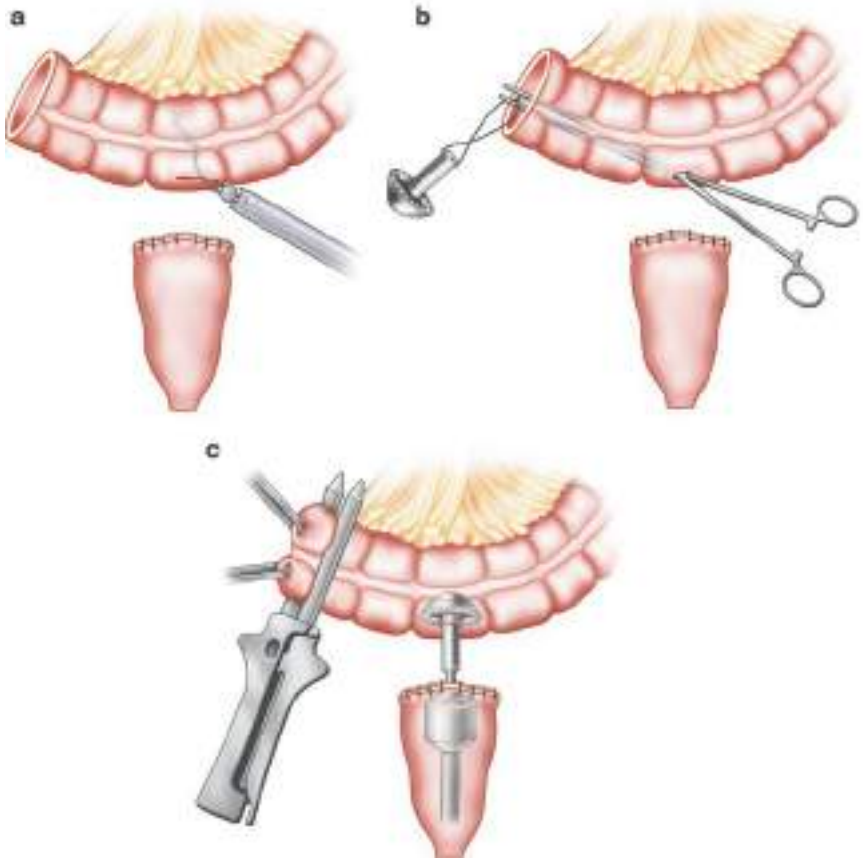

FIGURE 9-9. Side-to-end coloanal anastomosis. (**a**) A colotomy is made proximal to the open end of the colon. (**b**) The EEA anvil is passed through this opening. (**c**) The colonic opening is closed using a linear stapler, and the anastomosis is performed using an EEA stapler.

In order to perform a hand-sewn anastomosis, the surgeon must have good visualization of the cut edge of the anal canal. Manufactured self-retaining elastic hook retractors provide effacement of the anus and facilitate exposure of the anastomosis. With larger patients or when visualization is still difficult, better exposure of the anal canal can be achieved by placing multiple circumferential sutures from the anal verge to the skin several centimeters away on the thigh, groin, and buttocks. The transanal dissection, either intersphincteric dissection or mucosectomy, should be performed as appropriate for the pathology. Adequate colon length should be confirmed by assuring that the proximal colon reaches easily below the pubic symphysis. If not, further maneuvers to increase length must be performed before attempting to mature the anastomosis. When ready to perform the anastomosis, the orientation of the colon mesentery should be confirmed, and two noncrushing clamps are passed transanally by the perineal operator. Orientation of the clamps is established, and the open colon specimen is secured into the clamps by the abdominal surgeon while maintaining orientation of the colon. The colon is then coaxed through the pelvis down to the level of the anal anastomosis by rocking it back and forth. The abdominal operator can assist by using both hands to guide the colon into the deep pelvis. A simple full-thickness suture is then placed in each quadrant of the anal canal, making sure that the proximal colon lumen is proportioned equally around the circumference of the anastomosis. The anastomosis is then completed by placing intervening sutures in the remaining gaps.

Baik et al. reported on a case series of patients that had straight hand-sewn coloanal anastomoses after proctectomy for cancer [81]. In their series, 31 % of patients had anal incontinence at 6 months. The percentage of patients with incontinence decreased to 14 % at 1 year. Frequency was also noted, with 20 % of patients reporting more than six bowel movements a day at 1 year.

In the only randomized controlled trial comparing hand-sewn to stapled coloanal J-pouch anastomoses, Laurent et al. randomized 37 patients to the two techniques [82]. While the two groups had tumors at equivalent distances from the anal verge, the hand-sewn anastomoses were constructed nearly a centimeter closer to the anal verge. Functionally, the two groups appeared equivalent, but the very small sample size must be considered in the interpretation of these results.

The hand-sewn coloanal anastomosis can only be performed for very low anastomoses, and when feasible, a stapled anastomosis is preferable to the hand-sewn technique. This technique should be reserved for those anastomoses so low that they cannot be performed using the double-stapled technique.

Assessment of Pelvic Anastomosis

Some form of intraoperative anastomotic assessment should be performed at the time of creation. Multiple tests have been described including endoscopic visual evaluation and mechanical tests such as rectal insufflation with air, betadine, or methylene blue. Mechanical tests of anastomoses demonstrate intraoperative leaks in 5–25 % of anastomoses [83]. The air insufflation test is the simplest to perform. Multiple studies show this test reduces postoperative anastomotic leak rates, leading some to call for insufflation testing to be included as a quality process measure [84–87]. In addition to allowing for an air-leak test, intraoperative flexible endoscopic assessment of the anastomosis allows for visualization of the anastomosis. To date, there is no definitive confirmation that intraoperative endoscopy is more effective than a simple air-leak test [88–90]. Proponents of this technique point out the ability to assess for anastomotic bleeding, mucosal perfusion, and visual defects in the anastomosis.

Whether performing a simple leak test with a proctoscope or as part of an assessment with flexible endoscopy, the principles of the air-leak test remain the same. The bowel several centimeters proximal to the anastomosis should be occluded manually or with a bowel clamp. Saline is added to the pelvis to cover the anastomosis. Air is then insufflated into the rectum. While some feel that insufflation to high pressures may create defects in the anastomosis, it is the authors' opinion that air testing with rigorous rectal insufflation will stress the anastomosis and mimic or exceed the harshest physiologic conditions that may occur in the postoperative period. It is important to visualize the colon proximal to the anastomosis to ensure that it is indeed being distended. During insufflation, the anastomosis should be manipulated in all directions to confirm that a small leak is not being hidden or occluded by extraneous tissue. If there is bubbling, the saline should be slowly removed with suction down to the level of the anastomosis in order to localize the leak.

When an intraoperative leak is discovered, options include suture repair, proximal diversion, or takedown and refashioning of the anastomosis. For small leaks, suture repair is often adequate; however, the anastomosis must be tested again following the repair. Some authors suggest that recreating the anastomosis is the safest way to deal with any positive intraoperative leak test [87, 90]. Recreating the anastomosis usually requires further rectal resection with potential functional consequences. Diversion, rather than reconstruction, remains another option when there is a question about the integrity of the anastomosis. There is no argument that larger leaks, circumferential leaks, and leaks that cannot be visualized or adequately repaired require takedown and refashioning of the anastomosis.

Troubleshooting Problems with Pelvic Anastomoses

Unanticipated Pelvic Anastomosis

Despite thoughtful preoperative planning, situations will arise in which the surgeon must create an unplanned pelvic anastomosis. Frequently, the patient is positioned so that access to the perineum is not possible. If circumstances permit, skin closure and repositioning are an option that allows for the standard double-stapled anastomosis to be created. It is not always necessary or possible to reposition the patient in lithotomy position to create colorectal anastomoses. While a hand-sewn anastomosis remains an option, this becomes more difficult lower in the pelvis. It is also possible to create a stapled side-to-end anastomosis similar to the Baker anastomosis with the patient in supine or even lateral position. This technique requires placement of a purse-string suture in the open end of the rectum in order to secure the anvil for the circular stapler (Figure 9-10a–d). The stapled end of the colon is opened, allowing the circular stapler to be introduced into the colon lumen. The stapler is then guided down the colon over a distance of several centimeters and the stapler spike delivered out through the antimesenteric wall of the colon. The anvil is secured to the stapler, and it is closed and fired. The open end of the colon distal to the anastomosis can then be closed with a transverse stapler.

Inadequate Colonic Length

As emphasized earlier, adequate colonic reach is necessary before anastomotic construction begins. For a left colectomy, adequate reach is usually achieved by performing basic maneuvers including splenic flexure mobilization, division of the inferior mesenteric artery at its origin, and division of the inferior mesenteric vein at the inferior border of the pancreas cephalad to the vein branch that drains the splenic flexure. Splenic flexure mobilization requires more than just freeing the peritoneal attachments of the flexure in the left upper quadrant. Complete mobilization necessitates separation of the omentocolic attachments to the distal transverse colon, deliberate division of the renocolic attachments of the mesentery to Gerota's fascia of the left kidney, and lysis of the gastrocolic attachments between the posterior gastric wall and the transverse colon mesentery. Additionally, the distal transverse colon mesentery can be divided back to the middle colic vessels. These routine maneuvers will almost always allow adequate mobilization to perform any colorectal or coloanal anastomosis.

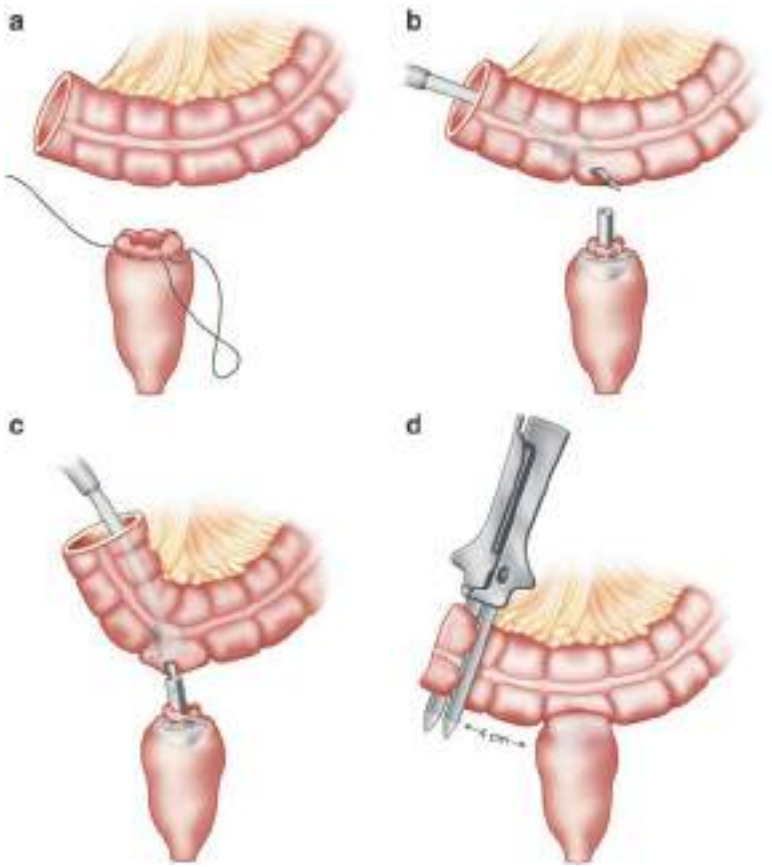

FIGURE 9-10. Unexpected colorectal anastomosis. (**a**) A purse string is sewn into the open end of the rectum. (**b**) The EEA anvil is placed through the rectal stump and the EEA stapler is passed retrograde through the open end of the colon. (**c**) The anastomosis is completed with firing of the EEA stapler. (**d**) A liner stapler is used to close the open end of the colon.

Resection of the splenic flexure as part of an extended left hemicolectomy often presents a challenge in obtaining adequate colonic length to create a tension-free anastomosis. In this case, the transverse colon is tethered by the middle colic vessels, and further mobilization will not increase the reach. In such circumstances, serial ligation of the middle colic vessels proceeding from left to right provides more length. The middle colic pedicles should be divided only as necessary to allow the colon to reach to the level of the anastomosis. After the pedicles have been divided, the blood flow to the distal colon must be reassessed, as the flow through the marginal artery to the anastomosis is frequently dependent on the middle colic vessels. Unfortunately, adequate blood supply and adequate reach sometimes find themselves at odds. If, after division of the middle colic pedicles, there is a compromise of the blood flow to the pre-anastomotic colon, it should be resected back to the point where there is good arterial inflow and satisfactory venous drainage.

Ideally, the colon can be extended around to the left of the ligament of Treitz and delivered into the pelvis to create the anastomosis. If the colon will not reach in this fashion, another route to the pelvis must be pursued. Simply draping the transverse colon over the small bowel is not a good alternative path to the anastomosis. This route rarely provides sufficient length and may lead to avulsion of the anastomosis if the patient develops an ileus and the bowel becomes distended. An option that avoids these pitfalls is to create a window in the terminal ileal mesentery that allows passage of the colon through this retroileal opening (Figure 9-11a, b). The window is created in the space between the ileocolic artery and the distal superior mesenteric artery. This technique, originally described by Rombeau et al., allows an unobstructed path to the anastomosis and also avoids the risk of anastomotic separation should the patient develop a postoperative ileus and small bowel dilation [91]. This technique usually requires mobilization of the proximal transverse colon by dividing the remaining omentocolic and gastrocolic attachments. The window should be large enough to accommodate the colon without causing strangulation. After adequate blood flow to the pre-anastomotic colon is verified, the anastomosis can be created in the usual fashion.

Sometimes, when a significant portion of the transverse colon has been resected, even this retroileal window does not allow adequate reach into the pelvis. In these situations, mobilization of the hepatic flexure and counterclockwise rotation of the colon provide one last opportunity to salvage a colorectal anastomosis (Figure 9-12a–c). This procedure is sometimes referred to as Deloyers' procedure, after the surgeon who published the first description [92]. This technique requires complete mobilization of the hepatic flexure and right colon—including dividing all of the retroperitoneal attachments and mobilization of the small bowel mesentery up to the duodenum. Any remaining middle colic vessels are ligated, leaving the colonic segment's blood supply based off

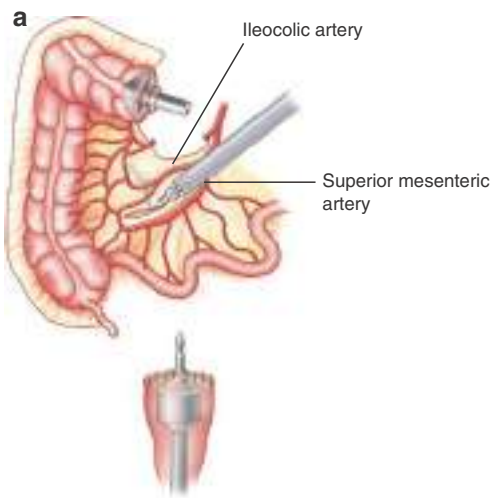

FIGURE 9-11. Retroileal pull-through. (**a**) A window is made on the anterior aspect of the ileocolic pedicle after the terminal ileum is mobilized from the retroperitoneum. (**b**) The colon is passed through this window and into the pelvis to perform the end-to-end anastomosis.

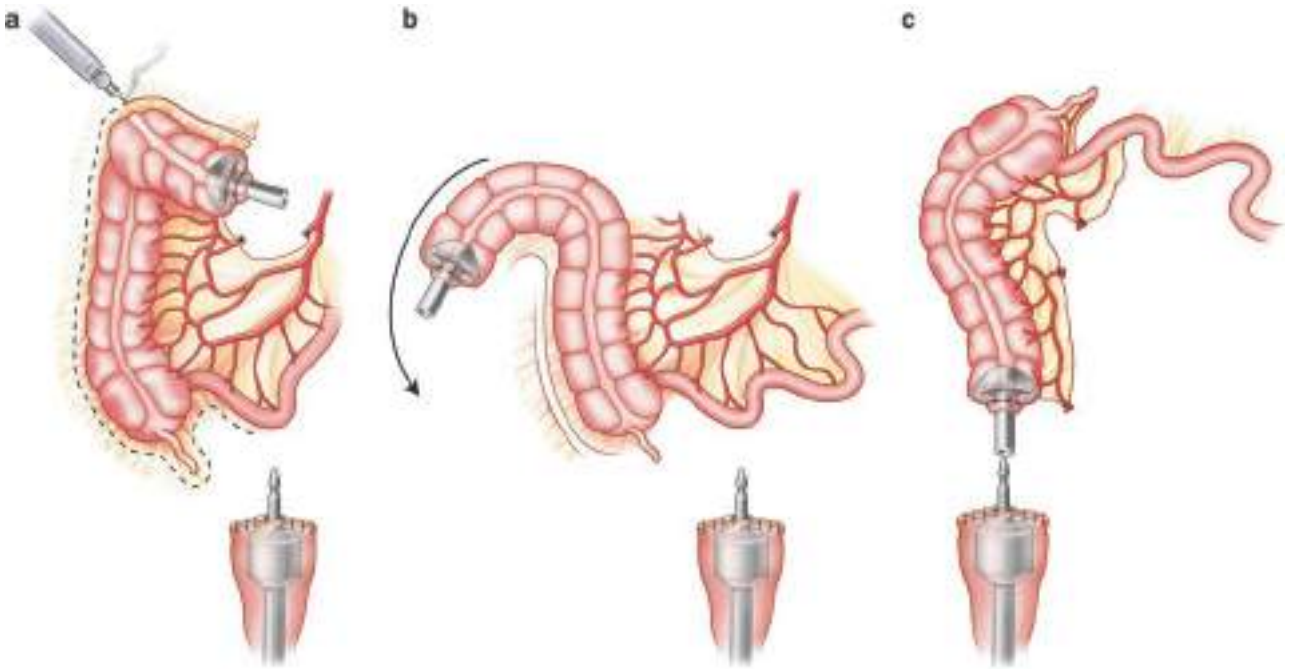

FIGURE 9-12. Deloyers' technique. (**a**) The hepatic flexure and right colon are mobilized laterally along with the terminal ileum from the retroperitoneum. (**b**) The colon is rotated in a counterclockwise direction and delivered to the pelvis. (**c**) The anastomosis is constructed.

of the ileocolic artery. The colon is then rotated in a counterclockwise direction to deliver the transverse colon into the pelvis to create the anastomosis.

Should all these salvage maneuvers fail to allow a tension-free colorectal anastomosis with adequate blood supply, remaining options include a completion colectomy with an ileorectal anastomosis or an end colostomy.

Intraoperative Anastomotic Failure

Unfortunately, failed anastomoses are inevitable in pelvic surgery. The ability to safely and effectively deal with a failure is essential for a colorectal surgeon. Misadventures such as a breakdown of the transverse staple line or the catastrophic failure of the circular stapled anastomosis present difficult challenges, especially low in the pelvis.

When a pelvic anastomosis fails, an attempt should be made to resect below the anastomosis and recreate it in a standard fashion. In refashioning the anastomosis, care must be taken to further mobilize the rectum from its surrounding structures, specifically the vagina, in order to allow sufficient room to create the new anastomosis.

Sometimes, it is impossible to place the transverse stapler below a failed anastomosis or separated transverse staple line. In this case, the anastomosis or failed staple line should be excised. The open rectal stump should be grasped with long Allis clamps and a purse string placed around the open rectum.

When low in the pelvis, placement of this difficult suture is facilitated by having an assistant apply pressure to the perineum in a cephalad direction. Manipulating a rectal sizer in through the open cuff may also help to better define the tissues and facilitate placement of the purse string. Once the rectal purse string is placed, the stapler anvil should be secured in the colon in the normal manner. The circular stapler is then passed through the anal canal and delivered to the point just below the open end of the rectum and purse string. Slowly, the stapler spike is advanced through the open rectal cuff. Once the spike has been fully deployed, the purse string is tied around the spike and inspected to confirm that the purse string is complete. The anvil is then fixed to the stapler, carefully closed, and fired. The anastomosis is evaluated by the usual means according to the surgeon's preference. As noted earlier, consideration should be given to diversion in these circumstances after an anastomotic mishap.

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10
Anastomotic Complications

Konstantin Umanskiy and Neil Hyman

Key Concepts

- Patients who develop diffuse peritonitis after intestinal resection with anastomosis should undergo prompt exploratory laparotomy.
- Colorectal anastomoses should be routinely tested prior to abdominal closure.
- Hemodynamically unstable patients who develop a leak after sigmoid resection should undergo a Hartmann procedure.
- Late anastomotic leaks commonly present with subtle and insidious symptoms such as failure to thrive.
- Endoscopic balloon dilation is the procedure of choice for short anastomotic strictures.
- Most cases of anastomotic bleeding resolve with conservative measures.
- Persistent anastomotic bleeding should be treated by colonoscopy with epinephrine injection and/or endoscopic clips.

Anastomotic Leak

Overview

Anastomotic leak is perhaps the most feared and dreaded complication after bowel resection [1]. The consequences of a failed intestinal anastomosis can be devastating to the patient, family, and surgeon alike. Management of an anastomotic leak typically necessitates a lengthy hospitalization with considerable morbidity, suffering, as well as the very real possibility of breathtaking cost and resource utilization [2]. This can include a prolonged stay in the intensive care unit, reoperations in a hostile and hazardous environment to control sepsis, and creation of an intestinal stoma when none was initially expected or planned [3]. Patients often require repeated imaging studies, a wide variety of invasive interventions, and many complex decisions surrounding the necessity, timing, and risk/benefit ratio of the pertinent diagnostic and therapeutic interventions.

Despite the serious and overwhelming burden that can be imposed by an anastomotic leak, we often do not know why the leak occurred in any particular patient or circumstance. There are a wide variety of factors that have been associated with an increased risk of anastomotic dehiscence, some of which may be at least partially remediable [4–10]. In general, sicker patients with more comorbidities are at higher risk. But we seldom know which of the associated factors are actually causative and particularly worthy of focus, since so many of them cluster together in the same patient. For example, patients with Crohn's disease may be considered to be at increased risk for anastomotic complications; but these patients may also be on steroids, other immunomodulatory agents, have preexisting local sepsis, and suffer from hypoproteinemia preoperatively [11].

Despite the critical importance of preventing leaks and understanding the pathophysiology of this potentially devastating problem, relatively little is known about why they actually occur. Avoiding tension on the anastomosis and assuring adequate perfusion to the two ends of the intestine to be joined remain valid and fundamental surgical principles; optimization of comorbid conditions and suspected risk factors is also of value [12]. But leaks often occur when no technical error, defect in surgical judgment, or patient-specific factor can be readily identified. Since we cannot confidently discern the causative element(s) that produced the leak, we are commonly unable to identify opportunities for improvement and devise a strategy to protect the next patient from this complication and its consequences. In short, it seems clear that our present concepts regarding the causes and prevention of anastomotic leak are lacking at best. New paradigms and avoidance strategies are badly needed.

Scope of the Problem

The reported incidence of anastomotic leakage after bowel resection varies from one to more than 20 %, based on the definitions used, location of the anastomosis, and length of

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follow-up [13–21]. A leak rate in the 5–8 % range is perhaps the most commonly reported incidence. Generally speaking, small bowel anastomoses have the lowest leak rate, and low colorectal or coloanal anastomoses carry the highest risk. The importance of definitions and the criteria utilized for diagnosis of a leak when assessing clinical data cannot be overemphasized; standardization of nomenclature across institutions would enable the more robust interpretation of incidence reporting for this key patient outcome. "Anastomotic leak" can signify anything from an apparently trivial, clinically meaningless radiologic finding to a profound septic insult causing a rapid decline, multiorgan failure, and death. In a systematic review, Bruce noted that there were 56 different definitions of "leak" used in the 97 constituent studies of gastrointestinal anastomoses that were reviewed [22].

It seems clear that there is a spectrum of radiologic findings and infectious complications in patients who have undergone an intestinal anastomosis that might reasonably be described as a leak. There is little question about the proper term or diagnosis in a patient who develops peritonitis after bowel resection and is found at laparotomy to have a dehiscence of their anastomotic site. But how should we classify patients who develop an intra-abdominal abscess after surgery? Should the patient who has an abscess around their anastomosis, but no contrast extravasation on an initial imaging study, be considered to have suffered a "leak"? What if a follow-up CT scan now reveals a communication from the abscess to the colorectal anastomosis: did an occult leak cause the abscess or did the abscess erode into the anastomosis? There are countless permutations on this theme, where reasonable surgeons might disagree; in truth, the precise pathophysiology of infectious events after an anastomosis in many patients may be uncertain. This makes comparative analysis of reported outcomes between different studies difficult to interpret.

We have described a spectrum of clinical entities with distinct clinical consequences that can complicate low pelvic anastomoses, for example [23]. These include "free" leaks, anastomotic sinuses, peri-anastomotic abscesses, and fistulas. Interestingly, even patients with "simple" fluid alone in the pelvis on a CT scan without any other evidence of a leak appeared to have impaired long-term function. Anastomotic infectious complications may be divided into leak, surgical site infection (SSI) organ space, and SSI deep. One can reasonably disagree about which category an individual postoperative complication may belong to. But a composite measure such as this may enable meaningful conclusions and avoid the largely arbitrary exercise of trying to distinguish between all of the nuanced findings that the surgeon may encounter in patients who develop an infectious complication associated with an intestinal anastomosis.

Consequences

An anastomotic leak is a potentially life-threatening complication, with a reported mortality in the 10–15 % range [24–29]. Most of these deaths occur in association with sepsis and progressive multiorgan failure, especially for the leaks that present early on in the postoperative course. For this reason, timely diagnosis and treatment prior to the onset of advanced organ dysfunction has been emphasized as a key factor in reducing the mortality rate for anastomotic leaks. However, patients with a more indolent course may also succumb to venous thromboembolic or other indirect complications owing to the prolonged hospital stay, limited mobility, and persistent inflammatory state that commonly occurs in patients who have leaked.

As noted earlier, patients with an anastomotic leak often require difficult and complicated reoperations in a hostile local environment, with considerable additional postoperative morbidity. Lengthy hospitalizations, the need for an intestinal stoma, repeated imaging studies, and trips to interventional radiology for catheter placement/replacement are commonplace [30]. True functional, physical, emotional, and psychological recovery is often measured in months or even years, especially when one considers the need for additional procedures such as stoma reversals even after the acute phase has resolved. Prolonged wound care, ventral hernias, bowel obstructions, and management challenges associated with gastrointestinal adaptation to the altered anatomy may continue to be active considerations for long periods of time, consume an enormous amount of resources, and delay return to the patient's "normal" lifestyle. Further, for many patients, an intestinal stoma is a permanent consequence of the leak [31].

In addition, local sepsis may lead to an impaired functional result, especially after low pelvic anastomosis, where fibrosis can markedly impair the reservoir function of the neorectum and/or be associated with a rigid and unyielding anastomotic stricture [32]. The adverse relationship between anastomotic leak and local recurrence after rectal resection for cancer is intriguing and may have several contributing explanations [33–36]. The leak may impair local and/or systemic immunity or may simply serve as a surrogate for a more aggressive tumor, suboptimal operation, or other host-/tumor-related factors that remain to be fully defined.

Prevention

As in almost any disease process or postoperative complication, prevention is always better than treatment. Unfortunately, we still do not know why most anastomotic leaks occur, and therefore we remain limited in our ability to prevent many of them. Nonetheless, even among high-volume surgeons, significant differences may be found in leak rates, suggesting that technical and/or judgment errors play a causative role in at least some leaks [37]. Time-honored principles such as avoidance of tension on the anastomosis and assuring adequate blood supply to the two ends remain pertinent and important considerations. The role of intraoperative assessment of anastomotic blood supply has received renewed interest in recent years.

Table 10-1. Reported risk factors for anastomotic leak

Patient factors
Overall physiological status
Steroids
Need for low rectal/anal anastomosis
Immunomodulators
Malnutrition/weight loss
Emergency surgery
Obesity
Male gender
Advanced age
Alcohol use
COPD
Cigarette smoking
Previous radiation
Prior abdominal surgery
Right vs. left colon (left increased)
Primary disease (e.g., Crohn's disease, diverticulitis)
Surgeon factors
Length of surgery
Blood loss
Use of pelvic drain
Bowel preparation
Use of vasopressors
Proximal diversion
Blood supply

Many patient- and surgeon-specific factors have been associated with an increased risk of an anastomotic leak (Table 10-1). However, many are simply markers for a sicker patient or serve as surrogates for various disease processes and/or a compromised host. So, it is unclear how many of the factors on this lengthy list are simply associated with a leak versus actually contributory, and how much effort or emphasis should be placed on trying to remediate them. Further, many factors (e.g., gender, age, disease process) are immutable and just a fact of life. Nonetheless, attention to controlling certain risk factors does seem prudent and worthwhile. These would include smoking cessation, optimization of nutritional status, and weight loss if possible [37–44].

Anastomoses should be tested intraoperatively when feasible, as occult disruptions may be identified and definitively treated [45–47]. A systematic review of the intraoperative assessment of colorectal anastomotic integrity documented an impressive reduction in anastomotic complications when the anastomosis was tested during surgery [11]. When a leak is identified intraoperatively, a sober and disciplined approach is required. Sometimes there is a focal, well-defined defect in an otherwise healthy-appearing anastomosis that can be readily repaired with a suture. However, in other circumstances, such as when there is concern about the blood supply, the defect is poorly visualized or there is a major disruption, it is best to start over, redo the anastomosis entirely, and retest. There is no sense trying to "perfume the pig" by placing a series of sutures into a poorly exposed, amorphous mass of tissue in the hope that the defect will be adequately addressed. With distal anastomoses, this will often include adding a proximal loop ileostomy. Mature surgical judgment, sometimes including intraoperative consultation with an experienced colleague, can enable optimal and objective decision making.

Intriguing work regarding the relationship of the microbiome and anastomotic leak has been reported by Alverdy and coworkers [48, 49]. It may be that the local microbial environment plays a critical role in anastomotic healing. Specific bacteria that produce locally destructive collagenolytic proteins (e.g., certain *Enterococcus*, *Pseudomonas*, or *Serratia* species) may be an important cause of anastomotic leaks, and perioperative suppression/eradication of these microbes may reduce leak rates. A large multicenter trial is underway to further explore this hypothesis.

Diagnosis

Perhaps one of the biggest fallacies perpetuated over the years about anastomotic leaks is that the diagnosis is typically straightforward and clinically obvious. This misconception is commonly exacerbated by surgical morbidity conferences where these cases are often reviewed. All attendees know or strongly suspect the patient in question suffered a leak (since it is being presented at a complication conference) and are often quick to suggest the diagnosis at the first mention of an abnormal vital sign, laboratory value, or upon review of radiologic studies.

Certainly, there are patients who present in the first few days after surgery with excruciating abdominal pain, hemodynamic instability, diffuse peritonitis, and a rapid and dramatic change in their clinical course; the diagnosis is often plainly evident and requires few if any ancillary studies (even in retrospect). However, in the nuances of actual clinical practice, medical decision making in the setting of a real patient where anastomotic leak is considered is usually far more difficult since, unfortunately, most leaks actually present in a more subtle and insidious manner [50, 51]. We reviewed the clinical course of 452 consecutive patients who had a bowel resection with anastomosis. Even in "uncomplicated" recoveries, tachycardia and tachypnea were almost routine, occurring in more than ½ of the patients frequently throughout the postoperative course. Hypotension, fever, and leukocytosis, factors commonly cited with the benefit of hindsight as reliable evidence of a leak, were also remarkably common in all patients and were poor indicators of a leak. The predictive value for abnormal vital signs or leukocytosis ranged from only 4 to 11 % [52].

Similarly, radiologic findings are often ambiguous and equivocal, commonly requiring careful and considered correlation with the clinical picture. On the one hand, the sensitivity for contrast radiography and CT scan in the setting of a leak has been reported to be in the range of 50 %, so a high index of suspicion must be maintained even when the imaging study appears to be negative [53]. On the other hand, Power has highlighted the broad overlap of radiologic findings in

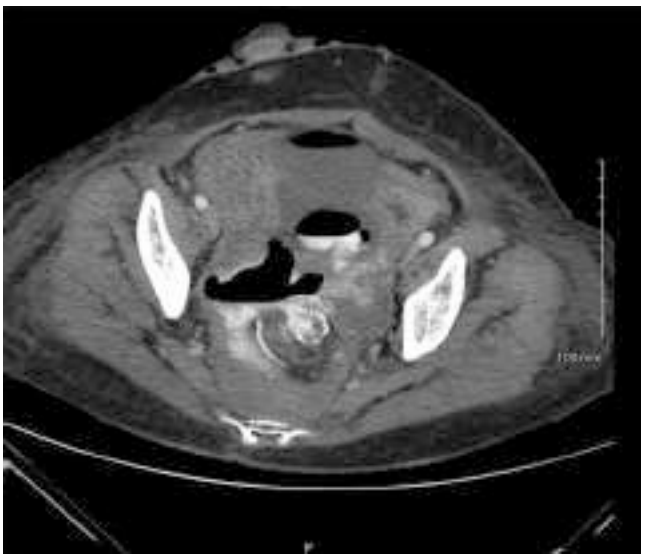

FIGURE 10-1. CT scan in a patient with anastomotic leak after low anterior resection.

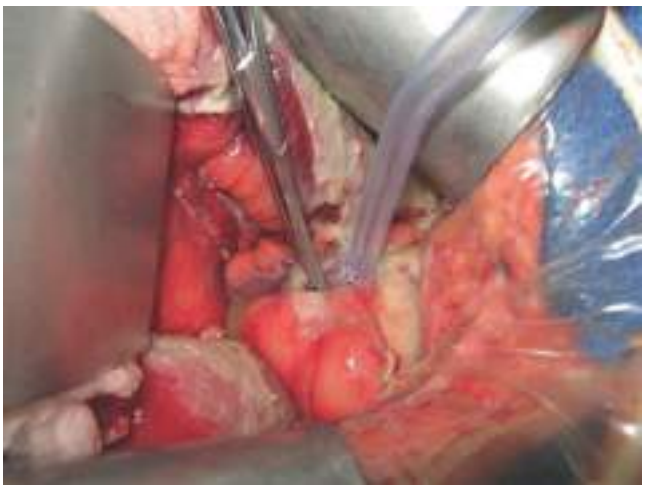

FIGURE 10-2. Diffuse peritonitis after major anastomotic disruption.

postoperative patients with or without a leak. For example, free air was seen on CT scan up to 9 days after surgery and localized extraluminal air up to 26 days postoperatively in patients without a leak. Of the many and varied radiologic findings that are often considered to be indicative of a leak, only loculated fluid with air (Figure 10-1) was observed more commonly in patients with an anastomotic leak [54].

With the foregoing as a background, it perhaps should not be surprising that the diagnosis of an anastomotic leak, in its many varied forms and presentations, is often quite delayed. In our review of 1223 patients undergoing an intestinal resection with anastomosis, the leak rate was 2.7 %. Of note, 14/33 leaks were only diagnosed upon readmission to the hospital, and 12 % were identified more than 30 days after surgery. The positive predictive value of CT scan was 89.5 % versus 40 % for contrast enema. However, these studies were used in somewhat different clinical settings, and the CT scans were often thought to be suggestive of a leak, rather than truly definitive [55]. Categorizing CT scans dichotomously into "positive" or "negative" can often seem to be a somewhat contrived exercise, in light of the open-ended and ambiguous terms that are often utilized to describe the radiologic findings.

So, the broad overlap in vital signs, clinical and radiologic findings between patients who have an uncomplicated postoperative course and those who are diagnosed with a leak, and the similarities in presentation between a leak and other common postoperative complications often make the diagnosis challenging in many clinical settings. The fact is that surgeons often worry or even agonize when things turn out to be fine and are commonly led astray by "reassuring" clinical data when patients have actually suffered an anastomotic leak. More reliable clinical, laboratory, and radiologic tools would be of great utility.

Treatment

Many factors need to be considered when deciding on the most appropriate management option for a patient with an anastomotic leak [56]. These include patient-specific factors such as the degree of hemodynamic derangement, physiologic reserve, nutritional status, comorbid complications, initial surgical indications/goals, and the potential need for additional treatments (e.g., chemotherapy for a malignant diagnosis). Similarly, features of the leak such as location (e.g., intraperitoneal vs. extraperitoneal), size of the defect, and the presence of concomitant tissue ischemia also play a major role in the surgeon's decision-making process.

Perhaps the most useful classification in outlining the principles of management is early versus late presentation. Patients with an early leak classically present in the first week after surgery with signs and symptoms of peritonitis, organ dysfunction associated with sepsis, and hemodynamic instability. In this clinical setting with a profoundly sick patient, the diagnosis is generally quite evident, and prompt return to the operating room is required (Figure 10-2). Radiologic studies are often unnecessary and may provide a false sense of reassurance as described above; hoping against hope it will just delay treatment and allow the septic picture to progress. The operating room is often the only place where this pivotal question can be definitively answered and addressed.

However, it bears repeating that even in the early postoperative period, patients with an anastomotic leak will often present with signs and symptoms that lead the surgeon astray and suggest other serious postoperative complications such as a pulmonary embolism, cerebrovascular event, or acute coronary syndrome. This is because patients with a leak will often appear short of breath and develop mental status changes, and the basic acute work-up will commonly reveal an abnormal chest X-ray or EKG. The surgical team must maintain a high index of suspicion for a leak in this setting and remain wary of alternative diagnoses.

Once the diagnosis is established in the first few days after the initial surgery, most patients will require operative exploration. Intravenous antibiotics and close observation may be appropriate in a few highly selected patients with small, contained leaks that otherwise appear reasonably well; most commonly, these are patients who have undergone a low colorectal anastomosis, especially if they have a proximal diversion. Otherwise, at reoperative surgery, the peritoneal cavity is thoroughly irrigated and appropriate cultures obtained. In general, patients with a small bowel to small bowel or ileocolic anastomosis are best treated with resection and repeat anastomosis. Patients who are hemodynamically unstable may be treated with an ileostomy and end-loop stoma, where the distal end is brought out through the same aperture as the ileostomy (Figure 10-3a–c). This markedly simplifies later reconstitution of the gastrointestinal track, which may be done without the need for laparotomy. This "minor" maneuver at the end of a taxing operation may be the difference between later stoma takedown and a permanent ileostomy, as many patients who are candidates for a stoma takedown will not be good candidates for another major laparotomy after a leak. Anastomosis with proximal loop ileostomy is another alternative to address this situation where primary anastomosis alone is deemed unwise.

When a colo-colic anastomosis breaks down, dividing the anastomosis and creating an end colostomy is usually the most appropriate option. Resection with anastomosis and proximal loop ileostomy is another option for hemodynamically stable patients. Performing an anastomosis without diversion in a hemodynamically unstable patient may greatly complicate diagnosing another leak after reoperation, and the second insult may prove too much for the patient to safely tolerate.

A leak after low anterior resection may create some challenging management decisions. If the anastomosis is divided and a colostomy created, then going back months later to attempt another low pelvic anastomosis to a short Hartmann stump may be a formidable endeavor; a pull through with hand-sewn coloanal anastomosis is often required. When there is no ischemia and the leak is relatively small and contained, loop ileostomy and drainage of the anastomosis is usually most appropriate. In stable patients with major disruptions, resection with anastomosis and proximal diversion may also be an option.

Although there is no hard and fast cutoff from "early" to "late" leaks, the management of anastomotic leaks diagnosed beyond the first week to 10 days postoperatively usually differs in many important regards from its earlier counterpart. These patients most commonly have a more insidious, subtle, and nonspecific presentation. Clinical features commonly include a poor appetite, low-grade fever, incomplete resolution of a postoperative ileus, and a generalized failure to thrive. Careful imaging including a CT scan of the abdomen and pelvis with intravenous and enteric (including rectal) contrast is typically the key to diagnosis and treatment planning. Reoperative surgery is usually unnecessary

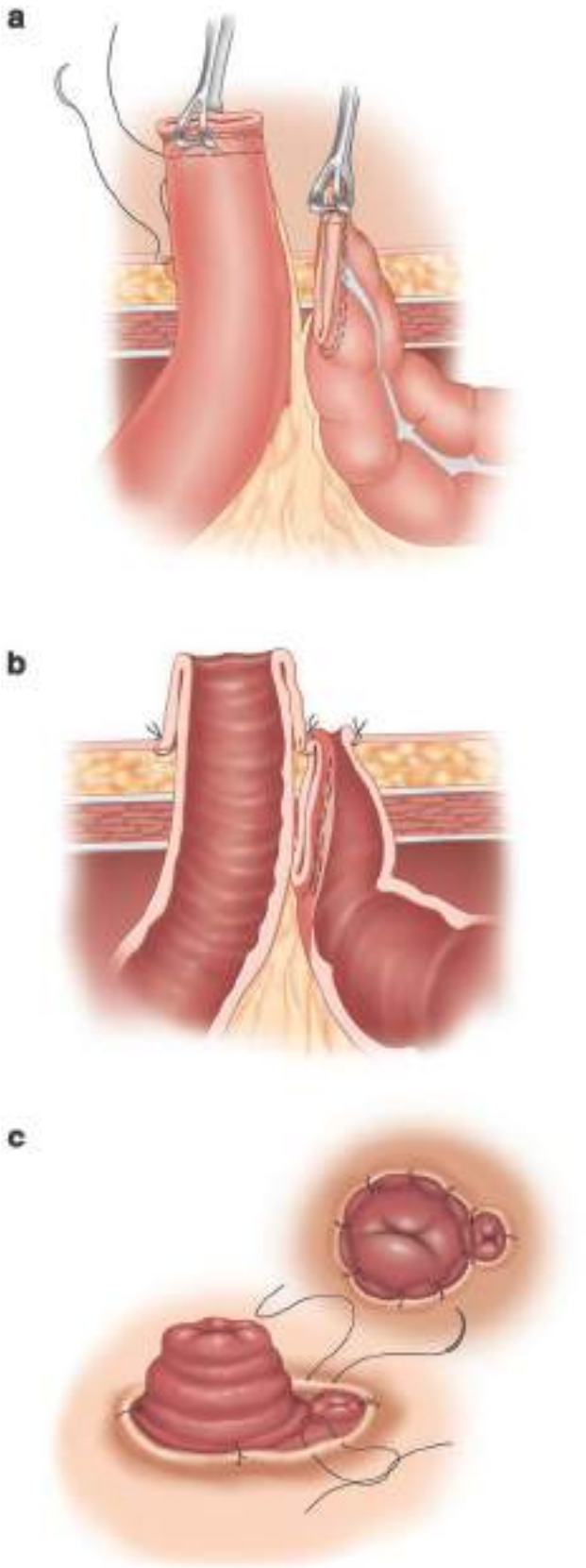

FIGURE 10-3. End-loop stoma. (**a**) The bowel is divided and each end is brought up through the opening. (**b**) The proximal portion is completely matured, while the distal end has only a corner matured. (**c**) Side and top view of the matured stoma.

and will quite often make things worse. Beyond a week to 10 days, patients will commonly have an obliterative peritoneal reaction, making dissection difficult and fraught with the danger of extending the damage to adjacent loops of small intestine as well as making the local situation worse. Adhesions are commonly dense and tenacious, leading to prolonged dissection, bleeding, and the need to anastomose, repair, or exteriorize fixed and friable bowel. If surgery is truly needed to control sepsis, the operation must be very carefully planned, focused, disciplined, and goal directed.

Most patients with late presentations are most often best managed by patience, antibiotics, and percutaneous drainage. Even in the presence of a demonstrable leak, percutaneous drainage alone may allow for complete resolution of the local sepsis and ultimate healing of the anastomosis. Unfortunately, this is commonly a slow process, requiring patience, serial imaging, and repeat percutaneous interventions. Both covered stents and vacuum-assisted devices have been used with anecdotal success [57–59].

Nutritional support, using the enteral route whenever possible, should not be neglected. Although patients are commonly restricted to clear liquids or nothing by mouth for prolonged intervals based on surgical custom, it is not at all clear that this enables healing of the anastomosis and may often exacerbate patient discomfort (physical and psychological) and diminish their ability to tolerate a prolonged recovery with repeated imaging studies and invasive interventions.

Anastomotic Stricture

Anastomotic stricture is a relatively common complication of colorectal or pouch-anal anastomosis, occurring in 3–30 % of cases [60], less commonly so following anastomosis elsewhere in the large intestine. The exact pathophysiology underlying anastomotic strictures remains unknown. Ischemia, incomplete "doughnuts" from stapled anastomotic reconstruction, anastomotic leakage, hemorrhage, and radiotherapy are probably contributing factors to this [61–66]. An anastomotic stricture may be defined as a chronic narrowing or obstruction to the flow of intestinal contents resulting in clinical signs or symptoms of complete or partial bowel obstruction [62]. Symptoms most commonly associated with rectal strictures are increasing constipation and partial large bowel obstruction. Other symptoms may include change in stool caliber or overflow diarrhea.

Asymptomatic patients with a stricture and diverting stoma can be identified based on digital rectal examination or upon radiographic or endoscopic evaluation prior to stoma reversal. Diagnosis is typically made by imaging (i.e., contrast enema) or endoscopically—the inability to pass a 12-mm-diameter sigmoidoscope through the anastomotic narrowing [60]. Anastomotic strictures frequently manifest at some delayed interval after surgery, except for cases associated with early postoperative anastomotic edema.

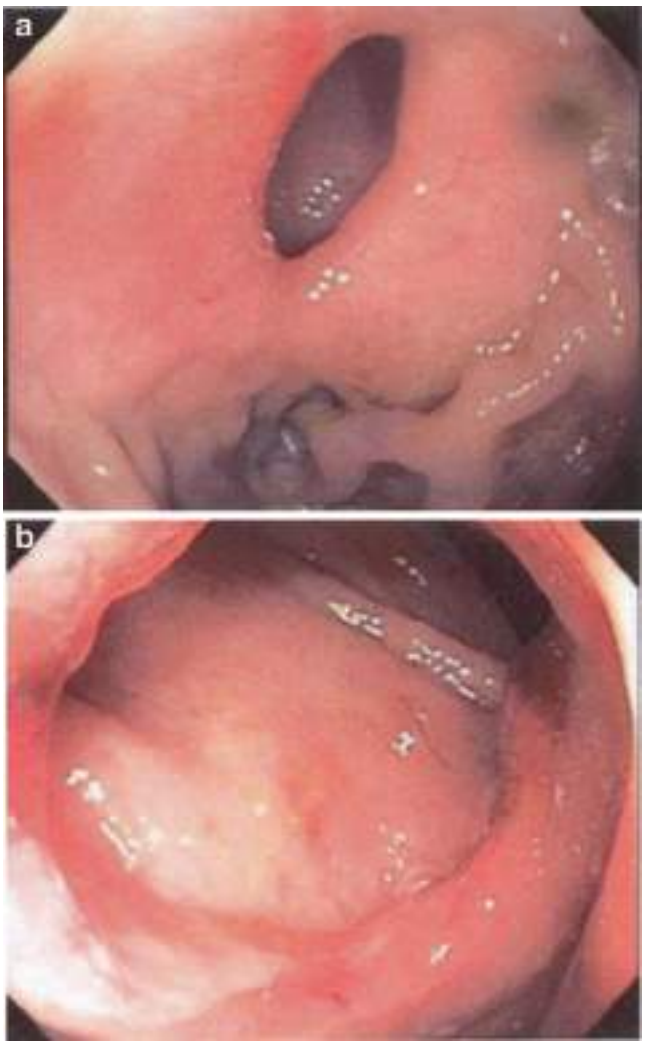

FIGURE 10-4. (**a**) Colorectal anastomotic stricture, before dilation. (**b**) Anastomosis after through the scope balloon dilation.

Luchtefeld [60] found that the stenosis was diagnosed at 1–6 months after surgery in 66 (54 %) of 123 patients, and at more than 6 months after surgery in 17 patients (14 %). Schlegel reported a series of 27 patients with a median time to diagnosis of 7.2 months [62]. Therefore, patients must be followed not only immediately after surgery but the diagnosis must be kept in mind for some time thereafter. Recurrent cancer must be considered as a cause of stricture prior to deciding on the treatment approach.

Short strictures in low colorectal, coloanal, and ileoanal pouch anastomoses can be treated by simple digital dilation, commonly performed in the outpatient setting or under anesthesia. Narrow distal strictures that do not admit the tip of the examining finger can be dilated with Hegar dilators, which are effective in achieving a sufficiently patent anastomosis with a low rate of restenosis.

Endoscopic balloon dilatation is highly effective, and the most commonly used method for treatment of short (<1 cm) colonic and colorectal anastomotic strictures (Figure 10-4a, b).

Several studies of balloon dilation of colonic anastomotic stricture reported success rates that range from 86 to 97 % [5–7]. Two types of balloon can be used for dilation: over the wire (OTW) and through the scope (TTS). The mechanical principles of these techniques are similar resulting in the dilating force being delivered radially and over the entire length of the stricture. Successful dilation is defined as an anastomotic lumen becoming wide enough to allow passage of a standard 12-mm diameter colonoscope and post-procedural relief of obstructive symptoms. Additional dilations may be required if the structure recurs.

The less frequently used method of bougie dilation of anastomotic stricture is accomplished by the radial vector of an axially directed force. Werre [67] treated 15 patients with a benign stricture after low anterior resection by using polyvinyl bougies (Savary-Gilliard). After a mean follow-up of 19 months, normal defecation was restored in ten patients; in five patients, there was only partial improvement, but only three required another form of treatment. No complications were reported. In a case study, Pietropaolo [68] found balloon dilation more effective than bougie dilation with respect to the proportion of patients successfully treated in a single session (76.9 % vs. 51.8 %).

Recurrent cicatricle strictures may be treated with the combination of incision plus balloon dilation [69]. Endoscopic stricturotomy with neodymium-yttrium aluminum garnet laser together with balloon dilation were performed by Luck in ten patients [70]. Treatment was successful, without recurrence or complication, in nine patients (median follow-up 82 months). In the remaining patient, the stricture recurred after 6 years. Brandimarte [71] treated 39 consecutive patients with an anastomotic colorectal stricture endoscopically by making six radial incisions electrosurgically with a precut papillotome. In all cases, satisfactory dilation of the stricture was obtained without complication, and no recurrence was identified at a mean follow-up of 25 months. Complications of electrocautery and laser strictureplasty are very low, with only one group reporting a 2.7 % technical failure rate [72]. Alternatively, transanal endoscopic microsurgical approach (TEM) strictureplasty with electrocautery or laser can be used. Endoscopic, TEM, or strictureplasty approach has been described as effective in 90–100 % of patients with a mean follow-up of 6–92 months [69, 70, 72–74].

Anastomotic strictures that are irregular, markedly angulated, fixed, or longer than 1–2 cm in length, may not be amenable to endoscopic treatment. In the ASCRS survey, surgery was required in 34 patients (28 %), including resection in 18 patients and permanent colostomy in 13 patients [60]. Reoperative rectal dissection in the presence of scarring from previous operations or from ongoing local sepsis is technically demanding and should not be underestimated. Shleigel [62] reported a series of 27 patients who underwent surgical correction of anastomotic stenoses. The authors performed seven colorectal anastomoses for upper rectal anastomotic strictures and 20 coloanal anastomoses for middle and lower rectal strictures (19 Soave's procedures and one colon J-pouch-anal anastomosis). Intestinal continuity was restored in all cases.

In long segment distal rectal strictures or after failure of local therapy, immediate or delayed coloanal anastomosis through a combined abdominal and perineal approach is recommended [75]. A less invasive technique using an end-to-end anastomosis (EEA) stapler may be applied to correct mid- to proximal rectal strictures without the need for laparotomy. Prior to stapling, the rectal anastomotic stricture is dilated and assessed by rigid sigmoidoscopy. Both the anvil and the rod of the circular stapler are introduced transanally, and the instrument positioned until the mural portion of the rectal stricture is caught between the anvil and the rod. The EEA is then fired so that a crescent-shaped rim of the stricture is stapled and resected. The biggest drawback to this method is its inability to treat any tight stricture that would not allow the anvil of the EEA to pass through its opening. An alternative method involves a laparotomy- or laparoscopy-guided approach to introduce the anvil of the stapler from above, via a small colostomy, and inserting the EEA stapler transanally until resistance from the stricture is met. Once positioned correctly, the stapler and anvil are mated and tightened, and the stricture is resected. Long-term results following this technique of stricture resection have been reported as 89–100 % return to normal bowel function with a mean follow-up of 12–49 months [62, 76].

Self-expanding metallic stents (SEMS) have been considered for medium-term symptom relief for recalcitrant benign colorectal strictures in patients who are otherwise unfit for surgery; but their use is associated with a high rate of delayed complications such as perforation, migration, and re-obstruction in up to 38 % of cases [77]. The SEM stents can be considered for short-term relief of acute obstruction and a as a bridge to elective surgery. Newer types of biodegradable stents [78] and fully covered self-expanding stents [79] have been evaluated, but their role in benign colonic and colorectal anastomotic strictures remains undefined.

Finally, diverting ileostomy or colostomy may be the only available treatment option for symptomatic relief of those patients who have failed all treatments or are not candidates for extensive surgical intervention to correct the anastomotic structure.

Anastomotic Bleeding

Anastomotic bleeding following stapled colorectal, colonic, or intestinal anastomosis is a common but usually self-limited complication, with the majority of cases resolving spontaneously with expectant management. Postoperative colorectal anastomotic bleeding can occur in up to 5 % of anastomoses [80–82]. Anastomotic bleeding may occur when the mesentery is incorporated into the staple line and can be further exacerbated by the use of anticoagulant and

antiplatelet agents. Continued hemorrhage is rare but, when it occurs, often requires further treatment.

The clinical presentation of anastomotic bleeding is similar to lower gastrointestinal bleeding from other causes, but interventional therapy is more difficult owing to the risk of ischemia or breakdown of the anastomosis. The optimal treatment choices depend on the site of bleeding, patient factors, and skill of the surgeon or endoscopist and may include conservative treatment with packed red blood cells and coagulation factors transfusion, endoscopic therapy, angiographic embolization, locally applied vasoactive substances, or reoperation with anastomotic refashioning.

The risk of postoperative bleeding can be decreased by avoiding the inclusion of mesocolon into the staple line. We also recommend intraoperative assessment of colorectal anastomoses with intraoperative flexible sigmoidoscopy. Ishihara found active and continuous bleeding from the stapled anastomosis intraoperatively in up to 9.6 % of colorectal anastomoses [83]. In the intraoperative setting, an actively bleeding vessel can be visualized and immediate hemostasis achieved by placement sutures under direct inspection, endoscopic injection of 1:200,000 epinephrine, or careful coagulation.

Postoperative anastomotic bleeding can occur from 4 h to 9 days following the operation [84]. Initial management includes correction of any associated coagulopathy and transfusion of blood and blood products if necessary. Attention should be paid to the amount blood and clots that patient is passing as a more accurate measure of the rate of bleeding; the hemoglobin and hematocrit changes may not occur until hours later. Between 2 and 10 units of packed red blood cells may be required in the nonoperative treatment of anastomotic bleeding [16]. It may be important to keep the patient warm by infusing warmed solutions and preventing hypothermia.

If anastomotic bleeding persists, the preferred next step is usually colonoscopic evaluation and management. Colonoscopy allows for direct inspection of the anastomosis with subsequent application of various means of hemostasis. Submucosal peri-anastomotic injection of up to 10 ml of 1:200,000 epinephrine in saline has been shown to result in control of anastomotic bleeding [84]. Cirocco reported the successful use of electrocoagulation, although it was noted that an anastomotic fistula that developed in one of six cases may have been related to this technique [85]. This may be due to the presence of staples at the bleeding site; the dissipation of energy may not be uniform and localized leading to increased tissue damage.

Endoscopic application of clips is an excellent alternative to coagulation and has been shown to be safe and effective in control of anastomotic bleeding [81]. Endoscopic therapy has obvious advantages in terms of less physiological stress on the patient, no requirement for general anesthesia compared with the surgical revision of anastomosis, and is clearly less invasive and more cost-effective. Colonoscopic hemostasis should be performed by a skilled and experienced provider proficient in advanced endoscopic techniques. An alternative course of action should always be entertained in the event endoscopic therapy is unsuccessful, particularly if the bleeding is severe, making a clear endoluminal view of the point of hemorrhage impossible.

Briskly bleeding anastomoses may be amenable to angiographic localization and treatment of the bleeding site. This strategy provides access for vasopressin infusion or embolization to control the hemorrhage. Vasopressin may be associated with significant complications such as myocardial or intestinal ischemia and infarction and therefore has to be carefully considered [86].

Angiographic embolization is an alternative to vasopressin infusion. Although this option avoids myocardial complications, it may precipitate bowel ischemia and infarction by interrupting the distal arterial blood supply [87]. These angiographic methods are best reserved for other intestinal anastomoses, such as in the small bowel, where the endoscopic approach is significantly limited. Although extremely rare, significant anastomotic bleeding after large bowel resection can be severe enough to require reoperation with surgical revision or reconstruction of anastomosis.

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Part II
Anorectal Disease

11
Approach to Anal Pain

Amir L. Bastawrous

Key Concepts

- A careful history should direct the diagnosis for patients with anal pain.
- A considerate yet thorough physical exam will usually establish the diagnosis by visualizing pathology or by palpating abnormalities. If not possible in the office, then an exam under anesthesia should be performed.
- Imaging is rarely needed to determine the etiology.
- An anal fissure will typically cause sharp anal pain during and after a hard bowel movement.
- The anal pain associated with a thrombosed external hemorrhoid is usually constant and accompanied by a palpable swelling but without systemic signs of infection.
- Cancer should always be included in the differential diagnosis.

Introduction

One of the more common complaints of patients consulting with colon and rectal surgeons, general surgeons, and primary care physicians is anal pain. In Western culture, the anus is generally taboo to speak about socially. In addition, it is a body region that is difficult for an individual to inspect on himself or herself. Yet anal and rectal pathologies can be inconvenient and are commonly debilitating. It is not unusual to have a patient with an acutely thrombosed external hemorrhoid or a perianal abscess completely incapacitated by their pain. Anal pain as a symptom encompasses a broad spectrum of diagnoses from the benign and self-limited to the neoplastic and life-threatening. A thoughtful and logical methodology is essential to efficiently diagnose and treat patients with anal pain.

Patient History

As with most things in medicine, taking a careful history is foundational when evaluating patients with anal pain. Listening to patients stories in their own words with a focus on their emphasis as much as on their words typically offers clues to the underlying problem. An experienced colorectal surgeon can often surmise the patient's diagnosis prior to any examination just by listening to key descriptions by the patient. An emphasis on pain characteristics is important. One should concentrate on the duration, location (intra-anal, external), character (burning, sharp, dull), causative agents (bowel movement, diarrhea, hard stool, exercise, fecal incontinence, drainage), associated signs and symptoms (fever, chills, weight loss, change in bowel habits), and items that provide any relief (warm water bath, bowel movement, topical creams).

Other elements of the patient history are also important and can provide some guidance. A personal history of diabetes may suggest an anal abscess or Fournier's gangrene. A history of inflammatory bowel disease may hint at anal fissures, fistulae, or abscess. A medication history of infliximab or etanercept may point to psoriasis as a cause for pruritus. A strong family history of colorectal cancer may lead to consideration to rule out rectal cancer as a cause for anal pain. A history of anoreceptive intercourse may raise the concern about sexually communicable infectious diseases, anal dysplasia, or anal cancer.

Finally, one should not be misled by either the patient's or referring physician's working diagnosis; for example, an alternate diagnosis should be considered for the patient who was told they have an anal fissure but whose history doesn't fit. Frequently anal symptoms or signs are called "a hemorrhoid" by default by the non-initiated when in fact the true pathology

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ranges from pruritus to anal cancer, with the occasional correctly diagnosed thrombosed external hemorrhoid.

A few symptom patterns are so common as to be nearly universal.

Anal Fissure (Figure 11-1)

Patients with a diagnosis of anal fissure typically describe sharp, "knife-like," pain during and immediately after a bowel movement [1, 2]. If the pain has not been too chronic, they may recall and describe a precedent hard, constipated bowel movement. They state that the pain may last for minutes or hours after passing stool. Sometimes the pain is so severe; they state they are afraid to have a movement. It isn't uncommon to hear a patient state that he/she will have spotting of blood on the toilet paper after wiping. Some patients will also describe relief with a warm water bath.

Acutely Thrombosed External Hemorrhoid (Figures 11-2 and 11-3)

Patients can usually tell you precisely when they developed an acutely thrombosed external hemorrhoid. They describe sharp, constant pain after straining, either with a bowel movement (loose or constipated) or lifting something heavy. The pain will coincide with a "bulge" they feel near the anal opening. The pain will last all day, usually increasing gradually, and then decrease over the week [3–6]. Depending on when the patient presents to the office, the pain may be either increasing or decreasing in intensity. They will say it hurts to sit or touch the area. They will not have fever.

Perianal, Perirectal, or Ischiorectal Abscess (Figure 11-4)

Some of the most uncomfortable patients will be those who have an acute abscess [7–11]. Their history is one of gradually worsening pressure and pain. The pain is worse before and during a bowel movement. There may be slight improvement afterward, but the pain lingers. They will typically describe fever and chills. These patients often refuse to sit due to the pain. There can be some similarity of symptoms with patients who have a thrombosed external hemorrhoid, but the primary difference in presenting symptoms is the presence of systemic symptoms of infection. Inability to urinate is a common associated complaint.

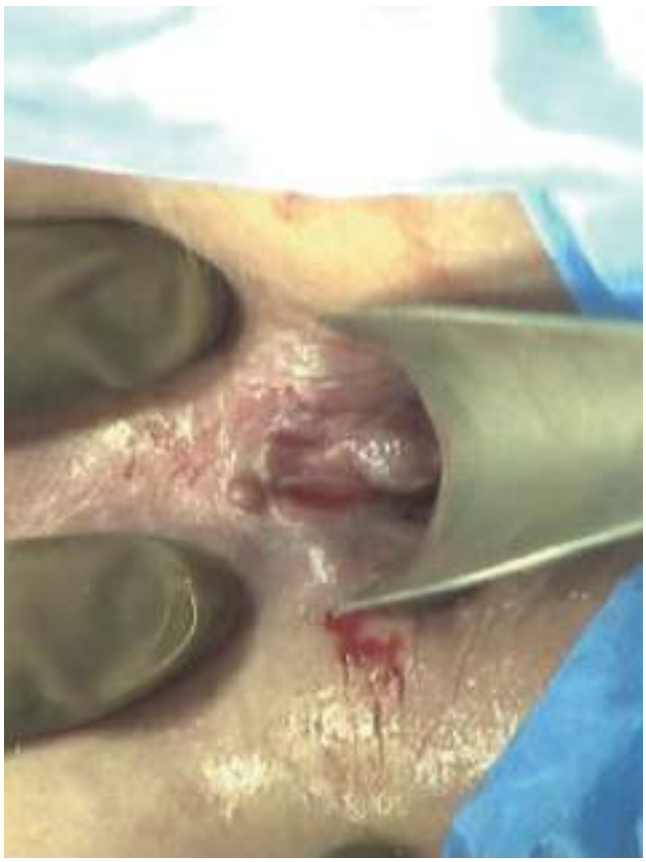

FIGURE 11-1. Anal fissure.

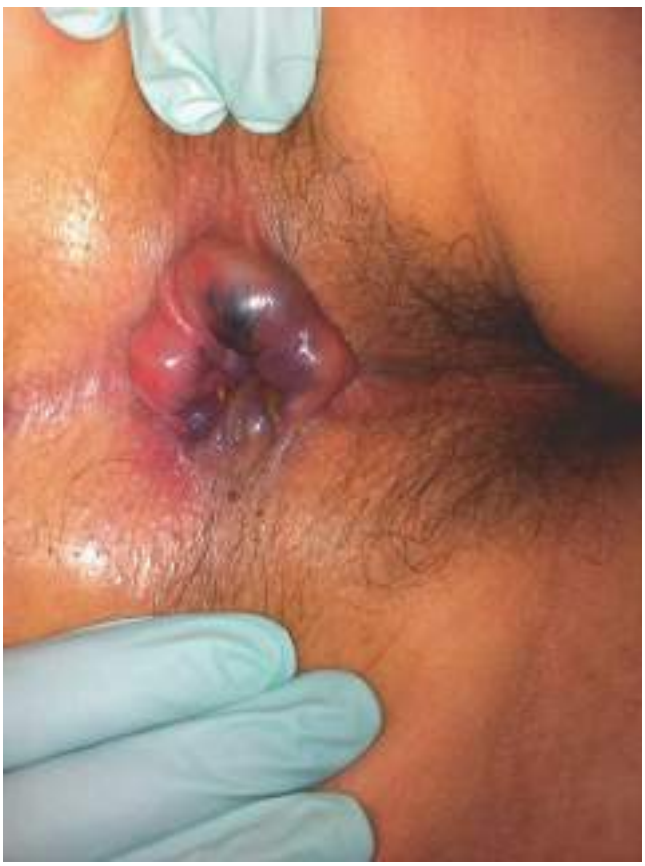

FIGURE 11-2. Acutely thrombosed external hemorrhoid.

FIGURE 11-3. Hemorrhoidal crisis.

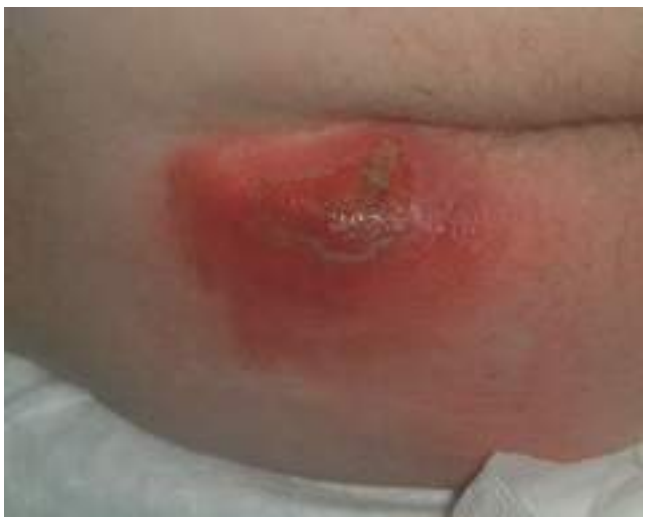

FIGURE 11-4. Perianal abscess.

Pruritus Ani (Figure 11-5)

The symptoms of patients with pruritus ani [12, 13] are occasionally described as painful but not often. Only after further discussion is the pain clarified to be burning or itching. It is clear that the sensory response of the anoderm and perianal skin is variable between individuals and may be less discriminatory (or may be just different) than other areas of the body. There does seem to be some overlap in the description of sensations of burning, itching, and pain. The irritation is nearly universally chronic in nature and may be associated with other synchronous diagnoses.

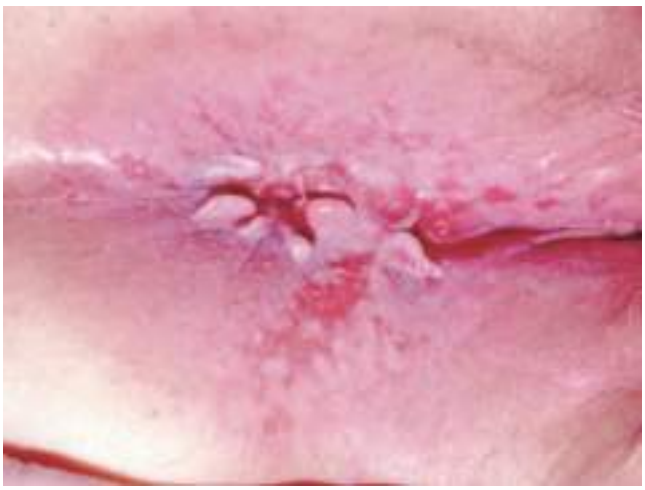

FIGURE 11-5. Pruritus ani.

Levator Syndrome

The pain history that patients with pelvic floor dysfunction (levator ani syndrome, proctalgia fugax, outlet obstruction constipation) [14, 15] describe is more variable than for the other diagnoses listed so far. This lack of fitting into a typical pattern itself often points to the diagnosis. The pain may be sharp, dull, burning, or achy. It may be intermittent or constant. The pain may or may not improve with warm water baths. It may be worsened or improved with bowel movement. Often the pain is chronic and worse late in the day. Unless there is associated other pathology, they will not describe fever or bleeding. Some will complain of difficulty with evacuation of stools.

Anal or Rectal Cancer (Figure 11-6)

The fear of malignancy is often part of the reason patients seek medical attention for anal pain. Thankfully, the vast majority of patients who present with anal pain have benign processes; however, the alert physician will always consider cancer within the differential diagnosis. Physicians should not become lulled into complacency after seeing several patients with typical anal fissures, only to misdiagnose a patient with an anal verge squamous

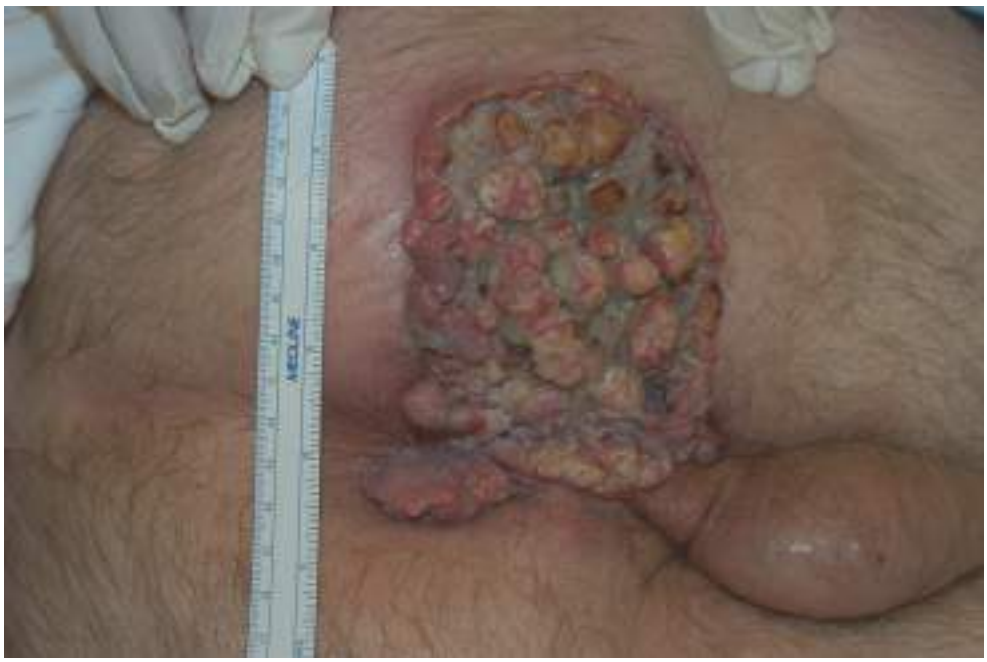

FIGURE 11-6. Anal squamous cell carcinoma.

cell carcinoma with a posterior midline ulceration. Anal and rectal cancers can present with pain [16–19]. Rectal cancers can cause pain (especially if low and advanced) with bleeding and change in bowel habits [16]. There is often weight loss associated with the presentation. Anal cancer can present more subtly. Symptoms may overlap with those of anal fissure with pain during and after a bowel movement along with spotting of blood on the toilet paper. There may or may not be an associated mass felt by the patient. Fever, chills, weight loss, and groin adenopathy may also be included in the patient history.

Physical Examination

Although an astute physician can often determine a cause for a patient's anal pain from the history, it takes a careful, systematic examination to confirm the working diagnosis. While a complete physical exam is important, the regional high yield focus of the examination includes the abdomen, inguinal, perianal skin and soft tissue, buttocks and gluteal cleft, anal canal, and rectum.

Abdominal Examination

Anal pathology can on occasion manifest with abdominal findings. An obstructing cancer can cause distention or alteration of bowel sounds. Metastases can present with hepatomegaly. Diverticulitis can manifest with anal abscess or fistula [20] in addition to abdominal pain or tenderness to palpation. Look for scars of prior operations that may suggest an associated diagnosis. Crohn's disease patients may be very thin and cachectic if they have both anal disease and bowel manifestations.

Inguinal Examination

The inguinal examination may identify adenopathy. Rectal adenocarcinomas can present with inguinal adenopathy if they are located low in the rectal vault or if there is high volume lymphatic metastatic disease in the iliac chains. Anal canal and anal margin squamous cell carcinomas, when metastatic, often present with inguinal adenopathy following anatomic drainage patterns [21–23]. This exam finding has implications for radiotherapy mapping and surveillance of disease regression or recurrence.

Perianal, Gluteal, and Intergluteal Examination

The anal examination requires extreme sensitivity to the patient's physical and psychological condition. They may be embarrassed, in pain, or fearful. Put the patient at ease. Many will appreciate a careful description of the exam as it is performed and an explanation of findings along the way. Take care to warn them before initiating any invasive component of the exam. Putting the patient at ease will foster trust and help the physician obtain more productive data in their analysis.

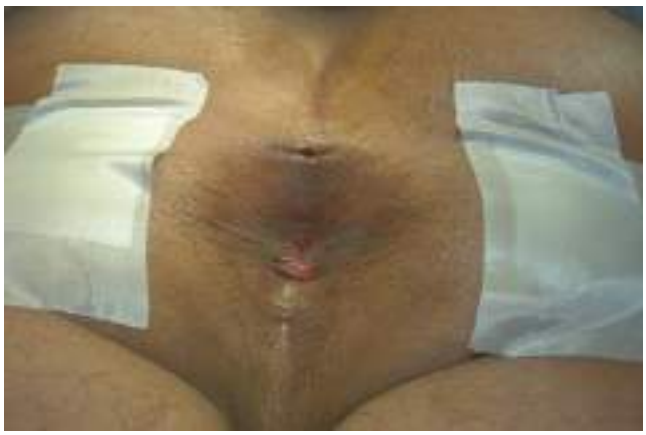

FIGURE 11-7. Anal fistula.

FIGURE 11-8. Anal stricture.

Visual examination of the anus is essential. One should look for abnormalities of the skin including color, scaly skin, thickened folds, masses, secondary openings of fistula-*in-ano* (Figure 11-7), evidence of abscess with swelling or redness, skin tags, and external hemorrhoid enlargement. Usually, anal fissure can be diagnosed by visualizing the anoderm before anoscopy with gentle retraction of the buttocks to evert the anoderm and expose the fissure. In the intergluteal cleft, look for sinuses, abscess, and pilonidal pits. Anal stenosis can be seen in some patients after anal surgery (Figure 11-8). The rare subcutaneous mass may be benign or malignant. An assessment of size, fixation, character, firmness, and tenderness is sometimes helpful in establishing the diagnosis (Figure 11-9).

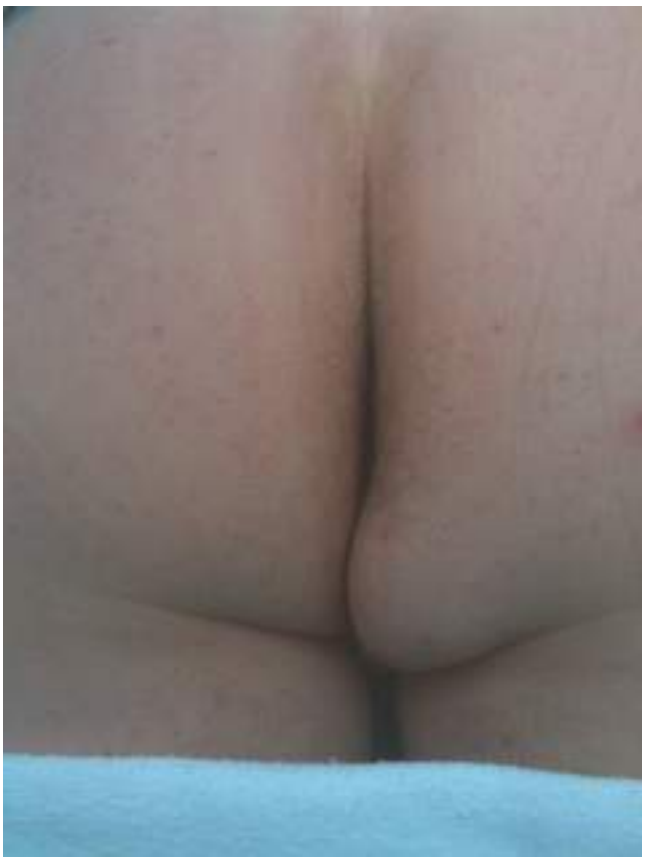

FIGURE 11-9. Solitary fibrous tumor.

Digital Rectal Examination

Next, the physician should assess the skin. Is the skin tacky to the touch, consistent with pruritus changes? Specific areas of pain, warmth, or masses should be examined. Prior to the digital rectal examination, the anus should typically be lubricated and a topical anesthetic used, especially if the patient is in pain. If for some reason, *Neisseria gonorrhoeae* is suspected, lubrication should be avoided prior to taking cultures. One should feel for any abnormal anal or distal rectal masses and anal tone. If low resting tone, stool seepage may be a cause for pruritus pain. If tone is high and there is twitching of the anal sphincter, even if there is no visible fissure, a diagnosis of anal fissure disease is likely. The tightness of levator muscles should be assessed bilaterally starting at the coccyx; this will often reproduce the pain or pressure of levator spasm. One should assess for the fluctuant swelling typical of an abscess, and the sacral hollow should be examined for presacral masses or cysts. The coccyx should

be distracted to assess for coccydynia; the prostate should be palpated since prostatitis may be the cause of anal pain. If the pain is too intense and the patient cannot tolerate the exam in the office setting, an examination under anesthesia should be scheduled.

Rectal Inspection, Anoscopy, and Sigmoidoscopy

After the digital rectal examination, particularly if the diagnosis is not clear and if the patient tolerated the exam without too much pain, an anoscopic or sigmoidoscopic examination should be performed. These endoscopic tools will help identify intra-anal and rectal lesions. Rarely, an anal melanoma may be seen (Figure 11-10). More common, abnormalities can include lesions from various sexually transmitted infections, mucosal changes of inflammatory bowel disease, internal hemorrhoid disease, or rare conditions, such as melanoma.

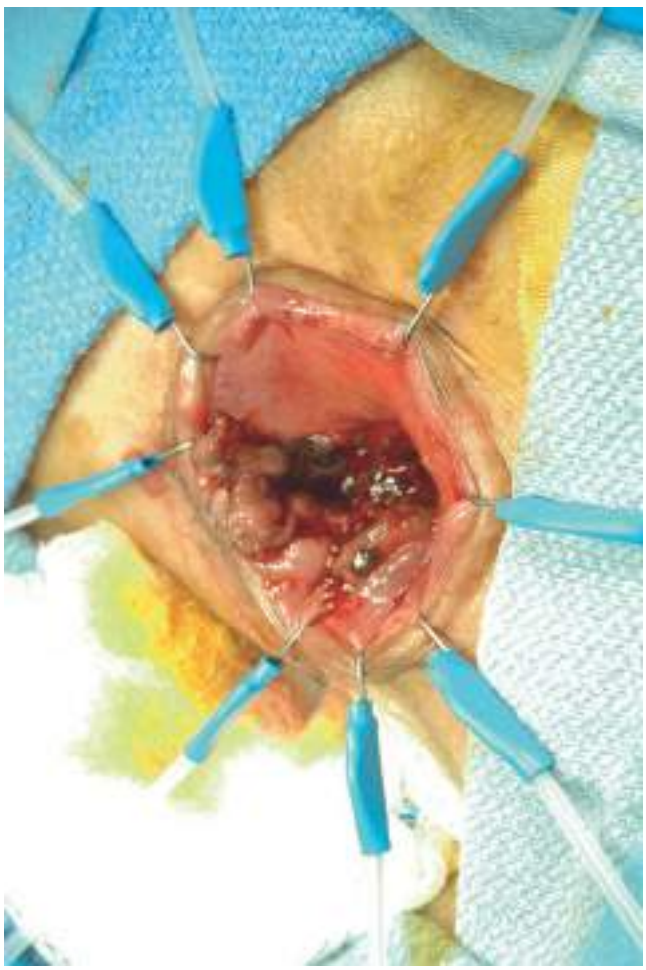

FIGURE 11-10. Anal melanoma.

Imaging and Diagnostic Testing

The history and examination will occasionally lead to a need to order confirmatory or diagnostic imaging studies. A rare patient whose history is consistent with anorectal abscess, but in whom an abscess cannot be found on exam, may benefit from a CT of the pelvis. A cine-videodefecogram or dynamic MRI of the pelvis may help confirm the diagnosis of a patient with suspected proctalgia fugax or other pelvic floor disorders. High-resolution anorectal manometry [24] and balloon expulsion can be used to differentiate outlet obstruction for patients with constipation. If an anal or rectal cancer is identified on examination, staging with ultrasound, MRI, and CT is appropriate. A pelvic radiograph can identify some foreign bodies (Figure 11-11).

Conclusion

A systematic approach to anal pain will ensure efficient diagnosis and initiation of effective treatments (Figure 11-12). A combination of careful history and detailed examination is nearly universal in obtaining the correct diagnosis. However, in the rare situation where the pain is still of unclear etiology, an examination under anesthesia may be warranted. Even more rarely, would imaging be necessary other than to further delineate an abnormality found on examination.

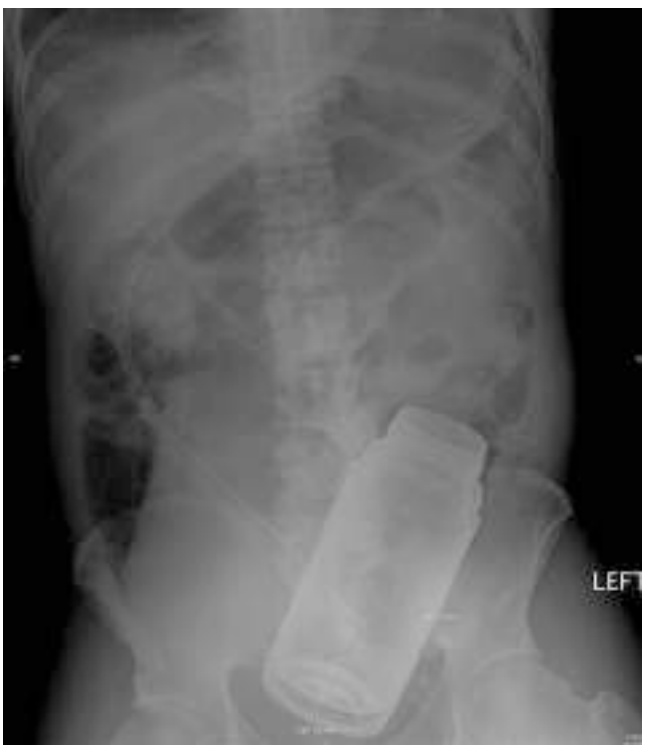

FIGURE 11-11. Foreign body.

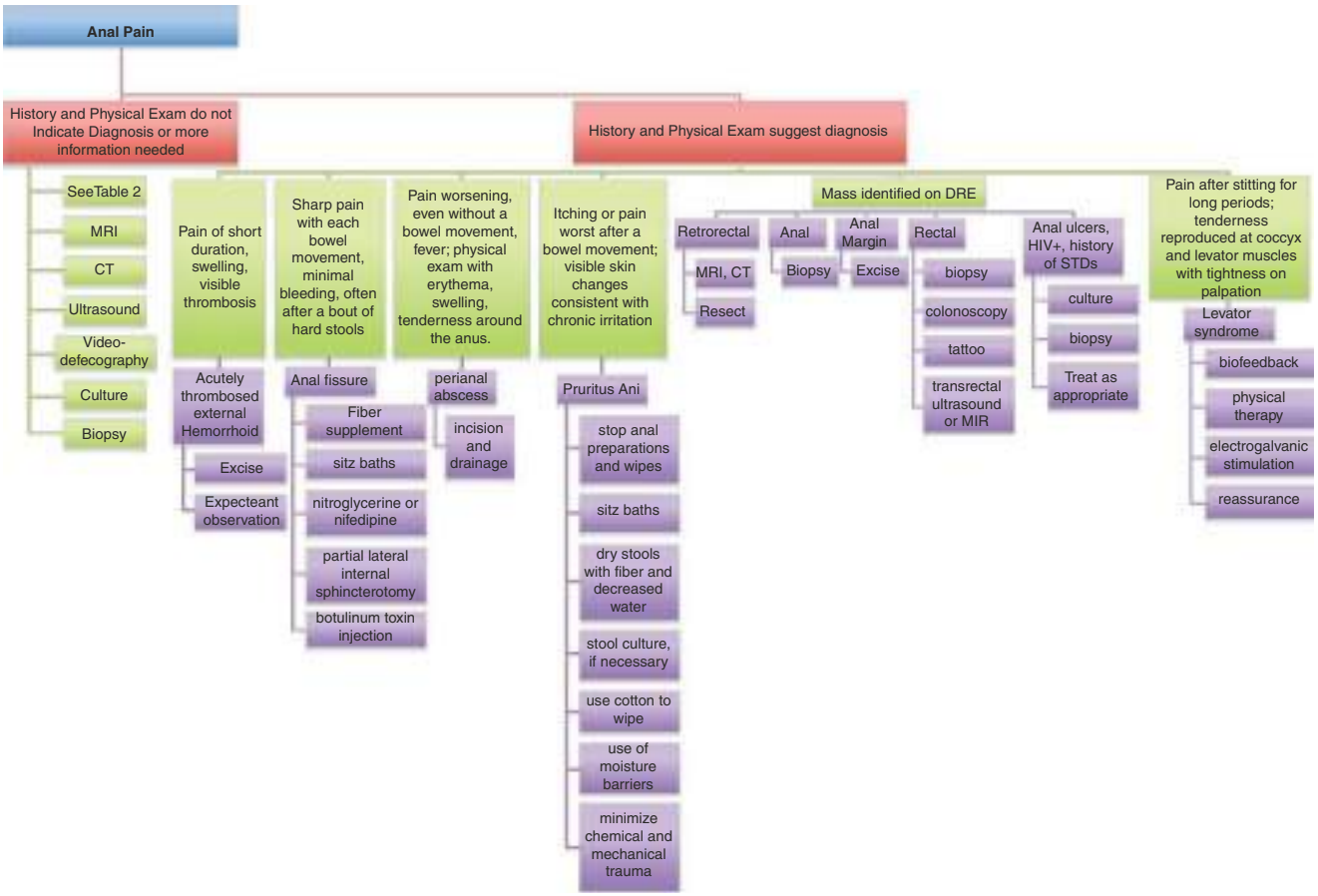

FIGURE 11-12. Systematic approach to anal pain. *With permission from Billingham R. Chronic anal pain. In*: *Steele*, *S.R.*, *Maykel*, *J.A.*, *Champagne*, *B.J.*, *Orangio*, *G.R.* (*Eds*). *Complexities in Colorectal Surgery. Decision-Making and Management. Springer*, *New York*, *2014. © Springer.*

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12
Hemorrhoids

Martin Luchtefeld and Rebecca E. Hoedema

Key Concepts

- The classification system of hemorrhoidal disease is based on the degree of clinical prolapse seen on the physical examination.
- Medical therapy for hemorrhoidal symptoms should be the initial treatment recommendation and can include dietary changes, increased water intake, fiber supplementations, and ointment therapy.
- Office-based procedures are offered mainly for internal hemorrhoidal disease with the most common procedure being rubber band ligation.
- Injection sclerotherapy may be performed on an anticoagulated patient due to the fibrotic reaction with almost no increased risk of bleeding.
- Excisional hemorrhoidectomy is the gold standard by which all surgical procedures are compared.
- Postoperative bleeding can occur at one of two different times, right after the procedure itself and delayed hemorrhage occurring 7–10 days post procedure.
- Urgent hemorrhoid surgery is usually reserved for the patient with strangulated, incarcerated, gangrenous hemorrhoids.

Hemorrhoids are one of the most common ailments that will be seen by a colon and rectal surgeon. While hemorrhoids can present in many different ways, there are a number of different conditions that are mistaken by patients and practitioners alike as "hemorrhoids."

Anatomy

Hemorrhoids are a normal part of the anal canal. Our understanding of hemorrhoid anatomy has not changed substantially since 1975 when Thomson published his master's thesis based on anatomic and radiologic studies and first used the term "vascular cushions" [1]. Per Thomson, the submucosa does not form a continuous ring of thickened tissue but instead is a discontinuous series of cushions. Anatomically the three main cushions are located in the left lateral, right anterior, and right posterior positions. Each of these thicker layers has a submucosa filled with blood vessels and muscle fibers. The muscle fibers arise from the internal sphincter and from the conjoined longitudinal muscle. These muscle fibers are thought to be important in maintaining the integrity of the hemorrhoid, and it is the breakdown of this tissue that can contribute to the hemorrhoids becoming symptomatic. The arterial blood supply to hemorrhoids is primarily from the terminal branches of the superior hemorrhoidal artery; branches of the middle hemorrhoidal artery also contribute. Venous outflow is from the superior, middle, and inferior hemorrhoidal veins (Figure 12-1) [2].

Etiology

There are numerous possible reasons why hemorrhoids become symptomatic. Dietary patterns, behavioral factors, anything that can cause excessive straining, and sphincter dysfunction are among the most common reasons. Thompson's vascular cushion theory states that normal hemorrhoidal tissue represents discrete masses of submucosa. During straining, the vascular cushions can become engorged and possibly prevent the escape of fecal material or gas. With the passage of time, however, the anatomic structures supporting the muscular submucosa weaken, allowing the hemorrhoidal tissue to slip or prolapse, leading to typical hemorrhoidal symptoms. Haas et al. noted that supporting tissues can be shown microscopically to deteriorate by the third decade of life [3].

Studies have investigated why this degradation occurs and what are the changes in the local microvasculature. Matrix metalloproteinases (MMPs) are enzymes present in the extracellular space and can degrade collagen, elastin, and

Electronic supplementary material: The online version of this chapter (doi:10.1007/978-3-319-25970-3_12) contains supplementary material, which is available to authorized users.

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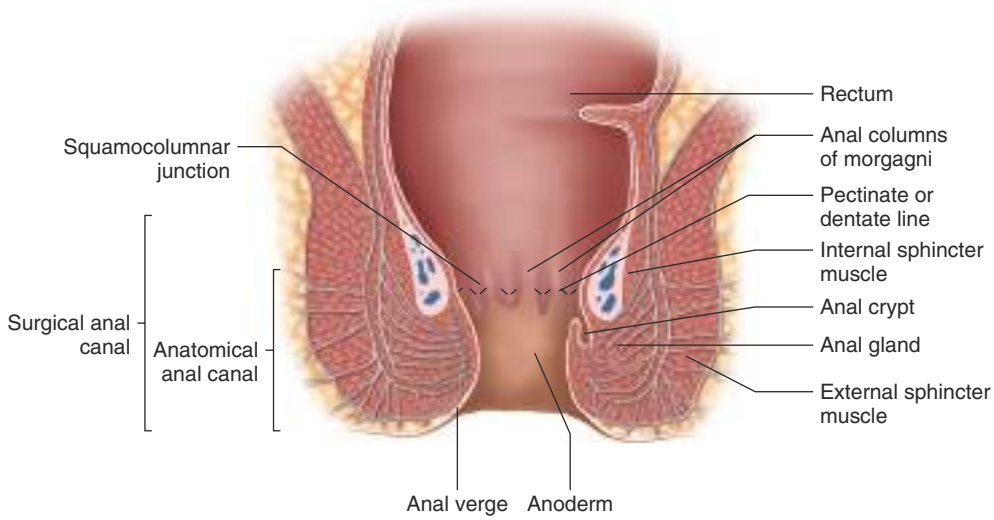

FIGURE 12-1. Hemorrhoid anatomy.

fibronectin. MMP-9 has been found to be overexpressed in hemorrhoid tissue in association with breakdown of elastic fibers [4]. Once the hemorrhoids start to prolapse, the internal sphincter can slow the rate of venous return and increase the hemorrhoid engorgement.

Increased vascular supply and neovascularization may play a role in making hemorrhoids more symptomatic. Aigner found that the terminal branches of the superior hemorrhoidal artery were larger in diameter, had greater flow, and higher peak velocity and acceleration velocity in patients with hemorrhoids compared to normal volunteers [5, 6]. Microvascular density has also been found to be increased in hemorrhoids. Chung et al. found that endoglin (CD105) which is a binding site for TGF-B and is a proliferative marker for neovascularity was found in over half of hemorrhoidal tissue specimens compared to none in normal anorectal mucosa [7]. Other researchers have found higher expression of angiogenesis-related proteins such as vascular endothelial growth factor (VEGF) in hemorrhoidal specimens [4].

Any process that can hinder venous return is thought to increase hemorrhoidal symptoms. Increased sphincter tone by itself can slow venous return [8, 9]; in fact, studies have shown that resting anal canal pressure is higher in patients with symptomatic hemorrhoids compared to normal subjects [10, 11]. Following hemorrhoidectomy, anal canal pressures drop so it is possible that the anal canal pressures are a result of the hemorrhoids rather than a cause [12]. Other possible causes include pregnancy, chronic cough, pelvic floor dysfunction, and simply being erect. Burkitt and Graham–Stewart suggested that Western diets emphasizing low-residue foods lead to increased straining with defecation [13] causing increased venous backflow predisposing to worsening hemorrhoid symptoms.

Despite the many theories that have been proposed, most of these are very speculative, and almost certainly hemorrhoidal symptoms result from a combination of multiple different factors.

Epidemiology

It is difficult to know the true incidence of hemorrhoids. As mentioned earlier, many patients who believe that they have hemorrhoids in fact have some other malady. One study done in 1990 suggested that the prevalence in the United States was 4.4% with the highest rate being in Caucasian patients between 45 and 65 years of age and elevated social economic status [14]. This sort of study has many potential obvious biases. In 2004, the National Institutes of Health noted that the diagnosis of hemorrhoids was associated with 3.2 million ambulatory care visits, 306,000 hospitalizations, and two million prescriptions in the United States [15].

Classification

Hemorrhoids are generally classified as internal, external, or mixed. Internal hemorrhoids are those located above the dentate line, and external hemorrhoids are located below the dentate line. This classification has important implications for treatment as the relative lack of pain fibers in the internal hemorrhoids allows for many more treatment options compared to the external hemorrhoids.

In addition, there is a classification system of the internal hemorrhoids based on the degree of clinical prolapse (Figure 12-2) [16]. This system is useful as it does allow some comparison of treatment methods between studies. Additionally, prolapse is one of the many main driving symptoms for patients to seek treatment. Unfortunately, this system does not address some of the other hemorrhoidal complaints such as pain, bleeding, and thrombosis since most hemorrhoid complaints are a combination of symptoms.

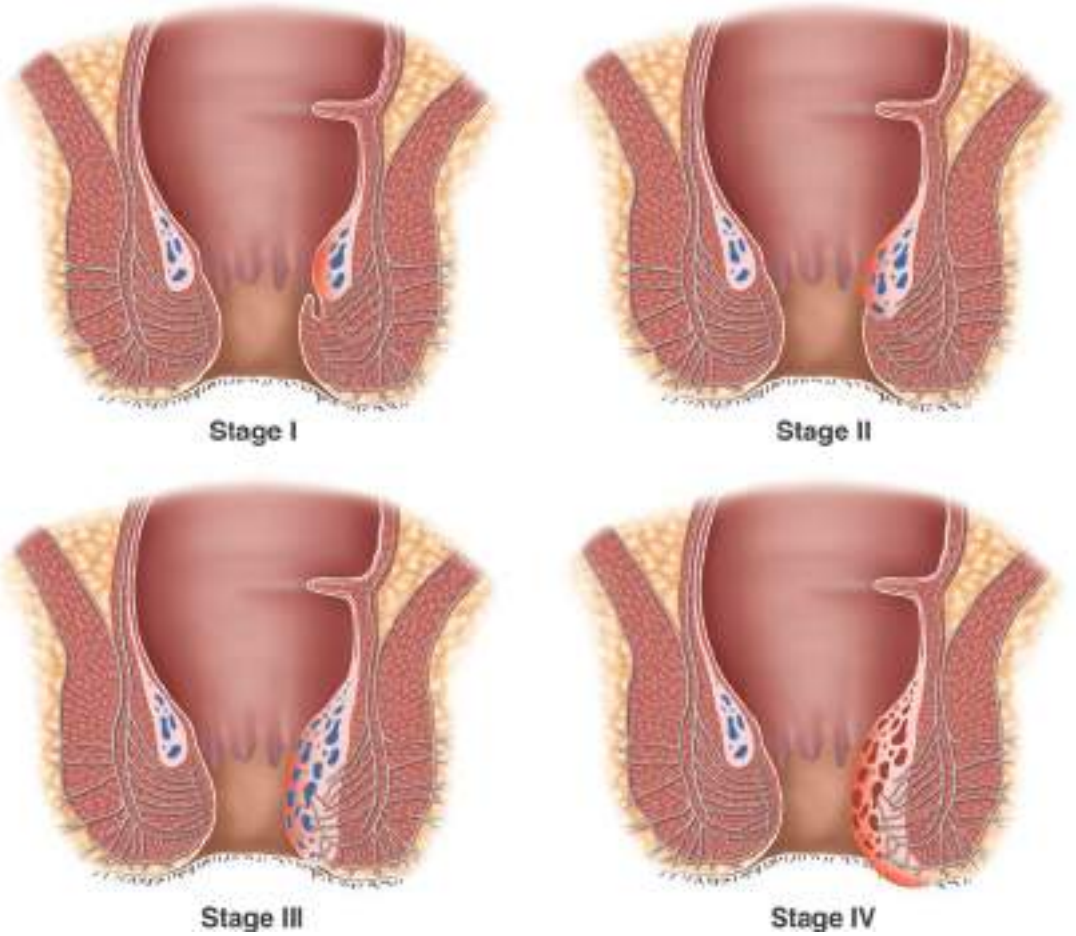

FIGURE 12-2. Hemorrhoid classification table/grading system.

Clinical Presentation

Most patients coming to an outpatient clinic visit with anorectal complaints will feel like they have "hemorrhoids." Bleeding, pain, and protrusion are the most common symptoms associated with hemorrhoids. Each of these components can vary in severity based on whether the internal hemorrhoids, external hemorrhoids, or a combination predominates. Itching can also be described, although itching as an isolated symptom is more often the result of pruritus ani.

When internal hemorrhoids are the primary source of the problem, the main symptoms are a combination of rectal bleeding and prolapse. Pain is very rarely associated with internal hemorrhoids, and in fact when this is a significant component of the presenting complaint, the practitioner should be very suspicious of another source of the problem. The bleeding that occurs with hemorrhoids is typically described as bright red in nature with the frequency ranging from rarely to several times per day. The blood can be seen on the toilet paper and in the toilet water, and sometimes patients even describe the sensation of the blood squirting out of the anus. Typically the frequency and severity will increase over time. Although it is very unusual, there can even be enough bleeding to lead to anemia. Another common symptom of internal hemorrhoids is prolapse. This can range from a simple swelling that quickly reduces after each bowel movement to an internal hemorrhoid that is chronically prolapsed and cannot be reduced. Many of the symptoms of internal and external hemorrhoids overlap. Certainly external hemorrhoids can lead to rectal bleeding in much the same way that internal hemorrhoids can. In addition, the intra-anal portion of the external hemorrhoids can also prolapse out of the anal canal along with the internal hemorrhoid. It can be difficult to distinguish by symptoms alone external hemorrhoids that are engorged and inflamed from prolapsing internal hemorrhoids.

On the other hand, external hemorrhoids are more likely to be associated with pain especially when they are engorged or inflamed. It is the presence of this pain that can help the clinician distinguish whether it is the internal or the external component of the hemorrhoids causing them the most problems.

Thrombosis is one distinct way that hemorrhoids can cause significant symptoms (Figure 12-3). A patient with a thrombosed hemorrhoid will typically describe a sudden onset of pain and swelling in the perianal region. The swelling that occurs will usually last at least days if not weeks,

FIGURE 12-3. Thrombosed external hemorrhoid. Courtesy of Richard Billingham.

TABLE 12-1. Hemorrhoid symptoms

- Rectal bleeding
- Bright red blood in stool
  - Dripping in toilet
  - On wiping after defecation
- Pain during bowel movements
- Anal itching
- Rectal prolapse (while walking, lifting weights)
- Thrombus
- Extreme pain, bleeding, and occasional signs of systemic illness in case of strangulation

whereas the protrusion that occurs with prolapse or edema usually resolves much quicker. The pain that results from the thrombosed hemorrhoid can vary greatly in severity but is typically constant and unrelenting. Thrombosed hemorrhoids typically occur in the external component but in severe cases can go on to involve the internal hemorrhoids as well. Thrombosed hemorrhoids can occur in patients who have had minimal hemorrhoidal symptoms in the past.

It is important to keep in mind the wide differential diagnosis in patients presenting with anorectal complaints (Table 12-1). Although many of these patients will indeed be found to have hemorrhoids, fissures, or fistulas, they may also harbor a more ominous diagnosis such as anal or rectal carcinoma. The practitioner should keep an open mind and consider other possibilities such as condyloma, Crohn's disease, proctitis, Paget's disease, or other types of dermatoses.

Evaluation and Physical Examination

History

A careful history should be done to guide the clinician to an accurate diagnosis. In addition, it is helpful to know which symptoms bother the patient the most. In some circumstances the patient is satisfied just to know that their symptoms are related to hemorrhoids and not something more serious. Part of the history should include the patient's bowel habits. If a patient has constipation, treatment of the constipation will be an important part of the treatment plan. Ulcerative colitis and Crohn's disease need to be considered in patients that have had significant diarrhea. If there has been a significant change in bowel habits, one also has to consider the many possibilities that can lead to this change.

For patients with rectal bleeding, the nature, color, and intensity of the bleeding should be noted. If also accompanied by a change in bowel habits, one needs to be suspicious of a malignancy or inflammatory bowel disease.

If pain is a significant component of the presentation, the intensity, frequency, and duration of the pain should be noted. If the pain is severe and described as a tearing sensation primarily at the time of the bowel movement, an anal fissure should be considered. Pain that is constant and has been present for days at a time should elicit consideration of a thrombosed hemorrhoid or perianal abscess as the underlying diagnosis.

Protrusion or swelling in the rectal area can be many different things. If the protrusion has been present constantly for weeks, months, or even years, it can be something as simple as a skin tag. However, one needs to also be mindful of diagnoses such as condyloma and neoplasm in this situation.

Physical Examination

A general physical examination should be conducted with concentration on the abdomen, groin, and perianal area. Typically the patient will be examined in the supine position first before switching to a prone jackknife or left lateral (Sims) position (Figure 12-4). It is important to be as reassuring as possible during this examination as it is inherently embarrassing and uncomfortable. It is always helpful to explain the steps of the examination so as to minimize surprise and discomfort.

The examination begins by gently spreading the buttocks and inspecting the skin, perineum, and the external anal opening. Anal fissures are usually diagnosed just with these simple measures, but if one is not thinking of this possibility,

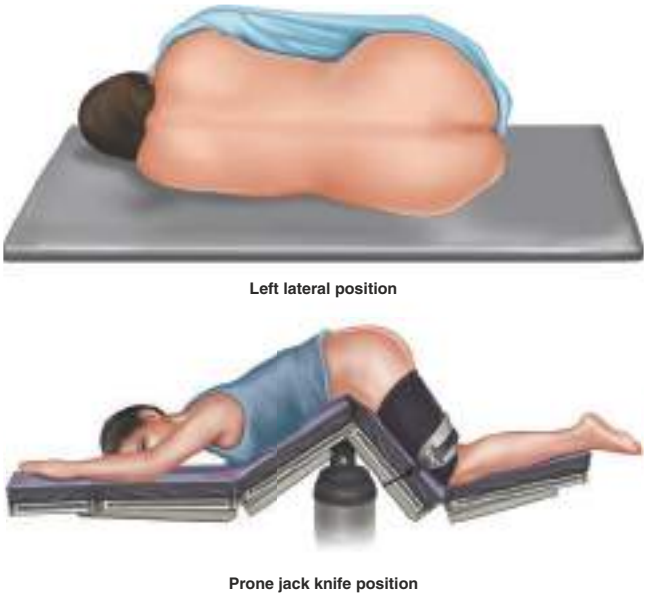

FIGURE 12-4. Patient positioning. (**a**) Left lateral position. (**b**) Prone jackknife position.

it is easy to miss a fissure. In addition, many other conditions can be identified: dermatitis, fistulas, abscess, anal cancer, skin tags, and condyloma. A digital rectal exam is then performed to assess for masses, pain, and sphincter tone. If there is any component of fecal soiling or incontinence, the sphincter tone should also be investigated by asking the patient to voluntarily squeeze during the digital exam.

Anoscopy is required to fully assess the hemorrhoids (see Figure 4.3). It is important that the anoscope is slotted or allows for side viewing to give the best view of the internal hemorrhoids. Asking the patient to bear down with the anoscope in place can give a better assessment of the severity of the hemorrhoidal problems and specifically the degree of prolapse.

Many patients should also undergo at least a rigid proctoscopy. This allows the surgeon to rule out malignancies or inflammatory conditions that could be mimicking hemorrhoids. This is especially true in older patients with bleeding, weight loss, anemia, or change in bowel habits.

The patient who presents with rectal bleeding should always be considered for full evaluation of the colon. An accurate history is very helpful in determining the need for colonoscopy. The young patient with typical hemorrhoidal bleeding that responds to treatment and with no family history of colon cancer likely does not need further evaluation. In a large series of classic "outlet" bleeding, colonoscopy revealed adenomas in less than 2% and no cancers in patients less than 50 years of age. When considering all age groups, 6.7% of the patients had a significant lesion (e.g., cancer, large polyps, or carcinoma in situ) [17]. Despite this evidence, some clinicians will still recommend colonoscopy in any patient over 40 years of age regardless of the type of bleeding.

Treatment

Treatment aggressiveness is determined by the degree of symptoms. Many patients have large inflamed hemorrhoids but desire nothing other than the reassurance of an accurate diagnosis. Other patients may have symptoms that seem far worse than the physical findings would suggest. The options for the treatment of hemorrhoids can be categorized into medical management, office-based treatments, and operative therapies.

Medical Management

Dietary

The most common problem associated with hemorrhoidal disease is constipation. As a result, the main components of dietary management are geared toward minimizing constipation and consist of a high-fiber diet accompanied by an adequate fluid intake. The recommended dose of dietary fiber is 25 g (for women) to 38 g (for men) per day [18]. This amount of fiber is difficult to attain and far exceeds the mean fiber intake of Americans of 16 g per day. Despite recommendations to increase fiber intake, this figure has not changed over the last 10 years [19]. Many patients find that attempting to reach the maximum amount of fiber leads to bloating and excessive gas, and this can be a limiting factor. Along with the increased fiber, patients should also drink at least 64 oz of fluid per day. The desired outcome of the increased fiber and fluid is a soft but formed bowel movement that can be expelled with minimal effort. Meta-analysis has confirmed that fiber supplementation can alleviate hemorrhoidal bleeding but is not useful for pain, prolapse, and itching [20]. It can take up to 6 weeks for the fiber therapy to show benefit [21].

Other options are available for patients that do not do well with fiber supplementation. Stool softeners are simple and safe and can be very helpful for patients that have exceptionally hard bowel movements. Hyperosmolar laxatives such as polyethylene glycol are a good choice for those patients that do not do well with fiber supplements. The goal of these supplements is ultimately the same as for dietary fiber and water.

For the occasional patient with diarrhea, the dietary focus must change. Evaluation must be carried out to determine the etiology if the diarrhea is significant. Even in the absence of a verified diagnosis, a few basic rules can be applied to the patient with diarrhea. In general, the diet should be high in fiber and low in fat content; caffeine, alcohol, and spicy foods are known to exacerbate diarrhea. Loperamide can be very useful to minimize diarrhea in patients with irritable bowel syndrome.

In many patients, the hemorrhoidal symptoms are tied into their toileting habits. The dietary changes mentioned above are designed to minimize straining and time spent on the toilet. Some patients will continue to have excessive straining time on the toilet despite having soft bowel movements. In this situ-

ation, the diagnosis of the obstructed defecation syndrome (ODS) should be considered. ODS will not respond to any type of surgical treatment of hemorrhoids and, in the ideal situation, would be recognized and treated at the outset.

Sitz baths are often used as part of the treatment for hemorrhoids. They are designed to decrease pain, burning, and itching following a bowel movement. They can also aid in hygiene as well as decrease anal canal pressures. Sitz baths tend to be more useful when warm water is used and when performed in the acute setting such as with a thrombosed hemorrhoid or an acute flare-up of hemorrhoidal disease [22]. Some patients with disabilities can have difficulty using them due to an inability to get in and out of a bathtub. In these situations, a portable sitz bath or even a warm shower can be useful. As comfortable as they can be, excessive use can lead to macerated skin and even more discomfort. Soaking time should be limited to 10–15 min two to three times per day.

Topical Therapies

Medical treatments such as topical ointments and suppositories deserve comment. Any trip to a local pharmacy will confirm that there is a vast array of over-the-counter hemorrhoidal treatments. Many of these products will combine a barrier protectant with some other active ingredient. The active ingredients can include vasoconstriction agents, local anesthetics, anti-inflammatory agents, and astringents [23]. There is very little science to support the use of these agents; however, some patients do claim to get relief from these products, and there appears to be little or no harm in their use.

A different approach to treating hemorrhoidal symptoms has been the use of topical nitrates, which have been shown to be beneficial in patients with high sphincter tone and hemorrhoids [24]. Calcium channel blockers are reported to be helpful in the setting of acute thrombosed hemorrhoids [25]. Since both are known to decrease internal sphincter tone, this may be the mechanism of action.

Patients will also sometimes try suppositories or will have them recommended by one of their caregivers. Similar to the ointments described above, suppositories are usually a combination of several different agents. Despite the fact that suppositories are difficult to maintain in the correct anatomic location, some patients do get relief with their use.

Oral Therapy

Flavonoids are a type of plant-based phlebotonics that were first described in the treatment of chronic venous disease and edema. They are reported to increase vascular tone, reduce venous capacity, decrease papillary permeability [26], increase lymphatic drainage [27], and have anti-inflammatory effects [28]. When used as oral therapy for hemorrhoids, a meta-analysis has shown decreased bleeding, pain, and itching with their use [29, 30]. However, many of these agents are not available in pharmaceutical grade in the United States. Calcium dobesilate is one of many synthetic phlebotonics. This agent has also been shown to be effective in decreasing bleeding and inflammation in hemorrhoids [31].

Office-Based Treatments

There are a number of treatments for hemorrhoids that can be carried out in the office. With the exception of a local excision of a thrombosed hemorrhoid, these treatments are all designed to be used for internal hemorrhoids. The relative lack of somatic innervation of the internal hemorrhoids allows such treatments to be considerably less painful than excisional treatments of the external hemorrhoids. Treatments that will be discussed are rubber band ligation, infrared coagulation, and sclerotherapy.

Rubber Band Ligation

Barron first described rubber band ligation of internal hemorrhoids in 1963 [32]. Even before that time, hemorrhoids had been tied off with various types of threads and ligatures [33]. Since Barron's description, it has become one of the most widely used techniques for the treatment of internal hemorrhoid problems. By applying a rubber band at the apex of the internal hemorrhoid, the hemorrhoid is fixed high in the anal canal, correcting the prolapse, and by decreasing the blood flow caudally, the hemorrhoids shrink in size.

The technique of rubber band ligation is straightforward but still must be done with care in order to minimize discomfort (Figure 12-5). No special preparation is required although some surgeons recommend an enema prior to the procedure. The patient is placed in either the prone jackknife or left lateral decubitus position depending on surgeon choice. Anoscopy is then done to determine which hemorrhoids will be banded. An assistant and adequate lighting are critical to get optimal visualization so that the procedure can be done precisely and with little discomfort to the patient. There are a number of different banders available (Figure 12-6). Some banders utilize a grasp, while others use suction to pull the internal hemorrhoid into the banding instrument.

Once the bander is in place, the rubber band is deployed to place it at the base of the internal hemorrhoid. It is important to place the band at least 1–2 cm above the dentate line. The anal transitional zone contains a variable amount of innervation, and bands placed in this area can cause significant pain. Even when proper precautions are taken and the hemorrhoid bands are placed in the appropriate anatomical site, there can be significant pain. Anywhere from 1 to 3 bands can be done at the same setting. Lee et al. found that placing multiple bands increases pain, urinary retention, and vasovagal reactions [34]. Maria et al. also found increased pain with multiple bands [35], and others have noted very similar complication rates [36, 37].

Postoperative care is straightforward. Patients can resume a normal diet and activity shortly after the procedure. They should be warned that there can be a show of blood 5–7 days following the ligation. An office appoint-

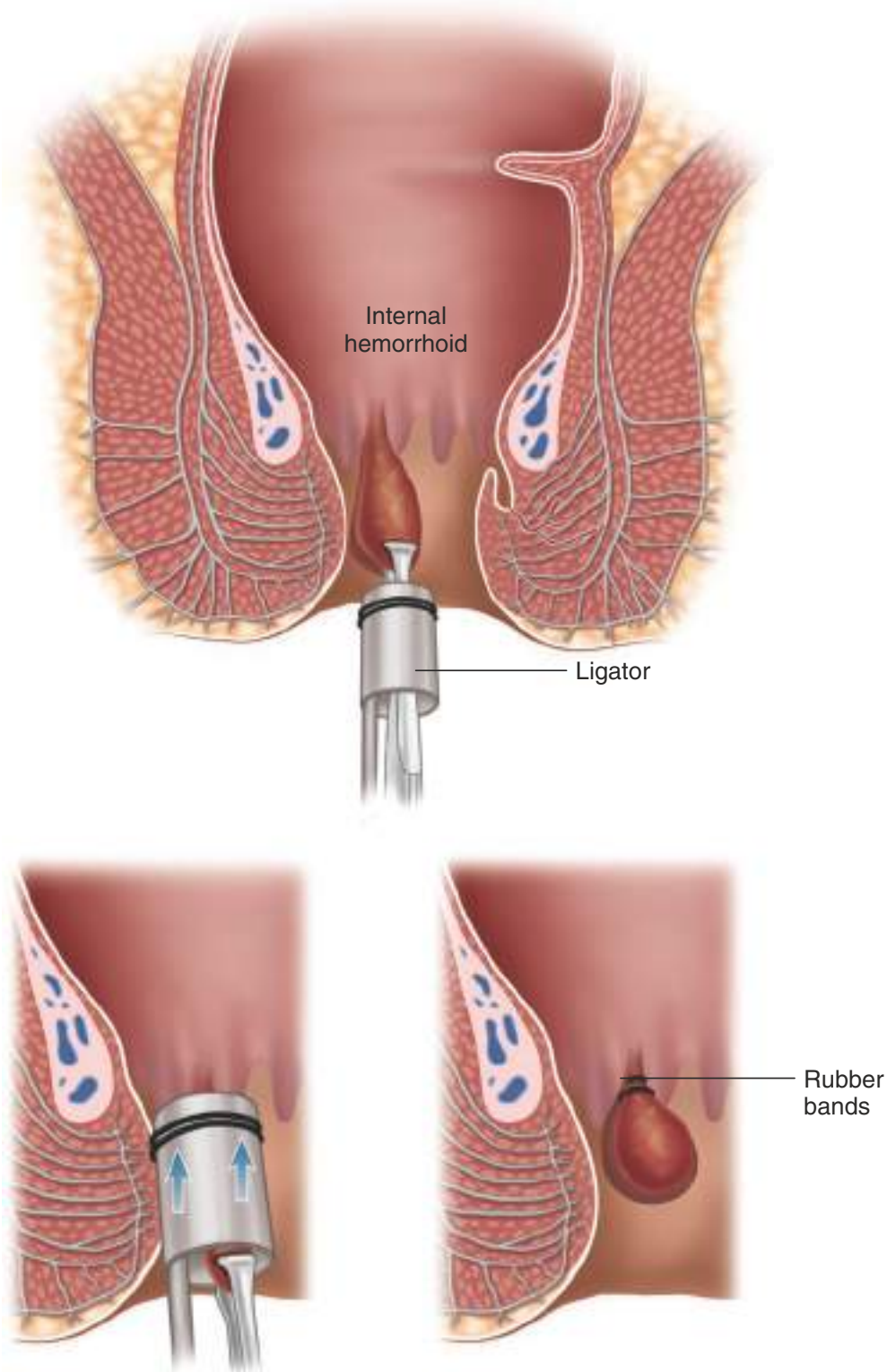

FIGURE 12-5. Hemorrhoid banding technique.

ment should be made in 2–4 weeks to evaluate the success of the banding.

Complications following banding are unusual, but the patient should be made aware of these possibilities. Delayed rectal bleeding of a significant nature occurs in approximately 1% of the patients [38]. Thrombosis can also occur especially in the remaining external component of the internal hemorrhoidal banding site [38, 39]. Abscess or urinary

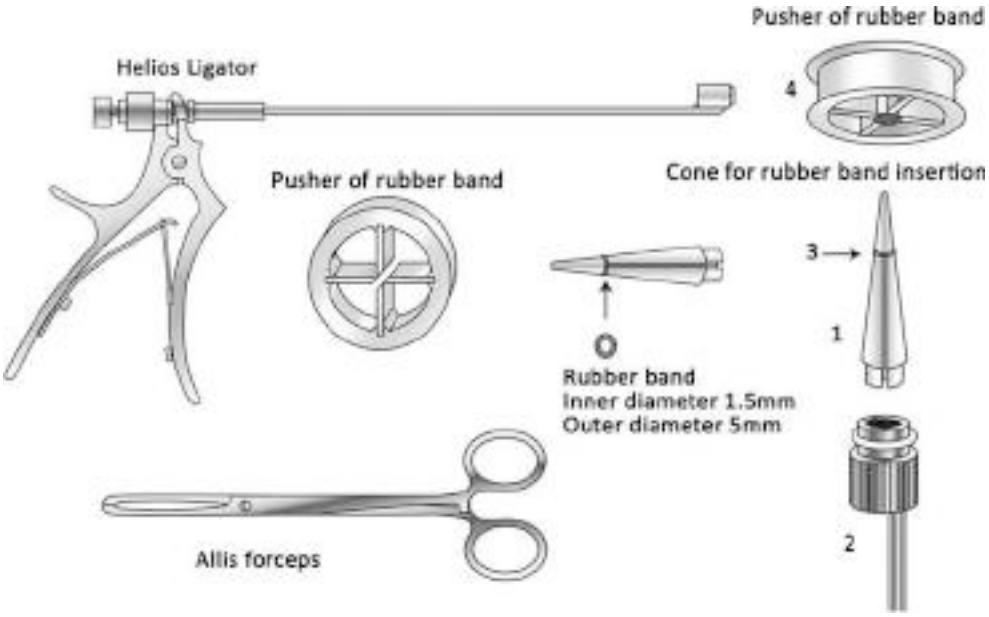

FIGURE 12-6. Hemorrhoid bander. Helio's product is easy to mount a rubber band. It uses a rubber band mounting cone (1), inserts rubber band at the end of cone (2), and pushes the rubber band to the bottom of the cone (3) using rubber band pusher (4). *With permission from Hyung Kyu Yang, Nonsurgical treatment of hemorrhoids. In: Hyung Kyu Yang, ed. Hemorrhoids. Springer, New York, 2014; pp: 47–63.© 2014 Springer.*

dysfunction is very rare [39]. A potentially devastating complication is pelvic sepsis. Although rare, several fatal cases have been reported [40–42].

Sepsis associated with hemorrhoidal banding usually presents with the triad of symptoms: increasing pain, fever, and urinary retention. Any clinician who does hemorrhoidal banding should be aware of this potential complication and be ready to treat it aggressively if it does occur. CT scan of the pelvis may illustrate air outside the rectum and/or inflammation. The diagnosis can also be made in the operating room with an exam under anesthesia. In earlier recognized and milder cases, debridement of the wound with intravenous antibiotics may suffice. In more severe cases, laparotomy with diverting colostomy and pelvic drainage may be necessary.

Rubber band ligation is very effective for the treatment of grade 1–3 hemorrhoids. Meta-analysis of multiple studies reveals that banding is the most effective non-excisional treatment available [43–45]. It should be noted, however, that 18–32% of patients require repeat treatments when followed long term [46, 47]. Still, many patients will find this to be a very acceptable alternative to the excisional treatments.

Infrared Photocoagulation

Energy ablation can be used to treat internal hemorrhoids; these options include infrared photocoagulation, bipolar diathermy, and direct current electrotherapy. Infrared photocoagulation is the most commonly used of these methods (Figure 12-7). Many of the concepts of rubber band ligation apply for infrared photocoagulation as well. Namely, ischemia of the internal hemorrhoidal vascular complex leads to scarring and fibrosis in the normal anatomic location [48]. Infrared radiation generates heat that coagulates protein and creates an inflammatory bed. The radiation is applied to the internal hemorrhoid typically at four different locations on

FIGURE 12-7. Infrared photocoagulation machine. *With permission from Hyung Kyu Yang, Nonsurgical treatment of hemorrhoids. In: Hyung Kyu Yang, ed. Hemorrhoids. Springer, New York, 2014; pp: 47–63. © 2014 Springer.*

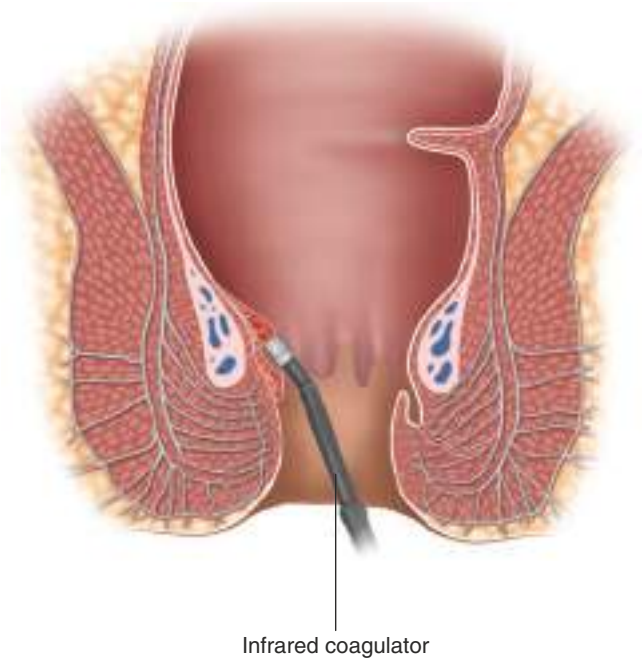

FIGURE 12-8. Infrared photocoagulation technique.

each hemorrhoidal complex. The depth of penetration is approximately 3 mm and leads to heat necrosis that causes tissue destruction and eventually fibrosis and scarring.

Positioning in preparation for this procedure is identical to that for hemorrhoidal banding and is based on physician preference (Figure 12-4). Once the patient is positioned, the tip of the infrared coagulator is used 3–4 times at the apex of each internal hemorrhoid. Each application of the photocoagulation is done for 1–1.5 s (although the device allows a range of 0.1–3 s) (Figure 12-8). The precise location of the treatment is just as important as it is for hemorrhoidal banding. If the treatment is done too low or too close to the dentate line, there will be significant post procedure pain. There is usually minimal discomfort once the treatment is complete, and all three hemorrhoid complexes can be treated at the same session [49].

Infrared coagulation is most effective for first- and second-degree hemorrhoids and may be less painful than hemorrhoidal banding [50]. While very effective for the treatment of bleeding, it is less useful for treating significant prolapse of hemorrhoids [41, 51]. Complications are rare following infrared photocoagulation and consist primarily of pain and bleeding due to excessive application of energy.

Bipolar diathermy and direct current electrotherapy have also been reported to be used in the same fashion as infrared coagulation. Bipolar energy does not penetrate as deeply as monopolar energy, and success rates for bipolar diathermy treatment have been reported from 88 to 100% [52]. Despite the good success rates, it has been noted that up to 20% of patient may require an operative surgical excision for hemorrhoid prolapse [53]. Neither energy ablation technique has been as popular as infrared coagulation.

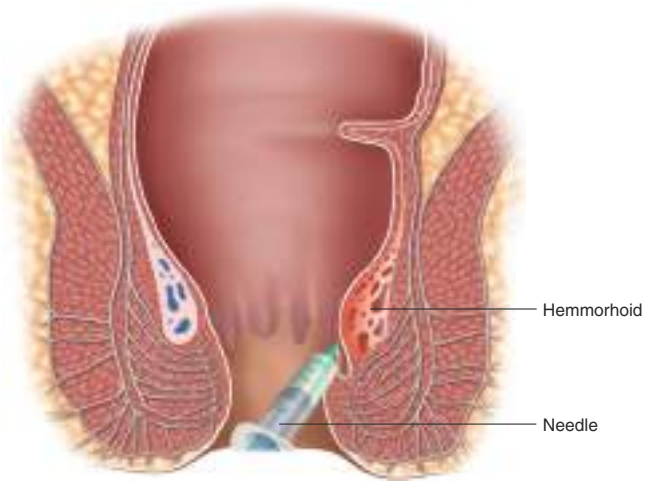

FIGURE 12-9. Sclerotherapy technique.

Sclerotherapy

Injection sclerotherapy was first attempted by John Morgan in 1869 [54]. The concept is analogous to that for infrared photocoagulation and hemorrhoidal banding: this solution is injected at the apex of the internal hemorrhoid complex which leads to scarring and fibrosis and, ultimately, to fixation of the internal hemorrhoidal complex. Many different agents have been tried including phenol, carbolic acid, quinine in urea, sodium morrhuate, and sodium tetradecyl.

The positioning of the patient, exposure, and placement of the sclerosing agent are identical to infrared coagulation. A spinal needle is used to place approximately 1–1.5 mL of the agent in a submucosal fashion at the apex of the internal hemorrhoid (Figure 12-9). The precise injection location into the submucosal space is important as placement too superficial can cause mucosal sloughing, while placing it too deep leads to more risk of infection, abscess, or significant pain. This complication usually occurs due to injection into a surrounding, unintended space [55]. Urinary retention and impotence postinjection sclerotherapy have also been reported [56].

Sclerotherapy is reported to be highly successful but is still not quite as effective as rubber band ligation especially for grade 3 hemorrhoids [57]. The best role for sclerotherapy may be in patients that require anticoagulation since the risk of bleeding is minimal with this technique. This is due to the fibrotic reaction rather than sloughing post procedure and can be safe in patients on anticoagulation. While bleeding is very unusual (approximately 1%) following hemor-

rhoidal banding, that bleeding risk can be very significant in the anticoagulated patient, and therefore sclerotherapy should be considered an option in this patient population. Multiple repeat attempts should be avoided due to the cumulative risk of stricture.

Operative Management of Hemorrhoids

Operative management of hemorrhoids is usually reserved for those patients who have failed medical management or have recurrent, persistent symptoms despite undergoing some of the internal hemorrhoidal treatments mentioned earlier in this chapter. Typically, only 5–10% of patients with hemorrhoidal complaints require operative hemorrhoidectomy [58]. Occasionally a patient will present with extensive thrombosed hemorrhoids or such advanced disease that it is clear from the initial encounter that a more aggressive approach is necessary. Strangulated, gangrenous hemorrhoids typically need immediate attention and operative intervention (Figure 12-10).

Excisional hemorrhoidectomy has excellent results, minimal recurrence rates, and few complications and remains the gold standard for surgical hemorrhoidal options. Unfortunately, it is also associated with significant postoperative pain. As a result, other newer therapies have been developed to treat hemorrhoids while attempting to minimize postoperative discomfort. The other primary operative management techniques include stapled hemorrhoidopexy and transanal hemorrhoidal dearterialization.

Excisional Hemorrhoidectomy-Closed Technique

Dr. Lynn Ferguson of the Ferguson Clinic first described the closed hemorrhoidectomy technique in the early 1950s [59]. It has remained the most common operation for hemorrhoids in the United States since that time [60]. A mechanical bowel preparation is not necessary, but preoperative enemas are useful to evacuate the rectum. Anesthesia can be tailored to the patient and can range from something as simple as local anesthesia plus intravenous sedation to a full general anesthesia with intubation. Positioning is per surgeon preference and includes the options of lithotomy, prone jackknife, and left lateral decubitus.

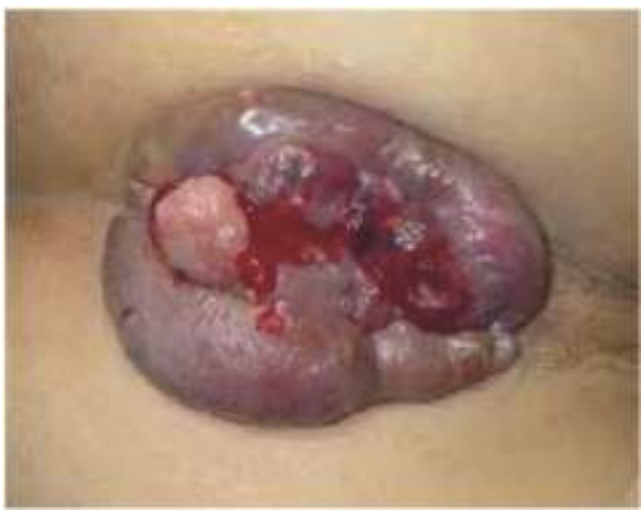

FIGURE 12-10. Strangulated, gangrenous hemorrhoids.

The operation starts with a digital exam followed by anoscopy to help clearly define which hemorrhoid complexes should be excised (Figure 12-11). Injecting the perianal skin and hemorrhoids with local anesthetic combined with epinephrine 1: 200,000 can help to decrease bleeding during the procedure. An elliptical incision is made around the hemorrhoid starting at the perianal margin, and a proportional incision should be made so that the length of the incision is approximately 3–4 times longer than its breadth. The hemorrhoid is then elevated off the underlying sphincter muscle fibers. It is useful to place the hemorrhoid under tension to facilitate this dissection. The dissection is carried out past both the external and internal component of the hemorrhoid. Sharp dissection with the scissors or scalpel or even electrocautery can be done to dissect the hemorrhoidal tissue off the underlying sphincter complex.

At the apex of the hemorrhoid, the vascular pedicle is then clamped and then the hemorrhoid excised. The vascular pedicle is then suture ligated with an absorbable suture; the same suture is then used to reapproximate the tissue. As the wound is closed, small bites of the underlying sphincter muscle can be taken in order to close the dead space. If the dissection is relatively bloody, a running locked stitch can be used to maximize hemostasis. Once the first hemorrhoid complex is excised, the remaining hemorrhoidal bundles can be examined to determine if they still need to be excised.

When multiple hemorrhoids are removed, it is important to maintain adequate skin and tissue bridges between the excision sites to minimize the risk of postoperative anal stenosis [61]. If one can still place a medium-sized Hill Ferguson retractor at the end of the procedure, then there is usually very minimal risk of anal stenosis.

A notable variation on the technique is the use of energy devices such as the LigaSure bipolar device or the harmonic device which both can be used to perform the excisional hemorrhoidectomy. The excision and dissection is done in the same fashion. It has been reported that there may be less postoperative discomfort following this approach and will be discussed in more detail later [62].

Excisional Hemorrhoidectomy Open Technique (Milligan–Morgan)

The open technique of excisional hemorrhoidectomy is very popular in the United Kingdom. This technique results in a very similar excision as the Ferguson technique except that the wounds are not closed other than suture ligating the vascular pedicle [63].

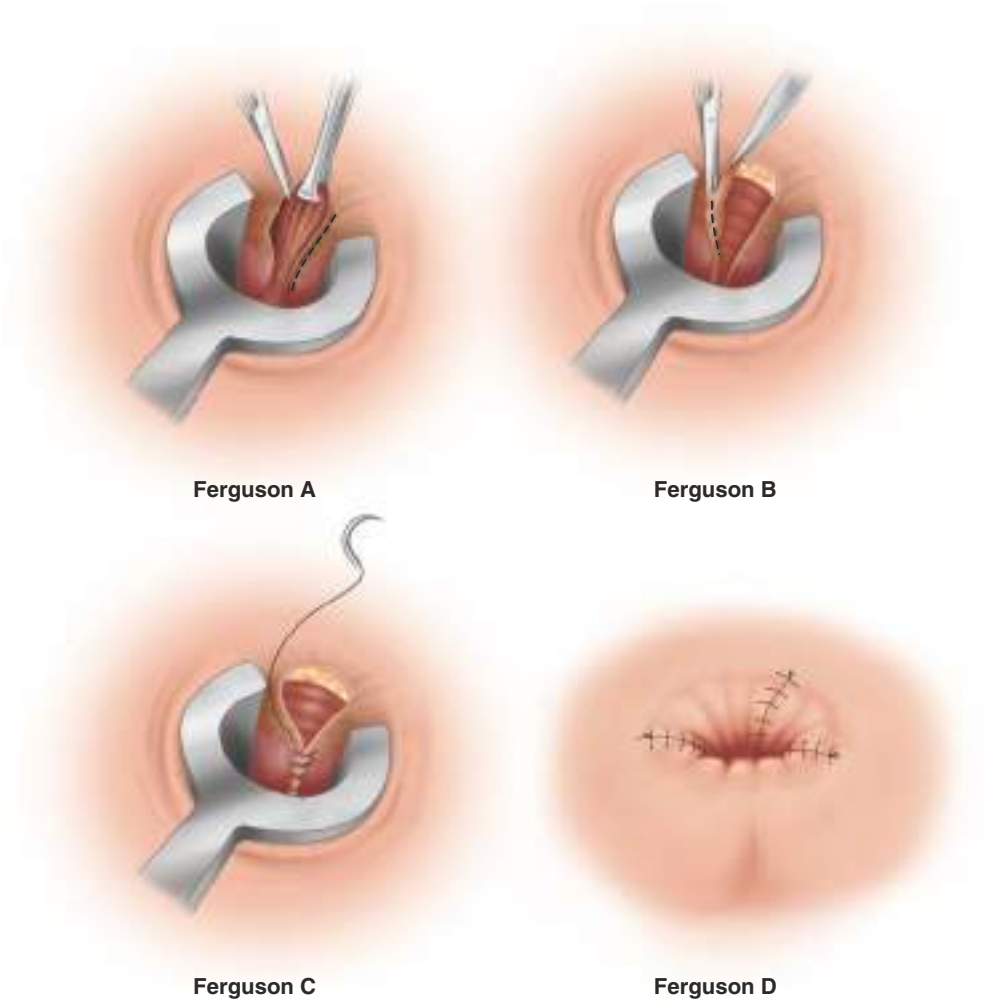

FIGURE 12-11. Closed hemorrhoidectomy.

The operation commences in a very similar fashion as the Ferguson closed hemorrhoidectomy technique. First, the external hemorrhoidal tissue is grasped, followed by the internal hemorrhoidal tissue and retracting them in a caudal fashion. An excision is then made at the perianal skin and extended into the anal canal. During the dissection it is of utmost importance to leave the sphincter muscles undisturbed. The apex of the vascular pedicle is then suture ligated and the hemorrhoid excised. The excision sites are then left open and allowed to granulate in (Figure 12-12).

Excisional Hemorrhoidectomy (Circumferential or Whitehead)

The Whitehead hemorrhoidectomy was designed to completely remove all the hemorrhoids at the time of surgery [64]. A circumferential incision is made at the level of the dentate line, and then the submucosal and subdermal hemorrhoidal tissues are dissected out and removed. Any redundant rectal mucosa is excised, and then the remaining proximal rectal mucosa sutured down to the anoderm. This operation is not in common use at this time due to the complication of a Whitehead deformity (Figure 12-13) [65].

Results of Hemorrhoidectomy

Excisional hemorrhoidectomy remains the gold standard for the long-term relief of hemorrhoidal symptoms. Although there are few longitudinal studies, MacRae et al. performed a meta-analysis that confirmed there is very little need for further treatment and that symptoms were well controlled [44].

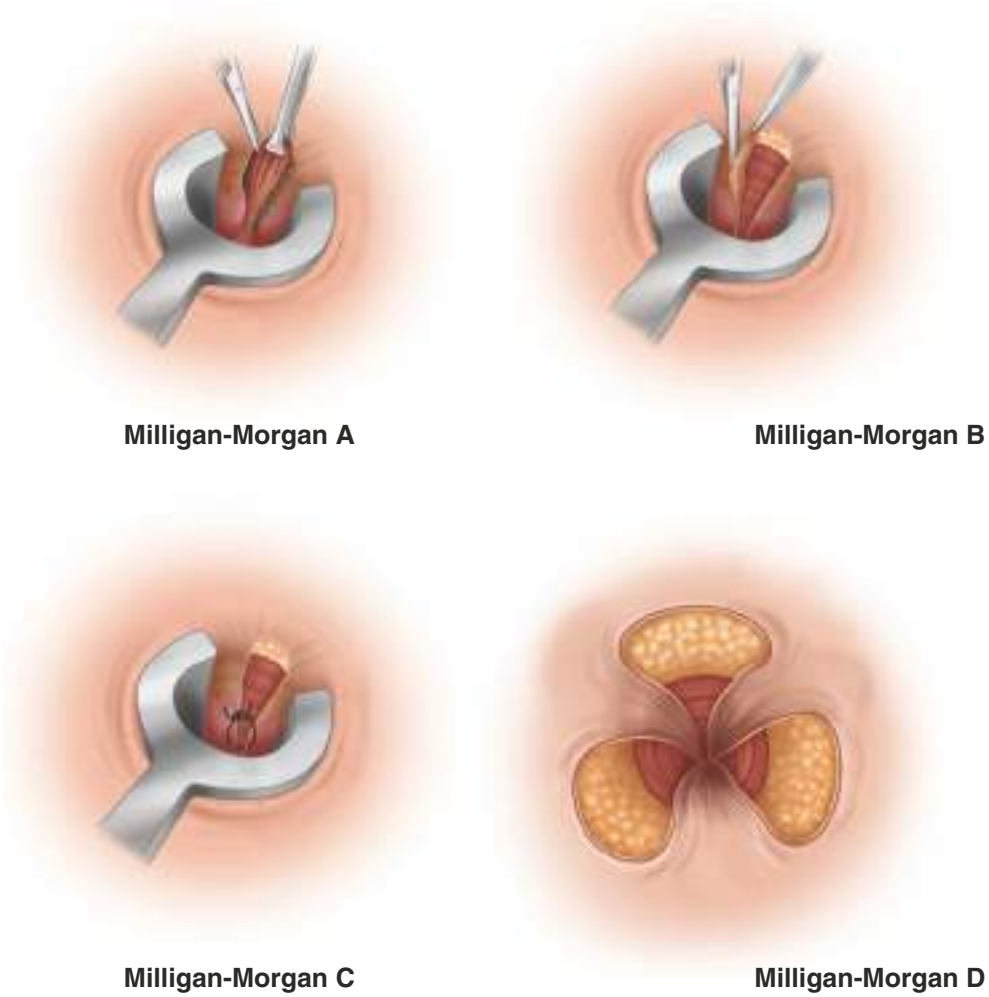

FIGURE 12-12. Open hemorrhoidectomy.

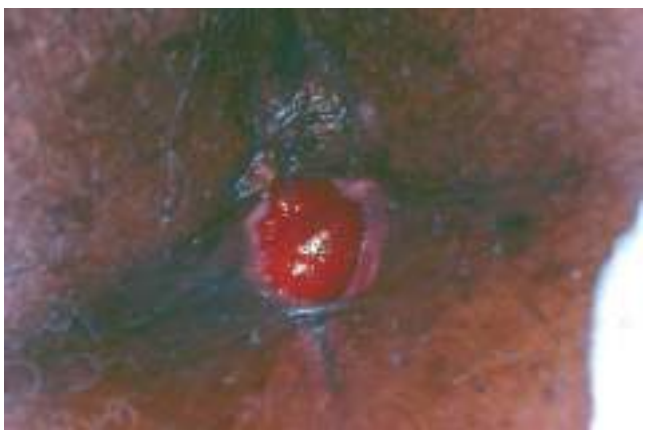

FIGURE 12-13. Whitehead deformity. Courtesy of American Society of Colon and Rectal Surgeons.

Although there has been considerable controversy over the relative merits of opened versus closed techniques, careful analysis in randomized, prospective trials suggests that there is very little difference between the two techniques [66–69]. One meta-analysis reviewed six trials with almost 700 patients and found no differences in cure rates, length of stay, maximum score, or complication rates [70].

The discomfort with hemorrhoidectomy has led to a search for less painful alternatives [71]. One such approach has been to use energy sources such as the harmonic scalpel or the LigaSure for the tissue dissection. A Cochrane review was done to compare LigaSure hemorrhoidectomy to excisional hemorrhoidectomy [72]. This review confirmed that the early postoperative pain was less when LigaSure™ (Covidien, CT) was used, but this difference disappeared by postoperative day 14. LigaSure hemorrhoidectomy was also found to be slightly faster. The same benefits appear to apply to Harmonic Scalpel™ (Ethicon, Brunswick, NJ) hemorrhoidectomy [73]. It is not clear that the increased cost of the LigaSure device or Harmonic Scalpel device would be offset by the decreased operating room time. Both LigaSure and Harmonic seem to offer patients less postoperative pain, but long-term follow-up data is not yet available. Other approaches in an attempt to decrease pain such as diathermy and the use of lasers have not shown any significant difference [74–76].

There have been other efforts to decrease the pain associated with hemorrhoidectomy. Mathai et al. described doing lateral internal sphincterotomy at the same time as the hemorrhoidectomy [77]. This additional procedure did decrease pain likely by minimizing the sphincter spasm associated with postoperative pain, but division of the sphincter muscle has prevented this approach from being widely accepted. Topical nitroglycerin has also been shown to decrease post hemorrhoidectomy pain [78]. Both oral and topical metronidazole have also been shown to decrease pain although the mechanism is not clear [79].

Complications of Hemorrhoidectomy

Urinary Retention

Urinary retention is one of the most common complications following hemorrhoidectomy and can increase hospital stay [80]. Zaheer found that disease severity, namely, number of quadrants excised, and analgesia requirements were both important risk factors for those patients who underwent hemorrhoidectomy. Although the exact reasons for this complication are not known, it is clear that both fluid restriction and pain control in the perioperative period is important to prevent this complication [81, 82]. There have been a few reports indicating that the stapled hemorrhoidectomy (PPH) is associated with a lower incidence of postoperative urinary retention [83].

Postoperative Hemorrhage

Postoperative hemorrhage is one of the more common complications after hemorrhoidectomy, although the risk is still relatively low. Bleeding typically occurs during one of two time frames post surgery. In approximately 1% of cases, the bleeding will occur in the immediate postoperative period. When this bleeding occurs, it is usually the result of a technical error and most commonly requires a return to the operating room for an exam under anesthesia and control of the bleeding.

Delayed hemorrhage can occur in up to 5.4% of patients and will typically occur 7–10 days after surgery [84, 85]. Post hemorrhoidectomy bleeding has been attributed to sepsis of the ligated pedicle in the past, although Chen et al. found that male patients and the operating surgeon may be risk factors in delayed post hemorrhoidectomy bleeding [86]. If postoperative hemorrhage occurs, immediate packing of the anal canal or tamponade with a Foley balloon catheter will control the bleeding. If the bleeding does not stop, then an exam under anesthesia may be warranted. Patients that require a trip to the operating room can be determined with the aid of rectal irrigation [87]. However, return to the operating room to investigate and control the bleeding is always a safe option.

Anal Stenosis

Anal stenosis can occur if excessive anoderm is removed at the time of the hemorrhoidectomy. The most common setting for this is when an emergency hemorrhoidectomy is done for prolapsed thrombosed hemorrhoids, and inadequate skin bridges remain post surgery. Treatment can be as simple as the use of bulk laxatives but may require dilation and or anoplasty (Figure 12-14) [88, 89].

Postoperative Infection

Postoperative infections are surprisingly uncommon. The risk of postoperative infection occurs less than 1%, but the rate may be underreported due to abscesses spontaneously decompressing. In the rare circumstance when an abscess or cellulitis occurs, it requires operative drainage and/or antibiotics as needed [90]. Prophylactic antibiotic therapy is not indicated for elective hemorrhoid surgery [91].

Fecal Incontinence

Fecal soiling or incontinence can occur following hemorrhoidectomy but is rather unusual. The etiology could be due to a combination of things like sphincter stretch during the procedure due to retraction, direct injury to the sphincter complex, or loss of the hemorrhoidal piles that have been thought to contribute approximately 10–15% of continence.

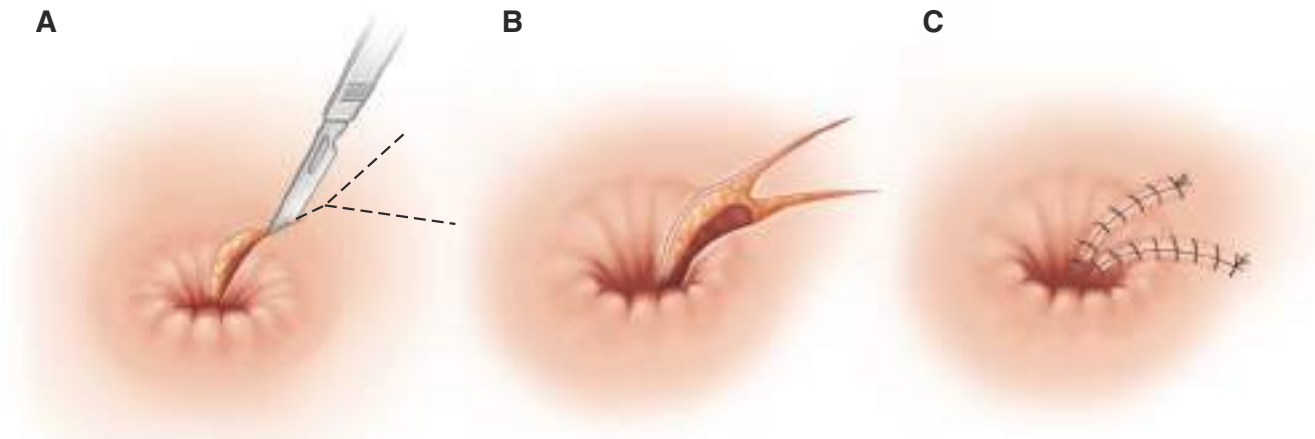

FIGURE 12-14. Y-V Anoplasty.

FIGURE 12-15. Stapled hemorrhoidectomy (PPH). *With permission from Schwandner O. Procedure for Prolapse and Hemorrhoids* (*PPH*; *Stapled Hemorrhoidopexy*). *In*: *Wexner SD*, *Fleshman JW. Colon and Rectal Surgery*: *Anorectal Operations. Wolter Kluwers*, *2011*. *© Copyright Wolters Kluwer 2011*.

Stapled Hemorrhoidopexy

Stapled hemorrhoidopexy was developed in Italy as an alternative form of operative therapy for hemorrhoids [92, 93]. It would be mistaken to refer to this procedure as a "hemorrhoidectomy" but is usually referred to as a procedure for prolapse using a hemorrhoidopexy technique (Figure 12-15). In this procedure, an end-to-end circular stapler is used to excise a circumferential ring of internal hemorrhoids, which includes the mucosa and submucosa above the dentate line (Figure 12-16). The result of the operation should be that the remaining hemorrhoids are pulled up into the anal canal and fixed in place. Some of the blood supply to the remaining hemorrhoids is also interrupted so that there is less engorgement of the remaining hemorrhoids.

Because the operation occurs above the dentate line, there has been reported less postoperative pain compared to a hemorrhoidectomy [94–96]. Indications for stapled hemorrhoidopexy include patients with second- or third-degree hemorrhoids who have failed previous nonoperative methods or have severe enough internal disease to go directly to a more aggressive approach. It is generally not used for patients with fourth-degree hemorrhoids or for thrombosed prolapsed hemorrhoids; however, some data do support this procedure in fourth-degree hemorrhoids if they can be reduced in the operating room [97].

Preparation for this operation is the same as for an excisional hemorrhoidectomy. As part of the kit that is provided with the circular stapler, there is a disposable circular translucent anoscope. With the anoscope in place, a purse-string suture is placed in a circumferential fashion into the submucosa approximately 2 cm above the transitional zone. The head of the stapler (similar to an EEA, but the head is not detachable) is then introduced into the rectum past the purse-string suture. The purse string is tied down around the stapler, and then the anvil is very slowly closed while giving gentle traction on the purse-string suture externally. Once closed, the stapler is fired and then removed along with the excised tissue. The staple line should be inspected carefully for bleeding as this is a common occurrence and may require suture ligation. In female patients the vagina should be inspected and palpated prior to firing the instrument to ensure that there is not a cuff of vaginal tissue included within the stapler.

Soon after the stapled hemorrhoidopexy technique was described, a number of randomized controlled studies were done that confirm there was significantly less postoperative pain compared to excisional hemorrhoidectomy and with equal relief of hemorrhoidal symptoms [94–96].

More long-term follow-up is now being accumulated on patients who have undergone the stapled hemorrhoidopexy. A recent Cochrane review was performed looking at seven trials with 537 patients comparing stapled hemorrhoidopexy to excisional hemorrhoidectomy. Patients undergoing excisional hemorrhoidectomy had fewer recurrences of prolapse and fewer symptoms than those undergoing stapled hemorrhoidopexy [98].

The multiple studies on hemorrhoidopexy confirm that it is a safe alternative to excisional hemorrhoidectomy; however, there are some unique complications that have been reported with this procedure including rectal perforation, persistent rectal pain, retroperitoneal sepsis, rectal obstruction, and rectovaginal fistula. The complication rate is similar between stapled hemorrhoidectomy and conventional hemorrhoidectomy, but stapled hemorrhoidectomy is associated with a higher rate of recurrent disease [99].

Transanal Hemorrhoidal Dearterialization

Transanal hemorrhoidal dearterialization is a relatively new technique first described by Morinaga in 1995 (Figure 12-17) [100]. Doppler is used to guide ligation of the arterial inflow to the hemorrhoids. Although not initially described, suture rectopexy can be done at the same setting to minimize prolapse.

Patient preparation and setup is identical to that for an excisional hemorrhoidectomy. Once proper anesthesia and positioning is accomplished, a specialized anoscope with a Doppler is introduced into the anal canal (Figure 12-18). The Doppler is used as the anoscope is rotated until one of the feeding arteries is identified and suture ligated. The Doppler can also be used to confirm that the artery was adequately ligated. The anoscope is rotated until all of the significant arteries are identified and ligated (generally 4–6 arteries, but this can be quite variable). Depending on the need to correct the prolapse, a suture mucopexy can be performed immediately following the ligation using the same stitch.

The arterial ligation and mucopexy are all done above the dentate line so one would anticipate that the pain would be less following this procedure when compared to excisional hemorrhoidectomy. Early studies seem to confirm that this procedure is less painful than a hemorrhoidectomy and equally as safe [101–104]. There seems to be a relative lack of good data to support this procedure. Giordano performed a systematic review of the available studies in 2009, and although there were 17 trials with 1996 patients, only one of these trials was a randomized controlled study. It was felt

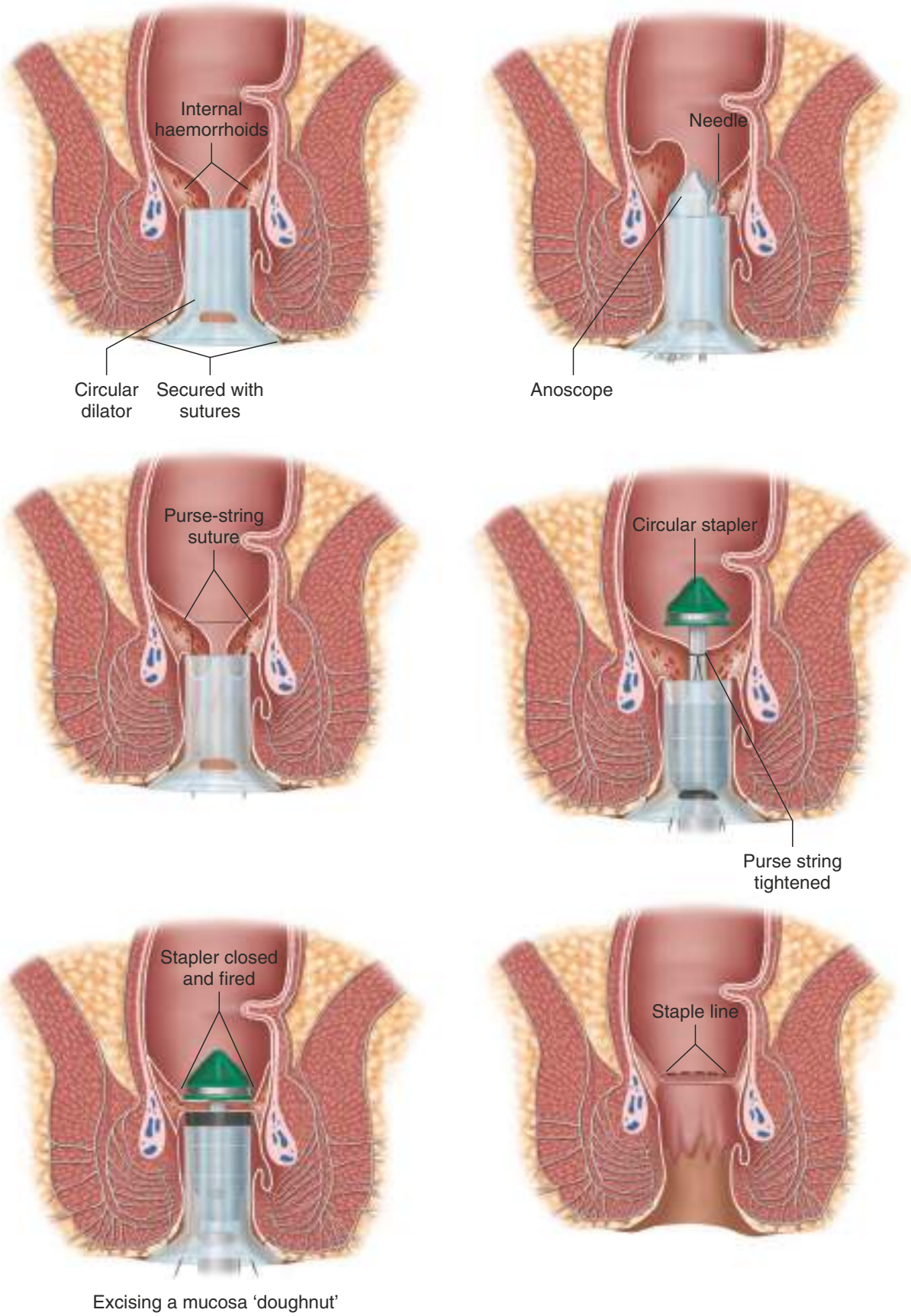

FIGURE 12-16. Stapled hemorrhoidectomy technique.

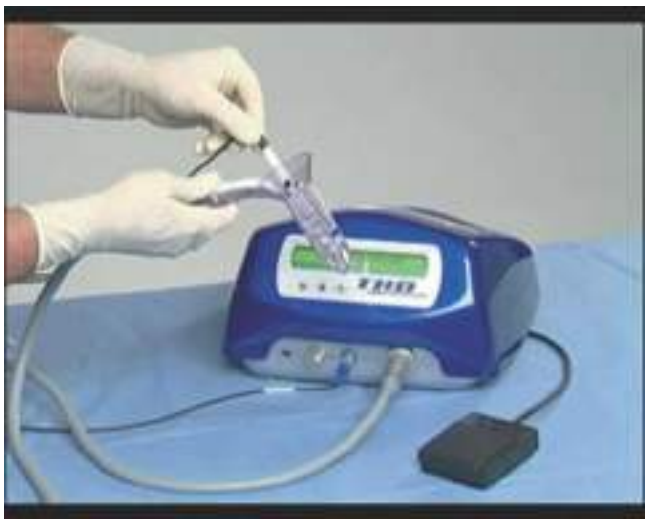

FIGURE 12-17. Transanal hemorrhoidal dearterialization device.

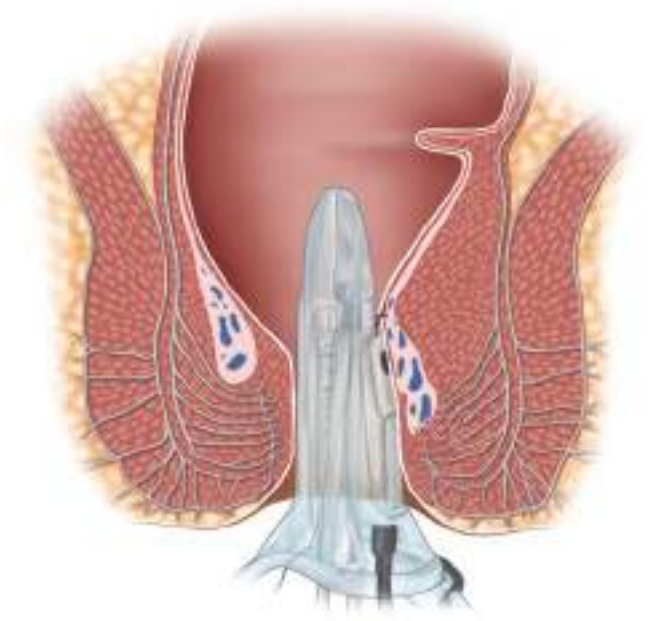

FIGURE 12-18. Transanal hemorrhoidal dearterialization technique.

that the quality of the studies included in this review was low overall. It appears to be a safe alternative with a recurrence rate of 10.8% for prolapse, 9.7% for bleeding, and 8.7% for pain at defecation at follow-up of 1 year or more [105].

Special Clinical Scenarios

Thrombosed External Hemorrhoid

A patient with acute thrombosed external hemorrhoids usually presents with the acute onset of anal pain along with a hard lump in the perianal region (Figure 12-3). Although the patient may describe a possible precipitating event, such as constipation or excessive straining, most of the time the thrombosis can occur for no apparent reason. The perianal pain and discomfort is constant and can be worse around day 3 or 4. If the patient delays long enough, the thrombosis can sometimes cause pressure ulceration and eventually skin necrosis leading to a spontaneous evacuation of the clot. In these cases, the patient will usually describe an immediate relief of the pain.

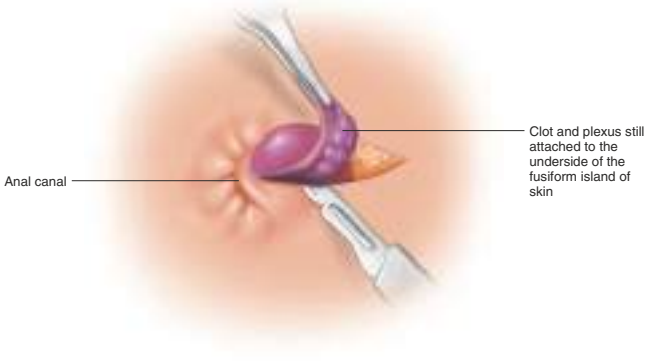

FIGURE 12-19. Enucleation of the thrombosed hemorrhoid.

The aggressiveness of the treatment is primarily driven by the patient's symptoms. Regardless of the size of the thrombosis, if the patient is relatively comfortable, it is usually best to allow the thrombosis to simply resolve on its own. On the other hand, many patients present to the physician's office due to severe, unrelenting pain, and in this circumstance, enucleation of the thrombus can be very helpful.

This procedure can usually be done under local anesthesia in the office although some patients may require sedation or even general anesthesia (Figure 12-19). In the office setting, local anesthesia can be used at the level of the thrombosed hemorrhoid. Once anesthetized, the skin should be excised overlying the thrombosis to allow as much of the clot to be removed. Bleeding is usually not troublesome and can be controlled with pressure, silver nitrate, and suture ligation if necessary. The wound can be left open or closed with absorbable sutures, depending on the preference of the surgeon (see Video 12-1) [106].

Strangulated (Thrombosed Prolapsed) Hemorrhoids

Strangulated or thrombosed, prolapsed hemorrhoids are internal hemorrhoids that are both incarcerated and irreducible (Figure 12-10). Patients typically have a previous history of prolapsing hemorrhoids and will present with an acute episode of pain and protrusion that is no longer reducible. They may also complain of urinary retention and referred pain. A thorough physical examination will demonstrate

both prolapsed incarcerated internal hemorrhoids and thrombosed external hemorrhoids. A significant amount of edema may be present and, if left untreated, may progress to ulceration, necrosis, and eventually gangrene.

Enucleation of the thrombus is inadequate treatment and not appropriate for this clinical scenario. Treatment usually consists of an urgent excisional hemorrhoidectomy in the operating room. The excisional hemorrhoidectomy can be performed in an open or closed technique, although some recommend an open technique in the face of necrosis. A newer option may include the bipolar device hemorrhoidectomy.

An alternative treatment option, if the patient does not wish to go to the OR or does not want surgery or if the OR is unavailable, can be performed in the office or ED setting. This includes using local anesthetic, applying pressure and/or massage to decrease the edema in the tissues, and then using a combination of rubber band ligations and thrombectomies. This will provide immediate relief for the patient and will not usually require a future surgical hemorrhoidectomy [107].

Portal Hypertension and Hemorrhoids

"Hemorrhoids" or rectal varices in patients with portal hypertension are a distinct entity compared to hemorrhoids in the general population. Rectal varices in patients with portal hypertension provide collateral circulation from the portal system into the systemic venous circulation. As previously mentioned, internal hemorrhoids drain into the middle rectal veins, then the internal iliac veins, and finally the systemic circulation. External hemorrhoids drain into the inferior rectal veins and then the internal iliac veins. The incidence of hemorrhoid symptoms in patients with portal hypertension is similar to the general population [108].

Anorectal varices are very common in patients with portal hypertension. There are reports of anorectal varices present in up to 78% of patients with portal hypertension [109]. Unlike esophageal varices, which are commonly present in this population, anorectal varices rarely bleed. Less than 1% of massive bleeding in these patients is attributed to anorectal varices or "hemorrhoids."

Treatment options for bleeding from the anorectal varices in this patient population are varied. Recommendations include conservative medical management, medical management of the portal pressures, sclerotherapy, suture ligation, stapled anopexy, and, lastly, TIPS and portosystemic shunts [110, 111].

Pregnancy

Hemorrhoid symptoms are not uncommon during pregnancy and can be exacerbated by the physiology of pregnancy, including increased circulating blood volume, impaired venous return, and change in bowel habits, namely, constipation and straining associated with labor. Usually the hemorrhoid symptoms present during pregnancy resolve after delivery and rarely need intervention. Surgical intervention is not warranted during pregnancy unless patients present with strangulated, gangrenous hemorrhoids. Local anesthesia is recommended in the left lateral position in order to rotate the uterus off of the IVC. It has been reported that only approximately 2% of pregnant women require emergent hemorrhoidectomy for strangulated hemorrhoids [112].

Crohn's Disease

Hemorrhoids can occur in patients with Crohn's disease and may require surgical attention; however, patient selection is very important. Hemorrhoid symptoms can be exacerbated in patients with Crohn's disease due to varied bowel habits, namely, diarrhea. Any anorectal surgical intervention must be performed with caution in patients with Crohn's disease due to prolonged wound healing and ulcerations. If the patient has well-controlled Crohn's disease and is not on steroids and there is little active inflammation, then Crohn's disease is not an absolute contraindication to surgical intervention. It has been reported to have a high rate of complications and can precipitate proctectomy for surgical complications not manageable with conservative means [113].

With the advent of newer medical therapies for Crohn's disease, the rate of prolonged healing and associated complications is much less. This was demonstrated in a study by Wolkomir and Luchtefeld where 90% of healing occurred in patients who underwent a hemorrhoidectomy where the ileocolic Crohn's disease was well managed. Hemorrhoidectomy, however, should not be performed in those patients with anorectal Crohn's disease or Crohn's proctitis [114].

Immunocompromised Patients

Immunocompromised patients with hemorrhoidal disease can be a very challenging and difficult clinical dilemma. Similar to the Crohn's disease population, extreme caution should be exercised when considering surgical therapies in this population. Again, poor wound healing and infectious complications are at the forefront of decision making. The HIV/AIDS population does suffer a higher degree of complications post hemorrhoidectomy [115]. Patients who are neutropenic should be offered nonoperative therapies first although the mortality rate in this patient population who undergoes a hemorrhoidectomy is not higher [116].

Symptomatic Hemorrhoids

Figure 12-20 shows a treatment algorithm for symptomatic hemorrhoids.

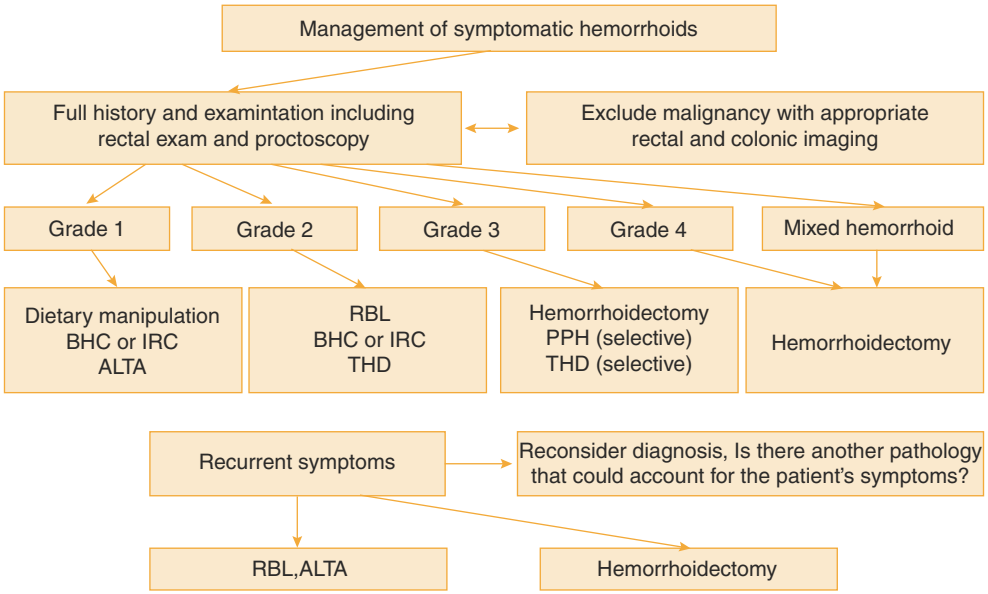

FIGURE 12-20. Treatment algorithm for symptomatic hemorrhoids. *RBL* rubber band ligation; *IRC* infrared coagulation; *THD* transanal hemorrhoidal dearterialization; *PPH* procedure for prolapsing hemorrhoids; *BHC* bipolar hyperthermic coagulation; *ALTA* Aluminum potassium sulfate and tannic acid (sclerotherapy). Adapted from Song G, Kim S. Optimal treatment of Symptomatic Hemorrhoids. J Korean Soc Coloproctol. 2011 Dec; 27(6): 277–81.

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13
Anal Fissure

Kim C. Lu and Daniel O. Herzig

Key Concepts

- An acute anal fissure (symptoms <6 weeks) is likely to heal (87%) with dietary modification and supportive care.
- In a chronic anal fissure (symptoms >6 weeks), topical nitroglycerin or calcium channel blockers are slightly better than placebo in inducing healing.
- Injection of botulinum toxin into the internal anal sphincter can heal fissures refractory to topical ointments; though this is not as effective as lateral internal anal sphincterotomy.
- Lateral internal anal sphincterotomy is the most effective therapy in healing fissures; there is an increased risk, however, of fecal incontinence.
- For anal fissures associated with decreased anal sphincter tone, a dermal advancement flap is a reasonable option.

Definition/Clinical Presentation

An anal fissure is a tear in the epithelial lining of the distal anal canal [1]. While this is likely an extremely common condition, it is difficult to know exactly how common. Many people assume this is a hemorrhoidal problem and initially avoid formal evaluation. Further, many fissures will resolve without intervention. Nevertheless, persistent anal pain and bleeding eventually push many patients to seek medical attention. In one single colon and rectal surgery clinic, anal fissures resulted in more than 1200 office visits over a 5-year period [2].

Fissures can be classified as acute vs. chronic and typical vs. atypical. Acute fissures cause bright red bleeding with bowel movements and sharp, burning, tearing anal pain or spasm that can last for hours after the bowel movement. Physical findings include a linear separation of the anoderm, at times visible with just separation of the buttocks (Figure 13-1). Often, elevated anal resting pressures are appreciated on digital rectal examination. If tolerated by the patient, the suspected diagnosis can be confirmed by visualizing the break in the anoderm with office anoscopy after using an anesthetic lubricant. If only one area can be examined, the posterior midline should be evaluated first, as it is the site of up to 90% of typical anal fissures. The remaining minority of typical fissures are found in the anterior midline [3]. Acute fissures generally resolve within 4–6 weeks of appropriate management; chronic fissures are therefore defined as those producing symptoms beyond 6–8 weeks. Chronic fissures have additional physical findings of an external sentinel tag at the external apex, exposed internal sphincter muscle, and a hypertrophied anal papilla at the internal apex (Figure 13-2).

Typical fissures are usually located in the posterior or anterior midline, have the characteristic findings described above, and are not associated with other diseases. In contrast, atypical fissures can occur anywhere in the anal canal (Figure 13-3), can have a wide variety of findings, and can tend to be associated with other diseases, including malignancy, Crohn's disease, human immunodeficiency virus (HIV) infection, syphilis, and tuberculosis (Figure 13-4).

Pathogenesis

Despite the common nature of this long-standing problem, the exact etiology remains uncertain. Many have described onset of a fissure after the passage of a large, hard stool or anal trauma.

By a mechanical theory, the occurrence in the posterior midline might be because the anorectal angle creates the greatest stress at this location [4]. Sphincter hypertonicity has been frequently described in early reports of the disease

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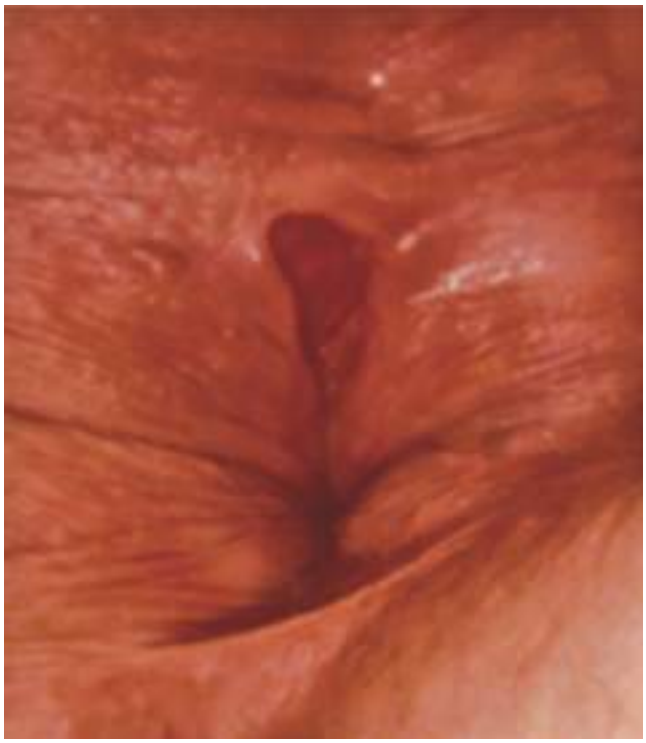

FIGURE 13-1. Acute fissure with clear edges and no signs of chronicity of sphincter hypertrophy. Courtesy of Dr. Richard P. Billingham, MD.

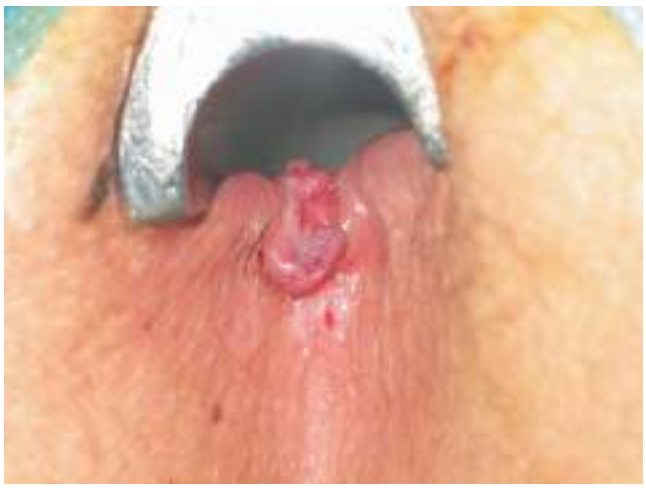

FIGURE 13-2. Chronic fissure with external sentinel tag, internal hypertrophied papilla, and thickened internal anal sphincter muscle.

and has been documented by manometry in multiple studies [5, 6]. It is not clear, however, if the elevated pressures are a cause of the disease or an effect [7].

A second common theory is relative ischemia of the posterior midline. This area of the anal canal has been shown to be relatively ischemic by both arteriographic studies and laser Doppler flowmetry [8, 9]. The theories of hypertonicity and ischemia may be related to some extent, particularly in that hypertonicity may aggravate the relative ischemia.

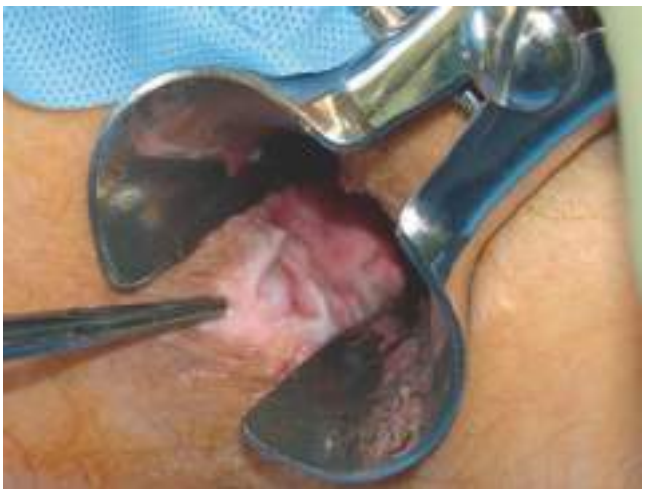

FIGURE 13-3. Atypical fissure with skin changes, broad base, and lateral location. Courtesy of Sam Atallah, MD.

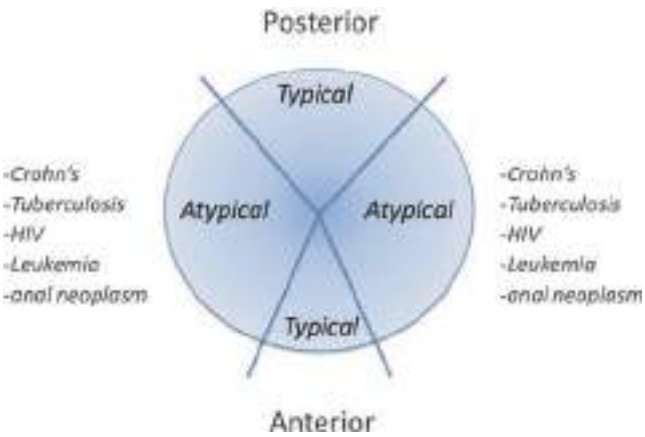

FIGURE 13-4. Type of fissure by location.

Nevertheless, tears in the anoderm undoubtedly occur with a great deal of frequency, whether from a large stool, anorectal intercourse, or instrumentation for surgical procedures, and the evolution to a chronic fissure is likely only seen in a minority of these instances. Furthermore, fissures can occur in the absence of any trauma or constipation.

Nonoperative Treatment

Healing Rates in Acute Anal Fissure

Practice parameters from the American Society of Colon and Rectal Surgeons state that conservative therapy is safe, has few side effects, and should usually be the first step in therapy [10]. Jensen reported a randomized trial done in patients with acute anal fissure. The control group in this trial was instructed to take 10 g of unprocessed bran twice daily and use a warm sitz bath for 15 min twice daily and after bowel

movements, if possible. Overall, 91% of patients were able to follow the study protocol. In that control group, the fissure healing rate was 87% [11].

Healing Rates in Chronic Anal Fissure

A more frequent problem for the surgeon is the patient who has had symptoms for several weeks and has failed an initial approach similar to that described by Jensen. In these patients, spontaneous healing rates are likely to be seen in only a minority of patients. A recent Cochrane review of the nonoperative treatment of anal fissure analyzed over 70 randomized trials of chronic anal fissure [12]. Unlike the acute fissure population, the healing rate in the combined placebo group is 35.5%.

Because internal anal sphincter hypertonicity is related to anal fissure, initial nonoperative treatment is targeted to alleviate internal anal sphincter activity through two topical agents, nitroglycerin and diltiazem, and one injectable agent, botulinum toxin A.

Topical

Nitroglycerin

Nitric oxide was reported to be the neurotransmitter mediating relaxation of the internal anal sphincter in the early 1990's [13]. Topical application of 0.2% glyceryl trinitrate ointment (GTN) was subsequently found to result in relaxation of the anal sphincter by manometric studies [14]. A landmark randomized trial was reported in 1997. That showed a healing rate of 68% with GTN treatment, compared with 8% in the placebo group [15]. The recent Cochrane analysis of 18 trials (four including children), however, showed a healing rate of 48.9% with GTN treatment, compared to 35.5% in the placebo or control group. With longer-term follow-up, recurrence varied from 51 to 67% [12].

The most common side effect of topical GTN treatment is headache, at a reported rate of 27% in the pooled analysis and may be as high as 50% [16]. While often minor and temporary, it may lead to discontinuation of therapy in 10–20% of patients [17–19]. In one prospective randomized trial comparing endoanal application vs. perianal application, endoanal application of 0.4% nitroglycerin bid was associated with decreased frequency and severity of headaches [20]. A second potential drawback to topical GTN is tachyphylaxis, which does not respond to escalations in dose or frequency.

There is was not an FDA-approved indication for nitroglycerin in the United States until 2011. The topical form of nitroglycerin was initially supplied as a 2% ointment. To achieve a 0.2% concentration, the prescription often needs to be filled at a compounding pharmacy. Jonas et al. reported that after application of 0.2% GTN, the reduction in mean anal resting pressure lasted only about 2 h, which may explain some of the treatment failures seen with GTN [16]. In 2011, the FDA approved Rectiv (0.4% nitroglycerin) which is applied endoanally bid for 6–8 weeks. At 24-week follow-up, there was a 77% healing rate [20].

Calcium Channel Blockers

Both diltiazem and nifedipine have been described either orally or topically to cause relaxation of the smooth muscle of the internal anal sphincter. Oral and topical nifedipine have been shown to lower mean resting anal pressure [21]. Similarly, diltiazem has been shown to decrease mean resting anal pressure, although the effect is greater with topical diltiazem [22, 23]. Since studies done with calcium channel blockers have more variability with respect to the medication, dosages, and routes, it is difficult to pool data for analysis. Multiple small trials suggest healing rates equivalent to GTN with fewer side effects [24, 25]. Neither diltiazem nor nifedipine are FDA approved for the treatment of anal fissure. There is no topical formulation available in the United States, so a compounding pharmacy needs to make a topical gel from an oral formulation.

Botulinum Toxin Type A

Botulinum toxins are a family of neuroparalytic proteins synthesized by *Clostridium botulinum*. They inhibit the release of acetylcholine at the neuromuscular junction [26, 27]. These agents can be used to induce a local paralysis that lasts for several months, depending upon the subtype used. The toxins are labeled A through G, according to immunologic specificity, with type A being most commonly used in the United States. Botulinum toxins are Food and Drug Administration approved for treatment of certain spastic disorders, but not anal fissures. They have been used off-label in other disorders, including chronic anal fissures. There is no uniformly recommended dose or site of injection. Botulinum toxin type A is supplied as a powder in 100-unit single-patient-use vials. Once reconstituted, any remaining solution after use must be discarded. Relaxation of the muscle occurs within days and lasts for 2–4 months. This has the theoretical advantage of allowing fissure healing while avoiding permanent fecal incontinence.

After the initial report in 1994, various methods of injection, including injection into the internal or external sphincter, at single or multiple sites, and in various doses, have been described [28]. In one small study of 50 patients with posterior anal fissures, patients were randomized to anterior vs. posterior internal anal sphincter injections. Those injected in the anterior internal anal sphincter were significantly more likely to heal [29].

Botulinum toxin injections of the internal anal sphincter have been compared with placebo, as well as other treatments, with mixed results. In a widely referenced, early, double-blind, placebo-controlled randomized crossover trial

of 30 patients, botulinum toxin A injection was found to be superior to saline injection, with a healing rate of 73% with Botox, compared to 13% with placebo ($p=0.003$) [30].

Trials have compared botulinum toxin injection with lateral internal sphincterotomy for fissures refractory to topical medical management. Arroyo et al. reported a randomized controlled trial of 80 patients and showed healing rates of 92.5% for the lateral internal sphincterotomy group, compared with 45% in the botulinum toxin group. They concluded, however, that botulinum toxin was still their preference in patients over 50 or at risk for incontinence due to a higher but not statistically significant incidence of incontinence after sphincterotomy [31]. Other small studies support the finding of higher number of treatment failures, but fewer complications in the botulinum toxin group [32, 33]. In a recent meta-analysis of seven randomized controlled trials, comparing botulinum toxin injection with lateral internal anal sphincterotomy, the healing and recurrence rates were worse with botulinum toxin [34]. In a recent randomized prospective trial comparing lateral internal sphincterotomy with Botox injection/topical diltiazem, 1-year healing rates were far superior with lateral internal anal sphincterotomy (94% vs. 65%) [35].

There is limited data regarding the long-term effectiveness of botulinum toxin. In one retrospective review of 411 patients who failed topical diltiazem, patients were treated with 100 units of botulinum toxin A and underwent fissurectomy under general anesthesia. 74% were healed at 2-year follow-up. Of note, the botulinum toxin was injected into the intersphincteric space.

Operative Treatment

Anal Dilation

One of the earliest forms of treatment was anal dilation, first described in 1829, and studied later in various trials for anal fissure [36, 37]. While extensively studied, there is considerable variability in the technique and a wide range of reported outcomes. Few well-controlled studies exist. The recent Cochrane review included an analysis of seven randomized controlled trials, comparing manual anal stretch to internal sphincterotomy [38]. They demonstrated that dilation was not more effective than sphincterotomy and had a higher rate of incontinence (OR = 4.03, 95% CI = 2.04–7.46). A more standardized and objective method of anal stretch, balloon dilation, has been reported. Renzi et al. evaluated the use of balloon dilation compared to lateral internal sphincterotomy in a prospective randomized trial [39]. Healing rates were high in both groups, and there was no difference between the groups. After 24 months of follow-up, however, incontinence was zero in the balloon dilation group, compared to 16% in the lateral internal sphincterotomy group ($p<0.0001$). While manual dilation is no longer indicated for anal fissure, balloon dilation may be one alternative.

Anal Sphincterotomy (Technique)

While also described in various forms since the early 1800's, isolated division of the internal anal sphincter muscle (sphincterotomy) was first described by Eisenhammer in the 1950's [40]. His technique of posterior internal sphincterotomy at the site of the fissure led to a posterior midline "gutter" or "keyhole" deformity, leading to fecal soiling in 30–40% of patients. Notaras described a simple modification: performing the sphincterotomy laterally, which eliminated this problem [41]. Since then, lateral internal anal sphincterotomy has become the main surgical intervention for failure of medical management. The procedure can be done under local anesthesia, as an outpatient. The variations currently include open vs. closed technique and conservative vs. traditional sphincterotomy. The closed technique is performed by inserting the scalpel blade in the intersphincteric groove and then turning it medially to break the fibers of the internal sphincter (Figure 13-5). The open technique is done through a radial incision overlying the intersphincteric groove. After dissecting the internal anal sphincter away from the anoderm, the distal internal anal sphincter is divided under direct vision (Figure 13-6). Division was originally described to the dentate line, but recent reports describe a more conservative approach, either with division of the muscle to the fissure apex or with division just until the band of hypertrophied muscle is released.

Outcomes Between Closed and Open Anal Sphincterotomy

From the Cochrane Library, a systematic review on the operative procedures for anal fissures was updated in 2011 [38]. The techniques of open and closed sphincterotomy have been compared in multiple reports, including five randomized studies that met inclusion criteria for the Cochrane analysis [42–46]. Combined, these reports show no difference in either persistence of fissure or incontinence with the two techniques. A prospective cohort study evaluated 140 consecutive patients undergoing open or closed sphincterotomy with postoperative endosonography [47]. Postoperative endoanal ultrasounds showed that open sphincterotomy was associated with a significantly higher proportion of complete sphincterotomies. The rate of incontinence and treatment failure was not different between the open and closed groups, but there was a strongly significant increase in incontinence scores ($p<0.001$) and decrease in recurrence rates ($p<0.001$) with increasing length of sphincterotomy.

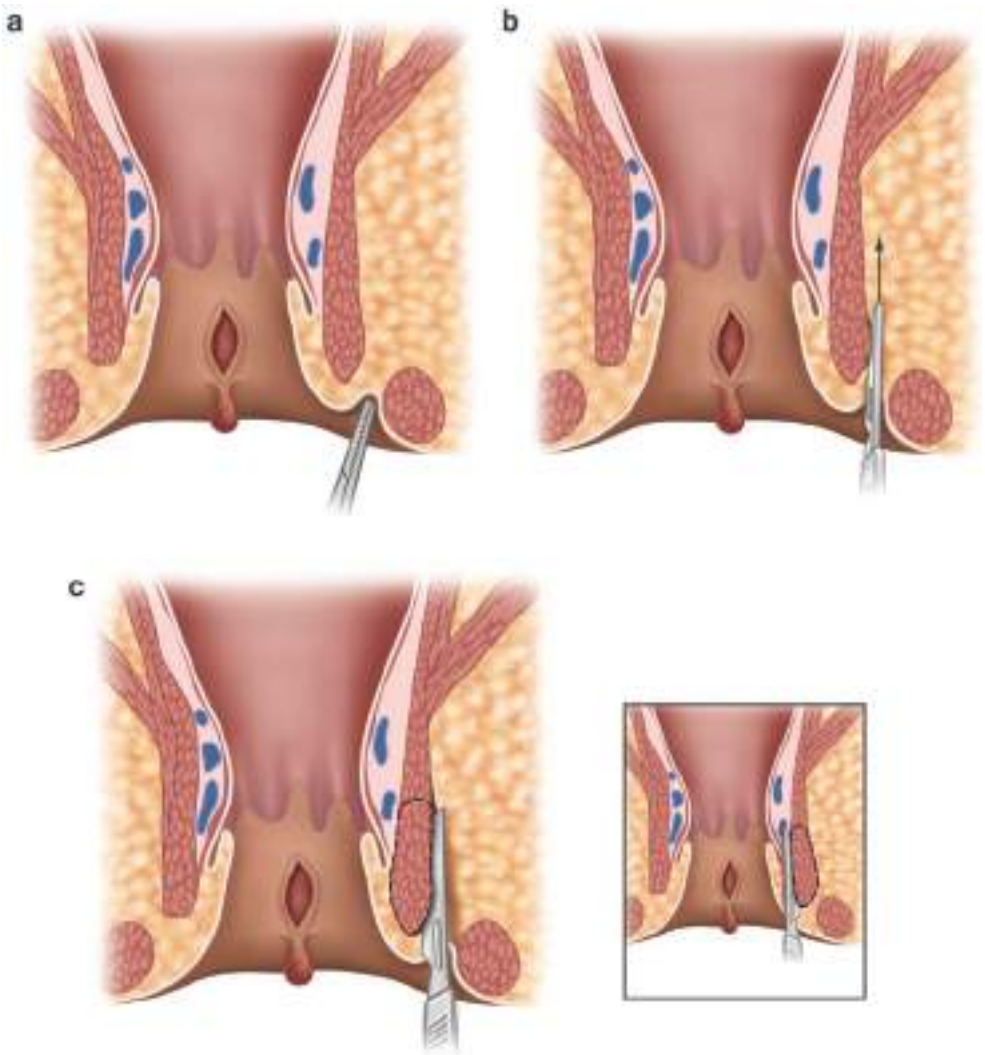

FIGURE 13-5. Closed lateral sphincterotomy. (**a**) Location of the intersphincteric groove. (**b**) Insertion of the knife blade in the intersphincteric plane. (**c**). Lateral to medial division of the internal anal sphincter (*inset*: medial to lateral division of the muscle).

Extent of Sphincterotomy

The decision regarding the extent of sphincterotomy performed in the operating room is a controversial topic. Excessive division increases the risk of incontinence, yet inadequate division increases the risk of persistence or recurrence. While many texts describe division to the dentate line, recent studies have examined a more conservative sphincterotomy. Mentes et al. prospectively randomized 76 patients with chronic anal fissure to lateral internal sphincterotomy to the dentate line or to the apex of the fissure [48]. Treatment failure was zero in the traditional group, and 13% in the conservative group after 1 year of follow-up, with most of the treatment failures occurring after 2 months. There was no statistically significant difference in the postoperative incontinence scores between the two treatment groups. There was, however, an increase in the postoperative incontinence score in the traditional group; this study may have been underpowered to detect a possible difference. In a similar manner, Elsebae et al. prospectively randomized 92 patients to sphincterotomy to the dentate line (traditional) or sphincterotomy to the apex of the fissure (conservative) [49]. Treatment failure was zero in the traditional group and 4% in the conservative group (p = NS); persistent incontinence was 4% in the traditional group and 0% in the conservative group (p = NS). The follow-up period, however, was only 18 weeks. In an even more recent study, Magdy et al. randomized 150 patients to traditional sphincterotomy, V-Y advancement flap, or conservative sphincterotomy + V-Y advancement flap. The healing rates were 84% in the traditional group and 94% in the conservative division/advancement flap group. The incontinence rates were 14% vs. 2%, respectively. The low healing rates with traditional sphincterotomy, however, are a bit hard to believe [50].

The techniques of division to the dentate line or to the fissure apex have objective definitions, yet many surgeons approach the sphincterotomy as a more subjective task. The band of hypertrophied internal anal sphincter muscle may or may not relate to either of these two landmarks. While division of the hypertrophied muscle segment is subjective, a subsequent report from Mentes et al. attempted to compare this method by creating a sphincterotomy that achieves an

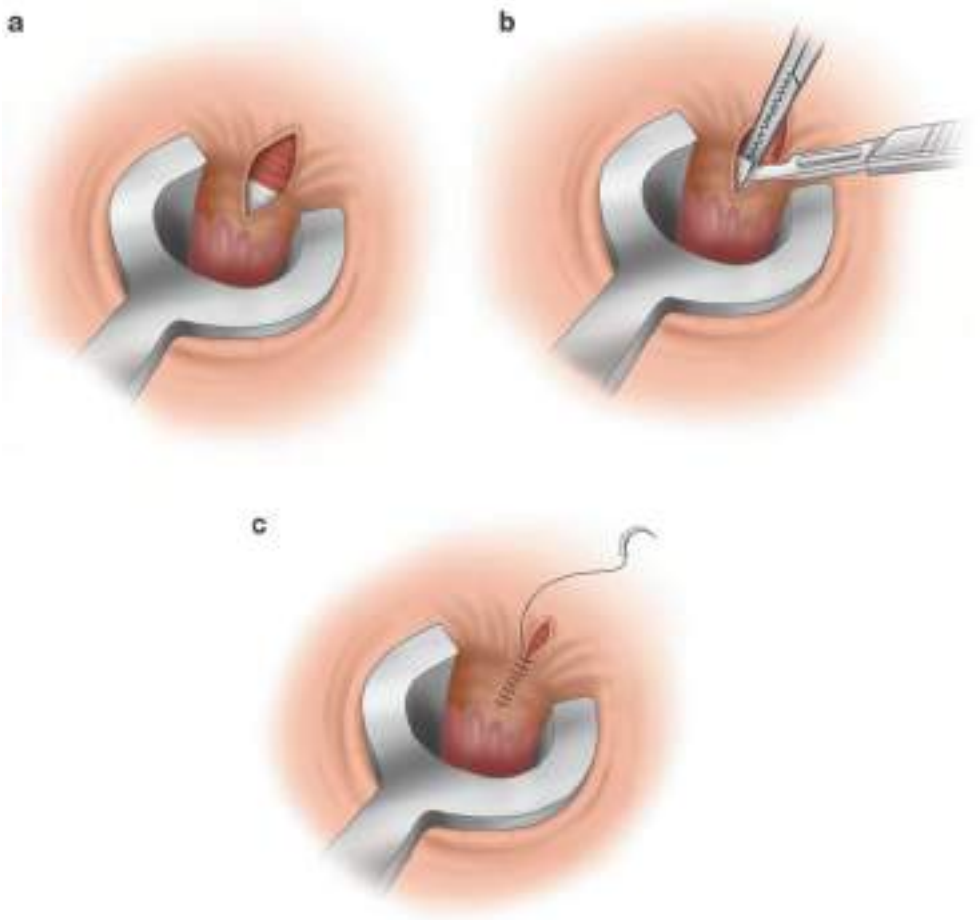

FIGURE 13-6. Open lateral internal sphincterotomy. (**a**) Radial skin incision distal to the dentate line exposing the intersphincteric groove. (**b**) Elevation and division of the internal sphincter. (**c**) Primary wound closure.

anal caliber of 30 mm. They prospectively compared this technique to division to the apex of the fissure [51]. Their findings showed the average anal caliber was greater in the group that underwent division to the apex, the incontinence rates were higher, and there was no significant difference in treatment failure.

Fissurectomy

The hallmark of chronic fissure is the triad of a hypertrophied internal sphincter, a hypertrophied anal papilla, and an external sentinel tag. Excision of the papilla and tag, or complete fissurectomy, is optional, but particularly useful if the fissure edges appear rolled and epithelialized, as this may promote faster wound healing. Renewed interest in fissurotomy (unroofing of superficial tract extending caudad from fissure) as primary treatment of the fissure has recently been reported [52].

Results of Sphincterotomy

In addition to these randomized controlled trials, a myriad of additional nonrandomized reports are available, describing a wide range of results from lateral internal sphincterotomy. While most reports cite low rates of treatment failure, the incontinence rate is widely variable and is as high as 30–40% [53, 54]. With a multimodal approach designed to minimize the risk of permanent incontinence, the trend is clearly moving away from lateral internal sphincterotomy and toward more medical therapy and/or botulinum toxin. It is not clear whether or not this strategy will be the most effective long-term solution with respect to morbidity, costs, and patient satisfaction. The disease, however, is largely measured by the subjective experience of the patient, who is ultimately the best judge of which treatment is worth pursuing and which risks are worth taking. Floyd et al. reported that with multiple options offered to patients, the ultimate time to healing is prolonged, but 72% of patients can avoid operative treatment, and 97% of patients can be healed [55].

In a similar report with a median follow-up of 47 months, Lysy et al. reported results from their approach of escalating from topical agents, to botulinum toxin, to sphincterotomy [56]. Like the cohort described by Floyd, 71% of patients resolved without lateral sphincterotomy. They also noted that the low rate of sphincterotomy came at the price of increased recurrences before complete healing, and a longer time spent in treatment.

Fissures Without Anal Hypertonicity

Treatments directed at relaxation of the anal sphincter, either pharmacologically or surgically, presume that relief of anal hypertonicity will lead to healing. A subset of patients with fissure, however, will not demonstrate hypertonicity, and hypotonicity may actually be found. Giordano et al. recently reported results from their prospective study of simple cutaneous advancement flap in 51 patients over a 6-year period for all patients, regardless of anal tone [57]. They found the procedure to be well tolerated, with a 98% treatment success rate. Nyam and colleagues evaluated 21 patients with fissures and below normal anal pressures. In this group, an island advancement flap resulted in complete healing and no incontinence in all patients [58]. A 2002 report from St. Mark's noted favorable results with advancement flaps for fissures with hypotonicity in a small series, with successful treatment in 7/8 patients with a median follow-up of 7 months [59]. While this technique might not be useful for all patients with refractory fissures, it holds particular promise in addressing the fissure in the setting of a hypotonic anus. Video 13-1 demonstrates the technique of an anal flap. While the video portrays anal stenosis, the technical points of the procedure are well demonstrated.

Crohn's Disease

Fissures are commonly seen in people with Crohn's disease, affecting approximately 30% of patients [60, 61]. When they occur, they tend to be in more atypical locations, deeper, and associated with other pathology, especially fistula. These fissures have atypical appearance as well, often creating deep ulcerations, and potentially creating significant deformity. As with other manifestations of Crohn's, it is reasonable to intervene only as complications dictate. Some authors have reported acceptable outcomes from interventions in these patients [62, 63], but caution should be the rule, and sphincter salvage is prudent. Multidisciplinary care is crucial in addressing anorectal disease in the patient with Crohn's, as appropriate medical management of the disease may lead to resolution of the anorectal disorders in 50% or more of these cases [64, 65].

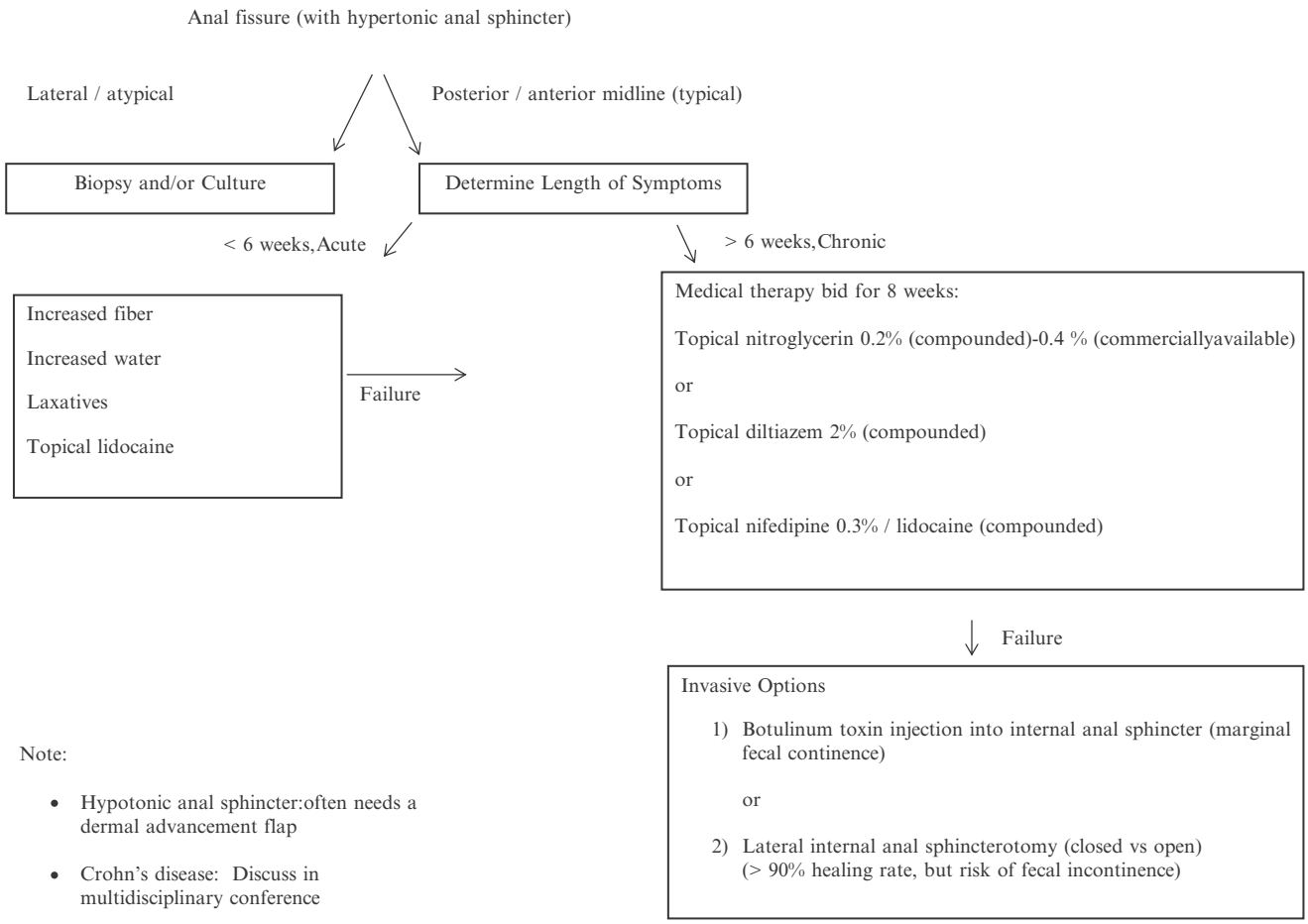

FIGURE 13-7. Treatment algorithm for anal fissure.

Human Immunodeficiency Virus

HIV-related anal disease includes both typical fissures and anorectal ulcers, which can appear as deep, broad-based, or cavitating lesions. Poor sphincter tone and function is a more frequent finding than the hypertonicity that accompanies typical, non-HIV-related fissures. Small studies have reported successful treatment of typical fissures, and the medical treatment of HIV continues to improve [66, 67]. Concerns about delayed wound healing and increased infectious complications, however, remain.

Conclusions

Anal fissure is a common disorder that is effectively treated and prevented with conservative measures in its acute form. Chronic fissures usually require medical therapy that can be effective in a small majority of patients. Initial therapy includes bulking agents, control of constipation, and topical medications to relax the internal anal sphincter. Botulinum toxin and lateral internal sphincterotomy can both be considered for treatment of refractory anal fissures, and the popularity of botulinum toxin is increasing. Sphincterotomy remains an effective operation, with a very high rate of resolution of symptoms, but at the price of some risk of permanent incontinence. A suggested treatment algorithm is provided in Figure 13-7.

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14
Anorectal Abscess and Fistula

Bradley R. Davis and Kevin R. Kasten

Key Concepts

- Successful management of anorectal abscesses requires an in-depth knowledge of pelvic floor anatomy and potential spaces through which sepsis can spread.
- The spaces occupying the anus and their anatomic landmarks will define the nomenclature of abscesses—perianal, perirectal, supralevator, and postanal space.
- Drainage of most abscesses can be performed in the office without drains or setons. If a fistula is encountered it should only be addressed if the anatomy in relationship to the sphincters is clearly identified.
- Necrotizing soft tissue infections are life-threatening emergencies that require aggressive surgical debridement and management of the offending anal gland.
- Fistulas will complicate a significant proportion of perirectal abscesses and are classified based on their relationship with the anal sphincter complex.
- Physical examination is often the only modality needed to determine the fistula track and selection of treatment, and preoperative imaging (MRI, US) is typically unnecessary except for patients with multiple external openings, when the internal opening cannot be identified, or for recurrent cases.
- Goodsall's rule, while being helpful, is accurate in about 60 % of cases and is more accurate for posterior fistulas.
- Fistulotomy is the most successful of the surgical treatments, but is also associated with the highest rates of continence disturbances—several non-cutting techniques have been described—all of which have limitations and varying degrees of success.

Introduction and Epidemiology

> It is difficult if not impossible to accurately assess the incidence of anorectal abscesses because they often drain spontaneously or are incised and drained in a physician's office, emergency room, or surgicenter.
>
> *Herand Abcarian* [1]

While seemingly a benign process, an anorectal abscess can produce significant distress and long-term morbidity. Delay in diagnosis, mismanagement of the disease, or failure to recognize the diagnoses can result in multiple procedures, increased cost, and protracted suffering. Further, confusion regarding the interplay between anorectal abscesses and fistula-in-ano may lead to inappropriate management. As such, it is important that treating clinicians have a good working knowledge of the diagnosis and management or refer the patient to a specialist.

Although the true incidence and prevalence are elusive, data from the operative management of anorectal abscesses provides a floor from which to extrapolate. The incidence of abscess is reportedly between 0.4 and 5 % of patients undergoing operative management [2, 3] translating to 8.6–20 patients per 100,000 population [4, 5], and yielding between 68,000 and 96,000 cases of anorectal abscess each year in the USA [1]. Patients are males at a 3:1 ratio, with both sexes presenting at a mean age of 40 years (range 20–60 years) [6]. Although often asked by patients, there is minimal data to suggest that inadequate hygiene, anal-receptive intercourse, altered bowel habits, diabetes, obesity, or race are associated with increased risk of abscess formation.

Pathophysiology

Anatomy

Management of anorectal abscess requires an in-depth knowledge of pelvic floor anatomy and associated potential spaces whereby purulent material can travel (see Chap. 1). A succinct description of the pelvis (funnel in funnel) illustrates the internal sphincter surrounded by the pelvic floor apparatus (external sphincter, levator ani, and puborectalis), and separated by the intersphincteric plane. The anal canal represents a connection between the anal verge and anorectal junction, with a length of 2–4 cm. At the anal canal's midpoint lies the dentate line, represented by undulating longitudinal folds of columnar

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endothelium (columns of Morgagni) proximally, and smooth squamous epithelium distally (anoderm). Between the columns of Morgagni, which number between 6 and 14, are unevenly distributed anal crypts whereby anal ducts empty. Importantly, ducts may extend into the internal sphincter, the intersphincteric space, or through the internal sphincter into the external sphincter [7, 8]. As a consequence of these extensions, select anorectal spaces are at risk for transmission of bacteria with subsequent formation of abscess.

The perianal space (Fig. 14-1a) lies immediately around the anal verge, with medial extension to the dentate line and lateral extension to the subcutaneous fat of the buttocks. This space is further connected to the rectal wall above the external sphincter by way of the intersphincteric space. The ischiorectal/ischioanal fossa is a pyramidal shaped potential space between the perineum and levator ani. It is bordered medially by the levator ani and external sphincter, with the obturator internus muscle and fascia along the ischium as its lateral border (Figure 14-1b). Anteriorly it is confined by the transverse perineal muscles. From a posterior standpoint, the ischiorectal fossa is bordered by the gluteus maximus and sacrotuberous ligament. Bilateral ischiorectal fossae are connected via the postanal space, under the anococcygeal ligament (Figure 14-1b). Above the anococcygeal ligament and below the levator ani, these fossae are continuous with the deep posterior anal space. Above the levator ani, between the pelvic wall and rectum, lies the supralevator space. Because this space is superiorly bordered by the peritoneum, abscesses may form from intersphincteric sources that track superiorly, or abdominal sources that track from the peritoneal cavity.

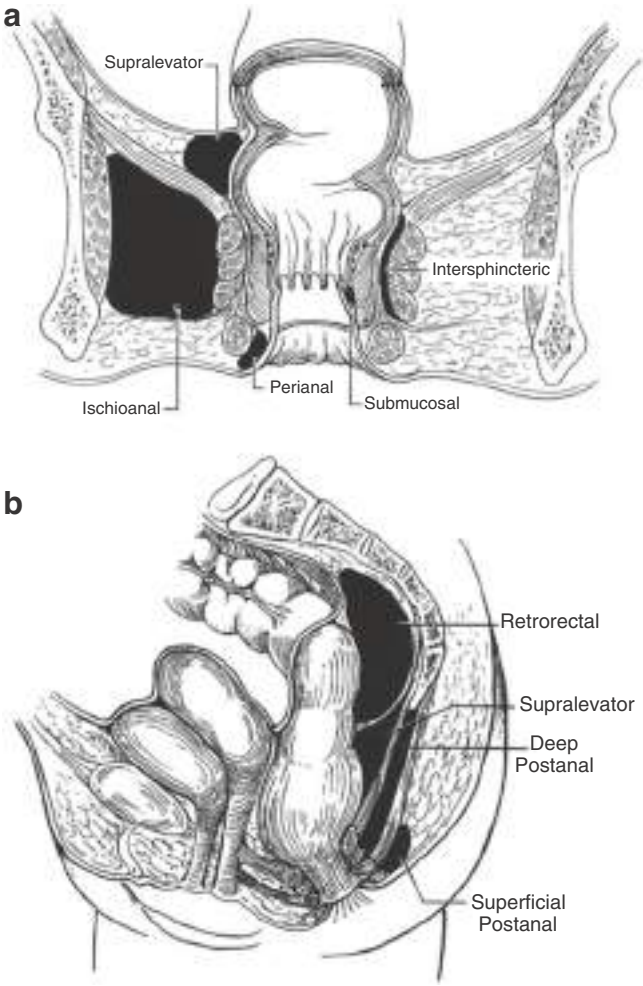

FIGURE 14-1. Anorectal spaces: (**a**) coronal section; (**b**) sagittal section. Vasilevsky CA. Anorectal abscess and fistula-in-ano [168] © 1997 David Beck, MD, with permission.

Etiology

Currently identified as vestigial organs with minimal role outside production of odiferous substances, anal crypts are considered the primary source for development of perianal abscesses [9]. The cryptoglandular theory underlying anorectal abscess formation was initially proposed by Eisenhammer [9] and later advocated by Parks [10]. They hypothesized that obstruction of a crypt by foreign body or perianal debris led to abscess formation due to stasis within the ducts. Predisposing factors for the development of cryptoglandular abscesses, which account for 90 % these infections, include liquid stool entering the anal duct, trauma, tobacco abuse, and cystic dilation of the duct resulting in poor emptying. The remaining 10 % are the result of specific disorders such as inflammatory bowel disease (IBD), trauma, and malignancy (Table 14-1).

Classification

Each anorectal abscess is classified based upon the potential space it inhabits (Figure 14-2). In general, perianal and ischiorectal abscesses are the most common, accounting for over 80 % of all diagnoses [11]. However, some implicate intersphincteric abscesses as the most common, with the ability to spread in any direction [5]. As expected, supralevator abscesses are the least common. The proverbial "horseshoe abscess" describes a process whereby bilateral disease occurs via connection through the intersphincteric, supralevator, or ischiorectal spaces. Recognition of this process is necessary to prevent undue operative intervention and patient suffering.

Evaluation

History and Symptoms

The patient with an anorectal abscess presents most commonly with acute pain in the perianal or perirectal region. Pain usually prompts an evaluation in the emergency room or physician's office. The pain is usually worsened with

TABLE 14-1. Etiology of anorectal abscess

Nonspecific
Cryptoglandular
Specific
Inflammatory bowel disease
Crohn's disease
Ulcerative colitis
Infection
Tuberculosis
Actinomycosis
Lymphogranuloma venereum
Trauma
Impalement
Foreign body
Surgery
Episiotomy
Hemorrhoidectomy
Prostatectomy
Malignancy
Carcinoma
Leukemia
Lymphoma
Radiation

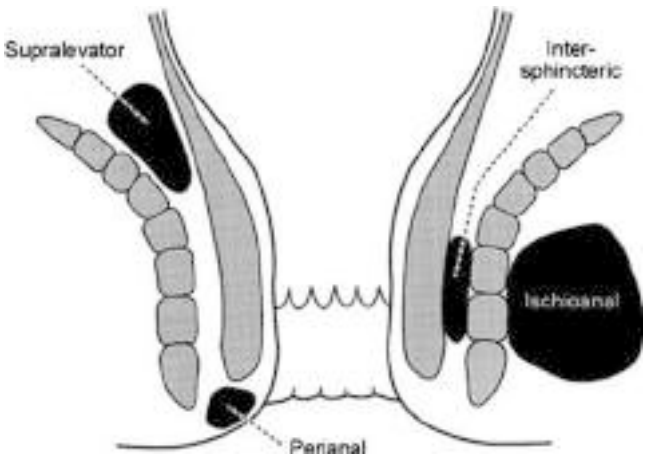

FIGURE 14-2. Classification of anorectal abscesses [169] © 1997 David Beck, MD, with permission.

sitting and defecation. For patient with chronic rectal pain, consideration should be given to an intersphincteric abscess. Further, associated symptoms of urinary dysfunction may distinguish the abscess as supralevator. For supralevator abscesses, pain may be described as a "dull ache" in the pelvic region or lower back. Of note, other symptoms include fever, chills, swelling, erythema, spontaneous drainage, and malaise. Rectal bleeding is unlikely in the majority of patients. Past medical history can alert the clinician to other possible causes of rectal pain including fissure, hemorrhoids, levator spasm, sexually transmitted infections, tuberculosis, human immunodeficiency virus (HIV), IBD, malignancy, and trauma. Given the possibility of surgical intervention, determining sphincter function and any history of fecal incontinence is important in these patients.

Physical Examination

Physical examination remains the single most important diagnostic study in patients with suspected anorectal abscess. In the prone position, external evaluation will reveal classic signs of infection including erythema, induration, fluctuance, pain, and spontaneous drainage. When completing an examination, ensure evaluation of the contralateral side to determine the existence of horseshoe extensions. For patients with an intersphincteric or supralevator abscess, external review is unlikely to reveal definitive signs. However, upon digital rectal exam, fluctuance or extreme discomfort should alert the clinician to this diagnosis. In this setting, if an internal opening is palpated, purulent drainage may also be noted. Unfortunately, pain oftentimes precludes an adequate rectal exam. When the diagnosis is in doubt, consideration should be given to performance of an exam under anesthesia with anoscopy and possible flexible sigmoidoscopy. In case of suspicion for supralevator abscess, or in patients with complicated medical history, further imaging may be warranted.

Imaging

Classically, imaging was rarely useful in the management of anorectal abscess. Some advocated for barium enema in young patients or those with recurrent fistula disease to rule out inflammatory bowel disease. However, modern techniques including computer tomography (CT), magnetic resonance imaging (MRI), endoanal ultrasound (EAUS), and transperineal sonography (TP-US) are especially helpful in the diagnosis of complicated anorectal abscesses and fistula-in-ano.

Computed Tomography (CT)

The use of CT for anorectal abscess is controversial [12]. However, such imaging is indicated in any patient in whom the diagnosis of anorectal abscess is unclear, those with complex suppurative anorectal conditions, anyone with significant comorbidities in which missing the diagnosis would prove harmful, or as a possible substitution for surgical evaluation. It can also be considered in patients with perianal Crohn's disease to assist delineation of rectal inflammation from anorectal abscess [13]. While high-resolution scanners are important for detailed images, just as important are the techniques utilized to maximize visualization. Triple contrast is often required, to include per os (PO), intravenous (IV), and *per rectum* (PR) modes. Slices of 2.5 mm are used

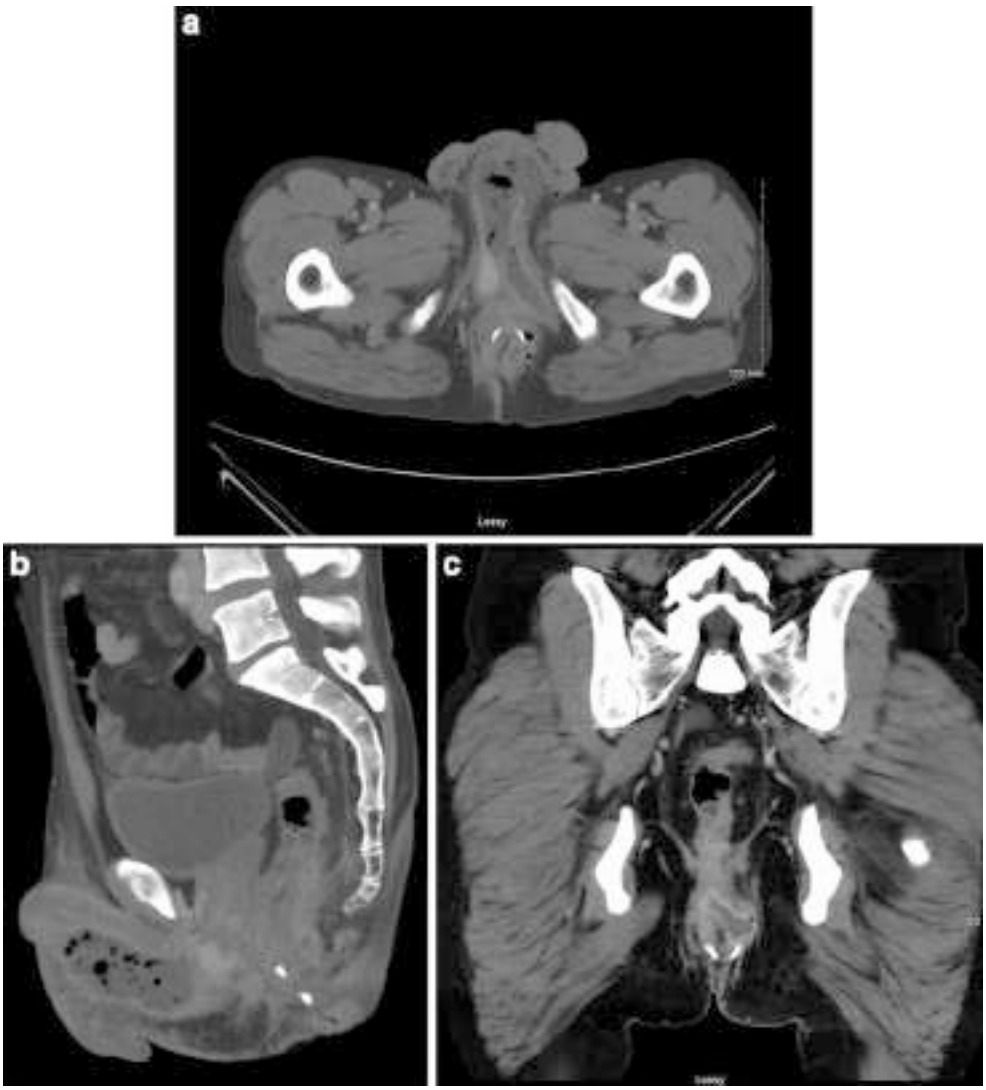

FIGURE 14-3. Computed tomography of complex anorectal abscess extending anteriorly towards scrotum. Axial images (**a**), coronal image (**b**), sagittal image (**c**).

to allow for appropriate reconstruction in sagittal and coronal planes (Figure 14-3a–c). When completed correctly, an abscess appears as an oval-shaped fluid collection with an enhancing wall, with or without demonstration of air. Additionally, fistulous tracts are readily identified by a tubular, air/fluid-filled structure that arises within the anal sphincter [6].

Magnetic Resonance Imaging

MRI for evaluation of anorectal abscess is uncommon, occurring more frequently in complex fistula-in-ano disease. Groups suggest the use of pelvic MRI for any recurrent of incompletely drained abscess to assist identification of horseshoe/postanal, supralevator, and other complex abscesses [14]. However MRI has limited value in the diagnosis of anorectal abscess in the acute setting.

Endoanal Ultrasound

Familiar to most colorectal surgeons, endoanal ultrasound utilizes a probe with 2D or 3D capabilities at a frequency of 5–16 MHz. Similar in discomfort to anoscopy, this technology allows effective characterization of abscesses and fistulae with reported accuracy of 85 % [13]. Normal EAUS demonstrates the interface between the cap and the submucosa (mixed echogenicity), internal sphincter (hypoechoic), intersphincteric space (hyperechoic), and external sphincter (mixed echogenicity) [15]. The probe is covered in a protective sheathing with all air removed, and gently inserted past the puborectalis before slow removal. Fluid is identified by hypoechoic, compressible ovals between or within specific planes. Limitations of this technique include user dependence, limited distance of detection from probe (extrasphincteric, supralevator abscesses), and requirement of intraluminal deployment, which may be precluded by discomfort in acute perianal sepsis.

Transperineal Sonography

A lesser known technique in the colorectal field, TP-US can be quite accurate in diagnosis of fluid collections, internal opening, and even existence and course of a fistulous track. Most importantly, in experienced hands it distinguishes perianal from perirectal abscess and sepsis. Using techniques similar to delineation of vascular structures, patients are evaluated in the left lateral decubitus position. In a comparison of TP-US and MRI, the former was more accurate for superficial fluid collections, while the latter was more accurate for perirectal infection. Overall, concordance between MRI and TP-US was 0.82 for diagnosis of perianal abscess, suggesting a significant advantage for this modality in the acute setting [16]. Clinicians with access to this technology should consider its use in applicable patients to help delineate fluid collection, fistulous tracts, internal openings, and reduce costs compared to MRI and CT studies.

Treatment

Role of Antibiotics

The surgical principles for management of abscesses, in general, hold true for the perianal and perirectal region, with prompt drainage and debridement being the cornerstone. Antibiotics are indicated when associated cellulitis is present, in patients who fail to improve following appropriate drainage, and those with immunosuppressed states. However, medication is rarely adequate in the absence of incision and drainage and at best does nothing to prevent subsequent fistula formation and at worse may increase the risk. In a randomized control trial evaluating treatment of anorectal abscess with and without antibiotics, the risk of fistula formation was unrelated to antibiotic usage. Fistula formation was, however, related to location of the abscess with an eight times higher risk associated with ischiorectal location, and a three times higher risk with intersphincteric compared to the perianal location [17]. (Isolated situations whereby antibiotics may be successful in this setting involve management of perianal Crohn's disease, and will be covered elsewhere.) Coverage is directed towards *Escherichia coli, Enterococcus species*, and *Bacteroides fragilis* in immunocompetent patients, and *Neisseria gonorrhoeae, Chlamydia trachomatis,* cytomegalovirus, and herpes simplex virus in immunocompromised patients [18]. Consider wound culture only in high-risk patient populations, and individuals with recurrent or non-healing disease [13].

Incision and Drainage

The appropriate setting for abscess drainage depends on the location of the abscess and the experience of the clinician. Simple, superficial perianal or ischiorectal abscesses requiring external drainage at the skin level are amenable to bedside drainage in the office, emergency room, or hospital ward. A simple rule of thumb recommends "outward" drainage whenever an abscess enters, or passes through, skeletal muscle (i.e., levator ani, external sphincter) [19]. All others should be drained internally through the rectum/anus. Standard procedure includes appropriate positioning, use of antiseptic prep, and local anesthesia of choice combined with 1:200,000 epinephrine. Starting with a local field block around the abscess prior to injection of skin overlying the point of maximal tenderness often provides more effective analgesia than injection of the cavity alone. The choice of elliptical incision, or cruciate incision combined with excision of skin flaps, prevents early closure and recurrence (Figure 14-4). When possible, the incision is made as near the anal verge as possible to limit the length of any potential fistula. Additionally, the predominant incision should run parallel to the external sphincter muscle fibers. Packing is not required in this scenario, and its absence yields quicker healing with less pain [20].

Patients requiring internal drainage, those with recurrent or bilateral disease, and those with large abscesses at risk for inadequate bedside drainage, should undergo operative drainage. For abscesses of significant size, consider multiple counter incisions with interposition of setons or Penrose drains to accelerate healing. Drains are removed at 2–3 weeks postoperatively when the base of the cavity has granulated and shrunk. Further candidates for internal drainage include (1) submucosal abscess, (2) intersphincteric abscess, (3) supralevator abscess from intersphincteric fistula, and (4) supralevator abscess from pelvic disease [19]. The diagnosis of intersphincteric fistula should be entertained in patients with pain out of proportion to exam findings. Definitive management involves incision of the internal sphincter along the length of abscess, with or without marsupialization of the wound edges. Individuals with delayed recurrence greater than 2 weeks likely have a fistula, and thus require EUA for delineation and control of fistula track.

Supralevator abscesses require delineation of the track by imaging before surgical correction is undertaken. When the inciting source is intra-abdominal, transrectal drainage is indicated in most scenarios. However, abdominal drainage can be considered depending upon ease of access and directionality of the abscess cavity. When the source is intra-abdominal, percutaneous management may prevent creation of a fistulous track through the levator plate via improper ischiorectal drainage, and is often more successful than transrectal drainage. The scenario of supralevator extension from ischiorectal abscess due to a transsphincteric fistula requires ischiorectal drainage. For instances where a supralevator abscess forms as an upward extension of an intersphincteric fistula, internal drainage via incision of the internal sphincter is best (Figure 14-5).

Bilateral abscess disease, or "horseshoe" abscess, requires operative drainage to delineate and control the source. This difficult-to-treat entity most commonly arises from a deep

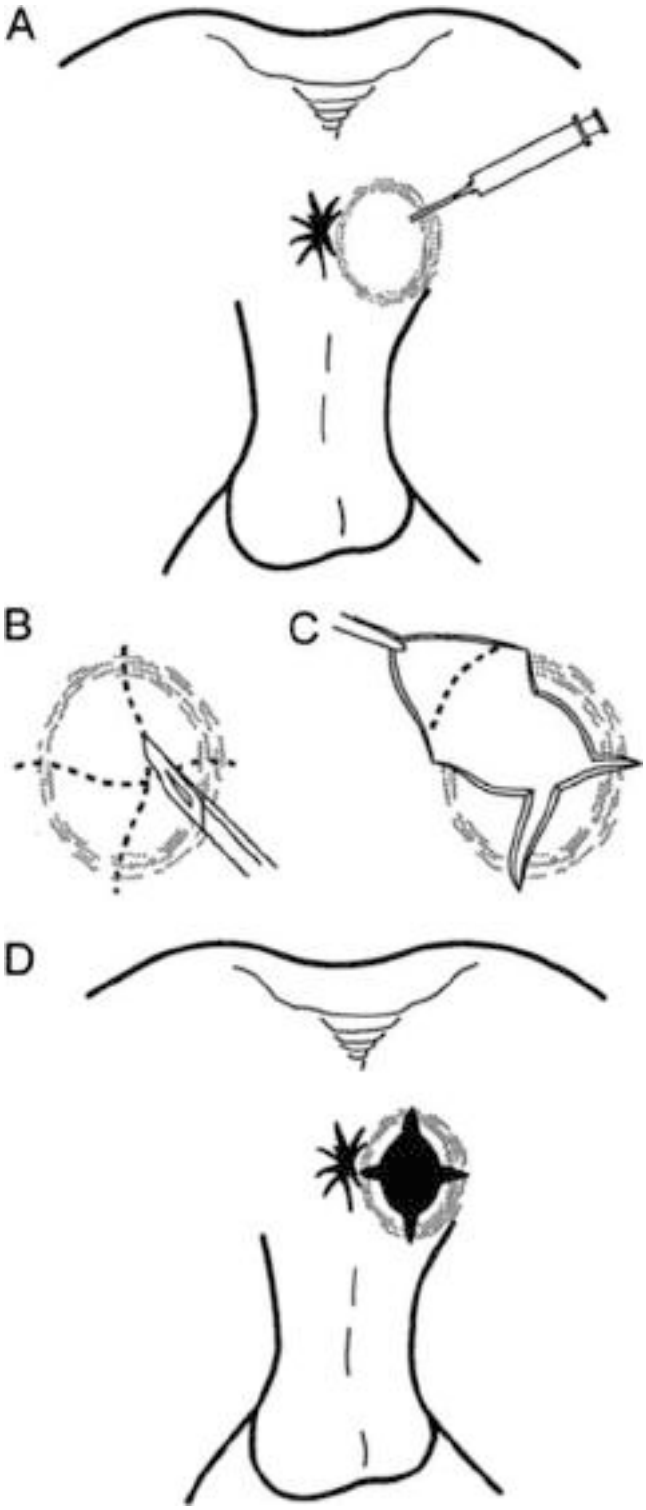

FIGURE 14-4. Drainage of abscess: (**a**) injection of local anesthesia, (**b**) cruciate incision, (**c**) excision of skin, (**d**) drainage cavity.

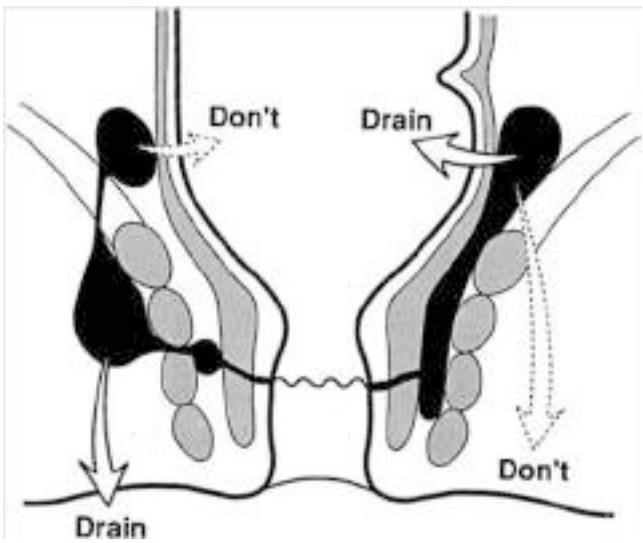

FIGURE 14-5. Drainage of a supralevator abscess.

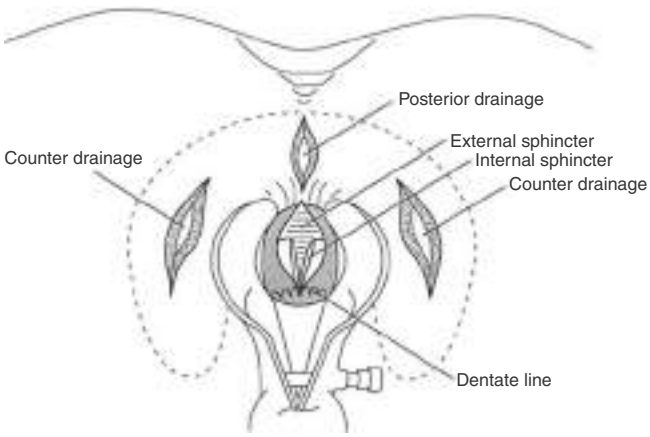

FIGURE 14-6. Drainage of a horseshoe abscess.

postanal space abscess. Many patients present with history of prior drainage procedures, and thus may have complex tracts. Options for management include the Hanley or modified Hanley procedures, consisting of open posterior drainage through the anococcygeal ligament, posterior midline incision of the internal sphincter and inciting anal duct, and open drainage of bilateral ischiorectal fossae to control lateral tracks (Figure 14-6) [21]. Modifications to this procedure include limiting drainage to internal sphincterotomy followed by elliptical incisions over bilateral ischiorectal fossae. If necessary, a seton (cutting or non-cutting) is placed in the posterior midline, with subsequent definitive management taking place at a later time (Figure 14-7). More recently, management of deep postanal space abscess was described using an intersphincteric technique. The intersphincteric space is dissected in the posterior midline until identification of the anal duct source, with subsequent continuation into the deep postanal space for drainage and curettage. Benefits included minimization of procedures necessary when using the loose seton technique, reduction in risk of incontinence compared with the cutting seton technique, and ease of learning for the surgeon [22].

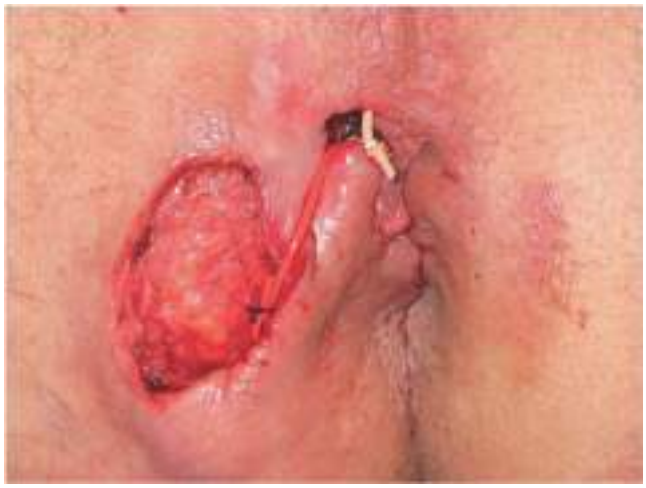

FIGURE 14-7. Horseshoe fistula managed with drainage and seton.

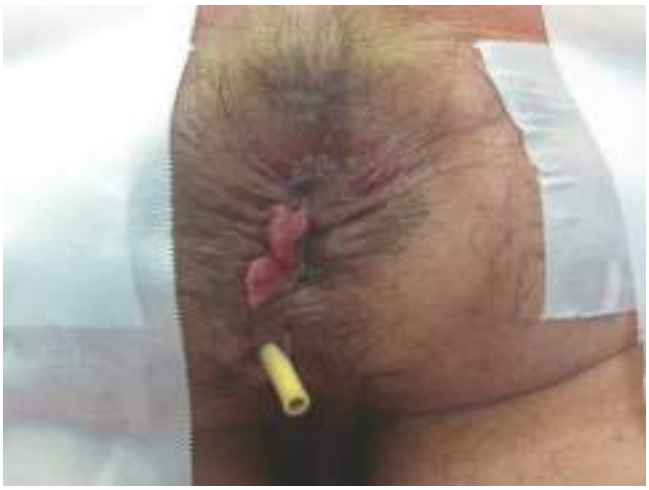

FIGURE 14-8. Pezzer catheter in an ischiorectal fossa abscess.

Catheter Drainage

Minimization of perianal incisions is possible using the placement of a drainage catheter within the abscess cavity. Appropriate size and external fixation of catheter are necessary to ensure adequate drainage, especially in patients with large abscess cavities, patients with severe systemic illness, and those with underlying comorbidities including diabetes mellitus and morbid obesity. To start, a small stab incision is made in anesthetized skin on the medial aspect of the abscess. A mushroom tip catheter (de Pezzer, Malecot, Cook Medical) between 10 and 14 Fr is inserted to full cavity depth. The external portion of the catheter is cut to length, leaving a 2–3 cm area with which you secure it to the perianal skin using a permanent suture (Figure 14-8). Recommendations differ with regard to duration of treatment, ranging from 3 to 21 days. However, removal prior to cessation of drainage usually results in recurrence, and should be avoided. For non-healing wounds, the catheter is utilized for drain studies to elucidate fistula tracks or other associated pathology.

Drainage with Primary Fistulotomy

Despite a paucity of recent studies on the management of anorectal abscess, controversy abounds regarding the use of primary fistulotomy at the time of abscess drainage. Historically, primary fistulotomy was performed when draining the abscess for source control, thereby increasing the rate of healing without the need for subsequent procedure [11]. In a meta-analysis of six randomized controlled trials, recurrence, persistent abscess/fistula, and repeat surgery were significantly reduced when primary fistulotomy was performed concurrent with abscess drainage (RR = 0.13, 95 % CI 0.07–0.24) [23]. However in the acute setting inflammation may inhibit clear determination of muscle involvement and the pooled relative risk of incontinence at 1 year was 3.06 (95 % CI 0.7–13.45), ranging between 2.03 and 4.77 in sensitivity analysis. This did not reach statistical significance when compared to the fistulotomy group and the study authors concluded that a fistulotomy at the time of abscess drainage was warranted. When an accurate estimate of muscle involvement is confounded by acute changes, thereby increasing the risk of excessive muscle incision, placement of seton may be indicated preventing the unintended consequence of incontinence [24, 25].

Despite these recommendations the risk of incontinence with all of the resultant patient morbidity may limit its application [26]. In fact several reports indicate a high rate of spontaneous healing following effective abscess drainage alone [27, 28] with the incidence of recurrent abscess reported to be 30 % and subsequent fistula formation between 26 and 50 % [23, 29, 30]. This may be even lower if the offending duct is identified and opened, confirming a limited role for primary fistulotomy in selected patients [23, 31].

In an effort to identify the crypt of origin when draining an acute abscess a probe can be carefully inserted into the suspected duct by direct visualization. Adjuncts for locating the duct include manual pressure on the abscess cavity while looking for purulent extrusion, identification of inflammation indicating the culprit duct, or simple blind probing. When identified, gentle probe advancement may elucidate the inciting fistula, but care is required to prevent creation of a false track. Unfortunately, a recent study reported successful internal opening (IO) identification of only 36 % using manual abscess cavity compression, consistent with prior published rates of failure exceeding 65 % [32, 33]. Interestingly, one randomized control trial reported 83 % success using simple abscess compression [34]. Because localizing the offending duct is difficult, and misidentification leads to complications, alternative methods are available. In patients who failed identification by abscess compression, injecting

2 cc of 2 % hydrogen peroxide combined with 1–2 drops of methylene blue into the abscess cavity resulted in localization of the internal opening in 90 % of cases. At median follow-up of 16.5 months, rates of recurrent disease were 2.8 % in those undergoing primary fistulotomy compared with 40 % in patients treated with incision and drainage alone [29].

Unfortunately, there is no clear answer to the question of primary fistulotomy at the time of abscess drainage. In fact, the ASCRS Practice Parameters for management of anorectal abscess advocate, "… weigh[ing] the possible decreased recurrence rate in light of the potential increased risk of continence disturbances" [13]. Surgeons who are inexperienced in the management of anorectal pathology should refrain from searching for a fistula due to higher rates of adverse events and poorer patient outcomes. Healthy patients *without* prior fistulous disease, IBD, or simultaneous anterior fistulas potentially benefit from primary fistulotomy at the time of abscess drainage in the hands of experienced surgeons. Superficial and low transsphincteric (<30–40 % external sphincter involvement) fistulas with minimal sphincter involvement provide the best opportunity for successful fistulotomy at the time of abscess drainage [5].

Postoperative Management

Postoperative care is similar to most anorectal procedures. Local wound care involves sitz baths two to three times daily followed by wound coverage using gauze. Packing is not necessary and should be avoided. Following catheter drainage, a dressing is similarly applied over the catheter end to prevent soiling of clothing. Irrigation of the catheter is not necessary. There is no data to support the use of topical antibiotics. Surgeon follow-up is indicated at 2–3 weeks in patients who undergo incision and drainage, and 7–10 days in those with mushroom-tip catheters. Endpoint for removal is cessation of purulent drainage from the drain, and closure of the wound around catheter. Patients are followed until complete healing of the wound or cavity; especially since recurrence and fistula formation are associated with delay/lack of surgical follow-up. Pain control is obtained with multimodality therapy to include local anesthetic at surgery combined with narcotic and non-narcotic oral medications for home use. Diet is advanced to regular once the patient is aroused from anesthesia, and a bulk-forming fiber supplement is advised for the first month. Activity level may proceed ad lib. Antibiotics are not warranted in the postoperative setting unless cellulitis is present, or in the immunocompromised patient.

Complications

Immediate Postoperative Period

Complications related to abscess drainage and fistulotomy include bleeding and urinary retention. Significant bleeding in the postoperative period following incision and drainage occurs at a rate of 1–2 %. The rate of urinary retention reported in the literature following uncomplicated incision and drainage is 2.3 %, increasing to 6.3 % in patients undergoing fistulectomy/fistulotomy [35]. This compares favorably to the reported incidence of 22 % in patients undergoing hemorrhoidectomy. Universal risk factors for urinary retention in anorectal procedures include age over 50, female sex, and intravenous fluid (IVF) greater than 1 L perioperatively [35].

Abscess Recurrence and Fistula Formation

Rates of abscess recurrence following drainage are estimated at 4–31 %, with a median of 13 % [36]. The only significant prognostic factor for patients presenting with their first abscess without other complicating factors such as IBD was time from disease onset to drainage procedure. Rates of recurrence were higher in those undergoing management more than 7 days after the onset of symptoms [37]. Early recurrence is usually the result of inappropriate technique, early skin apposition, and reformation of the abscess. Insufficient drainage leads to continued inflammation, prolonged healing, and fistula formation [1, 38, 39]. Reasons for semi-acute recurrence include missed loculations, prior intervention with associated scarring, and destruction of natural barriers to infection [26, 40, 41]. Because a large number of recurrent abscesses are due to inadequate treatment in patients who present with spontaneous drainage and receive outpatient care, one group advocated exam under anesthesia for all patients even if the abscess has apparently decompressed [39]. Horseshoe abscesses recur more frequently with a reported incidence between 18 and 50 %, usually requiring multiple operations before healing occurs [42]. The clinician must elucidate site of prior drainage and determine likelihood of horseshoe abscess in order to effectively treat the diagnosis.

Misdiagnosis

When an abscess is not effectively managed despite optimal medical and surgical intervention an alternative diagnosis must be entertained. Pilonidal disease, hidradenitis suppurativa, tuberculosis, herpes simplex virus, HIV, and inflammatory

bowel disease (specifically, Crohn's disease) must be part of the differential diagnosis [39]. While the incidence of pilonidal disease is 1:4000, only a few case reports exist detailing its presentation as an anorectal abscess or fistula [43]. In a study of 100 recurrent anorectal abscesses at a large tertiary care colorectal program, 32 % of patients treated for anorectal abscess actually had hidradenitis, underlying the importance of entertaining alternative diagnoses in patients with recurrence [39]. Incidence of HIV and other infectious sources are difficult to estimate, and will be predicated by the surrounding patient population. Between 5 and 19 % of Crohn's patients will demonstrate perianal manifestations prior to any other symptoms, suggesting a significant opportunity to make an early diagnosis.

Special Considerations

Necrotizing Anorectal Infection (Fournier's Gangrene)

Necrotizing anorectal infections are rare, representing less than 0.02 % of hospital admissions with an incidence between 1.6 and 3.3/100,000 [44]. Males outnumber females at a ratio between 9 and 50:1 [45]. Current estimates of mean age are between 45 and 55 years, which steadily increase as the worldwide population ages. The diagnosis is rarely made in children. Some countries report an increasing incidence; however, there is minimal data to support this conclusion in the USA. Medical risk factors commonly associated with necrotizing soft tissue infections include diabetes, hypertension, elderly age, obesity, immunosuppression (especially when due to malnutrition, liver disease, malignancies), drug use, and recent surgery [46]. As expected, rates of necrotizing fasciitis are increased in patients with perianal disease. Commonly, either long-standing or inappropriately managed perianal disease predates an episode of necrotizing fasciitis. In patients diagnosed with Fournier's gangrene, 50–60 % had underlying anorectal abscess as their inciting source [45].

Diagnosis

Presenting symptoms include severe pain out of proportion to exam, fever, chills, erythema, and induration at the site (Figure 14-9). In polymicrobial and clostridial infections, crepitance is often noted. Unfortunately, necrotizing soft tissue infections progress along fascial planes; thus the extent of disease is easily underestimated. Timing of disease progression ranges from 2 to 5 days. Laboratory values are nonspecific, but indicate disease severity. White blood cell count, creatinine kinase, and lactate are most helpful in estimating severity of infection and confirming the diagnosis.

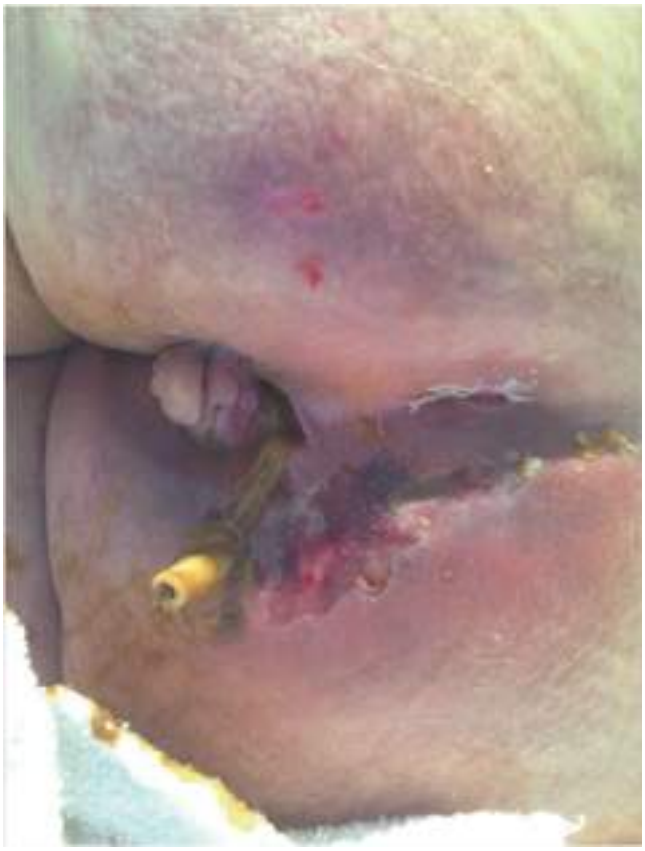

FIGURE 14-9. Necrotizing soft tissue infection in a patient with a supralevator fistula and abscess inadequately drained.

Cultures and gram stain are unhelpful at initial diagnosis, but can guide appropriate postoperative antibiotic therapy. Due to false negatives, bedside biopsy plays a limited role in the diagnosis except in tertiary care centers with experience. When the diagnosis is unclear, imaging is recommended using CT abdomen/pelvis to identify the source and extent of infection.

Treatment

Prompt diagnosis and treatment are necessary to maximize survival. Following diagnosis, treatment involves aggressive fluid resuscitation with crystalloid of choice and initiation of broad-spectrum antibiotics (penicillin g, metronidazole, third-generation cephalosporin, gentamicin). Next, the patient undergoes surgical intervention with wide local excision of affected tissue (Figure 14-10). Due to rapid spread, surgical excision should extend beyond visibly infected tissues. Additionally, the patient should be evaluated on a regular basis in the ICU for any wound changes. It is common to return to the operating room within 24–48 h to re-excise margins, and to ensure appropriate source control.

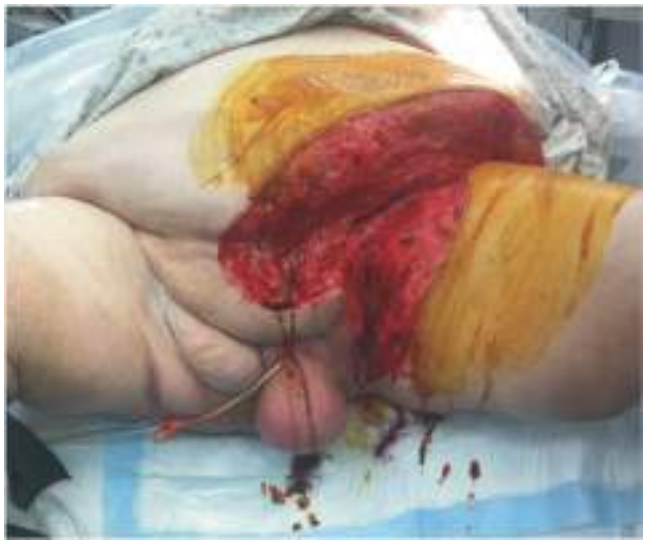

FIGURE 14-10. Extensive soft tissue debridement of necrotizing soft tissue infection starting as an anorectal abscess.

A useful adjunct when anorectal abscess incites necrotizing fasciitis involves the loose-seton technique [47]. Here, multiple radial incisions are made in the external sphincter at its outer margins. The incisions are widened manually, and loose setons placed between every other drainage incision. When combined with standard wide local excision at the outset, trips to the operating room are decreased, as is the overall wound size. Some advocate creation of a colostomy to help with wound care after extensive dissection. While no data currently supports this practice, higher consideration is given to patients with a grossly infected sphincter muscle, and anorectal perforation, or those in an immunocompromised state. Tailoring of antibiotics should occur when culture results return.

Outcomes

Necrotizing fasciitis remains a lethal disease, despite significant advances in diagnosis, surgical care, and supportive management. Mortality rates in the literature span 4–80 %; however, most large studies demonstrate a consistent range of 7–10 %. Death is usually the result of sepsis and sequelae of multi-organ system failure [45]. For survivors, long-term morbidity is dependent upon the extent of wound debridement and recovery of organ systems.

Use of the Fournier's Gangrene Severity Index (FGSI) predicts mortality by combining nine parameters such as temperature, heart rate, and other clinical values. In the sentinel paper, scores >9 predicted probability of mortality at 75 % [48]. Conversely, scores ≤9 predicted probability of survival at 78 %. Since 1995, multiple studies have validated this scoring system [45].

Anorectal Infections in Immunosuppressed Patients

Hematologic Abnormalities in Immunosuppression

In patients with hematologic malignancies, or those treated with myelosuppressive regimens, immunosuppression and low neutrophil count produce an incidence of anorectal sepsis approaching 10 % [49]. Despite the high incidence, diagnosis is often difficult and delayed. This occurs due to low neutrophil counts, whereby non-fluctuant induration with minimal erythema evades untrained eyes, leading to misdiagnosis in half of the patients [50]. If counts increase, normal clinical signs of abscess may occur, allowing for a diagnosis.

Complications of anorectal abscess in hematologically immunosuppressed patients are similar to healthy patients, including recurrence, fistula formation, and incontinence. However, systemic complications of sepsis are more likely in this patient population, including death. When untreated, mortality approaches 60 % [51, 52]. As such, aggressive management is indicated when anorectal sepsis is suspected.

Appropriate treatment of these high-risk patients involves determination of immune status and tailored therapy. Antibiotics are standard of care, aimed at coverage of standard gastrointestinal flora using a local antibiogram. For patients with absolute neutrophil count (ANC) <1000/mm^3, antibiotics are first-line therapy with rates of resolution between 30 and 90 % [49, 53]. Patients with higher neutrophil counts will demonstrate an abscess, which requires incision and drainage. Physical exam is limited in these patients, so imaging studies are indicated for delineation of size, extent, and involved structures. CT scans are rapid, easily obtained, and demonstrate supralevator components with high degree of accuracy. If concern exists for more complex anorectal sepsis, and possible necrotizing infection, MRI provides superior imaging for diagnosis. Using T1- and T2-weighted images, physicians can determine abscess vs. inflammation, adjusting treatment accordingly [50].

The decision on timing of surgical intervention is not always clear-cut. Patients with neutropenia suffer higher rates of morbidity following surgery, and mortality was upwards of 45 % in one study vs. 9 % in those treated only with antibiotics [54]. Published rates of failure in neutropenic patients range between 30 and 37 % [50]. If antibiotic therapy fails based on abscess formation, lack of improvement, or development of necrotizing infection, surgical debridement is indicated. While thrombocytopenia is associated with nonoperative management, fluctuance, erythema, and presence of purulent material indicate patients appropriate for surgical drainage [55]. Due to the high risk of morbidity and mortality in patients with incomplete evacuation of purulent material, operative washout is preferred to bedside management. Postoperative care and management proceed similarly to health patients.

Human Immunodeficiency Virus

There is little distinction between the management of HIV patients and otherwise-healthy individuals with anorectal abscess. However, prompt recognition and treatment are required due to concerns of underlying immunosuppression. In this patient population, alternative diagnoses including sexually transmitted infections and CMV are also common. Further, risk of neoplasm requires biopsy of tissue at the time of drainage.

Anal Fistula

The management of anal fistula cannot be undertaken without a thorough understanding of their etiology, and the anatomy of the anal canal and sphincter complex. The disease represents a wide spectrum of complexity and is often misdiagnosed and poorly treated by surgeons and physicians who lack experience. Complexity has certainly increased in large part due to the unwillingness of patients and surgeons to risk continence when managing fistulas, a fact underscored by the significant increase in the use of non-cutting techniques used to treat anal fistulas during the past 30 years [56].

Etiology

A fistula is defined as an abnormal connection between two epithelial lined surfaces such as a set of organs or vessels, which do not normally connect, e.g., the connection between the distal alimentary tract and the integument. The incidence is believed to be 2 per 10,000/year while the prevalence is not truly known [57]. The etiology of anal fistula is cryptoglandular in 90 % of cases, postoperative or traumatic in 3 %, inflammatory bowel disease in 3 %, as a result of anal fissure in 3 %, and tuberculosis related in less than 1 % of cases.

The cryptoglandular cause of anal fistula refers to the presence of the anal crypts, proposed to originate at the bottom of the rectal columns of Morgagni, which are epithelial lined tracts that penetrate to the submucosa and occasionally into and through the internal sphincter. Despite the use of the term "glandular" it is not always the case that these structures are functional and may be vestigial remnants from embryonic growth. Their frequency and location are varied but tend to concentrate posteriorly and are more commonly found in men [7, 58]. Kratzer and Dockerty examined over 100 anatomical specimens histologically, and found anal glands in 55 % of specimens; in 33 % the ducts penetrated the internal sphincter [59]. Parks evaluated 44 specimens and identified 6–10 glands originating from the anal crypts and held the belief that these were mucous producing. The glands terminated variably into the submucosa, internal sphincter, or intersphincteric groove. He postulated that these glands provided a free channel for infection to pass from the anal lumen deep into the sphincter muscles. He believed that chronic infection in the cystic portion of the gland, if deep to the internal sphincter, would result in a sinus forming to the skin. Though technically due to the epithelial lining of the duct it is in fact a fistula [10].

It is believed that the anal crypts become blocked by inspissated debris or stool. As a result, an infection develops at the anal glands, which extends in a path of least resistance, forming an abscess in the intersphincteric space leading to the development of a fistula [9]. Additionally anal fistula can occur as a result of Crohn's disease, malignancy, trauma, tuberculosis, lymphogranuloma venereum, and actinomycosis. Not all cryptoglandular infection results in the development of a fistula. Scoma et al. performed a retrospective analysis of 232 patients who had undergone a drainage procedure and found that 66 % of their patients subsequently developed anal fistula [60]. They did not classify the type of fistula or abscess in their study making generalizations difficult although 77 % of their patients were male. Hamadani et al. performed a similar review of 148 patients with a mean follow-up of 38 months. The cumulative incidence of anal fistula was 36 % with no differences seen in a multivariate analysis among men vs. women, nonsmokers vs. smokers, perioperative antibiotic use, or HIV status. Age less than 40 was the only significant predictor of fistula formation in their study [36]. Wang et al. reviewed the records of 1342 patients with confirmed anal fistula and matched these cases to a separate cohort of patients referred with other anorectal complaints but without fistula disease. Using multivariate analysis BMI exceeding 25 kg/m^2, prior diabetes, hyperlipidemia, dermatosis, sedentary lifestyle, regular alcohol intake, smoking, non-fistula anorectal surgery, prolonged sitting on the toilet for defecation, and a previous history of enteritis were independently correlated with a risk of anal fistula [61].

It is likely that the true incidence of anal fistula following abscess formation is closer to 30 % and should be suspected in any patient with a recurrent perirectal abscess especially if it occurs at the same site of a previous abscess as fistula-in-ano is thought to be responsible for 40–50 % of recurrent abscesses [39].

Classification

Anal fistula can be characterized as simple or complex. The definition of a complex fistula is not standardized but most authors agree that any fistula that is high transsphincteric or when a fistulotomy would result in incontinence should be considered complex. The definition also includes suprasphincteric, extrasphincteric, all anterior transsphincteric fistulas in women, and those caused by Crohn's disease, malignancy, surgery, and trauma. Roughly 50 % of all fistulas are considered complex giving rise to significant challenges in the treatment of this disease.

Anal fistulas are also classified based on their relationship to the anal sphincter complex. In 1934 Milligan and Morgan suggested a classification of anal fistula based on the position of the internal opening relative to the anorectal ring [62]. This was subsequently modified by Parks et al. (Table 14-2) based on his analysis of 400 cases of treated anal fistula over a 15-year period [63]. He anchored his classification system on the external sphincter due to the importance it played in the surgical management (Figure 14-11a–d).

Table 14-2. Classification of fistula-in-ano

Intersphincteric
Simple low intersphincteric
High blind tract
High tract with an opening in the rectum
High tract with rectal opening, no perineal opening
Extra-rectal extension
Secondary to pelvic disease
Transsphincteric
Uncomplicated
High blind tract
Suprasphincteric
Uncomplicated
Horseshoe extension
Extrasphincteric
Secondary to anal fistula
Trauma related
Pelvic inflammation
Inflammatory bowel disease or other anal disease

An intersphincteric fistula (Figure 14-11a) occurs in 20–45 % of cases [64] and does not penetrate the external sphincter and "ramifies only in the intersphincteric plane." Parks et al. additionally classified seven subtypes of intersphincteric fistula with the most common having a high blind track, which as its name suggests has an extension in the intersphincteric groove cephalad towards the rectum. The other subtypes are less common.

A transsphincteric fistula (Figure 14-11b) occurs in 30–60 % of cases and penetrates the external sphincter below the level of the puborectalis muscle exiting into varying levels within the ischiorectal fossa. A high blind track may also confound a transsphincteric fistula and can end at the apex of the ischiorectal fossa or alternatively pass through the levator plate into the true pelvic cavity. The latter can be felt if a probe is passed from the opening in the perineal skin, the tip of which will be palpable above the anorectal ring through the wall of the rectum. Care should be taken *not* to iatrogenically perforate the rectum or an extrasphincteric fistula will be the result. The significance of this high blind track is the inability to cannulate the internal opening using a probe passed from the perineal skin as it will preferentially follow the high blind track and not the transsphincteric portion, which comes off at a right angle. It may be possible to cannulate the internal opening through the anus with a right-angle probe in order to secure a seton or if feasible perform a fistulotomy. A flexible tip glide wire can sometimes be used when this sharp angulation is encountered but again care must be taken to avoid creating a false passage (Figure 14-12).

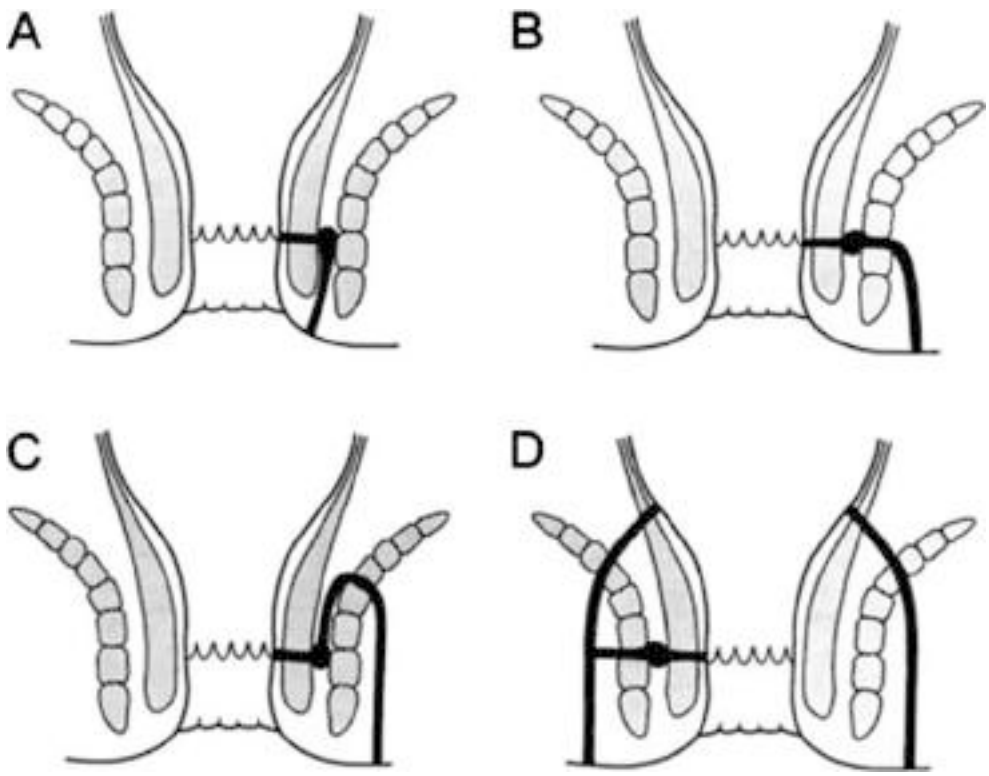

Figure 14-11. Classification of anal fistula. (**a**) intersphincteric, (**b**) transsphincteric, (**c**) suprasphincteric, (**d**) extrasphincteric.

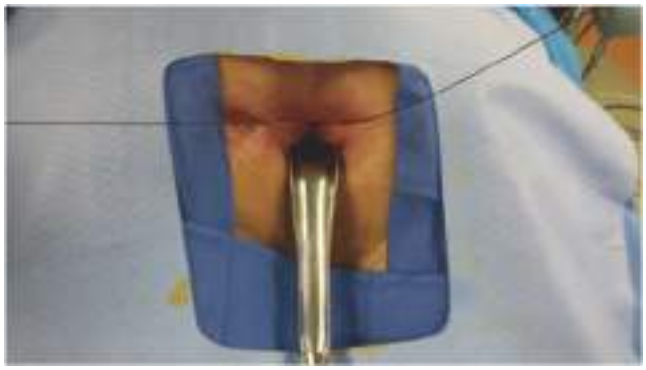

FIGURE 14-12. Flexible glide wire to delineate a transsphincteric fistula with a high blind extension.

A suprasphincteric fistula (Figure 14-11c) occurred in 20 % of cases in the series by Parks et al. but has been reported at a much lower frequency by other authors (<2 %) [64, 65] and in this group the track is over the top of the puborectalis, then downward again through the levator plate to the ischiorectal fossa, and finally the skin. As it passes over the puborectalis it is anatomically in the supralevator space and abscess formation here can be palpated by rectal exam. Abscess formation in this space can result in a horseshoe extension around the rectum.

Lastly extrasphincteric fistula (Figure 14-11d), which only occurs in 2–5 % of cases, passes from the perineal skin through the ischiorectal fat and levator muscles into the rectum. It is outside the external sphincter complex altogether. An extrasphincteric fistula may result from a transsphincteric fistula with a high blind tract that penetrates through the levator plate as described earlier or it may be due to trauma, inflammatory bowel disease, malignancy, or pelvic inflammation that necessitates through the levators to the perineal skin (ruptured appendicitis, terminal ileal Crohn's disease, or diverticulitis are the most common causes).

Submucosal fistulas are likely the result of anal glands that terminate in the submucosa and track just beneath the submucosa not involving the sphincter complex at all. These fistulas may be opened without compromising fecal continence.

Diagnosis

The symptoms of an anorectal fistula will be quite variable based on the location of the external opening, the complexity of the tract, the patient's tolerance, as well as the underlying cause. Fistula that results from cryptoglandular disease will usually be preceded by a history of an anorectal abscess that was drained (either purposefully or spontaneously). Patients will often assume that their symptoms are related to "hemorrhoids" and/or be referred after a biopsy of the external opening by referring physicians. Bleeding is common due to the hyper-granulation tissue that forms on the external

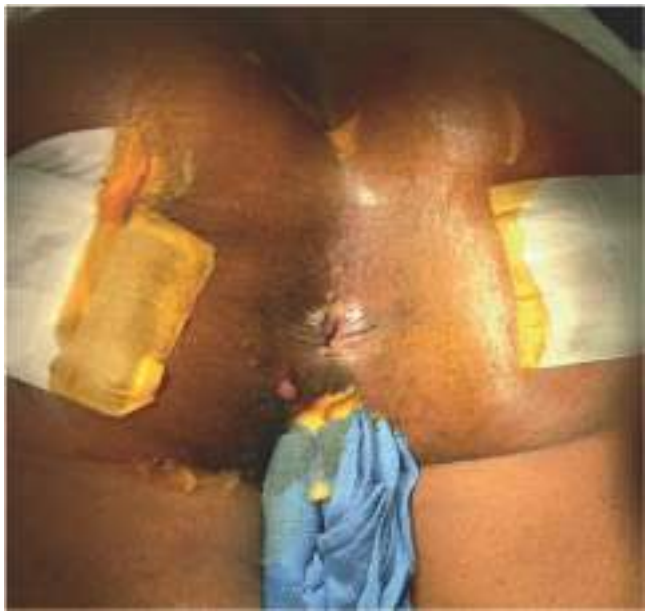

FIGURE 14-13. External opening noted left anterolateral with heaped-up edge.

opening and often irritation of the anal margin skin ensues from chronic moisture or from fecal contact. Pain may be a feature for patients with chronic infection or ongoing inflammation and is often cyclical as a result of spontaneous abscess formation and drainage. Severe pain should be a red flag for another etiology of the fistula such as malignancy or Crohn's disease. If a patient has concomitant gastrointestinal symptoms such as abdominal cramping, bloating, early satiety, or weight loss an associated diagnosis such as IBD or malignancy must be excluded.

Physical exam findings are usually pathognomonic for an anal fistula with an opening on the anal margin skin with heaped-up granulation tissue that is tender and often draining (Figure 14-13). The nature of the drainage can vary and may be serous, purulent, or feculent depending on the fistula. Often the location of the fistula can tell the examiner two things: the location of the internal opening and the depth of the fistula through the sphincter muscles. External openings that arise directly in the posterior midline close to the anal verge are usually submucosal while openings off the midline close to the anal verge are frequently intersphincteric. Low transsphincteric fistulas have been shown to occur more often in the anterior location and are less likely to be preceded by an abscess [66]. External openings in the ischiorectal fossa are usually the result of transsphincteric or suprasphincteric fistula and the examiner should suspect that the external sphincter muscle will be involved. In addition Goodsall's rule can be applied to help locate the internal opening. Goodsall described his observations of anal fistula in a book chapter written in 1900 [67]. He subdivided the anal margin skin into quadrants by two lines intersecting at right angles in the center of the anal aperture. The first was

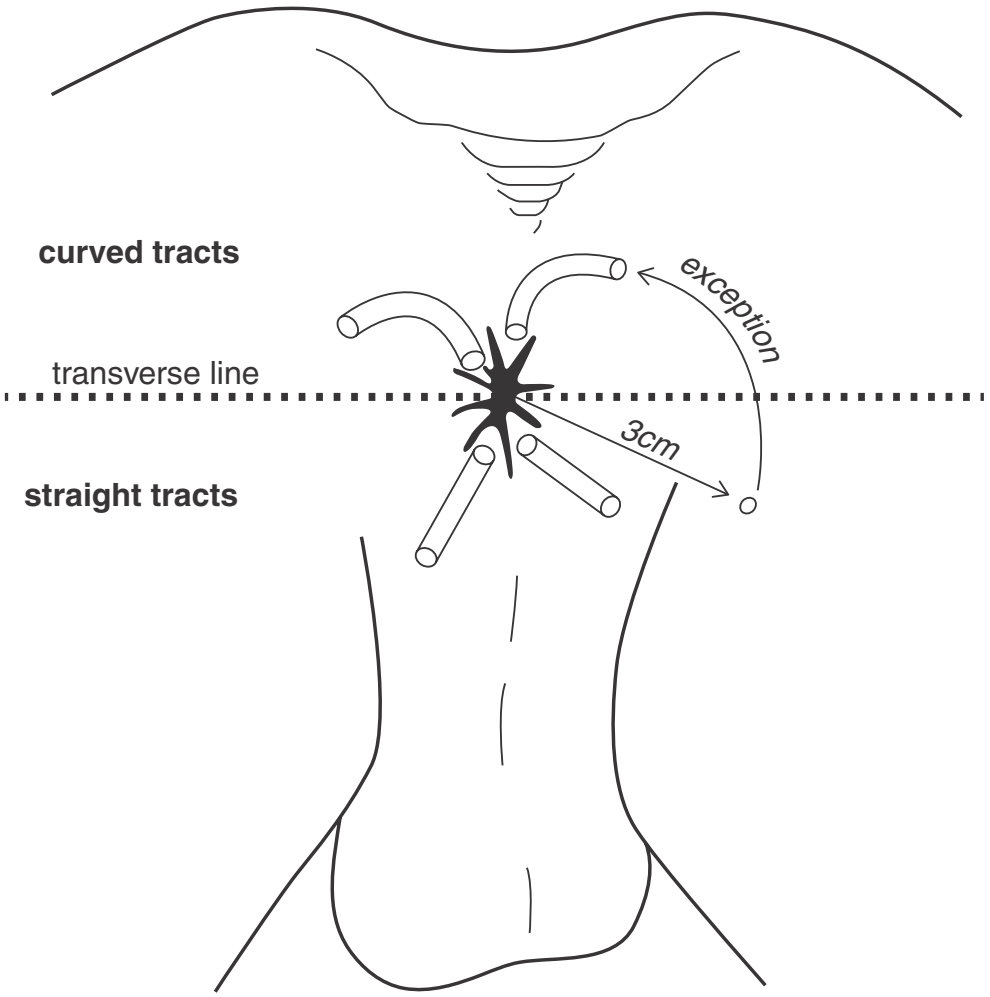

FIGURE 14-14. Goodsall's rule for anal fistula.

drawn connecting the ischial tuberosities and was referred to as the transverse anal line and the second from the coccyx to the pubic symphysis (Figure 14-14). The transverse anal line is of importance as external openings of anal fistulas that are located anteriorly are postulated to drain to an internal opening radially situated while posterior external openings drain to the posterior midline. This observation has proven accurate for external openings situated posteriorly but less so for anterior fistula. Cirocco et al. demonstrated in their retrospective review of 216 patients with transsphincteric fistula that 81 % of all fistulas drained to the midline. They confirmed that posteriorly located fistulas drain to the posterior midline in 90 % of cases (97 % for women, 87 % for men) while 71 % of anteriorly located fistulas drain to the anterior midline [68]. The positive predictive value of Goodsall's rule has been estimated to be 59 % and is more accurate for posteriorly located fistulas [69, 70].

Palpation of the anal canal using the pad of an experienced finger can frequently determine the location of the internal opening by subtle changes in the anoderm [71]. Anoscopy is helpful to exclude inflammatory conditions of the anal canal or other potential causes of the fistula but the internal opening is rarely seen unless pus is draining from it. In patients that have abdominal symptoms or findings in the office concerning for a cause other than cryptoglandular a colonoscopy can be performed. However as a general rule most patients with anal fistula require little if any work-up other than a physical exam.

Preoperative imaging is reserved for patients that present with multiple external openings, those in which an internal opening cannot be identified on physical exam either preoperatively or intraoperative or in cases of recurrence following surgical procedures especially a fistulotomy in which cure would be expected. Increasingly patients presenting with anal pain in the emergency room are undergoing CT scans with rectal contrast that can occasionally demonstrate an anal fistula. However as a rule this is not a helpful test for the evaluation of anal fistula and should not be routinely ordered [72].

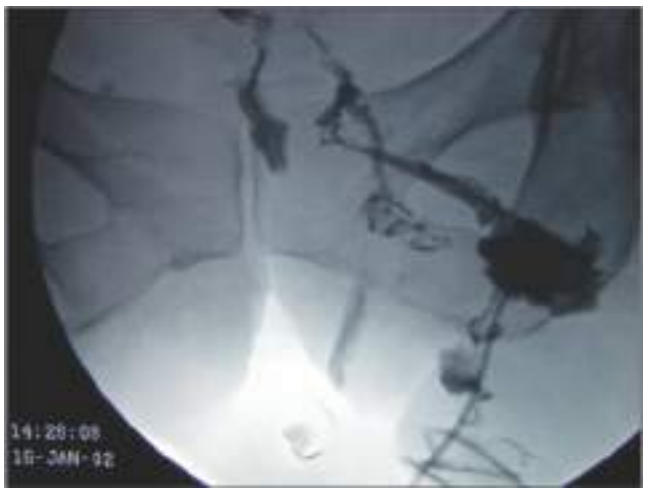

FIGURE 14-15. Fistulography of complex anal fistula (*arrow* on fistula tract).

Fistulography

Water-soluble contrast injected into the external opening under fluoroscopy using a small feeding tube has proved historically to be useful in the evaluation of complex anal fistulas (Figure 14-15). Weisman et al. retrospectively evaluated the utility of fistulography in 27 patients with anal fistula and found that in 13 of the 27 patients (48 %) information obtained from the fistulograms revealed either unexpected pathology ($n=7$) or directly altered surgical management ($n=6$) [73]. However Kuijpers et al. found fistulography to be inaccurate for the detection of internal openings (5/21 patients) and high extensions (9/21 patients) compared to surgical findings [74]. Using a modified technique in which contrast was injected through a Foley catheter inserted into the rectum Pomerri et al. demonstrated an accuracy of 74 % for the detection of internal openings and 92 % for secondary tracks when compared to surgery [75].

Due to the limitation of plane film imaging to delineate anatomic landmarks more recent attempts at fistulography have incorporated CT imaging in combination with contrast injection. Liang et al. prospectively evaluated 18 patients with anal fistula and found that CT fistulography had excellent concordance with intraoperative findings including the identification of the fistula tracks, internal opening, and deep abscesses [72]. They failed to demonstrate that CT fistulography was superior to the intraoperative assessment or compare their findings to other imaging techniques. More data is needed to determine if CT fistulography will be a valid tool to assist in the management of patients with complex anal fistula. However it is likely that fistulography as a diagnostic tool for complex anal fistula will be of limited value given the alternatives available in modern radiology suites or colorectal offices.

Endoanal Ultrasound

Surgeon-performed endoanal ultrasound (EAUS) can be performed in the office as a way to characterize complex fistula and its relationship to the sphincter complex. Fistulas appear as a hypoechoic track, which can be enhanced by the instillation of hydrogen peroxide or a Levovist™ [76]. These agents are injected into the external opening during the ultrasound examination to create air within the tract and increase the hypoechoic signal although the advantage of such agents has not been well established [77, 78]. EUS can also help determine the presence of secondary tracts as well as horseshoe extensions. Muhammed et al. performed a meta-analysis of studies comparing EUS with MRI for the detection and characterization of anal fistula. 240 patients were evaluated in the EUS group. The combined sensitivity and specificity in detecting fistulas were 0.87 (95 % CI: 0.70–0.95) and 0.43 (95 % CI: 0.21–0.69), respectively [79]. EUS performed better in the detection of transsphincteric fistula vs. intersphincteric and suprasphincteric tracts that can be difficult to localize [80, 81]. Buchanan et al. evaluated the utility of EUS compared to *preoperative* clinical assessment in determining the *classification* of anal fistula in 104 patients. EUS was superior to physical exam, which correctly predicted 87 (81 %) vs. 66 (61 %) patients, respectively ($p<0.01$). It was also superior in identifying the internal opening (91 % vs. 78 %), and undrained fluid collections (75 % vs. 33 %) [82]. Nagendranath et al. evaluated the performance of hydrogen peroxide-enhanced EUS in 68 patients undergoing surgery for anal fistula. EUS performed no better than *intraoperative* findings in determining the presence and course of the primary tract. EUS outperformed the surgical findings in detecting the presence of secondary tracts (92.65 vs. 79.41 %; $p<0.001$) and course (91.18 vs. 77.94 %; $p<0.001$) [78]. In 13 patients the findings on the EUS changed the operative approach from fistulotomy to seton placement but the authors do not comment as to the reasoning. Conversely, Toyonaga et al. were able to demonstrate that EUS was superior to *intraoperative* findings in the identification of acute and chronic anal fistula in a prospective series of 400 patients. EUS was superior to physical exam in correctly identifying the fistula track (88.8 % vs. 85.0 %, $p=0.0287$) and horseshoe extension (85.7 % vs. 58.7 %, $p<0.0001$) and in localizing the internal opening (85.5 % vs. 69.1 %, $p<0.0001$) [83]. The concordance with EUS findings intraoperatively has not been demonstrated to improve long-term outcomes of anal fistula surgery [84, 85] but more data is necessary to determine which patients and how often surgeons should perform EUS in the management of anal fistula. The results of these studies are influenced by the expertise and experience of the endosonographer and results may not be reproducible in all surgeons' hands. The images are subject to a high degree of interpretation and standards are not well described. Previous surgery, scars, and

trauma as well as the presence of undrained fluid collections can negatively influence the results of EUS. The presence of an abscess can lead to acoustic shadowing and render the results less accurate [86]. As MRI begins to supplant EUS for the evaluation of rectal cancer it is likely that the expertise in evaluating endoanal ultrasounds will diminish.

Magnetic Resonance Imaging

MRI of the sphincter complex has some advantages in diagnosing anal fistulas. No instrumentation of the anus is required and the exam is not operator dependent. The importance of MRI lies in its ability to demonstrate hidden areas of sepsis and secondary extensions, both of which contribute to the high rate of recurrence after surgery. Furthermore, MR imaging can be used to define the anatomic relationships of the fistula to predict the likelihood of postoperative fecal incontinence.

Two types of coils can be used: the endoanal and the external phased array coils. The endoanal coil was utilized to improve the imaging evaluation of perianal fistulas, but anal insertion is not well tolerated by patients [87]. The external phased array coil has a wider field of view and is better for assessing complex tracts, lateral extension, and fistulas crossing the levator ani muscle. Additionally, MR imaging with phased array surface coils requires no patient preparation or insertion of anything inside the anus. The introduction of the 1.5 Tesla (T) and 3.0-T magnets in the acquisition of images has negated the need for the endoanal coil in the evaluation of anal and rectal disease. A prospective trial comparing the use of the endoanal coil to the body coil found that surgical concordance was better using the body coil (96 % vs. 68 %), presumably due to field of view limitations [87]. The 3.0-T imaging improves spatial resolution and diagnostic accuracy over the 1.5-T magnet [88]. The finer detail helps in detecting and characterizing even small fistula tracks. However, comparative studies with 1.5-T or 3.0-T have not been reported.

On axial T2-weighted images, the internal and external anal sphincters appear as circular structures with low signal intensity. After intravenous administration of gadolinium, the internal and external sphincter can be easily distinguished on T1-weighted images by their different contrast enhancement. The internal sphincter muscle enhances to a higher degree than the external sphincter muscle [89]. On T2-weighted MR sequences, active fistulas and abscesses are hyperintense.

The potential of MR imaging in assessment of anal fistulas was demonstrated in a study of 16 patients with cryptoglandular fistulas, when MR imaging findings were compared with the subsequent findings from examination under anesthesia [90]. The authors concluded that MR imaging is the most accurate method for determining the presence and course of anal fistulas and that it may help reduce recurrence due to inaccurate surgical assessment. These conclusions were confirmed in a follow-up study of 35 patients that reported correct MR imaging assessments in 33 of the patients (94 %), including two cases in which examination under anesthesia failed to identify distant sepsis [91]. In a prospective study of 42 patients with suspected anal fistulas [92], the results of digital rectal examination, dynamic contrast-enhanced MR imaging, and surgical exploration were compared. MR imaging had a sensitivity of 97 % and specificity of 100 % for detection of fistulas. In addition, it allowed identification of more secondary tracks and was more accurate in identification of complex fistulas than either digital rectal examination alone or surgical exploration. Beets-Tan et al. reported that preoperative MR imaging provided important additional information in 12 of 56 patients with anal fistulas (21 %). This was further subdivided as 4 of 17 patients with recurrent fistulas (benefit in 24 %) and 6 of 15 patients with Crohn's disease (benefit of 40 %) [93]. In a larger study of 71 patients with recurrent anal fistula in which MR imaging findings were revealed after initial fistula surgery, the postoperative recurrence rate was as low as 16 % when surgeons always acted on the MR imaging findings, suggesting that areas of infection had been missed. By contrast, the rate of recurrence was 30 % when surgeons only sometimes acted on MR imaging results and 57 % when MR imaging results were ignored. Furthermore, in the 16 patients who required further unplanned surgery, MR images had initially correctly indicated the site of disease in all cases [94]. The results of MR imaging, anal endosonography, and clinical examination were compared to determine the optimal technique for classifying perianal fistulas. It was concluded that MR imaging is the optimal technique for distinguishing complex from simple perianal fistulas [95]. Finally in a small series of patients with supralevator abscess MRI was used to correctly characterize the fistula track as transsphincteric or intersphincteric, a distinction that is important in determining the correct drainage procedure (transrectal vs. transperineal) [14].

Taken together, the results of these studies confirm that MR imaging is an accurate modality for evaluation of perianal fistulas and associated complications. The most cost-effective algorithm for managing all patients with anal fistula has yet to be established but preoperative imaging should be considered when recurrent fistulas are encountered following treatment, in cases in which multiple external openings exist and when the anatomy is unclear either in the office or at the time of surgery.

Treatment

Treatment of anal fistulas has always been difficult and apparently the chief reason for the opening of the St Marks Hospital in England in 1836. The goals however of any surgical treatment are summarized as:

1. Elimination of sepsis.
2. Closure of the fistula track.

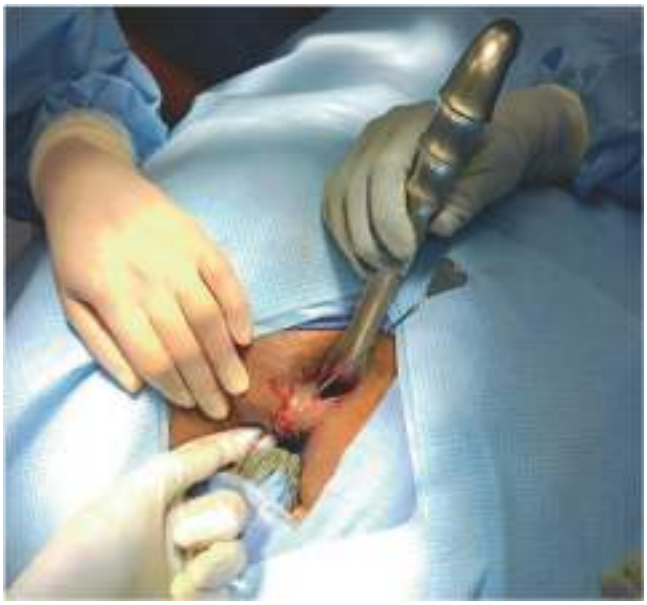

FIGURE 14-16. Probe through the external and internal opening of the anal fistula.

3. Preservation of patient's fecal continence and sphincter function.
4. Minimizing recurrence.

Identification of the external and internal opening is critical and several intraoperative techniques have been described. Physical examination is quite reliable in determining the location of the internal opening in the operating room but if not palpable a catheter can be used to inject either methylene blue or hydrogen peroxide into the external opening with a retractor in the anus. This has been associated with successful identification of the internal opening in 83 % of cases [71].

A gently curved probe inserted into the external opening is an alternative technique for finding the internal opening (Figure 14-16) but care must be taken not to create a false passage and it is better to have an idea of the location of the offending crypt prior to attempts at probing. Chronic tracks will have granulation tissue within them and its absence should raise the suspicion that a false track was created following a fistulotomy.

The ultimate choice of treatment will depend on the amount of sphincter involved in the fistula track with cutting procedures more likely for intersphincteric and low transsphincteric fistula and non-cutting techniques for all others. Patient preference will also influence the procedure choice with most patients opting for sphincter-preserving technique [96]. Surgeons must rely on their experience and comfort for the various non-cutting techniques as the overall quality of evidence to guide decision making is poor [97].

Lay Open Technique (Fistulotomy)

> *For the confident and successful surgical treatment of fistula-in-ano, one must be practiced and skilled in palpating and recognizing the anorectal ring, for whereas, if this ring be cut, loss of control surely results, yet as long as the narrowest complete ring of muscle remains, control is preserved. All the anal sphincter muscles below this ring may be divided in any manner without harmful loss of control.*
>
> *Lockhart-Mummery* [58]

For simple and most distal or intersphincteric fistula, conventional surgical treatment such as lay open of the fistula tract as a complete transection of the tissue between the fistula tract and anoderm is very effective (Table 14-3). Fistulotomy wounds typically heal after 4–6 weeks, which may be shortened by marsupializing the wound edges [98, 99]. This technique may also reduce the incidence of postoperative bleeding [100].

Recurrence and incontinence are the most significant complication and rates vary widely by author. In a retrospective review of 365 patients, Garcia Aguillar reported recurrence in 4 % of patients with intersphincteric fistula, 7 % with transsphincteric fistula, and 33 % for suprasphincteric and extrasphincteric fistulas [101]. Incontinence after surgical treatment of these fistulas also increased with the complexity of the fistula, lowest being for intersphincteric fistula (37 %) and highest for extrasphincteric fistula (83 %). Factors associated with recurrence included type and extension of the fistula, lack of identification or lateral location of the internal opening, previous fistula surgery, and surgeon experience. Incontinence was associated to female sex, high anal fistula, type of surgery, and previous fistula surgery. Visscher et al. reported on 116 patients who had undergone fistula surgery (both cutting and non-cutting) in whom both a fecal incontinence and quality-of-life questionnaires could be obtained. Median follow-up from the first perianal fistula surgery was 7.8 years (range, 2.1–18.1 years). Thirty-nine patients (34 %) experienced incontinence. Surgical fistulotomy, multiple abscess drainages, and a high transsphincteric or suprasphincteric fistula tract were associated with incontinence. As compared to simple fistula (Wexner score, 1.2 [SD, 2.1]), incontinence was worse after surgery for complex fistula (Wexner score, 4.7 [SD, 6.2], $p=0.001$), as were quality-of-life elements, including lifestyle ($p=0.030$), depression ($p=0.077$), and embarrassment ($p<0.001$) [102].

Setons

Setons are used to treat anal fistula when a lay open technique is not possible or not advisable. Most complex anal fistulas and fistulas associated with Crohn's disease are specific examples in which a lay open technique would have significant or complete impairment of fecal continence or

TABLE 14-3. Experience with fistulotomy in treating anal fistula

Author	Year	Surgical procedure	# Patients	Outcome	Follow-up
Kronborg	1985	Fistulotomy	26	Recurrence 11 %	12 Months
Hebjorn	1987	Incision and drainage with fistula surgery	20	Recurrence 10 % Minor incontinence 8.3 %	12 Months
Schouten	1991	Incision and drainage with fistula surgery	36	Recurrence 3 % Minor incontinence 39 %	42.5 Months
Tang	1996	Incision and drainage with fistula surgery	24	Recurrence 0 % Minor incontinence 0 %	12 Months
Ho Y	1997	Incision and drainage with fistula surgery	24	Recurrence 0 % Minor incontinence 0 %	15.5 Months
Ho	1998	Fistulotomy	52	Healing time 10 weeks Minor incontinence 11 %	9 Weeks
Belmonte Montes	1999	Fistulotomy	24	Incontinence 5 %	12 Months
Oliver	2003	Incision and drainage with fistula surgery	100	Recurrence 5 % Minor incontinence 6 %	12 Months
Pescatori	2006	Fistulotomy	52	Minor incontinence 8.3 % Recurrence 8.3 %	10 Months
Atkin	2011	Fistulotomy	180		
Tozer	2013	Fistulotomy	50	Recurrence 7 % Minor incontinence 20 %	11 Months
Hall	2014	Fistulotomy	146	Recurrence 6 %	3 Months

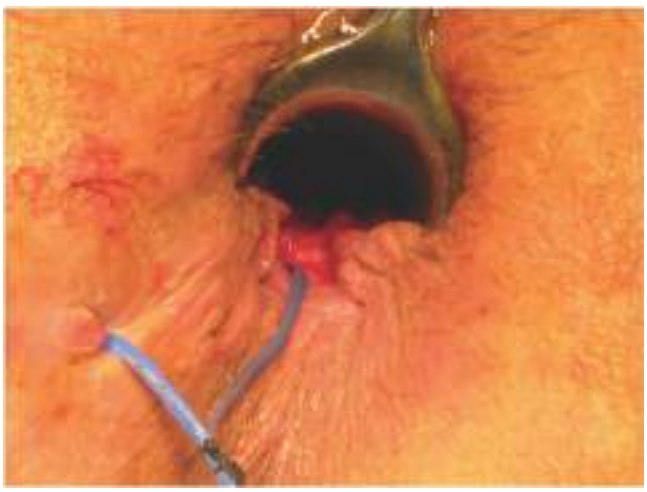

FIGURE 14-17. Seton in an anal fistula.

when healing of the subsequent wound would not be expected to occur (Figure 14-17). A variety of materials have been described for use as setons including wire, non-absorbable suture such as silk, vessel loops, and silastic catheters. Setons can be placed loosely in an effort to promote drainage and fibrosis of the fistula track either as a bridge to a non-cutting repair or as definitive treatment. Alternatively they may be tightened sequentially over time as a cutting seton in an effort to slowly divide the sphincter muscle and preserve continence by allowing a scar to form between the cut ends of the sphincter complex.

With cutting setons, the overlying skin and anoderm are divided at the time of surgery. The seton is then secured tightly around the remaining sphincter complex and is further tightened in the office at varying intervals. A variety of creative ways have been described to facilitate tightening of the seton [103, 104], and intervals vary from days to weeks but in general enough time must lapse for the seton to slowly divide the sphincter muscle. The time to complete healing will depend on the amount of tissue incorporated in the seton and the schedule of visits for tightening and has been reported between 1 month to as long as 1 year [105, 106]. Patients will often experience pain after tightening the seton and must be counseled as to the expected recovery and time frame to healing.

In a meta-analysis of 18 studies including 448 patients who were treated with cutting setons, recurrence rates were reported between 3 and 5 %. Overall fecal incontinence was reported as 5.6 % for patients in whom the internal sphincter was not divided at the initial surgery compared to 25.2 % when it was [107]. In another meta-analysis including 520 patients the average rate of incontinence following cutting seton use was 12 %. The rate of incontinence increased as the location of the internal opening of the fistula moved more proximally in the anal canal. In the studies that described the types of incontinence, liquid stool was the most common followed closely by flatus [108]. In a retrospective review of 112 patients undergoing cutting seton for transsphincteric or suprasphincteric fistulas ($n=84$) and extrasphincteric fistulas ($n=28$) the mean duration the seton was in place was 28.7 days. The mean time to complete wound healing was 9.3 weeks. With a median follow-up of 38.6 months recurrence was noted in one patient (0.9 %). Twenty-seven patients (24.1 %) had continence disorders, including gas incontinence in 21 patients (18.6 %) and liquid stool incontinence in 6 patients (5.4 %). There were no incidents of solid stool incontinence [109].

Non-cutting or draining setons are usually used as a bridge for definitive treatment in an effort to promote fibrosis, decrease the inflammatory response, and aid in identifying the internal opening at the time of the secondary procedure [110]. They can also be left in place to prevent recurrent abscess formation in patients with Crohn's disease or in patients who are not deemed candidates for additional surgery. Setons of any type can fall out due to wear and breaking. Vessel loops tend to be durable and can be left in place for years. If setons are to be left for prolong periods of time they should be loose but not so big that their presence becomes a problem for the patient in terms of hygiene and skin irritation. Setons that are secured in a circular configuration can rotate and the knots can migrate into the fistula track occasionally causing plugging and discomfort. Patient can be advised to twist them occasionally if this happens. The knots themselves can also cause irritation of the contralateral skin if too bulky.

Advancement Flap

Endorectal advancement flap (ERAF) has been advocated as an effective treatment for high transsphincteric or suprasphincteric fistulas. The techniques used are variable but the essential elements include debridement or excision of the fistula tract, mobilization of a vascularized, tension-free mucosal flap, and coverage of the internal opening, which is usually closed with absorbable suture. The procedure can be performed with locoregional anesthesia, but to optimize exposure of the anal canal and lower rectum a spinal anesthetic can be advantageous. A complete bowel preparation with oral purgatives is recommended combined with preoperative antibiotics.

Technique

1. With the patient in prone jackknife position or in lithotomy position, the internal opening of the fistula is exposed—this can be accomplished by everting the anal canal with the Lone Star® retractor system (Figure 14-18a).
2. The internal opening is identified and the crypt-bearing tissue excised.
3. A small rim of the anoderm, below the internal opening, is excised to create a neo-dentate line.
4. The defect in the internal anal sphincter is closed with absorbable sutures (2-0 Vicryl, Ethicon Inc., Somerville, NJ) (Fig. 14-18b).
5. A curvilinear incision is made at the level of the internal opening extending laterally to create a wide tissue flap.
6. Dissection is performed in the submucosal plane consisting of mucosa, submucosa, and few superficial fibers of the internal anal sphincter and then mobilized over a distance of 4–6 cm proximally.
7. The fistulous tract is alternatively curetted or cored out, and the defect in the internal anal sphincter is closed with absorbable sutures.

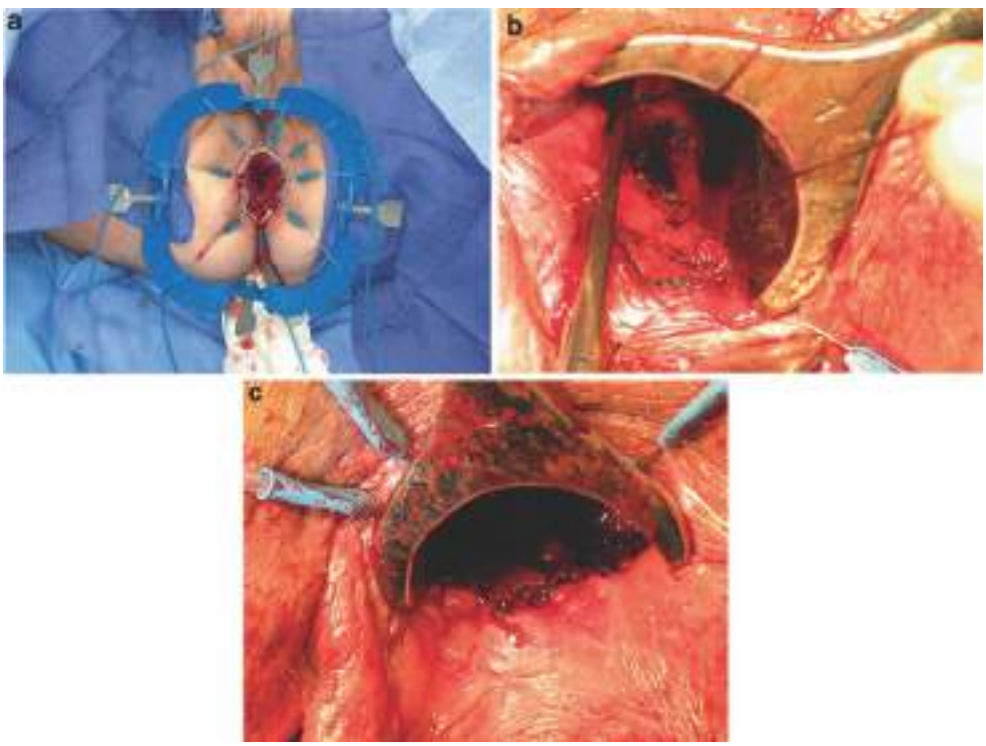

FIGURE 14-18. (**a**) Lone star to ever the anal canal. (**b**) Closing the internal opening. (**c**) Securing the flap.

8. The flap is advanced and sutured over the top of the internal opening with absorbable sutures (Figure 14-18c).
9. Vascular supply of the flap is maintained through the submucosal plexus.

The reported healing rates after flap repair vary between 60 and 100 % [111–119]. Ortiz et al. reported on 91 patients who underwent ERAF with a median follow-up of 42 (range 24–65) months. Eighteen patients had recurrence of the fistula during follow-up, with a median time to relapse of 5.0 (range 1.0–11.7) months. There were no recurrences after 1 year [120]. VanOnkelen et al. reported on a series of 252 patients with a high transsphincteric fistula of cryptoglandular origin that underwent ERAF with a median length of follow-up of 21 months (range 6–136 months). Before the procedure, patients underwent endoanal MRI to depict the course of the fistula tract and to determine the presence and location of associated abscesses. Seventeen patient- and fistula-related variables were assessed to determine their influence on recurrence. The failure rate at 3 years was 41 % (95 % CI, 34–48) [121]. Failure was not influenced by age, sex, smoking, or obesity. Nor was it affected by previous attempts at repair, preoperative seton drainage, presence of associated abscesses, location of the internal fistula opening, or postoperative drainage. 46 % of the patients in this series had a horseshoe extension of their fistula. The presence of a horseshoe extension correlated with successful repair 32.0 % [95 % CI, 23–41] vs. 51.0 % [95 % CI, 40.6–61.4]; $p=0.005$.

Despite these findings there are many studies that demonstrate patient, disease, and technical factors associated with either improved or worse outcomes following ERAF repair of complex anal fistula. Which of these are real and which are not can be difficult to discern due to the heterogeneity of patients and methods studied as well as the paucity of high-quality evidence. Knowledge of the literature as well as experience will facilitate discussion with patients regarding the risk of recurrence and complications rates following ERAF repair of complex fistulas.

One study looked at curettage of the fistula track vs. excision by means of "core out" and found no difference in recurrence [116]. In this same study the postoperative maximum squeeze pressure was reduced in patients who had the core out technique but this was not clinically relevant. The location of the internal opening (posterior vs. anterior) has no impact on outcomes of advancement flap repairs in the published literature even though it can be harder to obtain adequate flap length during posterior dissections due to the angulation of the anorectal junction posteriorly [122]. Preoperative seton placement did not impact outcomes of flap repairs in 278 patients with cryptoglandular fistulas reviewed retrospectively. Setons were in place at least 2 months prior to definitive repair [123]. Repeat anorectal advancement flap after recurrence has been shown to be feasible with overall good outcomes [124, 125], but has been shown to be a risk factor for failure [126, 127]. Success of flap advancement was inversely correlated with the number of prior attempts, and in patients with no or only one previous attempt at repair the healing rate was 87 %. In patients with two or more previous repairs the healing rate dropped to 50 % [126]. The combination of fibrin glue with advancement flap repair has also been associated with worse outcomes when compared to just flap repairs alone [128]. The use of platelet-rich plasma in combination with advancement flap has better outcomes but limited data [129]. Medically induced bowel confinement has not been shown to improve outcomes [130].

Full-thickness flaps have been shown to be superior to partial-thickness flaps in several studies [131, 132]. In one series 34 patients underwent surgery using a partial-thickness flap and 20 a full-thickness flap. Continence was not affected by choice of technique. Recurrence was 35 % and 5 %, respectively.

Patient-related factors that impact outcome include smoking, which both decreases the mucosal blood flow [133] and negatively impacts success of flap repairs [134]. Obesity negatively impacted advancement flap repairs in a study looking at 220 patients with complex anal fistula undergoing advancement flaps. After a median follow-up of 6 months, primary healing rate for the entire cohort was 82 % (180/220). In non-obese patients, recurrence rate was significantly lower than in obese patients (14 % vs. 28 %; $p<0.01$). Moreover, reoperation rate due to recurrent abscess with the need for seton drainage in the failure groups was significantly higher in obese patients when compared to non-obese patients (73 % vs. 52 %; $p<0.01$). Using multivariate analysis, obesity was identified as independent predictive factor of success or failure ($p<0.02$) [135]. Crohn's disease has also been shown to be a risk factor for failure [136].

While anorectal advancement flaps are chosen to preserve the sphincter muscle many reports have demonstrated some degree of fecal incontinence following surgery. Uribe et al. demonstrated significant reductions in maximum resting pressure 3 months after advancement flap repair of complex anal fistula (83.6 ± 33.2 vs. 45.6 ± 18.3, $p<0.001$) and maximum squeeze pressure (208.8 ± 91.5 vs. 169.5 ± 75, $p<0.001$). Before surgery, five patients (8.9 %) reported symptoms of incontinence. After surgery, 78.6 % patients had normal continence, seven patients (12.5 %) complained of minor incontinence, and five (9 %) had major problems with continence [113].

Ligation of Intersphincteric Fistula

The ligation of the intersphincteric fistula track is a sphincter-preserving procedure that can be performed under locoregional, spinal, or general anesthesia. The procedure is appropriate for all patients with high transsphincteric fistulas assuming that a well-formed fistula track has been established. The advantages of the procedure are its simplicity and applicability to most patients with fistula-in-ano (Table 14-4).

Table 14-4. Experience with LIFT procedure

Author	Year	# Patients	Procedure	Follow-up (weeks)	Percent healed (%)	Type of study
Rojanasakul et al.	2007	18	LIFT	4	94	Prospective observational
Shanwani et al.	2010	45	LIFT	7	82	Prospective observational
Ellis et al.	2010	31	bioLIFT	6	94	Retrospective
Bleier et al.	2010	39	LIFT	10	57	Retrospective
Ooi et al.	2011	25	LIFT	6	96	Prospective observational
Tan et al.	2011	93	LIFT	4	92	Retrospective review
Steiner et al.		18	LIFT	6	83	Retrospective
Aboulian et al.	2011	25	LIFT	24	68	Retrospective review
Mushaya et al.	2012	25	LIFT	4	68	Prospective randomized
Abcarian et al.	2012	50	LIFT	15	74	Retrospective
Lo et al.	2012	25	LIFT	2	98	Retrospective
van Onkelen et al.	2012	42	LIFT	12	51	Prospective
Chen et al.	2012	10	LIFT	6	100	Retrospective
Lehmann et al.	2013	17	LIFT	4	47	Prospective
Liu et al.	2013	38	LIFT	26	61	Retrospective
Madbouly et al.	2014	35	LIFT	56	74	Prospective randomized
Ye et al.	2015	43	mLIFT	60	87	Retrospective
Bastawrous et al.	2015	66	mLIFT	21	71	Retrospective

bioLIFT: biological LIFT; mLIFT: modified LIFT

Technique

A preoperative rectal enema is given to patients in the morning of surgery. Patients are placed in the prone jackknife position and regional anesthesia is used. The steps involved in the procedure are as follows [137]:

1. Identify the internal opening by injecting peroxide or saline through the external opening.
2. Incise circumanally in the intersphincteric plane at the site of fistula using a 3–4-cm curvilinear incision.
3. Identify the intersphincteric tract using a soft catheter or Lockhart–Mummery and lacrimal probes.
4. Dissect around the intersphincteric portion of the fistula tract being careful not to injure or disrupt the tract. A right-angle probe can be used for this purpose. Using narrow malleable retractors can facilitate exposure of the intersphincteric plane. A Lone Star retractor can also facilitate this exposure.
5. Hook the intersphincteric tract using a small right-angle clamp.
6. Doubly ligate the tract close to the internal and external sphincter with 2-0 Vicryl (Ethicon Inc., Somerville, NJ), and transect it between the sutures. Some surgeons prefer a transfixation suture.
7. Inject the external opening to confirm that the tract was divided completely.
8. Curette the external portion of the fistula tract.
9. Drain the external opening.
10. Re-approximate the intersphincteric incision wound loosely with an interrupted 3-0 Vicryl (Ethicon Inc., Somerville, NJ).

Variations in this technique include orienting the incision in a radial fashion and performing a partial fistulotomy up to the external sphincter [138, 139]. Other modifications include unroofing the fistula from the internal opening to intersphincteric groove, ligating the fistula tract, but preserving the external sphincter [140]. In an effort to increase the success of this procedure the use of biologics has also been examined including inserting a biologic mesh in the intersphincteric groove or as a plug in the external tract [141–143]. Series are small and conclusions cannot be drawn about the efficacy of these approaches.

Postoperatively patients are maintained on a bulk laxative and can be prescribed oral ciprofloxacin and metronidazole although the benefit of antibiotic in the postoperative setting has not been evaluated.

Abcarian et al. reviewed their experience with all-cause transsphincteric fistula treated with the LIFT technique [144]. Median follow-up was 18 weeks and closure was achieved in 74 % of patients. Success of the procedure was inversely correlated with the number of previous attempts at closure, a finding seen by other authors looking at their outcomes with the LIFT procedure [145]. No changes in continence were reported. Hall et al. reported in their multicenter prospective trial of anal fistula procedures a success rate of 79 % at 3 months of follow-up using the LIFT technique. Hospitals that performed more LIFT procedures had higher rates of healing [115].

In a meta-analysis looking at the success of the LIFT procedure 18 studies were reviewed including 592 patients (65 % male). The most common type of fistula was transsphincteric (73.3 % of cases). The mean healing rate reported was 74.6 %. The risk factors for failure were obesity, smoking, multiple previous surgeries, and the length of the fistula tract. The median length of fistula tract was shorter in the healed group compared with the failed group (4 cm vs. 6 cm, $p = 0.004$).

The mean healing time was 5.5 weeks, and the mean follow-up period was 42.3 weeks. The patient satisfaction rates ranged from 72 to 100 %. No de novo incontinence developed secondary to the LIFT procedure. There is not enough evidence that variants in the surgical technique achieve better outcomes (Bio-LIFT, LIFT-Plug, LIFT-Plus) [146].

A more recent meta-analysis of 24 original articles including 1110 patients was performed which included 1 randomized controlled study, 3 case control studies, and 20 case series. Most studies included patients with transsphincteric or complex fistula, not amenable to fistulotomy. During a mean follow-up of 10.3 months, the mean success rate was 76.4 % while incontinence, intraoperative, and postoperative complication rates were negligible (0 %, 0 %, and 5.5 %, respectively). There was no association between pre-LIFT drainage seton and success of the procedure [147].

In another review of 498 patients undergoing the LIFT procedure success rates ranged from 40 to 95 %, with a pooled success of 71 % (352 of 495 patients; 3 of 498 were lost to follow-up). Follow-up ranged from 1 to 55 months, with a reported mean or median of 4–19.5 months. One hundred and eighty-three patients were formally assessed for continence, out of whom 11 (6 %) had a minor disturbance [148].

When the LIFT procedure does fail several authors have noted that the resultant discharge presents at the intersphincteric incision and endoanal ultrasound has confirmed that these were simple fistulas that were subsequently managed with fistulotomy or local wound care [149, 150]. This has been shown in other studies but not as consistently [151].

Fibrin Glue

Fibrin sealants were introduced in the 1990s as an alternative to more invasive surgical procedures in an effort to shorten recovery, prevent incontinence, and simplify surgery in patients with complex anal fistulas. Hjortrup et al. instilled fibrin sealant into the fistula tracks of eight patients who had failed previous surgical attempts at closure and achieved a 50 % success rate after a single injection [152]. The advantages of fibrin glue are that it is simple and repeatable with no significant learning curve and no division of the sphincter muscle.

Generally fibrin sealants consisted of two components: fibrinogen concentrate and thrombin. Factor XIII is added to stabilize the fibrin monomers. Aprotinin is also added to prevent fibrinolysis. The glue is infused into the fistulous tract with the idea that collagen formation within the tract will stimulate healing. It also stimulates the migration and proliferation of fibroblasts and pluripotent endothelial cells to heal the fistula. Between 7 and 14 days postoperatively, plasmin that is present in the surrounding tissue lyses the fibrin clot as the tract is replaced by synthesized collagen [153].

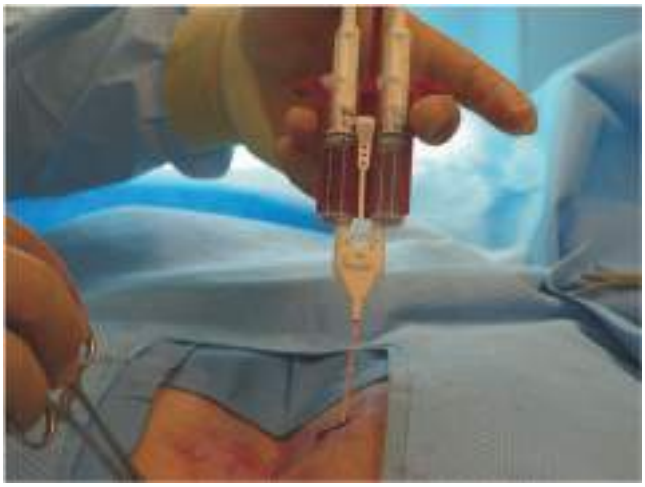

FIGURE 14-19. Fibrin glue injection into an anal fistula.

Technique

1. The patient is placed in the prone jackknife position and anesthesia is introduced (spinal, general, or locoregional).
2. Both openings of the fistula track are identified and mechanically curetted and irrigated with normal saline or hydrogen peroxide.
3. If extensive side branching or undrained abscess is encountered the procedure is aborted and a seton is placed.
4. A double-barreled syringe, containing the two components of the glue, is inserted into the external opening until the tip is seen at the internal opening (Figure 14-19).
5. At this point the internal opening can be variably sutured closed or left opening depending on the surgeon's preference—there is no significant advantage of one technique over the other [154].
6. The syringe is depressed, which mixes the two components as they are injected into the canal while withdrawing the syringe. The tract is filled completely until a bead of glue is seen at the external opening.
7. The glue is allowed to set for 30–60 s to form its stable clot.

Postoperatively, the use of antibiotics and diet restrictions do not seem to confer any benefit to the patient [155], but sitz baths, excessive straining, or vigorous exercise should be avoided to prevent dislodgement of the plug.

The efficacy of fibrin glue injection as a curative procedure remains in question. Success rates vary greatly depending on the etiology and complexity of the fistulas, type of fibrin glue used, and length of patient follow-up (Table 14-5).

Cintron et al. have reported the largest series of patients with perianal fistulas treated with fibrin glue [156]. Seventy-nine consecutive patients in this non-randomized prospective study were treated using one of the three different types of fibrin glue: autologous, Viguard-FS (V. I. Technologies,

Table 14-5. Experience with fibrin glue

Author	Year	# Patients	Success rate (%)	Follow-up (months)
Cintron et al.	1999	26	81	3.5
Cintron et al.	2000	79	61	18
Patrlj et al.	2000	69	74	28
Park et al.	2000	29	68	6
Sentovich	2001	20	85	10
Lindsey et al.	2002	42	63	4
Sentovich	2003	48	69	22
Loungnarath et al.	2004	39	31	26
Zmora et al.	2005	60	53	6
Gisbertz et al.	2005	27	33	7
Singer et al.	2005	75	21[a]	27
Maralcan et al.	2006	36	83	12
Ellis and Clark	2006	28	54	22
Dietz	2006	39	31	23
Witte et al.	2007	34	55	7
Adams et al.	2008	36	61	3
de Parades et al.	2010	30	50	12

Inc., New York, NY), and Tisseel VB (Baxter, Deerfield, IL). The majority of fistulas were transsphincteric and 8 % were secondary to Crohn's disease. The overall success rate was 66 %, with a mean follow-up of 1 year. Healing rates correlated with fistula complexity: intersphincteric 82 %, transsphincteric 62 %, and Crohn's related 33 %. The type of glue used did not affect success rates, and the use of commercial glue over autologous was recommended due to ease of preparation, increased strength in laboratory evaluations, and more consistent bonding. The average time to fistula recurrence was 3.3 months while the latest was seen at 11 months. This led the authors to stress the importance of long-term follow-up.

Many authors have suggested reasons for failure of fibrin glue in the treatment of anal fistula but little evidence exists to support these conclusions. Type of glue used, inadequate removal of granulation tissue, incomplete filling of fistula track(s), and track length have all been postulated to play a role in recurrence or persistence of the fistula [153]. In a meta-analysis of 12 published studies of 378 patients with complex anal fistula overall healing rate was 53 % with a wide variation between studies (10–78 %). The only factor that was found to account for this diversity was fistula complexity, with series including a high proportion of complex fistulae reporting worse outcomes [157].

Long-term follow-up of patients who show healing of their fistula tracks at 6 months demonstrated that few recur. Of 60 patients treated with fibrin glue 32 experienced healing. 23 (72 %) of these patients were available for long-term follow-up and 17 (74 %) remained disease free at a mean follow-up of 6.5 years. Six (26 %) patients had variable degrees of recurrence; four needed further surgical intervention and two were treated with antibiotics only. Recurrent disease occurred at an average of 4.1 years (range, 11 months to 6 years) from surgery, and on several occasions was at a different location in the perianal region. None of the patients experienced incontinence following the procedure [158].

Despite the varied success with fibrin glue treatment there is good evidence that patients experience no disturbances in continence as a result of treatment and treatment with fibrin glue does not preclude subsequent treatments of their fistula using alternative approaches. However the heterogeneity of published data regarding the success of this treatment makes it difficult to recommend as a first-line therapy of complex anal fistula.

Anal Fistula Plug

The concept of "filling" the fistula track spurred further innovation in the use of biological materials and in 2006 Johnson et al. performed a prospective trial in which a piece of Surgisis® (Cook Surgical, Inc., Bloomington, IN), a bioabsorbable xenograft, made of lyophilized porcine intestinal submucosa, was fashioned into a plug and secured into the fistula track of 15 patients with complex fistulas achieving an 87 % closure rate. As with the fibrin glue technique no sphincter division is required, so continence is not impaired. Since this initial study the Surgisis Anal Fistula Plug (AFP) (Cook Surgical, Bloomington, IN) has been introduced as a prefabricated cone-shaped device that can be easily secured into the fistula track. It acts as a tissue scaffold for host fibroblasts to promote healing and ingrowth of tissue into the fistula track [159].

TABLE 14-6. Experience with anal fistula plug

Author	Year	Type of study	# Patients	Success rate (%)	Follow-up (months)
Johnson et al.	2006	Prospective	25	87	3
Champagne et al.	2006	Prospective	46	83	12
O'Connor et al.	2006	Prospective	20	80	10
Ellis	2007	Retrospective	13	92	6
Ky et al.	2008	Prospective	45	55	6.5
Christoforidis et al.	2008	Retrospective	47	43	6.5
Safar et al.	2009	Retrospective	36	14	4.2
Ortiz et al.	2009	Prospective randomized	15	20	12
El-Gazzaz et al.	2010	Retrospective	33	25	7.4
van Koperen et al.	2011	Prospective	31	29	11
Chan et al.	2012	Prospective	44	50	10.5
Cintron et al.	2013	Prospective	73	42	15
Tan et al.	2013	Retrospective	26	13	15
Adamina et al.	2014	Prospective	46	43.5	68

Technique

1. The patient is placed in the prone jackknife position and anesthesia is introduced (spinal, general, or locoregional).
2. Both openings of the fistula track are identified and irrigated with normal saline or hydrogen peroxide.
3. The plug is rehydrated, usually in a 0.9 % normal saline solution for 3–5 min, before insertion.
4. The tapered end of the fistula plug is then tied to the anal side of the seton or silk suture and pulled into the fistula tract through the primary opening until it fitted snugly.
5. The plug is then trimmed flush with the primary opening. A 2-0 Vicryl (Ethicon Inc., Somerville, NJ) suture is used to anchor the plug to the mucosa/submucosa and internal sphincter at the primary opening with a figure-of-eight stitch, completely covering it with mucosa at the completion of the stitch.
6. The excess plug protruding from the external opening is trimmed such that the external opening is partially open to allow drainage and prevent infection.

Since introduction of the AFP, success rates have varied widely between 14 and 87 % (Table 14-6). Several technical and perioperative factors have been ascribed to the failures including the absence of preoperative seton placement, overly aggressive curetting of the fistula track resulting in widening of the track, inadequate fixation of the plug into the internal opening, and the presence of multiple tracks. Data is lacking to recommend one surgical technique over another. In one of the largest series by Citron et al. 73 patients underwent anal fistula plug closure of 72 transsphincteric and 1 suprasphincteric fistula [160]. There were eight fistulas secondary to Crohn's disease. Pre-procedure setons were used in patients at the discretion of the operating surgeon. Otherwise all aspects of the procedure were standardized. In their study the plug extrusion rate was 9 % (7/78). There was no difference in closure rates between primary and recurrent fistulas (primary = 20/53 = 38 % and recurrent 8/20 = 40 %). The overall patient success rate was 38 % (28/73) and the plug success rate was 39.5 % when plug fallouts were eliminated. The fistulas in four out of eight patients with Crohn's disease closed (50 %). There were no intraoperative complications and four postoperative abscesses (4/73; 5 %). Mcgee et al. looked at 41 patients with 42 fistula tracks who underwent AFP closures over a 39-month period. Complete closure was achieved in 18 of 42 (43 %) fistulas at a mean follow-up of 25 months. Closure was not associated with gender, age, tract location, duration of seton, or length of follow-up. Successful closure was significantly associated with increased tract length, because fistulas longer than 4 cm were nearly three times more likely to heal compared with shorter fistulas ((14/23, 61 %) vs. (4/19, 21 %), $p = 0.004$; relative risk = 2.8; 95 % CI 1.14–7.03) [161].

The diversity in study design and outcomes led O'Riordan and his colleagues to summarize the anal fistula plug literature for Crohn's- and non-Crohn's-related fistula-in-ano in a homogenous patient population [162]. Studies were included if results for patients with and without Crohn's disease could be differentiated and reported a mean or median follow-up of more than 3 months. Overall 530 patients were analyzed (488 non-Crohn's and 42 Crohn's patients). The plug extrusion rate was 8.7 % (46 patients). The proportion of non-Crohn's patients achieving fistula closure varied widely between studies, ranging from 0.2 (95 % CI 0.04–0.48) to 0.86 (95 % CI 0.64–0.97). The pooled proportion of patients achieving fistula closure in patients with non-Crohn's fistula-in-ano was 0.54 (95 % CI 0.50–0.59). The proportion achieving closure in patients with Crohn's disease was similar (0.55, 95 % CI 0.39–0.70). The authors noted that the divergent findings make it difficult for surgeons to quote an acceptable success rate during preoperative counseling of patients with anal fistulas considering treatment with the AFP.

A relatively new device for treating anal fistulas is a synthetic anal fistula plug (Figure 14-20) composed of a copolymer (polyglycolic acid:trimethylene carbonate) that is

FIGURE 14-20. Bio A absorbable fistula plug (W.L. GORE & Associates, Newark, DE, Courtesy of Michael Stamos, MD, with permission).

gradually absorbed by the body (Gore® Bio-A® Fistula Plug, W.L. Gore & Associates, Elkton, MD). There is limited data to assess the efficacy of this novel technique. Stamos et al. performed a multicenter prospective trial of 93 patients with non-Crohn's-related complex cryptoglandular transsphincteric anal fistulas treated with this device. The primary end point of the study was the healing rate at 6 and 12 months after plug implantation. 13 patients were lost to follow-up and an additional 21 were withdrawn (19 due to recurrence of their fistula prior to 6 months). Of the 66 patients remaining fistula closure at 6 months was 41 % (95 % CI, 30 %–52 %) which improved to 49 % (95 % CI, 38 %–61 %) at 12 months [163].

Novel Techniques

The use of laser in the treatment of anal fistula was initially described in 2011 in a pilot study by Wilhelm [164]. This sphincter-saving technique uses an emitting laser probe [fistula laser closure (FiLaC™), Biolitec, Germany], which destroys the fistula epithelium and simultaneously obliterates the remaining fistula tract. The procedure also includes the closure of the internal opening by means of an anorectal flap. In this pilot study, 11 patients with cryptoglandular fistula underwent FiLaC™ procedure with an overall success of 81 %. A subsequent study of 35 patients demonstrated healing in 71 % [165].

There is limited evidence for the use of adipose-derived stem cells (ADSC) to treat complex anal fistula mostly in patients with Crohn's disease. Autologous ADSC can be easily obtained with liposuction with minimal adverse effects on the patient. In a multicenter randomized controlled trial, Garcia-Olmo et al. [166] used ADSC to treat complex cryptoglandular, rectovaginal, and Crohn's-related fistulas. Initially they achieved a 71 % success rate with ADSC, compared with 16 % in the control group (fibrin glue only). However, at 1 year this had decreased to 62.5 and to 33 % at 3 years.

An injectable form of Permacol (Tissue Science Laboratories, Covington, GA), a type of porcine acellular collagen matrix, was modified by centrifugation to form a paste and has been used to inject anal fistula in combination with an ERAF. Studies are limited but success rates in non-Crohn's patients have been reported as high as 82 % [167].

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15
Complex Anorectal Fistulas

Giulio A. Santoro and Maher A. Abbas

Key Concepts

- The history and physical examination are the mandatory first step, providing in most cases the appropriate information to classify a fistula as "simple" or "complex." Anal continence should be evaluated using a validated incontinence score such as the Cleveland Clinic Florida Incontinence Score (CCF-IS) grading system.
- *Imaging procedures include (in order of authors' preference)* two- and three-dimensional endoanal ultrasound (2D/3D EAUS), pelvic magnetic resonance imaging (MRI), computed tomography (CT), and fistulography. Imaging can provide invaluable information on the anatomy of the fistula, including the primary track, internal opening, horseshoe extension, secondary cavities or extensions, and associated sphincter lesions and is a useful guide in surgical management.
- Complex anal fistula is challenging to treat due to the risk of postoperative anal incontinence and the high rate of recurrence. Three factors determine the outcome of surgical treatment: patient-related factors, fistula characteristics, and the surgeon's choice of operation inclusive of its technical conduct.
- Each surgical procedure has advantages and disadvantages, and the choice of operative intervention should be individualized based on patient-related factors and fistula characteristics taking into account success rate as well as impact on patient anal continence.
- Rectourethral fistula is often the result of prostate cancer treatment whether surgical or radiotherapy based. A multidisciplinary approach involving a urologist and a colorectal surgeon is essential. Small distal fistulas and those not radiation induced can be amenable to a local anal repair such as an endorectal advancement flap. Large fistulas, those induced by radiation, or persistent/recurrent fistulas are best approached by a transperineal approach with a gracilis interposition flap or in select cases by a transabdominal approach with rectal excision. Due to its rarity, rectourethral fistula is best managed in tertiary or quaternary centers with experience managing this condition.
- Ileal-pouch fistula is uncommon and can be extremely challenging to manage due to the morbidity associated with any intervention, failure rate of various surgical options, and long-term consequences to the patient. Simple procedures should be attempted first before more complex procedures are considered. Due to the low incidence of this condition, few centers worldwide have accumulated enough experience with ileal-pouch fistula management. Early referral to such centers is advisable.

Introduction

According to the standards practice task force of the American Society of Colon and Rectal Surgeons (ASCRS), an anal fistula may be termed "complex" when one or more of the following findings are present: the tract crosses more than 30 % of the external anal sphincter (high transsphincteric with or without a high blind tract, suprasphincteric, and extrasphincteric), horseshoe configuration, anterior location in a female, multiple tracts, recurrent, Crohn's disease, prior radiotherapy, or baseline incontinence [1]. In addition, anorectal fistulas with the following anatomical configurations and etiologies are considered complex: rectovaginal fistula, rectourethral fistula, anastomotic fistula following colorectal surgery, posttraumatic fistula, and malignant fistula. In this chapter, the definition, classification, pathophysiology, clinical assessment, diagnostic evaluation, surgical treatment, and outcome of complex anorectal fistula are described. The reader is provided with a comprehensive approach to the management of patients with complex anorectal fistula

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taking into consideration the various factors that influence outcome. Rectovaginal fistula and Crohn's-related fistula are not covered in this chapter but dealt with in other parts of this textbook.

Complex or Recurrent Cryptoglandular Fistulas

Definition, Classification, and Pathophysiology

An anal fistula may be termed "complex" when the tract crosses more than 30 % of the external anal sphincter (high transsphincteric with or without a high blind tract, suprasphincteric, and extrasphincteric), is horseshoe, is anterior based in a female, has multiple tracts, and is recurrent or the patient has preexisting incontinence [1]. The aim of anal fistula treatment is to eradicate the fistulous tract, prevent recurrence, minimize postoperative septic complications, and minimally impact anal continence. The selection of a surgical technique that is both safe and effective can be challenging. Sphincter-preserving operations such as injectable glues or plugs are associated with low risk of incontinence but high rate of persistent or recurrent disease [2]. Non-sphincter-preserving operations such as fistulotomy or fistulectomy have high success rate but can be associated with stool incontinence in some patients. Knowledge of the results of various surgical techniques coupled with good surgical judgment is essential when deciding on a surgical option for a patient.

Clinical Assessment and Diagnostic Evaluation

According to the standards practice task force of the ASCRS, a disease-specific history (demographic characteristics, smoking behavior, previous anorectal surgery, symptoms) and physical examination (inspection, palpation, digital rectal examination, careful probing, anoscopy, and/or rigid proctoscopy) is the mandatory first step, providing in most cases the appropriate information to consider a fistula "simple" or "complex" (strong recommendation based on low-quality evidence: 1C) [1]. The history should include the type of prior anal operations, obstetrical history in females, the presence of gastrointestinal disorders such as inflammatory bowel disease, medical comorbidities such as diabetes, prior radiation therapy to the pelvis, and current smoking status. Inquiry about the patient's bowel habits can provide useful information to guide postoperative care. Anal continence should always be assessed using a validated score such as the Cleveland Clinic Florida Fecal Incontinence Score (CCF-FIS) grading system (Figure 15-1) [3]. The scale reports the various types of incontinence (gas, liquid, solid), pad usage, impact of the incontinence on patient's lifestyle, and frequency of occurrence. A score of 0 corresponds to full continence, whereas a score of 20 is indicative of daily incontinence to gas, liquid, and solid. Physical examination can be helpful in delineating the fistula anatomy and reaches a very good accuracy in identifying superficial (100 %) and transsphincteric (100 %) tracts, but it appears inadequate for supralevator (63.6 %) and intersphincteric (33.3 %) tracts [4–6]. Deen and colleagues were able to identify only 50 % of the internal openings and 27.3 % of the horseshoe extensions [4]. Similarly, Poen and colleagues reported a correct diagnosis of primary tracts in only 38 % of patients, with 62 % of patients being unclassified [5]. The limitation of physical examination alone has been highlighted by others with an overall accuracy of 65.4 % for preoperative identification of the primary tract [6]. The additional challenges encountered included inability to identify suprasphincteric or extrasphincteric fistulas, to determine the internal opening, and to delineate ischioanal, pelvirectal, and horseshoe secondary extensions [6].

Type of incontinence	Never	Rarely <1/month	Sometimes <1/week >1/month	Usually <1/day >1/week	Always >1/day
Solid	0	1	2	3	4
Liquid	0	1	2	3	4
Gas	0	1	2	3	4
Wears Pad	0	1	2	3	4
Lifestyle Alteration	0	1	2	3	4

FIGURE 15-1. Cleveland Clinic Florida Fecal Incontinence Score (CCF-FIS). 0 = complete continence; 20 = complete incontinence [3].

Considering the limitation of physical examination, the standard practice task force of the ASCRS recommends (strong recommendation based on low-quality evidence: 1C) *performing* imaging procedures (two- and three-dimensional endoanal ultrasound (2D and 3D EAUS), pelvic MRI, and fistulography) for an accurate preoperative classification of the primary tract and its extensions [1]. These assessments can provide information on the anatomy of the fistula, including the primary tract, internal opening, horseshoe extension, secondary cavities or extensions, and associated sphincter lesions [7, 8]. On 2D/3D EAUS, the fistulous tract appears as a hypoechoic structure and can be traced in relationship to the internal and external sphincter muscles (Figure 15-2). Hydrogen peroxide enhancement of the tract can confirm its course as it traverses the anal sphincter complex and can provide accurate classification (Figure 15-3). Similarly, MRI can provide invaluable information to define the exact anatomy of a complex fistula (Figure 15-4). Clear delineation of the fistula anatomy to guide operative intervention can be helpful for surgical planning and may impact surgical outcome [9, 10]. In a large study of patients with recurrent anal

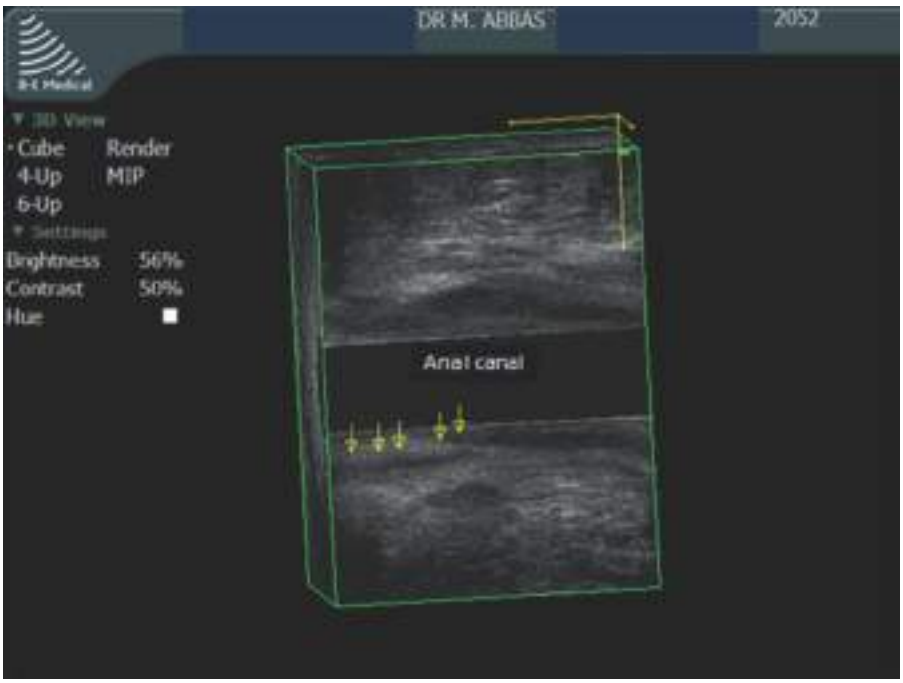

FIGURE 15-2. Recurrent low transsphincteric anal fistula secondary to cryptoglandular disease [3D endoanal ultrasound].

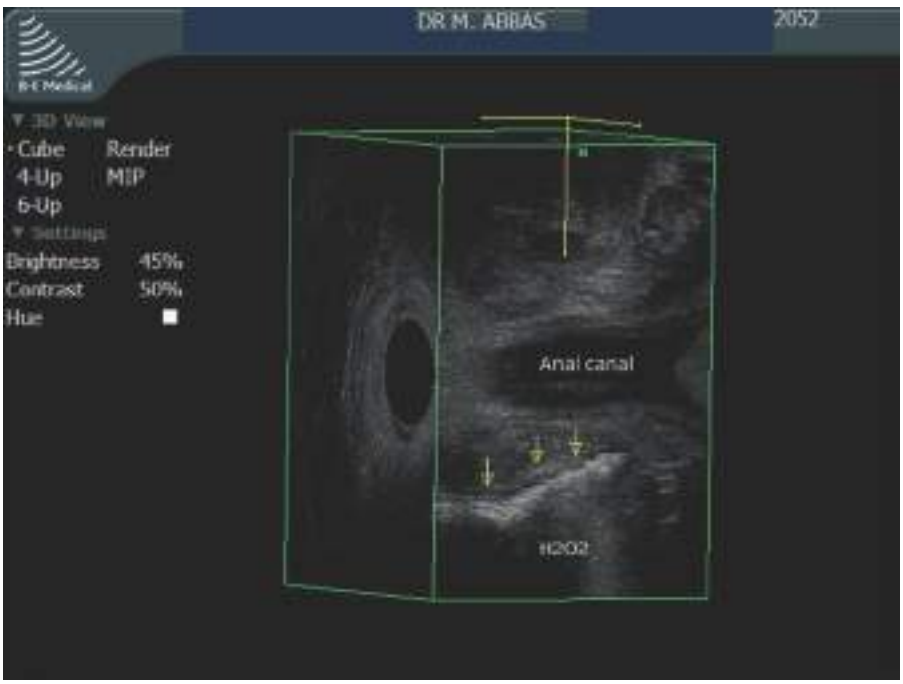

FIGURE 15-3. Persistent high transsphincteric anal fistula secondary to cryptoglandular disease [3D endoanal ultrasound].

fistulas, the postoperative recurrence rate was low (16 %) when surgeons always guided the patient's treatment based on the MRI findings. However, the recurrence rate rose to 30 % when the surgeons occasionally acted based on the MRI findings and 57 % when the MRI findings were ignored [10]. A variety of investigators have directly compared EAUS (2D/3D both with and without hydrogen peroxide injection through the external opening) with MRI (external phased array/endoanal coil), and these comparisons have found EAUS variously superior [11], equivalent [12–15], or inferior [16]. The difficulty in comparing these modalities is related to the ability to define a true reference standard for fistula-in-ano due to the following potential sources of bias: the operators who perform the assessments can have differing levels of experience with EAUS or with MRI and, similarly, the surgeons who perform the operations have different

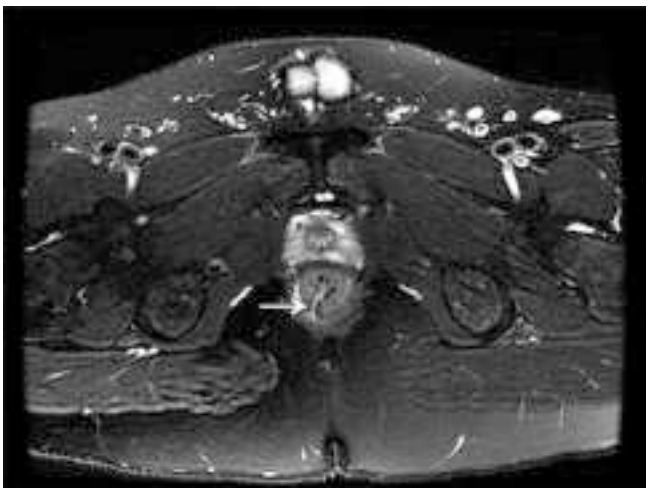

FIGURE 15-4. Suprasphincteric anal fistula secondary to anal trauma [magnetic resonance imaging]. White arrow points to fistula tract.

levels of experience. For this reason, Buchanan and colleagues proposed the "outcome-derived" reference standard [13]. If there is disagreement between findings at EAUS, MRI, and surgical examination, the findings associated with fistula healing should be assumed to be correct. Sahni and colleagues assessed the optimal technique for fistula classification using an "evidence-based medicine" method [17]. MRI was found to be more sensitive (0.97) than clinical examination (0.75) but comparable to EAUS (0.92) for discriminating between complex and simple fistula. MRI and EAUS can provide complementary information in some cases. However, our preference is to perform EAUS as the initial diagnostic test when available as it is a simpler and less costly modality compared to MRI. In centers where EAUS and MRI expertise is not readily available, fistulography can be performed to delineate tract configurations such as horseshoe fistula, high blind limb extension, or secondary branches (Figure 15-5). However, conventional fistulography is limited in its assessment of muscle involvement by the fistula tract. Computed tomography can be a useful imaging adjunct in select situations to identify recurrent abscesses secondary to complex fistula (Figure 15-6). Under such circumstances, computed tomography can guide drainage procedures to deal with acute sepsis, but in general it is not useful in elective surgical planning geared towards chronic fistula eradication.

In addition to imaging, baseline assessment of sphincter function with anorectal manometry can be helpful in select patients, such as multiparous females or in patients with prior anorectal surgeries [18, 19]. There are two different manometry systems including the low-compliance water perfusion system and the 3D high-resolution anorectal manometry. The low-compliance water perfusion system is equipped with six fluid-filled lumen and radially arranged ports throughout the cross section (Figure 15-7a, b). The pressure is recorded by pressure transducers that are

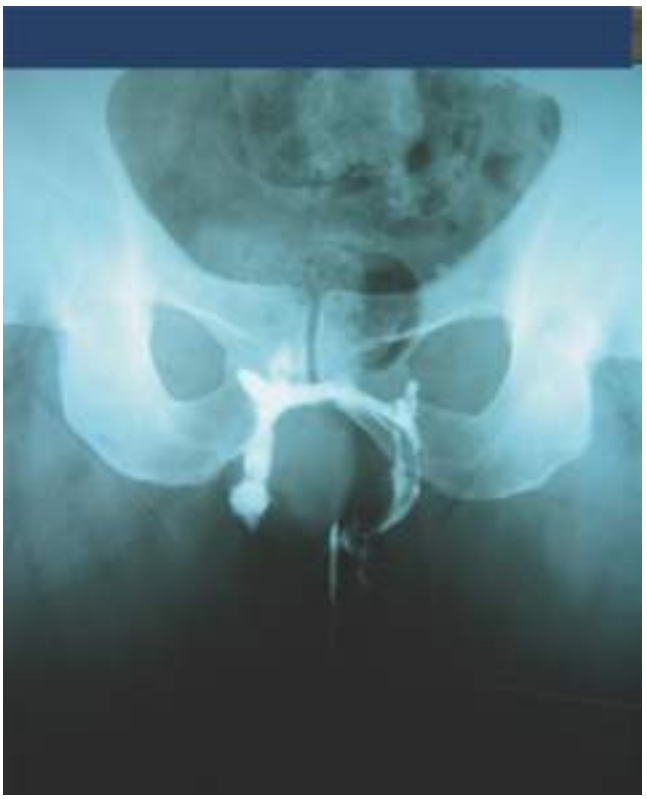

FIGURE 15-5. Fistulogram demonstrating a horseshoe fistula.

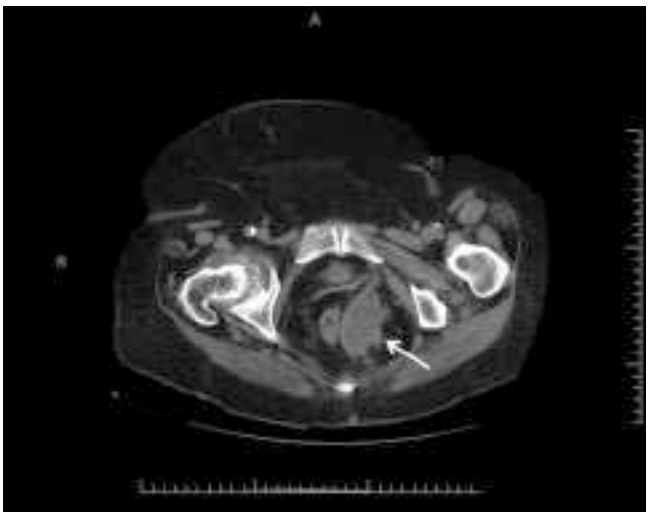

FIGURE 15-6. Computed tomography scan highlights recurrent supralevator abscess with fistula. *White arrow* demonstrates the abscess cavity on the patient's left.

located within each infusion line and are connected to a chart recorder. The 3D high-resolution anorectal manometry can simultaneously provide physiological and topographical data. The registration should include the maximum resting pressure and the maximum squeeze pressure [19].

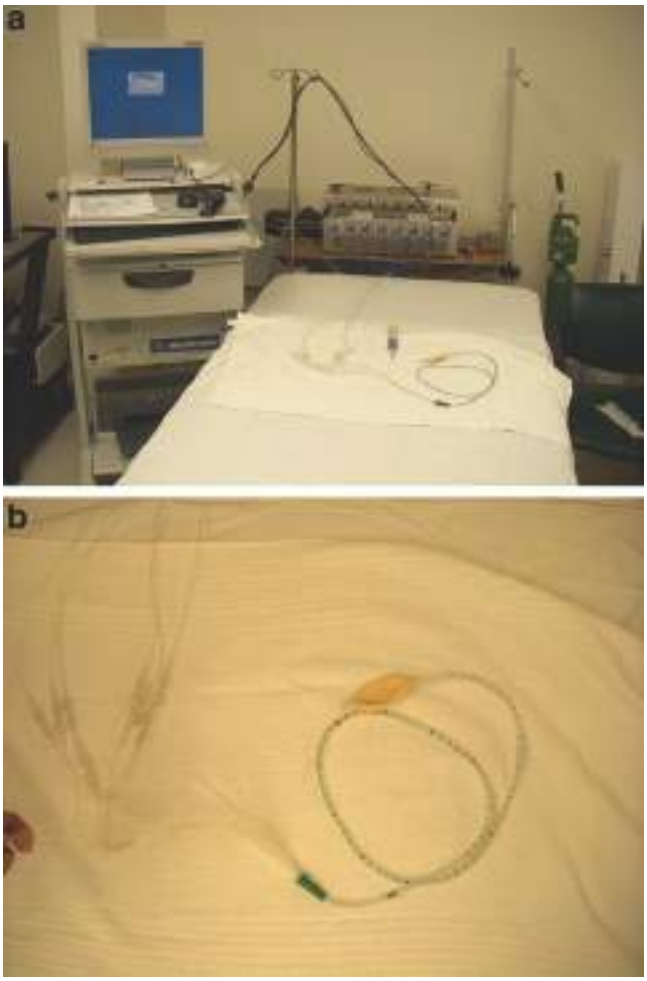

FIGURE 15-7. (**a**) Low-compliance water perfusion anorectal manometry system. (**b**) Anorectal manometry catheter.

Surgical Treatment

Surgical treatment of complex anal fistula involving a significant portion of the muscle can pose significant challenges to the surgeon and have long-term impact on the patient's well-being. The goal to eradicate the fistula should be balanced with the aim to preserve as much of the sphincter integrity to avoid impairment of continence. Similarly, in the case of recurrent fistulas, local structural alterations of the anal canal such as fibrosis or disruption of anal sphincter are often observed. Under such circumstances, surgical options may be limited because of the high risk of incontinence. Sound surgical judgment and familiarity with the outcome data of various operations is of paramount importance in order to pick the appropriate option from a modern armamentarium of surgical interventions [20]. Figure 15-8 provides a comprehensive carepath for a structured approach to guide the care of patients with anorectal fistula. It is based on our extensive experience with treating anorectal fistulas of various etiologies and complexity.

Seton

Seton is an important treatment option that can provide temporary control of fistula symptoms or can serve as a definitive intervention to control or eradicate a chronic fistula. A variety of materials have been used in the placement of setons including suture material (Ethibond, silk, nylon, polypropylene: suture size #2.0 to #2, depending on the tract width), vascular vessel loop, Penrose drain, rubber band, and chemically impregnated material [21]. A draining seton is tied loosely around a fistulous tract to promote drainage, to minimize acute abscess formation, and to allow for scarring of the fistulous tract. While a draining seton can be used as a definitive treatment in some patients [such as patients with multiple complex fistulas, radiation-induced fistula, or active Crohn's disease] (Figures 15-9 and 15-10), it is often a temporary measure as the patient awaits additional definitive fistula surgery. A period of 12 or more weeks is typically advisable during which the patient is assessed periodically to ensure adequate drainage. The seton may be used as a guide for gentle fistula irrigation if needed with solutions such as hydrogen peroxide, saline, antibiotics, or antiseptic. While a draining seton is in place, any new abscess or fistula formation should raise suspicion for inadequate drainage possibly due to having missed the correct fistulous tract at time of seton placement or due to progression of disease. Following an adequate period of drainage, a definitive sphincter-preserving fistula procedure can be performed.

A cutting seton is the second type of seton and typically entails encircling the fistulous tract. The skin and subcutaneous portion of the fistula are divided in the operating room to expose the anal muscle, which is encircled by the seton material (Figure 15-11a). The seton is connected to a Penrose drain which allows the patient over the course of several days to a couple of weeks to gradually pull the seton through the muscular portion of the tract (Figure 15-11b). Progressive cutting by the seton produces a slow fistulotomy, which allows for scarring of the divided tract minimizing wide separation of the divided muscle. An alternative variation of the cutting seton is the multiple seton technique. Two or more setons are passed through the tract, and at various time intervals, each suture is tightened progressively after taking out the previously tightened suture which becomes loose.

Anal Flap

Two types of anal flaps are available to treat anal fistula including transanal endorectal advancement flap and anocutaneous flap. The endorectal advancement flap is a good option for most complex anal fistulas, which typically are higher and involve more of the anal sphincter complex. Usually a noncutting draining seton is placed for 12 or more weeks to allow for fibrosis of the fistulous tract before the definitive flap repair is performed. The endorectal advancement flap is our

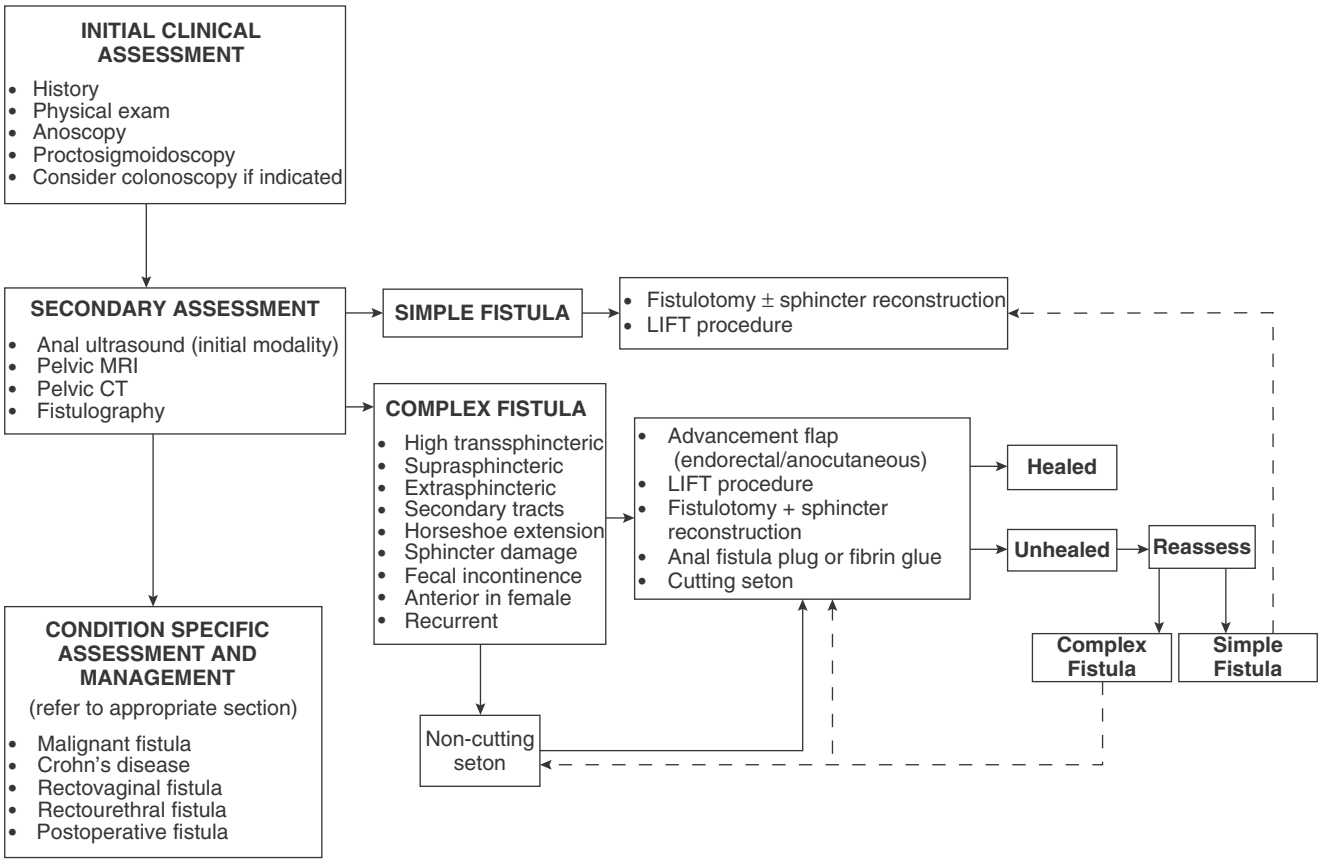

FIGURE 15-8. Carepath for evaluation and treatment of complex anal fistula secondary to cryptoglandular disease.

preferred method to treat most complex anal fistula secondary to cryptoglandular disease, except for posterior-based horseshoe fistula. The operation is typically performed in the prone position under general anesthesia. At time of flap repair, the draining seton is removed. The tract is irrigated with hydrogen peroxide and the tract is traced with a fistula probe. The anorectum is irrigated with Betadine, and the area of the planned flap is outlined and infiltrated with 1 % lidocaine with 1:100,000 epinephrine for hemostasis (Figure 15-12a, b). The subcutaneous portion of the external opening is excised, and the fistula is debrided with a curette (Figure 15-12c). A curvilinear incision is made approximately 1 cm distal to the internal opening and a partial or full thickness broad-based (3–4 cm wide) endorectal flap is raised (Figure 15-12d) [22]. It is important to avoid a mucosa-only based flap as it is associated with a higher failure rate due to ischemia. The flap should be dissected cephalad to ensure enough mobility to reach the lower anal canal. Once the flap is raised, the intramuscular portion of the internal opening is closed with interrupted 3.0 Vicryl suture (Figure 15-12e). The distal portion of the flap containing the mucosal portion of the internal opening is trimmed. The flap is matured over its muscular bed using 3.0 Vicryl single interrupted sutures (Figure 15-12f). Care is taken to spread any tension across the entire flap to provide adequate coverage of the intramuscular portion of the internal opening. Upon completion of the flap, an antibiotic impregnated gelfoam is placed inside the anal canal.

Ligation of the Intersphincteric Fistula Tract

The ligation of the intersphincteric fistula tract (LIFT) was described in 2007 by Rojanasakul and colleagues from Thailand [23] (Videos 15.1, 15.2, 15.3, 15.4, 15.5, 15.6, 15.7, and 15.8). The LIFT procedure is a sphincter-preserving operation that entails division and ligation of the fistulous tract in the intersphincteric plane. It is a good option for transsphincteric anal fistula. The LIFT procedure is the authors' second preferred surgical option when an endorectal advancement flap is contraindicated (i.e., anal stricture, incontinent patient, prior failed flap). Suprasphincteric and horseshoe fistulas can pose technical challenges and in general are not suitable candidates for the LIFT procedure. A draining seton is not mandatory prior to performing the procedure in fibrotic fistulas. However, wet fistulas with copious drainage and those associated with a cavity can benefit from a draining seton prior to the LIFT procedure. A metallic

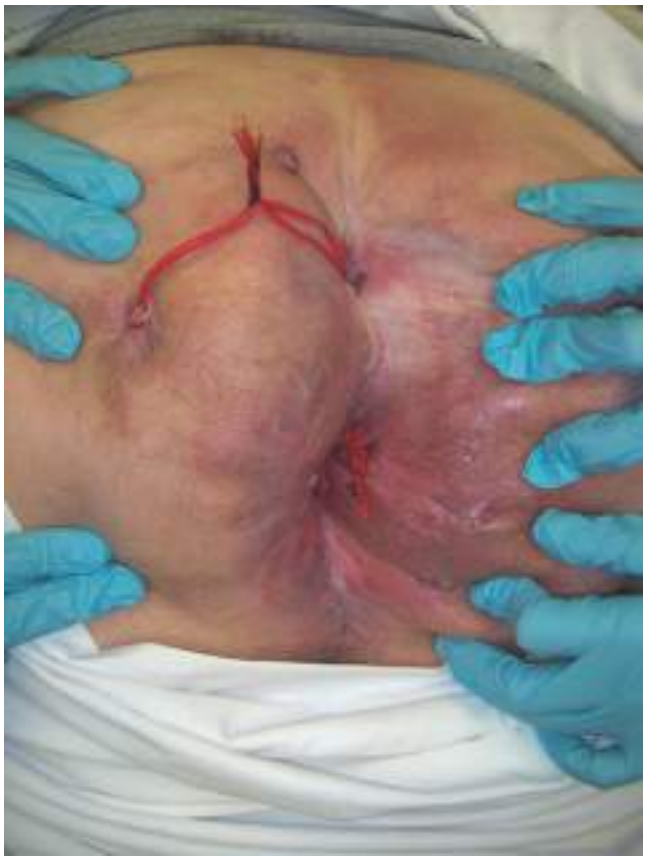

FIGURE 15-9. Draining setons in a patient with multiple complex anorectal fistulas and prior radiation therapy to the pelvis.

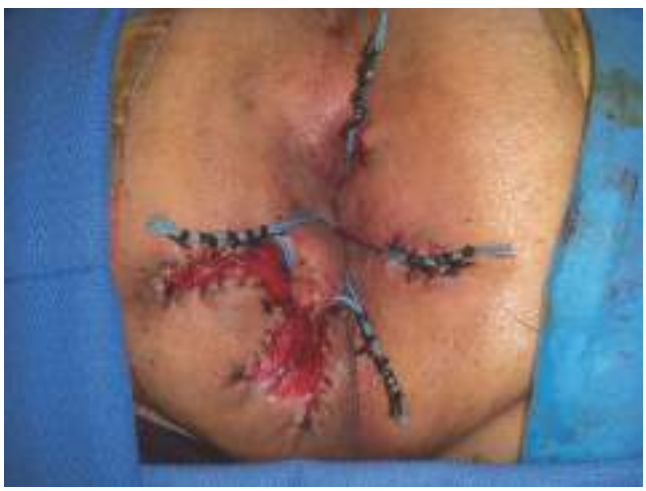

FIGURE 15-10. Draining setons in a patient with long-standing history of multiple fistulas emanating from different internal openings in all 4 anal quadrants.

FIGURE 15-11. (**a**) Cutting seton in a patient with suprasphincteric fistula. The skin and subcutaneous portion of the tract are divided before tightening the seton. (**b**) The cutting seton is connected to a Penrose drain to allow the patient to gradually pull through the fistula.

probe is inserted into the external opening and passed gently through the tract to exit through the internal opening (Figure 15-13a, b). The intersphincteric groove is identified externally, and a small circumanal skin incision overlying the fistula is performed to enter the intersphincteric space between the internal and the external sphincter muscles. The dissection in the intersphincteric plane is continued until to fistulous tract is reached and encircled (Figure 15-13c). Care is taken not to divide the tract prior to proper identification and dissection from surrounding sphincter muscle. This is achieved by palpating the fistula probe throughout the dissection. The fistula tract is then encircled by using a right-angle clamp, and two absorbable sutures (2.0 Vicryl) are used to ligate the fistula tract medially and laterally leaving a space in between to sharply divide the fistula (Figure 15-13d). Care is taken not to dislodge the tied sutures (Figure 15-13e). To confirm the integrity of tract division, hydrogen peroxide can be injected from the internal and external orifices while the wound is still open. The intersphincteric plane is closed in two layers (muscle approximation and the skin) by using

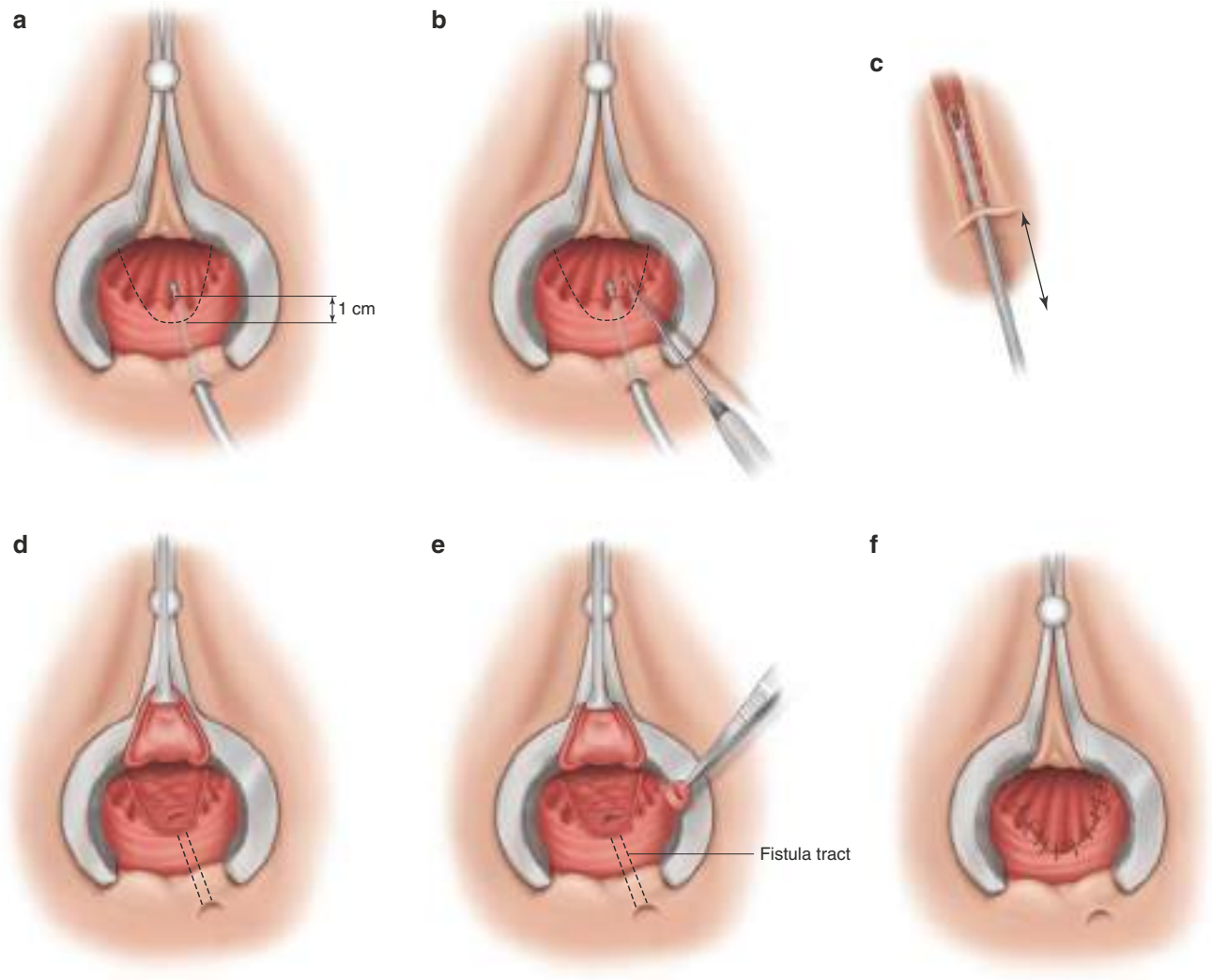

FIGURE 15-12. (**a**–**d**) Technical steps of endorectal advancement flap.

single interrupted 3.0 Vicryl (Figure 15-13f). Both the internal and external openings are left opened to allow drainage. The external opening nodular induration can be excised and left open. Patients have a normal diet on the day of surgery and are discharged within 24 h. A variation to the conventional LIFT procedure is the BioLIFT procedure which entails the use of a bioprosthetic porcine graft to reinforce the ligation and the closure of the fistula tract [24]. The graft is interposed between the internal and external sphincter muscles to overlap 1–2 cm area of the ligated and divided fistulous tract. Other modifications of the LIFT procedure are the LIFT-PLUS procedure which adds a partial fistulectomy of the subcutaneous portion of the tract from the skin to the external sphincter muscle and the LIFT procedure combined with endorectal advancement flap [25].

Fistulotomy with Sphincter Reconstruction

Fistulotomy with sphincter reconstruction is a suitable technique for complex or recurrent fistulas in incontinent patients or in patients who are at risk for incontinence [26]. Two enemas are given the evening before or the morning of the operation. Prophylactic intravenous antibiotics are given at time of operation and are continued postoperatively for 1 week. The operation is performed under general anesthesia in the prone jack-knife position. If a draining seton has been previously placed, it is removed, and a fistula probe is introduced through the external opening and guided through the tract until it protrudes out of the internal opening (Figure 15-4a). The fistula tract is completely divided using electrocautery (Figure 15-14b). Curettage of the tract and

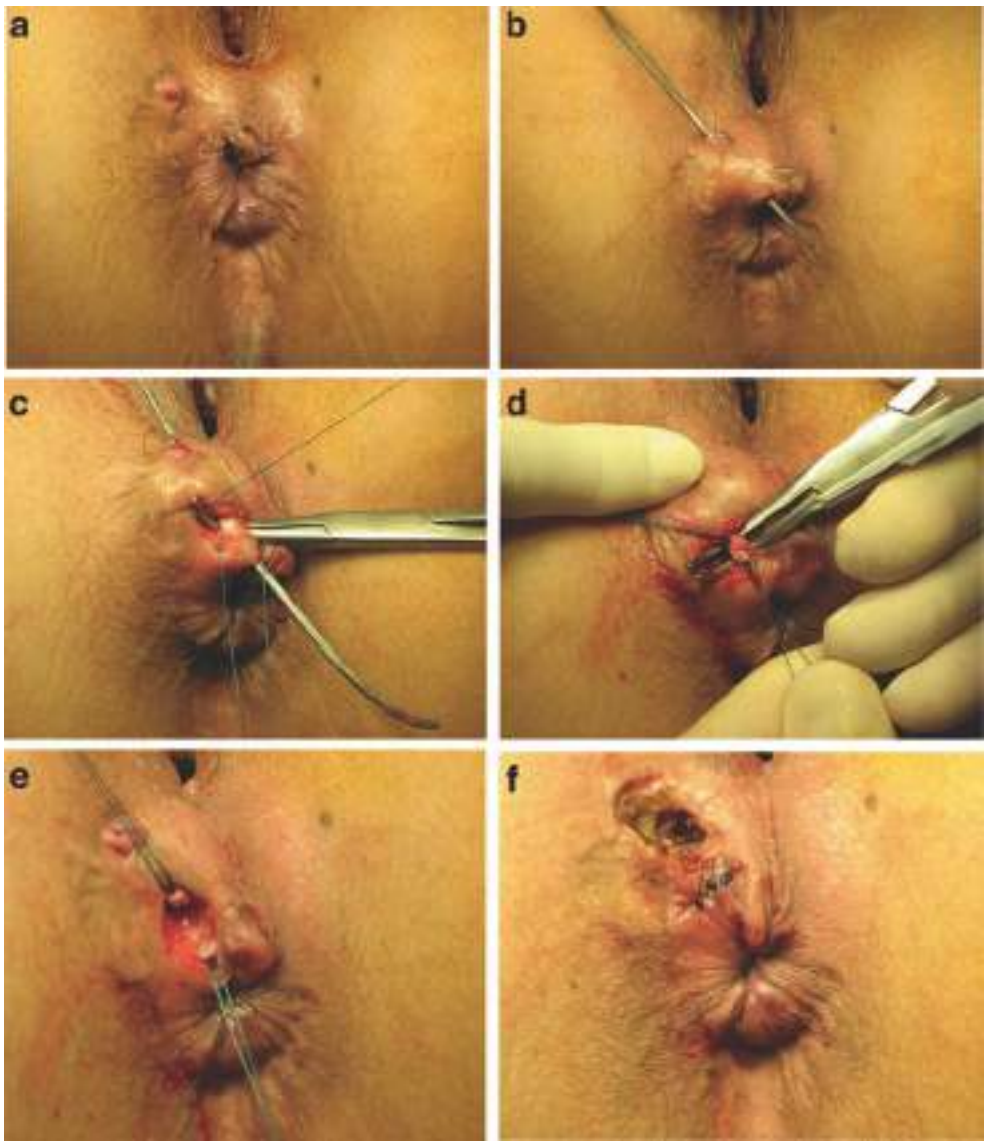

FIGURE 15-13. (**a**–**f**) Intraoperative demonstration of the LIFT procedure.

any associated cavities is performed to ensure that all granulation tissue is debrided. Excision of the fibrous tract can be performed taking care not to excise any muscle or alternatively the fibrous tract is left in situ. The amount of divided sphincter involved in the fistula is carefully assessed, and the edges of the transected muscle are identified for reconstruction. An end-to-end primary sphincteroplasty is performed using a series of horizontal mattress sutures using 2.0 Vicryl or PDS sutures (Figure 15-14c). The fistula bed of the divided fistulous tract is incorporated in the suturing to completely obliterate any potential space behind the muscle reconstruction. The edges of the open wound are finally marsupialized by tacking the divided mucosal and submucosal layer to the muscle repair (Figure 15-14d), keeping the most superficial aspect of the wound open to allow for drainage. 3.0 Vicryl or 3.0 Chromic suture is used for the marsupialization. Stool softeners and analgesic are given as needed.

Anal Fistula Plug

The anal fistula plug is used to close the primary internal opening and serves as a matrix for the obliteration of the fistulous tract. Initially, a bioabsorbable xenograft made of lyophilized porcine intestinal mucosa with conic shape was introduced to the market (Surgisis® AFP, Cook Medical, Bloomington, Indiana, USA) [27]. The tract is traversed with a fistula probe and then curetted. A 2-0 silk suture is tied to the tapered end of the plug and then pulled through the internal opening using the fistula probe until it is snug inside the fistula tract (Figure 15-15a, b). The excess end of the plug is trimmed inside the anal canal side using scissors (Figure 15-15c). The trimmed portion of the plug is fixed to the internal opening and internal anal sphincter muscle using 3.0 Vicryl suture (Figure 15-15d). The mucosal/submucosal

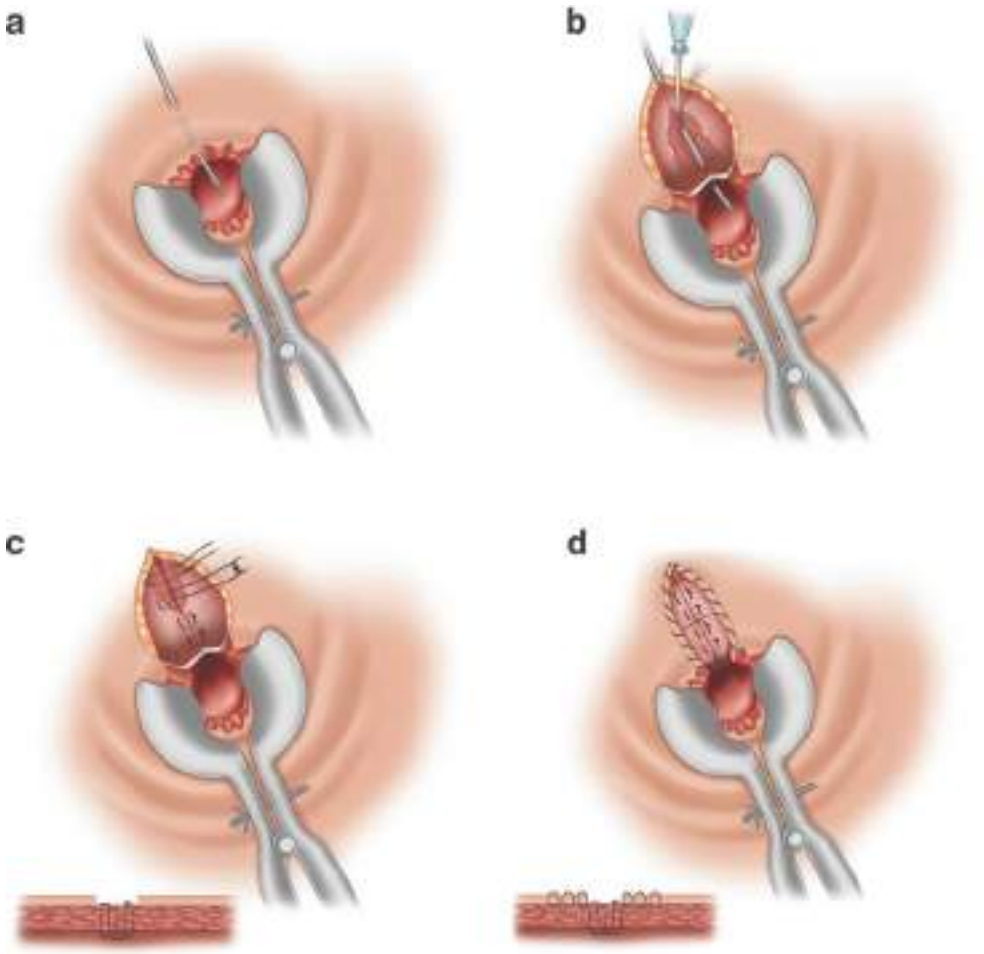

FIGURE 15-14. (**a**–**d**) Technical steps of fistulotomy with sphincter reconstruction.

opening at the internal fistula opening is approximated with the same suture. The external opening of the fistula is left open to drain after trimming the tapered end of the plug (Figure 15-15e). Due to the variable results of the Surgisis® AFP with failures related to migration, extrusion, and infection, a new absorbable plug was subsequently introduced (GORE® BIO-A® Fistula Plug, W. L Gore & Associates, Inc., Flagstaff, Arizona, USA) [28]. The plug is designed with a special flat disk head and six plug arms that can allow better anchoring to tissue (Figure 15-16a). The plug is made of 100 % synthetic bioabsorbable material that starts resorption at 6th week and is completed after 6–7 months. The general technical steps of the GORE® BIO-A® Fistula Plug procedure are similar to those of the Surgisis® AFP with some minor variations. After the identification of the fistula, the tract is debrided with a curette. The external opening is cored out to accomplish sufficient drainage. Inside the anal canal, a small submucosal flap is raised in the area of the internal opening. The plug is pulled through the internal opening (Figure 15-16b). In cases where the fistula tract is too narrow for the entire plug, one or more of the six arms can be excised at the junction with the flat disk. The head of the plug is fixed to the internal sphincter muscle using 2.0 Vicryl suture (Figure 15-16c) and then covered with the small submucosal flap.

Fibrin Glue

Fibrin glue (Tisseel®, Baxter, Deerfield, Illinois, USA) and synthetic glue (cyanoacrylate glue, Glubran® 2, GEM S.R.L., Viareggio, Italy) are injectable products that can be used in the treatment of anorectal fistulas [29]. They act as tissue sealants and are believed to stimulate the growth of fibroblasts and pluripotent endothelial cells into the fistulous tract. This physiologic response triggers collagen deposition and wound healing. Fibrin glue treatment is simple and repeatable and maybe a good initial option in patients with high fistulas. Although associated with an overall low success rate, failure of the glue to eradicate the fistula does not compromise further treatment options, and sphincter function is preserved. The procedure starts by identifying the external fistula opening, followed by the curettage of the fistula tract. Approximately 5 ml of reconstituted fibrin glue is injected through the external opening (Figure 15-17a) until it

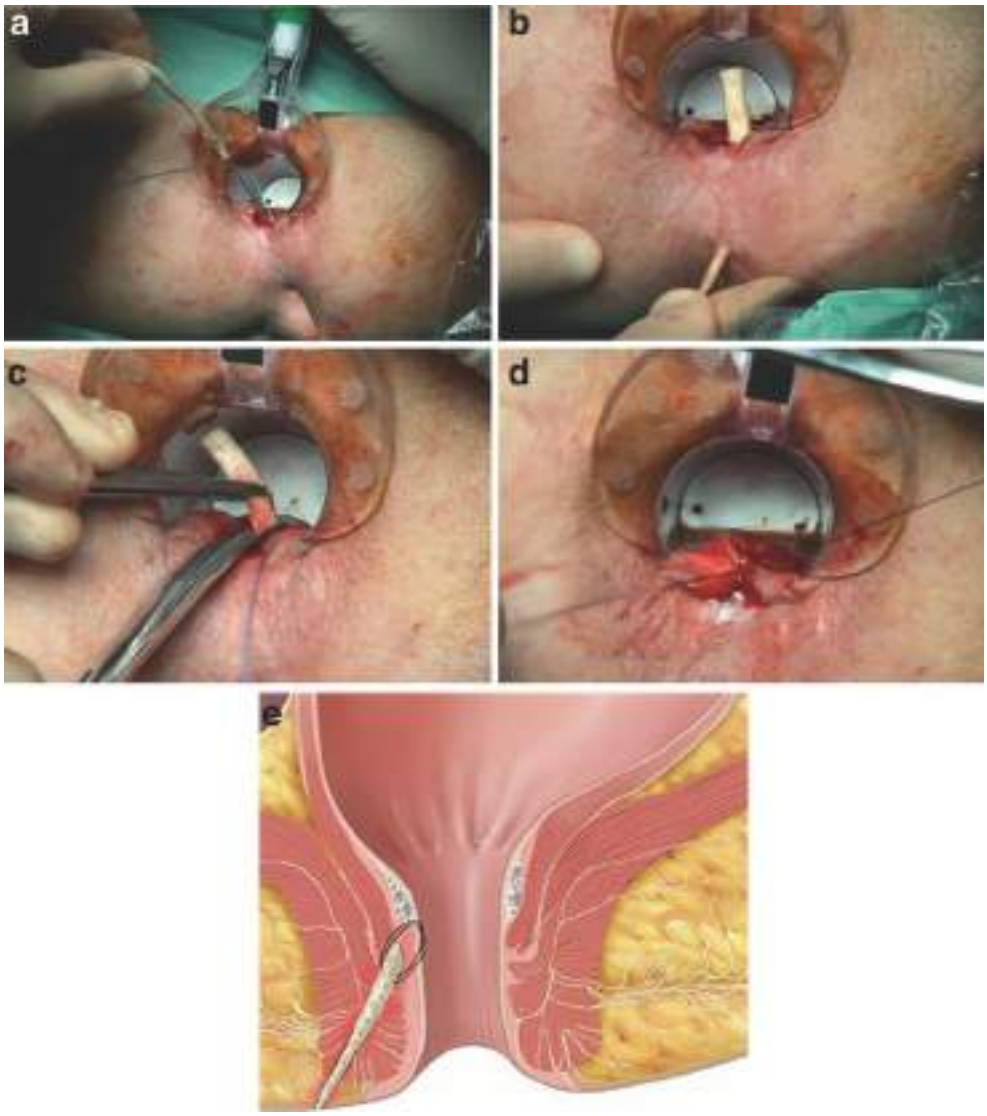

FIGURE 15-15. (**a**-**e**) Intraoperative demonstration of the anal fistula plug (Surgisis® AFP) procedure in a patient with high transsphincteric fistula. Anatomical view of obliterated fistula tract following placement of anal fistula plug (Surgisis® AFP).

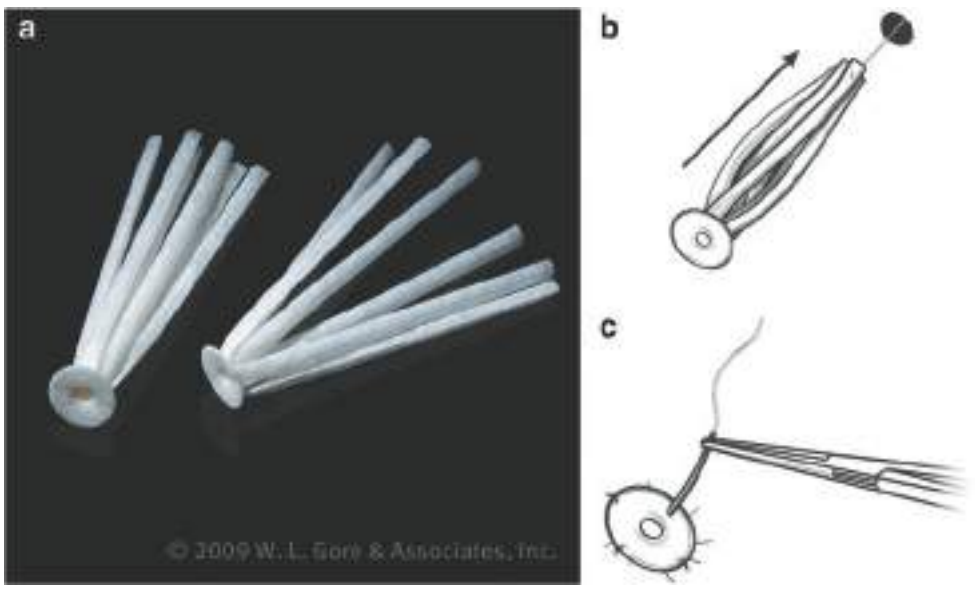

FIGURE 15-16. (**a**) GORE® BIO-A® Fistula Plug. With permission © W. L. Gore and Associates 2009. (**b**) Pulling of the GORE® BIO-A® Fistula Plug through internal opening. (**c**) Anchoring the flat top on the GORE® BIO-A® Fistula Plug to covering the internal fistulous opening.

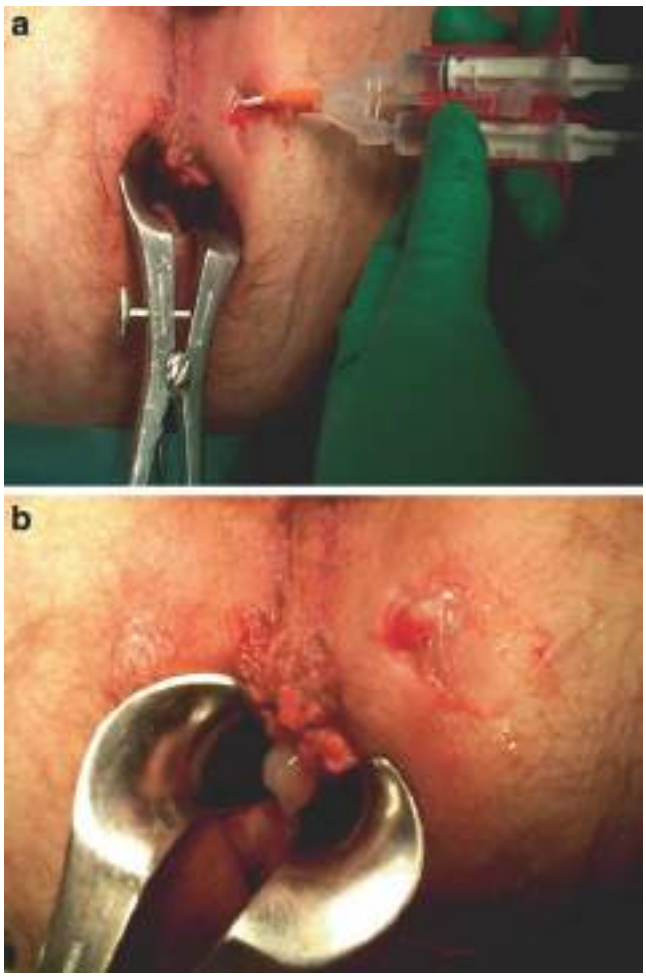

FIGURE 15-17. (**a**) Fibrin glue injection of a high transsphincteric fistula through the external fistulous opening. (**b**) Fistula tract sealed with the fibrin glue. Note the fibrin glue extruding from the internal opening inside the anal canal.

extrudes from the internal opening area (Figure 15-17b). The internal opening is closed with 3-0 Vicryl suture.

Newer and Evolving Technologies: VAAFT, FiLaC, and Stem Cell

The last decade has seen the introduction of three additional new technologies: the video-assisted anal fistula treatment (VAAFT), the fistula laser closure (FiLaC), and stem cell therapy [30–32]. At this stage of development, it is premature to tell what long-term roles these evolving technologies will play in the field of anorectal fistula surgery. The technical expertise with these three procedures has been concentrated in a limited number of centers globally. Thus, they have not formally been incorporated in the management algorithm presented in Figure 15-8, but they are worth describing in this chapter as potential future options pending additional long-term data.

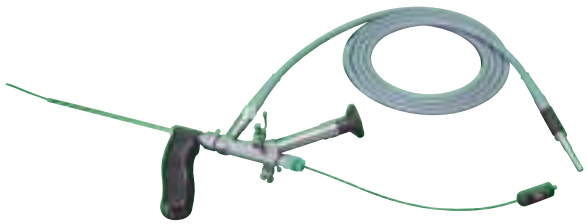

FIGURE 15-18. Anal fistuloscope (Karl Storz, Tuttlingen, Germany).

The video-assisted anal fistula treatment was initially described by Meinero from Italy [30]. The procedure is performed with a kit, which includes a rigid fistuloscope (Karl Storz, Tuttlingen, Germany) (Figure 15-18), an obturator, a unipolar electrical diathermy probe, an endobrush, an endoscopic grasper, and a synthetic cyanoacrylate glue. The fistuloscope video equipment is an 8°-angled endoscope with an optical working channel to introduce the instruments and an irrigation channel. VAAFT consists of a diagnostic phase followed by an operative phase. In the diagnostic phase, the fistuloscope is inserted through the external opening and advanced by the irrigation of the glycine-mannitol 1 % which expands the fistula tract. Both primary and secondary openings and tracts are explored via the fistuloscope. After the internal opening is located, absorbable sutures are taken at its site in the rectum or anal canal for applying traction. During the next operative phase, the aim is to destroy the fistula tract from the inside by curetting the tract, obliterating it, and closing the internal opening. Through the working channel of the fistuloscope, the fistula tract is cauterized, and necrotic material is removed using an endobrush and irrigation. Finally, the internal opening is closed by either suturing or stapling with a linear or semicircular stapler, or alternatively by advancing an anal flap. In order to reinforce the suture or staple line, 0.5 ml of synthetic cyanoacrylate glue can be applied.

The fistula laser closure is a novel sphincter-saving technique that uses an emitting laser probe [FiLaC™, Biolitec, Germany] to destroy the fistula epithelium and simultaneously obliterate the remaining fistula tract [31]. Since the main reason for operative failure is a persistent fistula tract or remnants of fistula epithelium which were not excised, it is postulated that the benefit of this newly designed radial-emitting laser probe is to eradicate the granulating and fibrous fistula tissue. FiLaC™ eliminates fistula epithelium and granulation tissue in a circular manner causing shrinkage and obliteration of the tract. The first step of the procedure is the identification and localization of the internal opening by hydrogen peroxide or methylene blue injection from the external opening. The fistula tract is debrided with a curette, and a plastic hollow 14 French catheter is inserted using a guide-wire. 400 μm radial-emitting disposable laser fiber is inserted into the catheter with its tip emerging at the internal orifice. The fiber delivers laser energy homogenously at 360°, and by applying continuous energy, the tract

is closed while withdrawing it at a speed of 1 mm per second. The procedure includes the closure of the internal opening by means of an anorectal flap. When some scar tissue prevents that, either a mucosal or anodermal flap is used for closure of the internal opening. A modified laser procedure consists of sealing the fistula tract by laser with no need for endorectal flap. The closure of the internal opening is allowed by a laser shrinkage effect.

The potential role of mesenchymal adult stem cells in differentiating into various types of cells may have a role in the treatment of anal fistula, suppressing inflammation and promoting differentiation. Application of autologous expanded adipose-derived stem cells (ASCs) represents a novel approach for enhancing regeneration of damaged tissues [32]. ASCs can be obtained from subcutaneous fat by liposuction, and this process yields 100 times more stem cells than bone marrow aspirates. Following curettage of the fistula tract and suture closure of the internal opening, ASC solution is injected into the tract and into the walls of the fistula. The tract is subsequently sealed with fibrin glue.

Outcome

Complex fistulous disease challenges even the most experienced surgeons. Successful management requires good surgical judgment, knowledge of anorectal anatomy, and technical proficiency in the surgical approaches available to ensure the highest possible postoperative continence and wound healing. Success rate in patients with complex or recurrent anorectal fistulas is lower than in patients with simple anal fistulas. Often more than one procedure is needed to eradicate the fistula. Risk for incontinence is usually higher due to the complexity of the fistula, recurrent or persistent disease, and/or prior failed interventions. A fundamental understanding of the advantages, disadvantages, limitations, and results of the various techniques is essential [33, 34]. The selection of a specific operation for an individual patient based on fistula characteristics, body habitus, gender, baseline continence level, and history of prior interventions if any is of paramount importance.

Seton

According to the standards practice task force of the ASCRS [1], use of a seton and/or staged fistulotomy for the treatment of complex fistula-in-ano has strong recommendation based on moderate-quality evidence [1]. Noncutting seton is usually used as a bridge to additional surgical intervention and typically is not curative. When removed the rate of persistent fistula is very high [35]. A high rate of incontinence (38 %) has been reported with cutting seton. In our practice, we rarely use a cutting seton, which we typically reserve for patients with high complex fistulas who failed multiple prior interventions or in fistulas not amenable to other techniques such as high posterior-based fistulas in patients with deep buttock cleft. In a study performed by Garcia-Aguilar and colleagues comparing cutting seton with two-stage seton fistulotomy in the management of high anal fistulas, both techniques were equally effective in eradicating the fistula and were associated with similar incontinence rates [36]. When using a tight or cutting seton, the intraoperative preservation of the internal sphincter muscle appears to reduce the postoperative fecal incontinence without a substantial increase in recurrence rates as reported by Vial and colleagues in a systematic review of 19 series and 448 patients [37]. Overall, the fecal incontinence was 5.6 % when the internal anal sphincter was preserved compared to 25.2 % when it was divided. Hasegawa and colleagues reported their results with cutting seton in 32 patients with cryptoglandular fistula (81 % transsphincteric) [38]. Continence disturbance was noted in 54 % of the patients, and the fistula recurrence rate was 29 %. Women with prior vaginal deliveries experienced significant incontinence leading the authors to advice against the use of cutting seton in this subgroup of patients especially in the setting of an anterior fistula. Cutting seton is associated with new onset of gas incontinence. Isbister and Sanea reported their experience with cutting seton in patients with transsphincteric fistula [39]. Frequent gas incontinence developed postoperatively in 9.5 % of the patients, and 21.4 % developed occasional gas incontinence. Mentes and colleagues published their results with cutting seton in transsphincteric fistula involving greater than 50 % of the sphincter complex [40]. Recurrence rate was low (5 %), but the rate of postoperative incontinence was 20 %.

Advancement Flap

According to the standards practice task force of the ASCRS [1], the grade of recommendation for the treatment of complex fistula-in-ano with advancement flap is a strong recommendation based on moderate-quality evidence (1C). The Association of Coloproctology of Great Britain and Ireland (ACPGBI) recommends transanal advancement flap for the treatment of anal fistula when simple fistulotomy is thought likely to result in impaired continence [41]. Endorectal flap has demonstrated a success rate of between 60 and 93 %, and it has been advocated as the treatment of choice for complex fistula-in-ano [41, 42]. It can be technically challenging especially in posterior-based fistula in males and in patients with deep buttock cleft. Postoperative incontinence rate has been reported between 7 and 38 % [43]. Zimmerman and colleagues reported a healing rate of 69 % in patients with transsphincteric fistula at a median follow-up of 14 months [44]. Ortiz and Marzo reported a low recurrence rate of 7 % for high transsphincteric or suprasphincteric fistula [45]. When examining factors affecting success, the level of the fistula did not impact outcome. Continence disturbance was observed in 8 % of cases.

Table 15-1. Results of LIFT procedure

	Year	# of patients	Follow-up (months)	Success (%)	Incontinence (%)
Rojanaskul et al. [23]	2007	18	6.5	94	0
Ellis [24]	2010	31	15	94	0
Shanwani et al. [52]	2010	45	9	82	0
Aboulian et al. [53]	2011	25	6	68	0
Tan et al. [54]	2011	93	5.8	85	0
Abcarian et al. [55]	2012	40	4.5	74	0
Mushaya et al. [56]	2012	39	16	92	0
Ooi et al. [57]	2012	25	5.5	68	0
Wallin et al. [58]	2012	93	19	40	31
Han et al. [59]	2013	21	14	95	5
van Onkelen et al. [60]	2013	22	19.5	82	0
Lehmann et al. [61]	2013	17	13.5	65	0
Sirikurnpiboon et al. [25]	2013	41	4.8	83	0
Sileri et al. [62]	2014	26	16	73	0

Abbas and colleagues had an initial success rate of 83 % and a recurrence rate of 14 % during a median follow-up of 30 months [42]. Schouten and colleagues reported a recurrence rate of 25 %, and continence disturbance was observed in 35 % of their patients [46]. Prior drainage with a noncutting seton is believed to increase success rate. Patients who fail an initial flap can be considered for a repeat procedure. Jarrar and colleagues reported their experience in 98 patients treated by an advancement flap [47]. Primary healing occurred in 72 % of patients, and secondary healing (following a second flap after initial failure) occurred in 57 % of cases yielding an overall healing rate 93 %. There was a significant improvement in continence and a decrease in urgency after flap repair. The flap technique can impact success rate. Dubsky and colleagues compared the outcome of full thickness flap with mucosal based flap only [48]. 54 consecutive patients with high anal fistula secondary to cryptoglandular disease were retrospectively reviewed. The overall recurrence rate was 24 % and was much lower in the full thickness subgroup (5 %) compared to the mucosal subgroup (35.3 %). Patients with four or more previous anal surgeries were at highest risk for failure. No difference in postoperative incontinence was noted between subgroups. The addition of autologous platelet-rich plasma can increase success rate as described by van der Hagen and colleagues who reported a 90 % success rate during a follow-up of 26 months [49]. Smoking has been associated with a lower success rate. Zimmerman and colleagues studied the outcome of endorectal advancement flap in 105 patients [50]. During a median time of 14 months, healing rate was 60 % in smokers compared to 79 % in nonsmokers. In another study by the same researchers, blood flow was measured during endorectal advancement flap procedures. Blood flow was significantly lower in smokers compared to nonsmokers [51].

Ligation of the Intersphincteric Fistula Tract

According to the standards practice task force of the ASCRS, data are too preliminary to make a formal recommendation for the LIFT procedure in the treatment of complex fistula-in-ano [1]. The initial reported success rate of the LIFT procedure was 94 % [23]. However, subsequent studies with longer follow-up have shown a wider range of success rate from 40 to 95 % (Table 15.1) [23–25, 52–62]. Wallin and colleagues performed a retrospective review of 93 patients treated by LIFT procedure [58]. Fistula healing rate was initially 40 % and with secondary interventions increased to 57 %. Interestingly, the authors reported that in those patients with recurrence, the LIFT technique had transformed a complex fistula into a simple intersphincteric fistula that could be effectively treated by subsequent intersphincteric fistulotomy. Medialization of the fistula tract or conversion of a transsphincteric fistula into an intersphincteric fistula after LIFT ("downstaging") has been also described by Tan and colleagues in patients with persistent discharge [54]. A recent systematic review including 13 articles and 498 patients reported an overall success rate ranging from 40 to 95 %, with a pooled success of 71 % [63]. Minor continence disturbance was observed in 6 % of cases. The conclusion of this review was that the LIFT procedure appears to be an effective sphincter-conserving approach for the treatment of complex fistula-in-ano. In another review, Vergara-Fernandez and colleagues analyzed 18 studies with 592 patients [64]. The mean healing rate reported was 74.6 %. No de novo incontinence developed secondary to the LIFT procedure. A recent meta-analysis of 24 original articles reported a mean success rate of 76.5 %, an incontinence rate of 0 %, and a postoperative complication rate of 5.5 % (mean follow-up of 10 months) [65]. Lehmann and colleagues assessed the efficacy of the LIFT procedure in 17 recurrent anal fistulas [61].

Table 15-2. Results of the anal fistula plug

	Year	# of patients	Follow-up (months)	Success (%)	Extrusion (%)
Johnson et al. [70]	2006	15	3.5	87	N.R.
Champagne et al. [71]	2006	46	12	83	4
Schwandner et al. [72]	2008	18	9	61	2
Christoforidis et al. [73]	2008	47	5	38	14
Theckkinkattil et al. [74]	2008	36	11	50	10
Starck et al. [75]	2008	32	12	59	N.R.
Lawes et al. [76]	2008	20	7.4	24	N.R.
Safar et al. [77]	2009	35	4.2	13.9	9.7
Ortiz et al. [78]	2009	15	12	20	15
Wang et al. [79]	2009	29	9	34	N.R.
McGee et al. [80]	2010	41	24	44	5
Anyadike et al. [81]	2010	33	14	73	N.R.
Van Koperen et al. [82]	2011	31	11	29	13
Ommer et al. [28]	2012	40	12	57.5	N.R.
O'Riordan et al. [83]	2012	488	3–24.5	54	8.7

The long-term healing rate was 65 %. No de novo incontinence was reported. In a retrospective study, Tan and colleagues compared the LIFT operation with the mucosal advancement flap [66]. The anal flap was more effective than the LIFT operation (93.5 % vs. 62.5 %, respectively). However, a recent prospective randomized trial comparing the LIFT procedure with mucosal advancement flap in patients with high transsphincteric fistula found similar long-term healing rate, recurrence rate, continence, and quality of life [67]. Ellis and colleagues reported a 94 % success rate with the BioLIFT procedure in a prospective study of 31 patients [24]. A lower success rate was noted by Chew and colleagues who reported comparable success of 63 % with both LIFT and BIOLIFT procedures [68]. The LIFT-PLUS procedure was compared to the traditional LIFT procedure in a prospective study on 41 patients [25]. The healing rate in LIFT-PLUS group was 85 % compared to 81 % in the LIFT group. No incontinence was reported.

Anal Fistula Plug

According to the standards practice task force of the ASCRS [1], there is weak recommendation based on moderate-quality evidence (2C) for the treatment of complex fistula-in-ano with AFP. Several studies have reported variable results with this minimally invasive procedure. In an attempt to standardize the indications for use of bioprosthetic Surgisis® AFP and techniques for its placement, a consensus conference was held in 2007 [27]. According to the consensus, the use of the Surgisis® AFP should be recommended in transsphincteric anal fistula without any acute inflammation or infection. It was also suggested that a frequent issue affecting the Surgisis® AFP procedure was a failure in technique of the plug placement [27]. Reported success rate in various studies has ranged from 13.9 to 87 % (Table 15-2) [28, 69–83]. The postoperative abscess/sepsis rate has ranged from 4 to 29 %. Failures have been related to technical issues, plug extrusion, and infection. O'Riordan and colleagues conducted a systematic review (22 studies included, 488 patients) of the anal fistula plug [83]. Fistula closure was achieved in 54 % of cases. The success rate has been lower in patients with multiple tracts [69]. This can be due to undertreatment of the secondary tracts in which no plug was inserted. In one study, tract length was a predictor of outcome with longer fistula tracts carrying higher success rate [80]. None of studies evaluating the role of the noncutting seton before plug insertion found any significant change in closure rate. However, due to the heterogeneity of patient populations and fistula characteristics described in the various studies, further randomized controlled trial would be needed to settle this issue. Muhlmann and colleagues compared Surgisis® AFP and anal flap for the treatment of complex anal fistulas in 55 patients [84]. The results were disappointing, with 33 % healing rate after flap and 32 % following the plug. van Koperen and colleagues compared the Surgisis® AFP with the mucosal advancement flap for cryptoglandular high transsphincteric fistula in a double-blinded multicenter randomized trial [82]. At a follow-up of 11 months, the recurrence rates were 71 % for the plug and 52 % for the mucosal advancement flap. No significant differences were noted in postoperative pain, pre- and postoperative incontinence scores, soiling, and quality of life. Ortiz and colleagues conducted a randomized clinic trial comparing the Surgisis® AFP with the endorectal advancement flap in patients with high cryptoglandular fistula-in-ano [78]. The trial was closed prematurely due to a high failure rate of the plug (80 %) compared to the flap (12.5 %).

The variable success rates reported with Surgisis® AFP and the inability to reproduce high healing rates in most practice settings provided an opportunity to develop another plug from a different material with the aim to increase success rate. The GORE® BIO-A® Fistula Plug was the second

plug introduced in the field of fistula surgery. A German multicenter study investigated the GORE® BIO-A® Fistula Plug in the treatment of high anal fistulas [28]. The overall healing rate in 40 patients was 57.5 % without postoperative impairment of continence. In a retrospective review of 48 patients treated with the same plug, Heydari and colleagues reported an overall healing rate of 69.3 % without change in continence level [85]. No plug dislodgment or postoperative infection was noted. There is a paucity of data comparing the Surgisis® AFP with the GORE® BIO-A® Fistula Plug. Buchberg and colleagues published a retrospective study comparing the two plugs [86]. Twelve patients received the Surgisis® AFP, and ten patients had the GORE® BIO-A® Fistula Plug. The healing rate was 12.5 % in the Surgisis® AFP compared to 54.5 % in GORE® BIO-A® Fistula Plug. Due to the retrospective nature of the study and the small number of patients, it is early to tell whether this trend will be observed when additional data becomes available in the future.

Fibrin Glue

According to the standard practice task force of the ASCRS [1], the grade of recommendation for the treatment of complex fistula-in-ano with debridement and fibrin glue injection is a weak recommendation based on low-quality evidence (2C). The use of fibrin sealant injection initially demonstrated promising results with high success rates between 60 and 80 % [29]. However, subsequent studies with longer follow-up have reported lower success rates of 32–54 % [29]. At 1 year following injection of commercial fibrin sealant, Cintron and colleagues reported a 64 % fistula closure rate [87]. Most recurrences were noted within 3 months of the injection, but some up to 11 months. Sentovich treated 48 fistulas and observed a 60 % healing rate during a median follow-up of 22 months [88]. Retreatment with fibrin glue increased the closure rate to 69 %. Loungnarath and colleagues found that durable healing could not be sustained and was achieved only in 31 % of cases [89]. Most failures were noted within 3 months. The success rate was not different in patients with previous failed treatment. Swinscoe and colleagues reported that following fibrin glue injection, a shorter fistula (<4 cm) tended to recur more frequently than longer fistula (>4 cm) with recurrence rate of 54 % vs. 11 % [29]. A possible explanation is that a short fistula tract does not hold the glue as well as longer tract. van Koperen and colleagues conducted a retrospective study to assess the potential value of fibrin glue in combination with transanal advancement flap compared to advancement flap alone [90]. The overall recurrence rate in their group of cryptoglandular high transsphincteric fistula was 26 %. Recurrence rate for advancement flap alone was 13 % compared to 56 % when fibrin glue was injected in the subgroup of patients without previous fistula surgery and 23 % vs. 41 % in the group with previous fistula surgery. The authors concluded that the obliteration of the fistula tract with fibrin glue was associated with worse outcome after rectal advancement flap. Singer and colleagues randomized patients to three groups prospectively: group one received injection of antibiotic plus the sealant, group two had surgical closure of the internal opening, and group three had both [91]. At a mean follow-up of 27 months, initial healing was 21, 40, and 31 %, respectively ($P=0.38$). Therefore, neither of these technical alterations improved the success rate. In a quest to improve the healing rate for the injectable procedure, Jain and colleagues reported good results using cyanoacrylate glue to treat complex fistulas [92]. Seventeen out of 20 patients (85 %) healed following an initial injection, and two patients required one additional injection without further signs of fistula discharge. A second injection can be beneficial as reported by Barillari and colleagues who increased healing rate from 71.4 to 90.2 % after additional injections [93].

The high success rate of fibrin glue injection reported in some series has not been reproducible in the majority of practice settings, and studies that have carefully evaluated patients following fibrin glue injection have reported low success rate. Buchanan and colleagues from St. Mark's hospital conducted a prospective study to evaluate the efficacy of fibrin glue injection in patients with complex anorectal fistula [94]. During a median follow-up time of 14 months, the healing rate was 14 %. Careful long-term assessment of the patients was performed with physical examination and magnetic resonance imaging. The high failure rate associated with fibrin glue injection has been attributed to the difficulty in ensuring the glue remains in the fistula tract, failure of closure of the internal opening, and lack of autologous tissue ingrowth to seal the tract. A Cochrane database systematic review analyzed ten randomized controlled trials [95]. Comparisons were made between various treatment modalities. There was no significant difference in recurrence rate or incontinence rate in any of the studied operation except in the case of advancement flap which carried higher success rate. A higher recurrence rate was noted when fibrin glue injection was added to an endorectal advancement flap, favoring a flap-only technique. Both fibrin glue injection and advancement flap had low incontinence rate, but the higher success rate of the flap favors its use over fibrin glue.

Fistulotomy with Sphincter Reconstruction

Fistulotomy with sphincter reconstruction is an effective surgical treatment for complex anal fistula. Patients with baseline incontinence, those at risk for incontinence (such as patients with previous childbirth, anterior fistula in females, existing sphincter defect from prior anal surgery), and patients with recurrent disease can be suitable candidates for this technique. Overall healing rates range from 83.3 to 97.4 % and the incontinence rates between 3.7 and 21.4 % (Table 15-3) [26, 43, 96–100]. However, studies analyzing

TABLE 15-3. Results of fistulotomy with sphincter reconstruction

	Year	# of patients	Follow-up (months)	Success (%)	Incontinence (%)
Parkash et al. [96]	1985	120	6–60	83.3	3.7
Christiansen and Ronholt [97]	1995	14	12–48	85.7	21.4
Perez et al. [43]	2006	35	32	92.9	12.5
Roig et al. [98]	2010	75	13	89.4	18.3
Kraemer and Picke [99]	2011	38	N.R.	97.4	9.4
Arroyo et al. [100]	2012	70	81	91.4	16.6
Ratto et al. [26]	2013	72	29.4	95.8	11.6

the degree of continence in patients who were treated with this procedure reported a minor degree of incontinence (flatus incontinence and soiling). Ratto and colleagues conducted a prospective study in 72 patients with complex fistulas [26]. The recurrence rate was 4.2 %, and de novo incontinence (soiling) was noted in 11.6 % of patients. In another study of 70 patients with complex anal fistula who underwent fistulotomy with sphincter reconstruction, 70 % of the patients with preoperative anal incontinence improved [100]. The postoperative improvement was assessed subjectively using the CCF-IS scale (*mean score*: 6.75–1.88, $P<0.005$) and objectively measuring anal pressures using anorectal manometry. During a follow-up period of 81 months, recurrence rate was 8.6 % with the majority of recurrences treated successfully with a repeat procedure. Perez and colleagues studied 60 patients in a randomized clinical trial comparing fistulotomy and sphincter reconstruction to fistulectomy and advancement flap [43]. No difference was noted in recurrence rate between the two subgroups (7.1 % vs. 7.4 %) or postoperative incontinence as measured by CCF-IS score. Roig and colleagues retrospectively analyzed 146 patients who underwent endoanal advancement flap (71 patients) or fistulectomy with sphincter repair (75 patients) [98]. Forty-two fistulas (28.7 %) were recurrent, 98 were transsphincteric, and 37 were suprasphincteric. Twenty-six (17.7 %) patients had some degree of preoperative continence disturbances, without significant differences between the two groups ($P=0.47$). After a mean follow-up of 13 months, fistula persisted or recurred in 18.3 % of advancement flap vs. 10.6 % of sphincter reconstruction ($P=0.19$). In 2011, the first German guideline for the treatment of anal fistulas considered "fistula excision with direct reconstruction" to be a therapeutic option [101]. Based on extensive positive experience with this technique (a decade of personal experience of the chapter senior author at Kaiser Permanente Los Angeles Medical Center is pending publication), we concur with the German guideline and do believe that there is a role for fistulotomy with sphincter reconstruction in patients with complex anal fistula. While the majority of available data has been from European centers, we hope that future studies will report results from the United States.

Newer and Evolving Technologies: VAAFT, FiLaC™, and Stem Cell

Using the VAAFT procedure, Meinero and Mori achieved an overall success rate of 73.5 % in 136 patients with non-Crohn's disease-related anal fistula [30]. Recurrence rate was 26.5 % within 2–3 months of follow-up. No worsening in continence was noted in their study. Kochhar and colleagues recently examined the results of the VAAFT procedure in a prospective study in 82 patients [102]. The recurrence rate was 15.8 %. Postoperative pain and discomfort were minimal. Another recent report of the VAAFT procedure revealed a recurrence rate of 17 % without major complications or incontinence [103]. Due to the limited data on VAAFT and its recent introduction, it is premature to draw any firm conclusion about its long-term efficacy, additional benefits, and limitations compared to the existing surgical options. Further studies are needed to determine what future role if any it will play in the management of patients with anal fistula.

Giamundo and colleagues studied the outcome of the FiLaC™ procedure in 35 patients with cryptoglandular and Crohn's disease-related fistulas [31]. The overall success rate was 71 % at 20 months of follow-up. No continence impairment was noted in any of the patients, but significant postoperative pain and anismus were noted in 8 patients (22.9 %) who were treated with the 980 nm diode laser. For this reason, the authors consider that the use of a 1479 nm diode laser for FiLaC™ is preferable to the 980 nm. In addition, they recommend the placement of a draining seton prior to the procedure to help create a more homogenous tract caliber and may contribute to the closure of secondary tracts. More recently, Oztürk and colleagues reported their results in 50 patients treated for intersphincteric and transsphincteric anal fistulas [104]. Healing rate was 82 % during a 12-month follow-up. The FiLaC™ procedure remains investigational at this stage, and additional data is needed prior to making firm recommendations for its use. So far it appears not to impact continence level; however, long-term success rate is unknown. The blind introduction of the laser catheter into the fistulous tract does not provide direct visualization of any secondary tracts which may lead to persistent disease.

Learning curve appears short based on the report of early adapters, but a significant investment in equipment is needed, and this may prove cost ineffective in the long run.

Autologous adipose-derived stem cell is a novel approach for the management of complex anal fistula [32]. A phase III multicenter, randomized, single-blind, add-on clinical trial was performed to investigate the safety and efficacy [105]. In this trial, 200 adult patients from 19 centers were randomly assigned to receive 20 million stem cells (group A), 20 million adipose-derived stem cells plus fibrin glue (group B), or fibrin glue (group C) after closure of the internal opening. Fistula healing was defined as reepithelization of the external opening and absence of collection >2 cm by MR imaging. If the fistula had not healed at 12 weeks, a second dose (40 million stem cells in groups A and B) was administered. Patients were evaluated at 24–26 weeks (primary end point) and at 1 year (long-term follow-up). In treatment of complex anal fistula, a dose of 20 or 60 million adipose-derived stem cells alone or in combination with fibrin glue was considered a safe treatment, achieving healing rates of approximately 40 % at 6 months and of more than 50 % at 1-year follow-up. It was equivalent to fibrin glue alone. No statistically significant differences were found when the three groups were compared [105]. To date, it is difficult to make a judgment of this technique because available data is limited and many questions still remain unanswered.

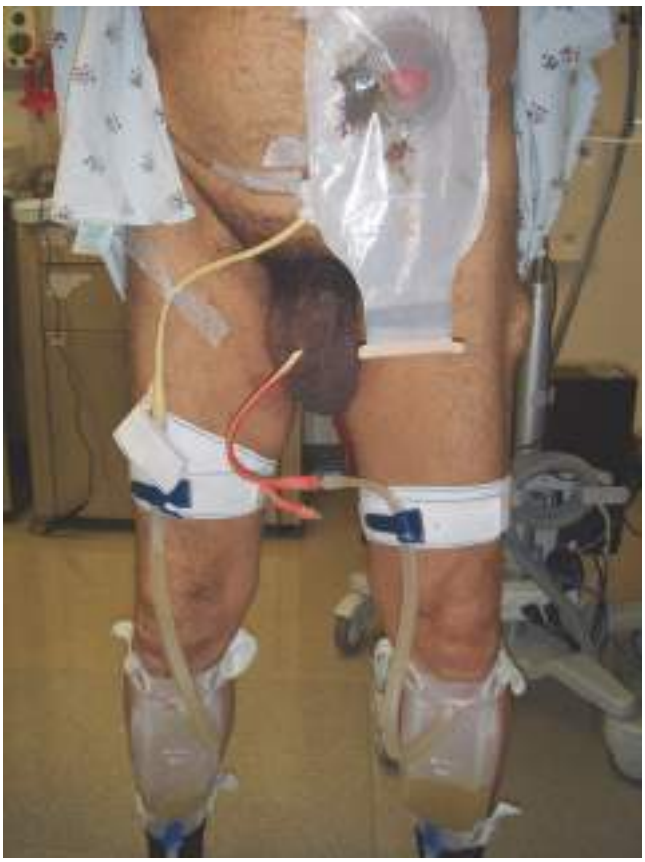

FIGURE 15-19. Patient with radiation-induced rectourethral fistula with diverting colostomy, suprapubic catheter, and urethral catheter.

Rectourethral Fistulas

Definition, Classification, and Pathophysiology

The prostatic urethra is in close proximity to the rectal wall, and it is separated from the rectum by the capsule of the prostate and the Denonvillier's fascia. Rectourethral fistula (RUF) is uncommon and can be congenital or acquired, resulting from surgery, radiation, inflammatory bowel disease, malignant neoplasm, pelvic infections, or trauma. RUF is a very complex condition that negatively impacts the patient's quality of life, can lead to permanent urinary dysfunction, and often requires multiple initial interventions for symptomatic control and additional definitive repair in a significant number of patients (Figure 15-19). In the Western world, the most common mechanism of RUF is multimodality treatment for prostate cancer, including surgery, external radiation therapy (EBRT), or brachytherapy, with an incidence of 0.1–3 % in patients who received these therapies [106]. Less commonly, RUF is the result of rectal or anal cancer treatment. Radiation leads to microvascular injuries and mucosal ischemia. It has been reported that up to 50 % of patients with RUF have a history of irradiation [107]. A review by Hechenbleikner and colleagues reported that radiation-induced RUF was due to EBRT in 17.8 % of cases, brachytherapy in 29.6 %, and combination therapy in 42 % [108]. The mean time from the last radiotherapy session and the diagnosis of RUF ranged from 14 months to as long as 14 years, supporting the data that the RUF is a late complication of radiotherapy. It is likely that the increased use of brachytherapy and EBRT for prostate carcinoma will increase the incidence of this condition [109]. Other causes of RUF include surgical intervention (65 %), trauma (22 %), and inflammatory bowel disease (6 %). RUF can occur following open, laparoscopic, or robotic prostatectomy for prostate cancer or abdominoperineal resection for low rectal carcinoma or anal carcinoma. Rectal injury during radical prostatectomy is uncommon with a reported overall incidence ranging from 0.12 to 9 % (0.47–2 % of laparoscopic cases) [110]. RUF can develop if the rectal injury is unrecognized at the time of operation or when primary repair of the rectum fails to heal properly [111]. The main types of trauma-related RUF are penetrating injuries, pelvic trauma/fracture, and motor vehicle accident. The etiology of the fistula greatly affects treatment choice and success, with the greatest difference occurring between irradiated vs. nonirradiated RUF.

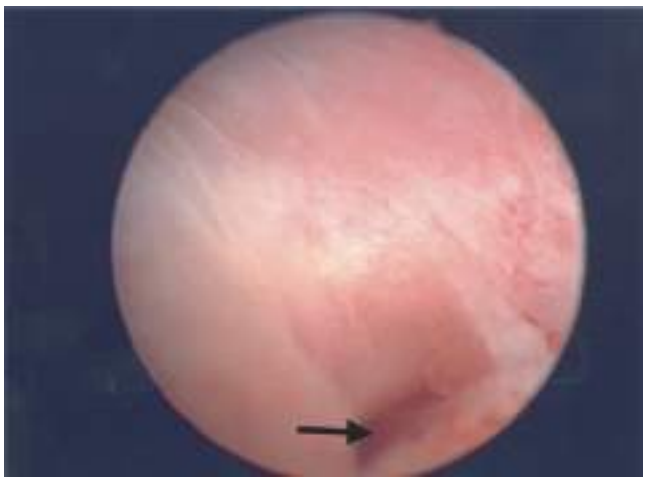

FIGURE 15-20. Cystoscopic view of external beam radiation-induced rectourethral fistula.

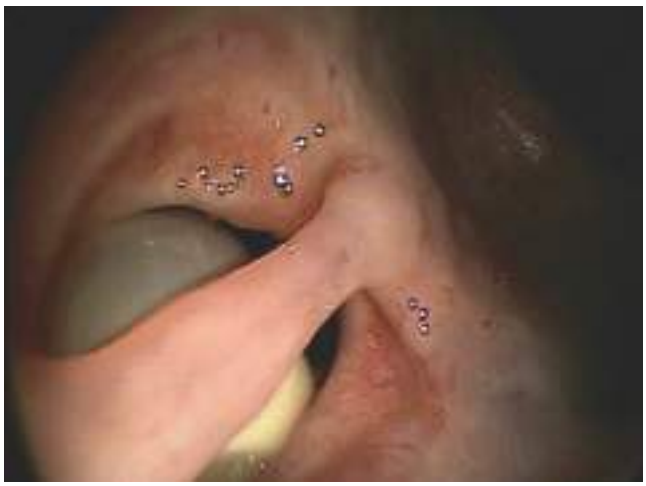

FIG. 15.21 Reflex view during flexible sigmoidoscopy demonstrates post-radical prostatectomy rectourethral fistula. Note the urethral catheter on the bladder side

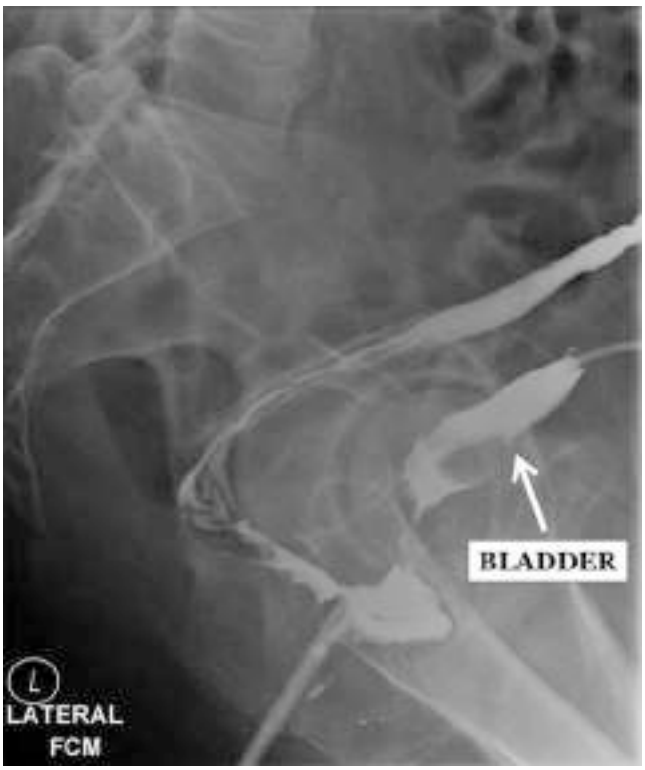

FIGURE 15-22. Gastrografin enema reveals a rectourethral fistula secondary to laparoscopic radical prostatectomy. Note the contrast flow into the bladder (*white arrow*).

Clinical Assessment and Diagnostic Evaluation

A disease-specific history (demographic data, past medical history, previous surgical and trauma history, prior radiation, onset of symptoms) is solicited from the patient. Symptoms of RUF include fecaluria, pneumaturia, hematuria, recturia, rectal bleeding, urinary tract infection, and severe rectal or pelvic pain. Physical examination (inspection, palpation, digital rectal examination) is performed to determine the size and location of the fistula in relationship to anal verge. RUFs related to prostate cancer treatment are anteriorly based and are about 5–6 cm from the anal verge in a normal size adult. The size of the fistula can vary from 5 mm to several centimeters depending on mechanism of injury and prior radiotherapy. Diagnostic modalities include cystoscopy (Figure 15-20), colonoscopy or flexible sigmoidoscopy (Figure 15-21), voiding cystography, retrograde urethrography, gastrografin enema (Figure 15-22), computed tomography scan, and magnetic resonance imaging. These investigations allow a direct visualization of the fistula and provide information of the concomitant colorectal, urethral or bladder pathology [112]. If feasible, urodynamic evaluation can be performed for the preoperative assessment of urinary function. This may impact clinical decision making as those with total urinary incontinence, or severe voiding dysfunction may be treated with a permanent urinary diversion. These diagnostic modalities are useful in the baseline assessment of the patient and are also essential to document healing after conservative management, fecal diversion alone, or definitive RUF repair. It is critical to assess complete healing prior to stoma closure in patients with fecal diversion.

Surgical Treatment

Treatment of RUF poses substantial challenges to the surgeon. Few centers have gathered a large experience in treating this rare condition. A multidisciplinary team approach involving a colorectal surgeon, a urologist, and in some instances a reconstructive surgeon is needed for optimal management. It is important to note that the management of RUF has not been standardized and large variations in treatment approaches exist due the rarity of the condition, surgeon's familiarity with a particular surgical technique, and/or patient population seen at a particular medical institution.

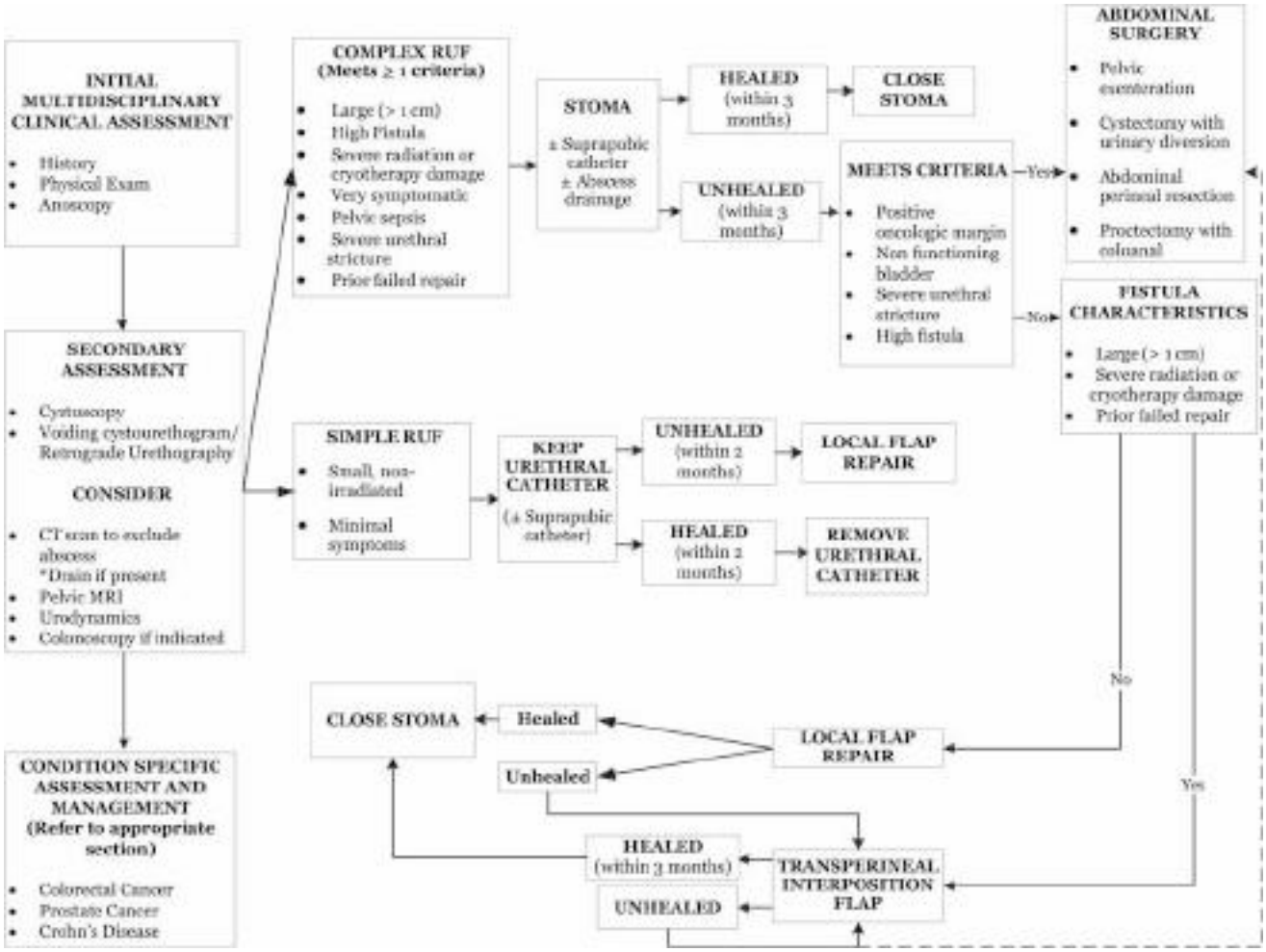

FIGURE 15-23. An algorithm-based approach to the management of rectourethral fistula.

Recently the senior author has proposed an algorithm-based approach to RUF based on his experience managing this rare entity at a tertiary center over a decade period [106].

Figure 15-23 provides the carepath algorithm. RUFs related to malignant neoplasm or Crohn's disease are managed according to these condition-specific treatment algorithms. RUFs related to radiation, cryotherapy, trauma, or prior surgical intervention such as prior prostatectomy are classified according to etiologic factor, degree of symptomatology, presence of pelvic sepsis, degree of urethral stricture, and history of prior repair. Small, minimally symptomatic, nonirradiated RUF can be managed initially with a urethral catheter and if needed suprapubic catheter drainage. Despite extensive recommendations in the literature for routine fecal diversion [113–117], cases meeting the stated criteria do sometime heal spontaneously without fecal diversion. Such cases include post laparoscopic or robotic radical prostatectomy. Chun and Abbas reported that 60 % of RUFs resulting from laparoscopic radical prostatectomy healed spontaneously with urinary +/− fecal diversion [110]. If RUF remains unhealed for 2 or more months, surgical intervention is usually warranted. Local transanal flap repair is a good option for small nonirradiated RUF. If RUF remains unhealed following local flap repair, a diverting stoma followed by additional local flap repair or transperineal repair with gracilis interposition flap or dartos flap would be the next step.

Patients with large RUF (>1 cm), prior radiation or cryotherapy, significant symptoms, severe urethral stricture, or prior failed repair require fecal diversion with suprapubic catheter drainage. Patients with postoperative or trauma-related RUF should undergo computed tomography scan of the pelvis, and if an abscess is present, it should be drained percutaneously under imaging guidance. After 3 months of fecal diversion, the RUF should be reassessed. If healed, the patient can then undergo stoma closure. It is important to reassess the patient with a minimum of two diagnostic studies (endoscopic or imaging) from the bladder and rectal side to confirm complete healing prior to closing the stoma. Patients with unhealed RUF have several options including permanent fecal diversion. Patients who desire definitive

repair can be approached via a transabdominal (proctectomy with coloanal with or without omental flap, pelvic exenteration with or without sphincter preservation), transanal flap, transperineal (gracilis flap interposition or dartos flap), transsphincteric, or transsacral technique [106–132]. The first three approaches in our opinion are the most suitable. We consider a transabdominal approach in the form of pelvic exenteration (can be anal sphincter preserving with coloanal) for patients with positive oncologic margins or nonfunctioning bladder. Otherwise, a transanal or transperineal approach is considered. Transanal repair consists of endorectal advancement flap with or without biologic mesh reinforcement [117]. It is most effective for small fistula without extensive tissue damage from radiation or cryotherapy. Patients who fail transanal repair and those with extensive tissue damage, large fistula, or significant urethral stricture are best approached with transperineal repair with gracilis interposition flap. Urethral reconstruction can be achieved with a buccal mucosal flap or biologic mesh. It is important to convey to the patient the expectations and limitations of surgical treatment, including the need for multiple operations, the risk of failure, and the potential poor anorectal and urinary functions.

Transanal Approach

For a nonirradiated small RUF, a transanal approach with rectal advancement flap is a good option in patients without anal stricture [117, 121, 129]. The technical details of the flap operation have been described earlier in this chapter for complex anal fistula. After mobilization of the flap, the urethral opening is identified. Gentle debridement of any granulating tissue is performed. The procedure is typically performed in the Jack-knife prone position under spinal or general anesthesia. A modified technique of biologic mesh reinforcement of the transanal endorectal flap has been previously described [117]. The addition of biologic material can be helpful in patient with larger defect and good vascularized tissue which can facilitate tissue ingrowth. Figure 15-24a–h demonstrates the technical steps of the flap repair with mesh interposition between the prostate and rectal wall. The flap is mobilized, and gentle debridement of the fistula edges on the prostate side is performed. Tissue approximation over the urethral opening is performed if enough pliable tissue is available. Multiple 2.0 Vicryl sutures are introduced into one aspect of the biologic mesh and through the tissue at the apex of the exposed flap bed, ideally one to two centimeters proximal to the fistula opening. The biologic mesh is then parachuted into the exposed flap bed and secured in placed with the sutures. Any excess mesh is trimmed along with distal aspect of the endorectal flap. Finally the flap is secured to the edges of the dissection using 2.0 Vicryl sutures. A urethral catheter is kept for 4–6 weeks postoperatively before assessing fistula healing.

A limitation of the transanal approach is limited exposure in some patients with long anal canal and deep buttock clefts which can make it difficult to adequately mobilize the rectal flap.

Posterior Approach

High RUF can be approached via a posterior approach either through a York-Mason transsphincteric dissection or a Kraske approach [123]. The York-Mason technique involves posterior sagittal division of the anal sphincter and levator muscles as well as the posterior wall of the rectum to gain access to the fistula. Repair of the fistula is performed, followed by closure of the proctotomy and all divided tissue planes. The Kraske approach entails resection of the coccyx, division of the tissues between the coccyx and the sphincters to provide access to the posterior wall of the rectum, which is then opened to provide access to the fistula. The use of a transsphincteric approach has decreased significantly over the past years, because of the risk of fecal incontinence as a complication of anorectal sphincter surgery. Additional concern is poor tissue healing in patients with prior radiotherapy. We rarely consider this approach and favor an abdominal approach if access is needed for a high RUF.

Transperineal Approach

The transperineal approach is the preferred method for most RUFs that require interposition of healthy and well-vascularized tissue. This technique provides a good plane of dissection and exposure for low and mid RUFs. Tissue interposition can be provided with a dartos flap or gracilis muscle for larger irradiated RUF [120, 122, 125, 128, 132, 133]. The dartos flap is harvested from the posterior aspect of the scrotum and rotated inward to interpose between the repaired urethra and rectum. The operation is performed in the prone position. After harvesting the dartos flap, the interposition of the flap is performed through a perineal incision.

The transperineal gracilis muscle interposition flap is an excellent option to repair large irradiated RUFs. The procedure entails two phases: initial harvesting of the gracilis flap in the lithotomy position and then RUF repair through a perineal dissection in the prone position. The gracilis flap is traced externally about 4 cm posterior to the adductor muscle (Figure 15-25a). Three incisions are made over the course of the muscle which is isolated with Penrose drains (Figure 15-25b). The distal insertion of the muscle is then disconnected at the medial aspect of the knee, and the gracilis is dissected off surrounding tissue from distal to proximal, gradually rotating it medially. Small perforators from the superficial femoral vessels are clipped and divided. Care is taken to preserve the major neurovascular bundle which is typically located within 10 cm of the pubic symphysis (Figure 15-25c). The freed portion of the muscle is

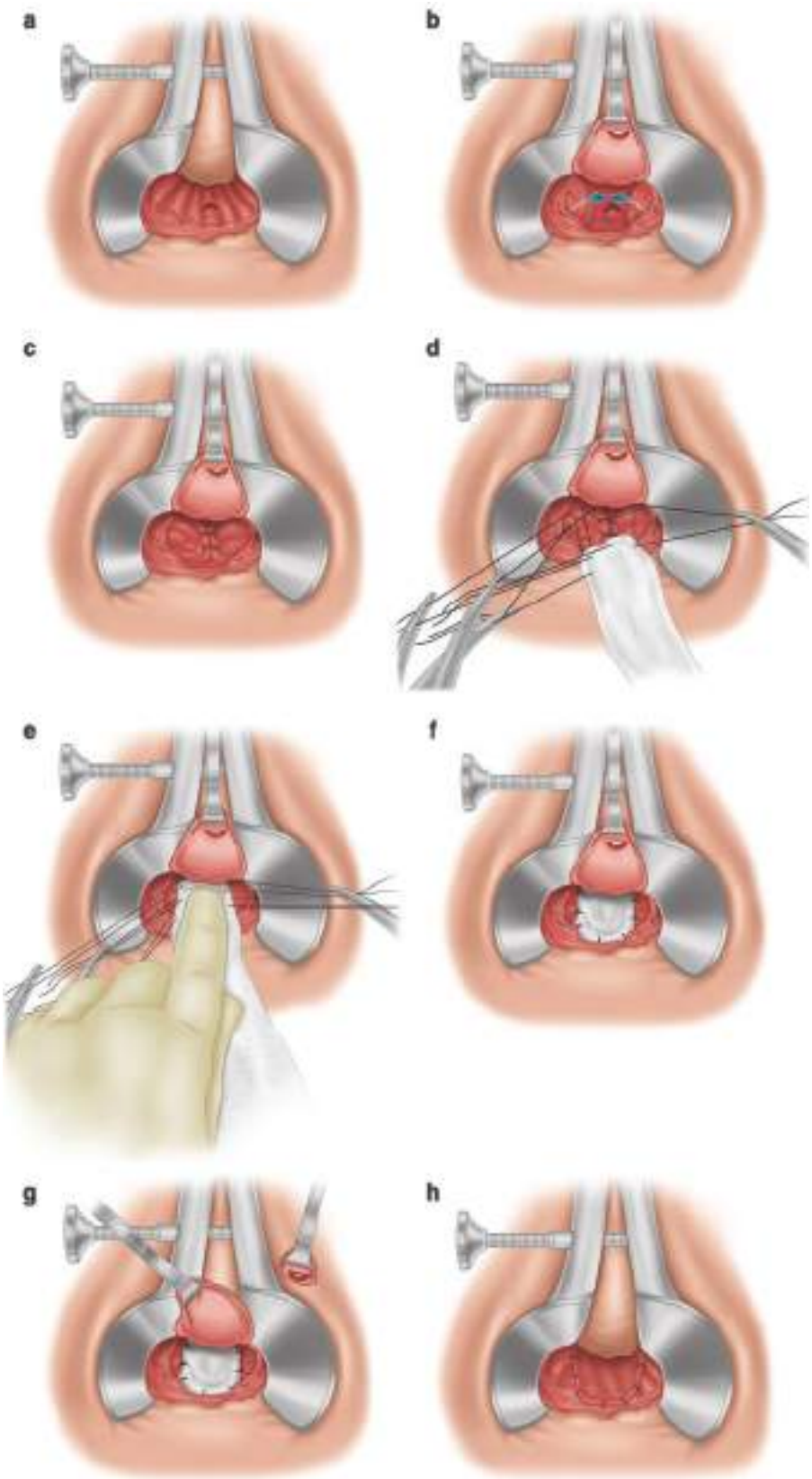

FIGURE 15-24. (**a**–**h**) Transanal endorectal advancement flap with biologic mesh interposition.

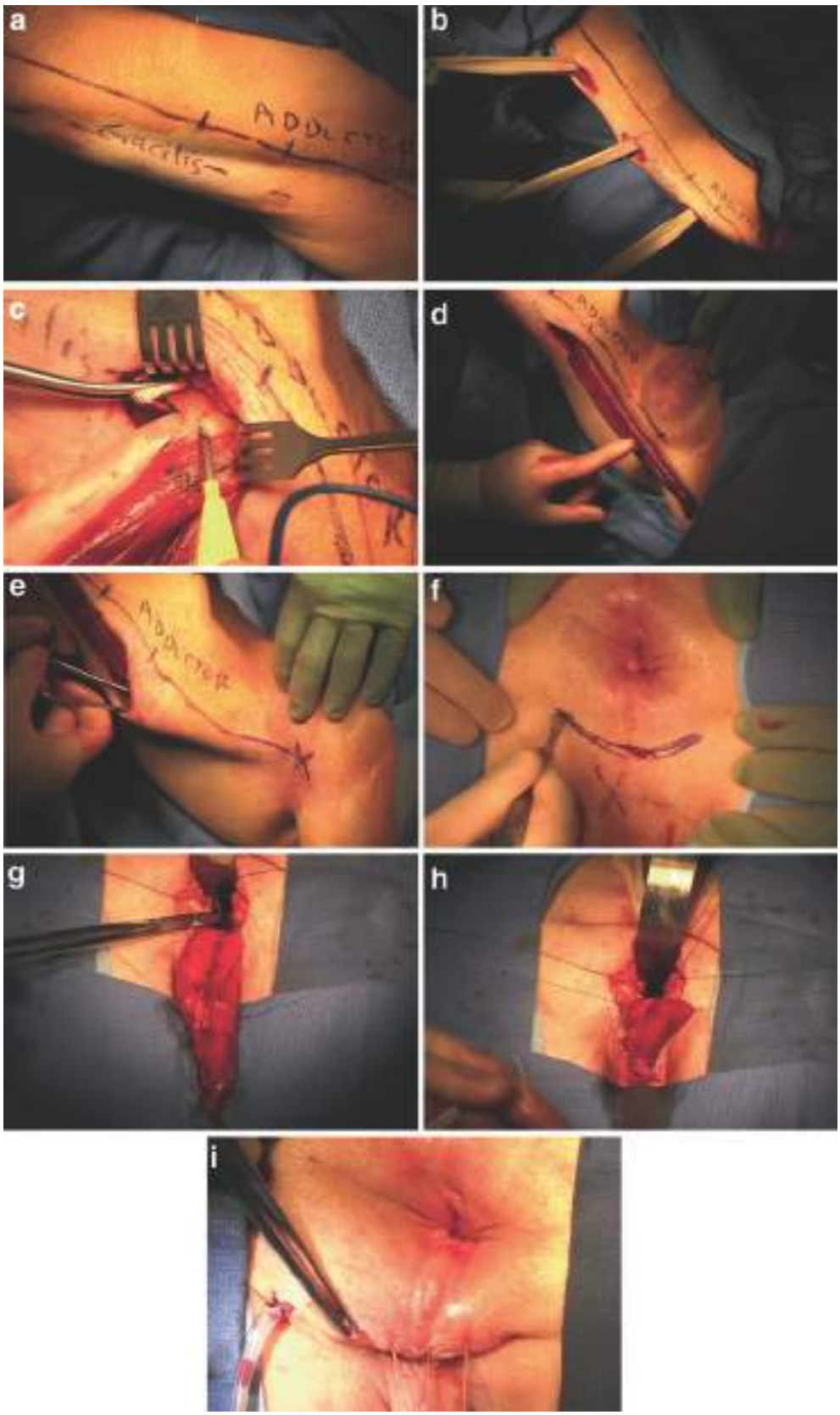

FIGURE 15-25. (**a–i**) Intraoperative pictures of transperineal repair of rectourethral fistula with gracilis interposition flap.

Table 15.4 Outcome of patients with rectourethral fistula in various series

	Year	# of patients	Procedure	Follow-up	Closure (%)
Youssef et al. [120]	1999	12	Dartos flap	9–42 months	69
Garofalo et al. [121]	2003	14	Rectal flap	31 months	68
Lane et al. [107]	2006	22	Transabdominal (68 %)	29 months	88
Wexner et al. [122]	2008	36	Gracilis flap	N.R.	78
Ghoneim et al. [125]	2008	25	Gracilis flap	28 months	100
Gupta et al. [126]	2008	10	Gracilis flap	24 months	100
Ulrich et al. [127]	2009	26	Gracilis flap	22 months	100
Kasraeian et al. [123]	2009	12	Transsphincteric	22 months	75
Vanni et al. [124]	2010	74	Gracilis flap + tissue rectal flap	20 months	92
Samplaski et al. [128]	2011	13	Gracilis flap	2.5 months	92
Hechenbleikner et al. [108]	2013	416	Gracilis flap (72 %)	N.R.	87.5
Keller et al. [106][a]	2015	30	Transperineal (54 %) Transanal (31 %) Transabdominal (15 %)	72 months	90

[a]43 % required definitive fistula repair

exteriorized through the most proximal skin incision and rotated to ensure adequate length for perineal coverage (Figure 15-25d). A subcutaneous passage is created using a large clamp to tunnel the muscle from the medial aspect of the thigh to the perineum (Figure 15-25e). The skin incisions over the medial thigh are closed after placing a subcutaneous drain. The patient is then placed in the prone position. Using curvilinear incision centered over the perineum, dissection is carried anterior to the anal sphincter muscle and through the rectoprostatic plane (Figure 15-25f). Once the plane of the fistula is entered, the dissection is carried another 3–4 cm cephalad. If urethral reconstruction is needed, it is carried out at this phase of the operation using either biologic mesh or buccal mucosa flap harvested from the mouth [124]. The next step is interposing the gracilis flap. Sutures are placed in the muscle edges using 2.0 Vicryl (UR6 needles) and the apex of the dissection cephalad to level of fistula (Figure 15-25g). The muscle is then parachuted into the wound and gently guided to cover the entire bed of the dissection (Figure 15-25h). Additional sutures are placed as needed to secure the muscle in place. The subcutaneous portion of the wound is then closed in layers over a drain and skin is closed (Figure 15-25i).

Transabdominal Approach

In general, we reserve a transabdominal approach for select group of patients with RUF. Patients with postoperative RUF following prostate or rectal surgery and positive oncologic margins can be offered a transabdominal approach. Additional indications include high RUF not accessible to a transanal or transperineal approach, patients with nonfunctioning irradiated bladder or severely stricture urethra which requires excision with urinary diversion, and patients with prior failed repairs. The type of abdominal operation is individualized based on patient- and disease-related factors. Options include cystectomy with urinary diversion, proctectomy with coloanal anastomosis, abdominoperineal resection, and pelvic exenteration. An omental flap or rectus abdominis flap interposition can be used if needed. The omentum is dissected preserving the left gastroepiploic artery as main blood supply. The flap is placed between the rectum and the urethra after pelvic dissection is carried out to divide and resect the fistula. Primary repair of the rectal wall is performed and covered with the omental flap. If the rectal defect is too large to close and tissue quality is poor, proctectomy with or without sphincter preservation is indicated. Dissection is carried down to the levator muscles to reach below the level of the fistula. For high RUF, the rectum is divided with a stapler at the level of the anorectal junction if technically feasible, and a stapled coloanal anastomosis can be performed. For mid to low RUF, mucosectomy or intersphincteric dissection is performed from below to complete the dissection, and intestinal continuity is restored with a handsewn anastomosis. Abdominoperineal resection can be performed if not sphincter preservation is indicated.

Outcome

The outcome of RUF treatment is difficult to evaluate because published studies with large number of patients are scarce. Significant heterogeneity exists in the various reports due to differences in patient populations and operative techniques. Table 15-4 summarizes the results of several large series [106–108, 120–128]. The reported success rate following definitive operative intervention ranges from 68 to 100 %. However, it is important to emphasize the various management strategies in the published reports. Not all patients require definitive repair. A spontaneous closure rate of 14–46.5 % has been reported after fecal diversion, and some patients can heal small RUF with urethral catheter drainage alone [106]. In a systematic review, Hechenbleikner and colleagues reported similar RUF closure rate in nonirradiated

and irradiated patients (89 % vs. 90 %), but the permanent fecal diversion rate was 25 % in irradiated patients compared to 3.8 % in nonirradiated patients [108]. The overall permanent urinary diversion rate was 8.3 % and was significantly higher in irradiated patients (42.5 %) compared to nonirradiated patients (4 %).

The transanal approach with rectal advancement flap is safe and effective in the absence of prior radiation therapy [106, 121]. Garofalo and colleagues reported 85 % closure rate with this technique in 12 patients at the Cleveland clinic [121]. Indication for local flap is small nonirradiated fistula, whereas large fistula requires a more complex procedure. The gracilis muscle interposition is currently the most commonly used method for treating complex, large, recurrent, and/or irradiated RUF. In a systematic review, including 416 patients (40 % with previous pelvic irradiation and/or ablation), most RUFs (90 %) underwent 1 of 4 categories of repair: transanal (5.9 %), transabdominal (12.5 %), transsphincteric (15.7 %), and transperineal (65.9 %) [108]. Tissue interposition flaps, predominantly gracilis muscle, were used in 72 % of repairs. Fistula closure was successful in 87.5 %. Overall permanent fecal and/or urinary diversion rates were 10.6 and 8.3 %. Wexner and colleagues reported their results in 36 males who underwent the gracilis interposition for RUF, mainly due to prostate cancer treatment [122]. Thirteen patients (36 %) had a mean of 1.5 prior failed repairs (range 1–3) [122]. Seventeen patients (47 %) experienced postoperative complications. The initial success rate was 78 %. After a second procedure in 8 patients, the overall clinical healing rate was 97 %.

Proctectomy with coloanal procedure can be considered in select cases in presence of a hostile pelvis, previous radiation therapy, previous attempt at repair, and under a defunctioning stoma. Patsouras and colleagues reported a success rate of 50 % in four patients treated with this technique [118].

Postoperative Fistulas

Definition, Classification, and Pathophysiology

Restorative proctocolectomy (RPC) with ileal-pouch-anal anastomosis (IPAA) has evolved as the mainstay surgical treatment for patients with intractable ulcerative colitis and familial adenomatous polyposis. Ileal-pouch fistula is uncommon but a highly morbid complication. The fistula tract can be classified as pouch anal, pouch vaginal, and pouch perineal. Pouch-anal fistula is defined as a fistulous tract with an internal opening at or above the ileoanal anastomosis and an external opening below the IPAA at the anal canal or perineal skin. Pouch-vaginal fistula may be classified relative to the anastomotic suture line (above, below, or at the level of anastomosis). Fistula is defined as complex if there are multiple tracts and/or the internal opening is at or above the IPAA (high fistula) [134, 135]. Perianal fistula may occur as a postoperative complication after ultralow anterior resection, coloanal anastomosis, Hartmann reversal procedure, abdominoperineal resection, or transanal endoscopic microsurgery for distal rectal cancer [136, 137]. Major risk factors associated with development of postoperative fistulas include elderly age, diabetes, vasculopathy, smoking, preoperative/postoperative radiotherapy, operative technique, and postoperative pelvic sepsis. Good surgical technique, avoidance of postoperative pelvic sepsis, careful dissection through the rectovaginal septum to avoid incorporating the vagina in the anastomosis when firing the stapler, a tension-free anastomosis with good blood supply, staged procedures, and temporary diversion are of fundamental importance for successful healing of bowel anastomosis and avoidance of such complications.

Clinical Assessment and Diagnostic Evaluation

A disease-specific history includes demographic characteristics, diagnosis at the previous anorectal surgery (inflammatory bowel disease, familial adenomatous polyposis, rectal cancer), and type of surgery (coloanal or colorectal anastomosis; one-stage, two-stage, or three-stage RPC; mean time between the different stages; pouch configuration; stapled or handsewn anastomosis; mean distance of anastomosis from anal verge; postoperative pelvic sepsis), symptoms, and the median time to fistula presentation. Fistulas often present with pelvic and perianal sepsis or drainage and pain. Careful physical examination (inspection, palpation, digital rectal examination, probing) should be performed. Patients with acute pouch-anal sepsis or complicated perianal disease or an inadequate clinical assessment should undergo examination under anesthesia. Preoperative imaging to evaluate the anatomy of the fistula tract includes endoanal ultrasound, pelvic MR imaging, CT scan, pouchography, and fistulography.

Surgical Treatment

Because of the low incidence of these fistulas, the optimal management continues to be controversial. The guiding principles are to control pelvic and perianal sepsis and eliminate the fistulous tract. An acute abscess should be drained, and when necessary, a noncutting seton may be placed to control anorectal infection. Operative techniques include gracilis muscle interposition, lay-open fistulotomy, collagen plug insertion, ileal advancement flap, transvaginal advancement flap, fibrin glue, transperineal repair, Martius (i.e., bulbocavernosus) flap, pouch excision, or redo pouch [134–142]. Pouch-vaginal fistula can persist and recur indefinitely, even after repeated repairs. Simple procedures should be attempted first, if there is a chance of success, before more complex procedures are considered. Temporary diverting ileostomy, permanent end ileostomy with/without pouch excision, and

redo-RPC should be considered in patients with ileal-pouch fistulas. Temporary diverting colostomy with/without coloanal/colorectal anastomoses or permanent end colostomy with/without anastomoses removal or completion proctectomy should be considered in rectal cancer patients [138]. Complex perineal fistula occurring after APR or pelvic exenteration can be treated by the use of an omentoplasty or rectus abdominis musculocutaneous flap to fill the dead space of the pelvis with well-vascularized tissue. If the omentum is not sufficient or the rectus abdominis is not an option due to the presence of a colostomy and urostomy through both muscles, a biological mesh and/or a gluteal flap can be utilized. Medical treatment including anti-TNF agents should be the first-line therapy for patients who present delayed onset of pouch fistula and a suspicion for Crohn's fistula.

Outcome

Gaertner and colleagues conducted a retrospective review on 342 patients who underwent RPC and found 25 patients (7 %) who presented with symptomatic ileal-pouch fistula [140]. Complete fistula healing occurred in 64 % of patients at a median follow-up of 29 months. Operative techniques were heterogeneous, and each patient underwent an average of 2.8 procedures. Mallick and colleagues reviewed the Cleveland Clinic experience with pouch-vaginal fistulas [141]. Fistula occurred in 102 females: 59 at ≤12 months (early fistula) and 43 at > 12 months (late-onset fistula). Local repair was performed in 77.3 % of patients (ileal-pouch advancement flap in 49.5 % of cases and transvaginal repair in 27.8 % of cases). The healing rate after ileal-pouch advancement flap was 42 % when performed as a primary procedure and 66 % when performed secondarily after a different procedure. The healing rate for transvaginal repair was 55 % when done as a primary procedure and 40 % when performed secondarily. Nineteen patients underwent redo ileal-pouch construction, with an overall pouch retention rate of 40 %. At median follow-up of 83 months, 57.7 % of the 102 patients had healed the pouch-vaginal fistula, whereas pouch failure occurred in 34 women (35 %, 12 early onset and 22 late onset). Heriot and colleagues assessed the short-term and long-term outcomes of surgical repair of 68 patients with pouch-vaginal fistula after RPC at St. Mark's Hospital [142]. Surgery was undertaken in 87 % of patients: 24 % pouch excision/diversion or seton drainage and 66 % primary repair. Overall primary healing rate was 40 % at a median follow-up of 19 months. The overall pouch failure rate for patients with pouch-vaginal fistula was 35 %.

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16
Rectovaginal Fistula

Jamie A. Cannon

Key Concepts

- Repair of rectovaginal fistulas should be tailored to the individual patient based on the anatomy of the fistula and associated conditions.
- Perianal sepsis must be controlled prior to attempting a definitive repair.
- Patients with RVFs from obstetric trauma should be evaluated for concomitant sphincter defects.
- Patients who have a Crohn's-related RVF should have their disease medically optimized prior to repair of the fistula.
- Introduction of healthy, well-vascularized tissue such as a Martius flap or gracilis interposition should be considered in patients who have attenuated tissues or have undergone multiple previous unsuccessful repairs.
- Fecal diversion should be considered in patients undergoing major repairs.

Rectovaginal fistulas (RVFs) are abnormal communications between the anus or rectum and the vagina. RVFs are uncommon in the general population, but are seen frequently by colorectal surgeons. The condition can be extremely disabling and is associated with significant distress in affected women. Patients may present with stool per vagina resulting in frank incontinence, or gas or drainage per vagina. These symptoms can also cause pelvic pain and interfere with intimacy.

Successful treatment of rectovaginal fistulas offers the opportunity to greatly improve a patient's quality of life. Unfortunately, success rates are not on par with other commonly performed operations. Many patients present after having undergone multiple previous attempted repairs, which can be frustrating for the patient and surgeon. Hoexter et al. reported 33% of their patients with previous attempted repairs were in litigation with their surgeons [1].

A number of different factors may contribute to the poor success rates following repair. Anatomically, there is little muscle in the thin rectovaginal septum, which may make it more difficult for this region to heal. Fistulotomy, the most successful surgery for managing perianal fistulas, is contraindicated as it invariably results in some degree of incontinence, either due to the paucity of sphincteric muscle in women anteriorly or a resulting keyhole defect.

Multiple different approaches have been described to treat rectovaginal fistulas, which reflects the fact that there is not an ideal operation with a uniformly high success rate. Interpreting the literature to determine the best approach can be challenging. Most papers report series with few patients, and the patients are far from uniform. Varied patient presentations make standardizing the multiple different approaches difficult, if not impossible. In addition, surgeons often vary techniques slightly, use different terminologies, or combine approaches, which prohibits a side-to-side comparison. In general, more complicated and extensive repairs are not associated with improved rates of success, which could leave one to believe that a less invasive approach is preferable. However, the complexities of the fistulas selected for a major procedure create a selection bias against these repairs. Preoperative fecal diversion has not been shown consistently to lead to better outcomes, but this again may represent selection bias in those patients chosen for diversion. These compounding factors make the likelihood of a randomized trial comparing different repair types impractical.

Therefore, it is imperative for the surgeon to have a thorough understanding of the patient's anatomy, disease process, and options for repair in order to determine the best approach. In this chapter, we will review the etiologies for rectovaginal fistula, the evaluation of a patient with a rectovaginal fistula, various approaches for repair, and finally discuss the decision making process in choosing the appropriate surgical procedure.

Etiology of Rectovaginal Fistulas

Rectovaginal fistulas can be the result of obstetric injuries, cryptoglandular disease, or Crohn's disease. These etiologies are discussed below. They can also be caused by malignancy,

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radiation therapy, or leaks from a colorectal, coloanal, or ileal pouch-anal anastomosis. These are beyond the scope of this chapter and addressed elsewhere in this book.

Obstetric Injury

Obstetric injury is the most common cause of RVFs. While many published case series have a higher proportion of patients with other etiologies, such as Crohn's disease, this is a reflection of specific referral patterns and the patient populations at different institutions. Rectovaginal fistulas are reported to occur following 0.1–0.5% of all vaginal deliveries [2]. Obstetric fistulas can arise from a fourth-degree tear in which the repair has broken down. This type of fistula will generally become clinically apparent 1–2 weeks after delivery and is most often located at the level of the anal sphincters. Prolonged labor resulting in compression of the rectovaginal septum by the infant's head can lead to necrosis of the RV septum and cause a rectovaginal fistula that presents in a more delayed fashion. These generally occur cephalad to the pelvic floor where the rectovaginal septum is thinnest. Traumatic injury from an instrumented delivery may result in an immediately apparent fistula and also generally occurs in the thin portion of the rectovaginal septum.

Repairs of RVFs caused by obstetric injury tend to be more successful than repairs of fistulas from other causes. Halverson et al. reported on 15 patients with obstetric-related RVFs that had failed previous repairs [3]. All fistulas were eventually able to be repaired for an overall success rate of 100%, but required a total of 23 procedures for a per procedure success rate of 65%. This cohort of patients was compared to patients with recurrent RVF from Crohn's disease that had an overall success rate of only 50% (6 of 12 patients healed with a total of 21 procedures).

Cryptoglandular Disease

Cryptoglandular disease, which is the most common cause of simple anorectal fistulas, can also cause rectovaginal fistulas. This occurs when an anteriorly located anal gland or its associated duct becomes occluded; the resulting abscess may form in the rectovaginal septum and decompress into the vagina. If the communication fails to heal, a rectovaginal fistula results. These are generally located at the level of the dentate line on the rectal side and course through the anal sphincters to the low vagina or introitus.

Crohn's Disease

Rectovaginal fistulas caused by Crohn's disease are variable in their presentation and location. As they are the result of transmural inflammation from the anorectum, they are frequently associated with perianal sepsis, branching fistula tracts, additional rectocutaneous fistulas, and scarring and stricturing of the anorectum. Approximately 10% of women with Crohn's disease will develop a rectovaginal fistula, and they are more common in those who suffer from colonic Crohn's disease [4, 5].

Surgical repair of rectovaginal fistulas caused by Crohn's disease is not as successful as repair of fistulas of obstetric or cryptoglandular origin. Prior to attempting any repair, control of perianal sepsis is required. This may require abscess drainage and seton placement. A discrete, epithelialized tract should be present before attempting repair, which is best achieved with initial seton placement. Multiple fistula tracts, a watering can perineum, or active inflammation of the rectal mucosa are contraindications to repair. Figure 16-1 shows a rectovaginal fistula from Crohn's disease. Multiple external openings with stool present are visible in the perineum. This patient would benefit from placement of a seton to allow the fistula to mature prior to definitive repair.

Repair should not be undertaken in the presence of active inflammation of the rectum as the repair is unlikely to heal. Those with significant Crohn's-related pathology of the anorectum are unlikely to be good candidates for repair and should be managed either medically, with a seton, or with a proctectomy. Athanasiadis et al. found

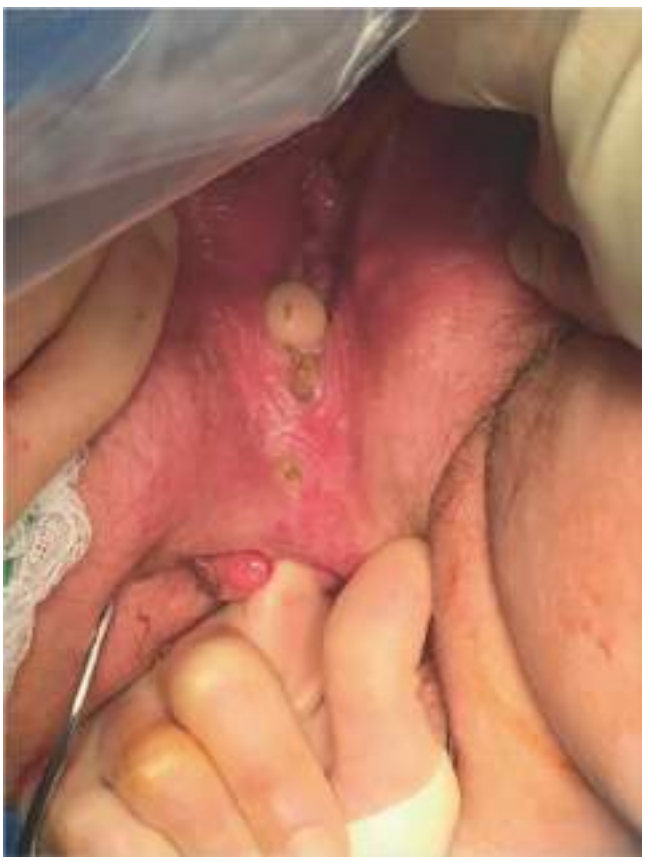

FIGURE 16-1. Large Crohn's-related rectovaginal fistula with multiple external openings in the perineum.

that of patients presenting with Crohn's disease and a rectovaginal fistula, only 51% were deemed appropriate for attempted repair [6]. Overall, 19% of patients eventually underwent a proctectomy for management of their disease.

The use of infliximab has been shown to lead to spontaneous healing of fistulas in Crohn's disease. Kraemer et al. reported healing of symptomatic fistulas in 8 of 19 patients with Crohn's-associated anorectal fistulas treated with infliximab prior to surgery [7]. Its role in the management of rectovaginal fistulas specifically is not well delineated, but multiple reports have shown spontaneous healing of RVFs. These results may not be durable once immunomodulators have been discontinued [8], but are promising enough to warrant a trial of medical therapy prior to surgical intervention. If the fistula does not close spontaneously, reducing the amount of associated inflammation will likely improve the chance of success with surgical repair. Sands et al. reviewed the ACCENT II trial which studied infliximab in patients with fistulizing Crohn's disease [8]. Twenty-nine patients in this trial had rectovaginal fistulas. Patients were evaluated at week 14 of treatment with infliximab, and 13 of those patients (44.8%) were found to have healed fistulas. While this success rate has not been duplicated in other studies, healing with infliximab therapy alone has been demonstrated elsewhere as well. Table 16-1 summarizes these findings.

Successful surgical treatment of Crohn's-related RVF varies in the literature, with success rates ranging from 30 to 70%. Selection bias may be responsible for some of this variation; the more highly selected the candidates the greater the chance of success. Patients most likely to have a successful repair are those with an isolated RVF without other perianal diseases and in whom their Crohn's disease is quiescent. The success rates reported below for repair of Crohn's-related RVFs can be compared to a success rate of 74% in simple fistulas that are not related to Crohn's [9].

Luffler et al. reported on 45 patients with Crohn's-related RVFs [10]. The patients underwent a total of 95 interventions, averaging 2.1 interventions per patient. Their long-term success rate was 53%, but 10 patients (22.2%) required proctectomy. They found levatorplasty and endorectal advancement flaps to have similar rates of success at approximately 50%.

Drs. Hull and Fazio reported on 48 Crohn's patients with RVF. [11] Nine required proctectomy and five were treated with a seton only. Of the 35 who underwent attempted definitive repair, 19 were successful (54%). Five of the failures underwent subsequent successful procedures for an overall success rate of 24/35 (69%). They also found that success was more likely among the patients who had fecal stream diversion, with 8/9 diverted patients having successful repairs.

El-Gazzaz et al. reported on 65 women with Crohn's disease who underwent RVF repair [12]. They had 30 successes (46.2%). They noted that many of the failures were late failures and thus recommended long-term follow-up in order to accurately determine success. It is difficult, however, to discern between actual treatment failures and recurrent disease with the development of new Crohn's-related fistulas.

Table 16-1. Medical therapy for Crohn's-related RVFs

Author	Year of publication	Drug utilized	No. of patients	No. of successful closures (%)
Present [45]	1980	6-MP	6	2 (33.3)
Ricart [46]	2001	Infliximab	15	5 (33.3)
Bodegraven [47]	2002	Infliximab	4	0 (0)
Sands [8]	2004	Infliximab	29	13 (44.8)
Parsi [48]	2004	Infliximab	14	2 (14.2)

Evaluation of a Patient with a Rectovaginal Fistula

The etiology of the fistula can often be determined from the patient's history. History taking should be directed toward the patients obstetric history, previous abdominal and anorectal operations, history of radiation treatment, and signs and symptoms of Crohn's disease or diverticulitis. Physical examination begins with a visual external examination. Care should be taken to search for signs of continuing perianal sepsis, such as undrained abscesses or purulent perineal drainage. Evidence of perianal Crohn's disease should be sought. Cloacal-type defects can be seen following severe obstetric injury.

On digital rectal examination, the condition of the perineal body and rectovaginal septum should be noted. Care should be taken to assess the quality and strength of the anal sphincters. Large rectovaginal fistulas may be readily apparent on rectal examination. Bimanual examination may be required to detect smaller fistulas. Careful palpation of the entire rectovaginal septum between the fingers of each hand may reveal the presence of a small fistula. Note should also be made of any strictures or scarring of the anal canal from previous or active Crohn's disease. The location of the fistula relative to the sphincter muscles and pelvic floor should be determined as this can affect the type of repair chosen.

If the fistula is not palpable, further investigations are needed. Baig et al. found that physical examination was successful in identifying the fistula in 74% of patients [9]. If it cannot be identified on examination, alternate etiologies to explain the patient's symptoms should be considered, such as a colovaginal fistula rather than a rectovaginal fistula. Colovaginal fistulas from diverticulitis are a more common condition, and a contrasted CT scan of the abdomen and pelvis will demonstrate inflammation of the sigmoid colon directly overlying the vagina if this is the case. However, very small or high RVFs may not be palpable on exam.

While other imaging studies are often employed, RVFs can be difficult to detect on routine imaging. Options include

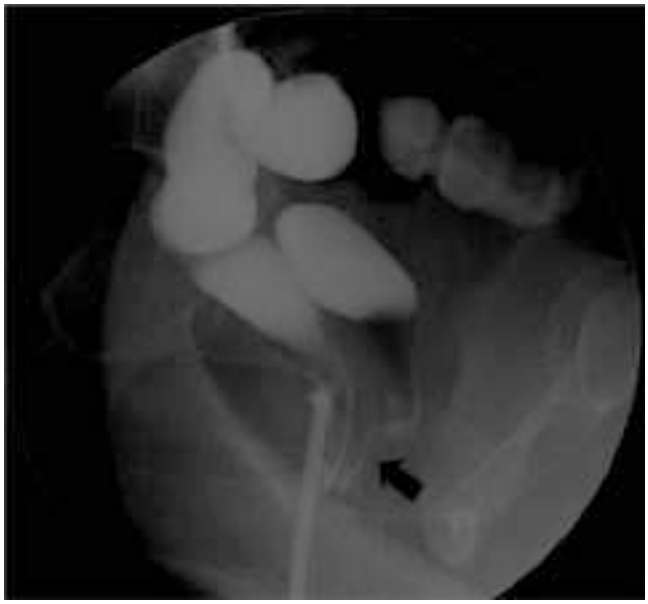

FIGURE 16-2. Gastrografin enema showing contrast passing through a rectovaginal fistula. © 2015 Kobayashi and Sugihara; licensee Springer. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly credited [53].

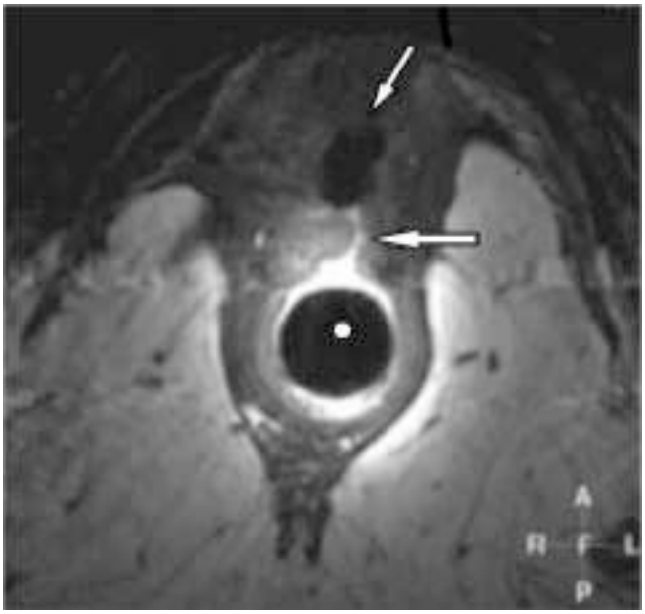

FIGURE 16-3. Rectovaginal fistula as seen on MRI.

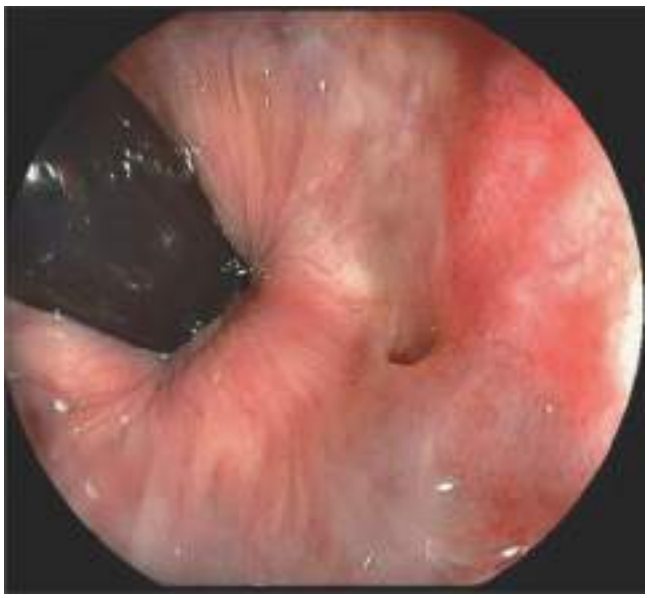

FIGURE 16-4. Rectovaginal fistula on retroflexed view on colonoscopy. © 2015 Kobayashi and Sugihara; licensee Springer. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly credited [53].

gastrografin enema and vaginography. These have a low yield, however, and are rarely successful in imaging distal fistulas. They rely on occlusion of the anal canal or vaginal introitus in order to generate enough pressure to show passage of contrast through the fistula, and balloon placement may occlude the fistulous opening itself. Figure 16-2 shows an RVF on gastrografin enema. Baig et al. found vaginography did not identify the fistula in any of the five patients in whom it was performed [9]. Defecography may rarely be useful, but may identify other pelvic floor pathologies.

Endoanal ultrasound and MRI are the most useful imaging studies to identify a fistula [13]. MRI also has the advantage of identifying other disease within the pelvis. Figure 16-3 shows the appearance of an RVF on MRI. Endoanal ultrasound has been reported to identify the tract in 73% of patients [9]. Injection of hydrogen peroxide through the tract may aid in identification [14]. Ultrasound is also useful in that it enables assessment of the anal sphincters. It should be performed routinely in patients with an RVF secondary to obstetric trauma as they may have associated sphincter damage. Anal manometry may be considered as well. Patients with Crohn's disease should undergo a complete evaluation of their Crohn's disease, to include colonoscopy and CT or MR enterography. While the fistula itself is rarely seen on colonoscopy, colonoscopy allows for identification of active disease and other Crohn's-related complications. Figure 16-4 demonstrates the appearance of an internal opening on colonoscopy.

The best option for identifying an occult RVF is an examination under anesthesia. This allows for probing of the rectovaginal septum with a fistula probe to elucidate the location (Figure 16-5). It also allows for inspection of the anal canal and rectal and vaginal mucosa to identify areas of inflamma-

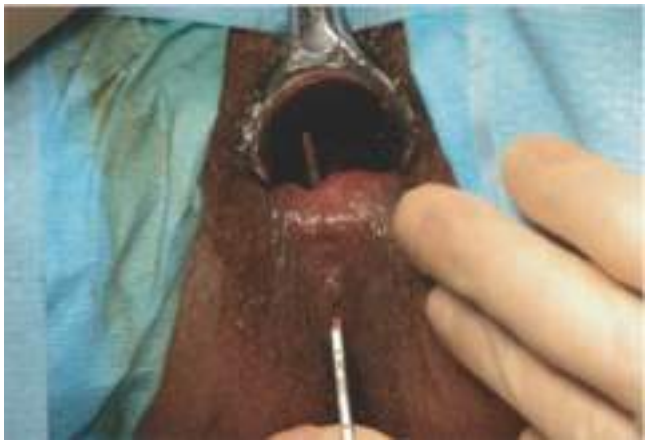

FIGURE 16-5. Fistula probe passing through a rectovaginal fistula.

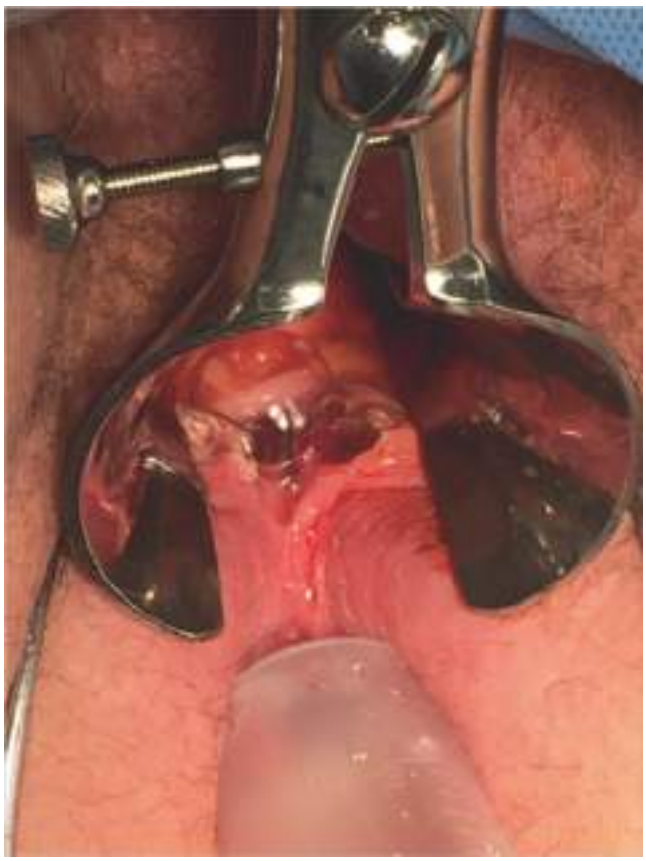

FIGURE 16-6. With the patient in Trendelenburg position, saline is placed in the vagina. An asepto syringe is used to inject air in the rectum. Bubbling in the vagina reveals the location of the rectovaginal fistula.

tion or dimpling for more targeted inspection. If this is not successful, other techniques may be employed. With the patient in Trendelenburg and lithotomy position, the vagina can be filled with saline while the rectum is insufflated with air (Figure 16-6). Air bubbling through the RV septum can elucidate the fistula's location. Alternatively, a tampon or operative sponge may be placed in the vagina. Saline with methylene blue dye can be introduced into the rectum via a flexible sigmoidoscope. Blue staining on the gauze within the vagina confirms that a fistula is present, but may not show the actual location.

Surgical Approaches to Repair of Rectovaginal Fistulas

A number of different techniques have been employed to repair a rectovaginal fistula, and for many patients more than one attempt at repair is necessary. For simple rectovaginal fistulas, defined as located in the mid or lower vagina and without Crohn's disease, Baig et al. reported successful repair in 14/19 patients (74%) using a variety of techniques. [9] For recurrent fistulas of various etiologies, Halverson and colleagues reported 23/48 procedures successful (48%) in 29 patients, for an overall healing rate of 79% [3]. Pinto and associates looked at 118 patients with RVF and found an overall success rate of 58.8% per procedure, with 103 patients eventually healing completely (87.3%) [15]. Among those with Crohn's, success was only 44.2% per procedure, but 78% of patients were eventually healed. They found recurrence rates were similar after various types of repairs. Tobacco use was identified as a risk factor for recurrence.

A list of the many surgical approaches to rectovaginal fistulas would be quite extensive. While the various approaches can be grouped into categories based on their similarities, each individual series will often describe a slight modification to previous reports. Patients are also frequently managed with more than one type of repair as treatments are customized to the fistula. For example, a rectal advancement flap may be combined with a transperineal repair or sphincteroplasty. This makes direct comparison of the various techniques difficult. The types of repairs are grouped together here for review as endorectal (rectal advancement flaps or sleeve advancements), transperineal (episioproctotomy or sphincteroplasty), tissue transposition (Martius flap or gracilis), transvaginal, and transabdominal.

Endorectal Repairs

Endorectal advancement flaps are the most commonly performed procedure for the management of a rectovaginal fistula. The procedure as described by Rothenberger et al. in 1982 [16] remains similar to what is described in most reports today with only minor variations in technique. The patient is placed in the jackknife prone position. A Pratt bivalve anoscope is used to expose the anterior rectal wall. Distal to the location of the fistula, an incision is made through the mucosa, submucosa, and down to the internal sphincter. A flap is raised in the rectum proximally. While some describe only raising

mucosa and submucosa, fibers of the circular muscle (internal sphincter) are generally included, and this is how Rothenberger described the procedure. The flap is raised for a distance of 4 cm proximal to the location of the fistula in order to allow for a tension-free anastomosis. Once the flap has been raised, the fistula itself is closed by approximating the fibers of the internal sphincter. This may require some lateral mobilization in order to bring the edges of the internal sphincter into approximation. The distal-most portion of the flap that contains the fistula is excised. The healthy flap is brought down to cover the fistula opening and secured in place. Figure 16-7 depicts these steps.

The most common cause for failure is thought to be flap retraction or necrosis. Therefore, it is essential that enough flap be mobilized so there is no tension on the anastomosis. The base of the flap should be at least twice the width of the apex of the flap in order to ensure adequate blood supply. Rothenberger reported overall good success with this technique. Out of 35 patients, 30 were successfully repaired with this approach (86%). This success rate is similar to that reported by Lowry et al. from the same institution with 43/49 (88%) successful [17].

Others, however, have not reported the same high degree of success with this technique. Ellis reported a

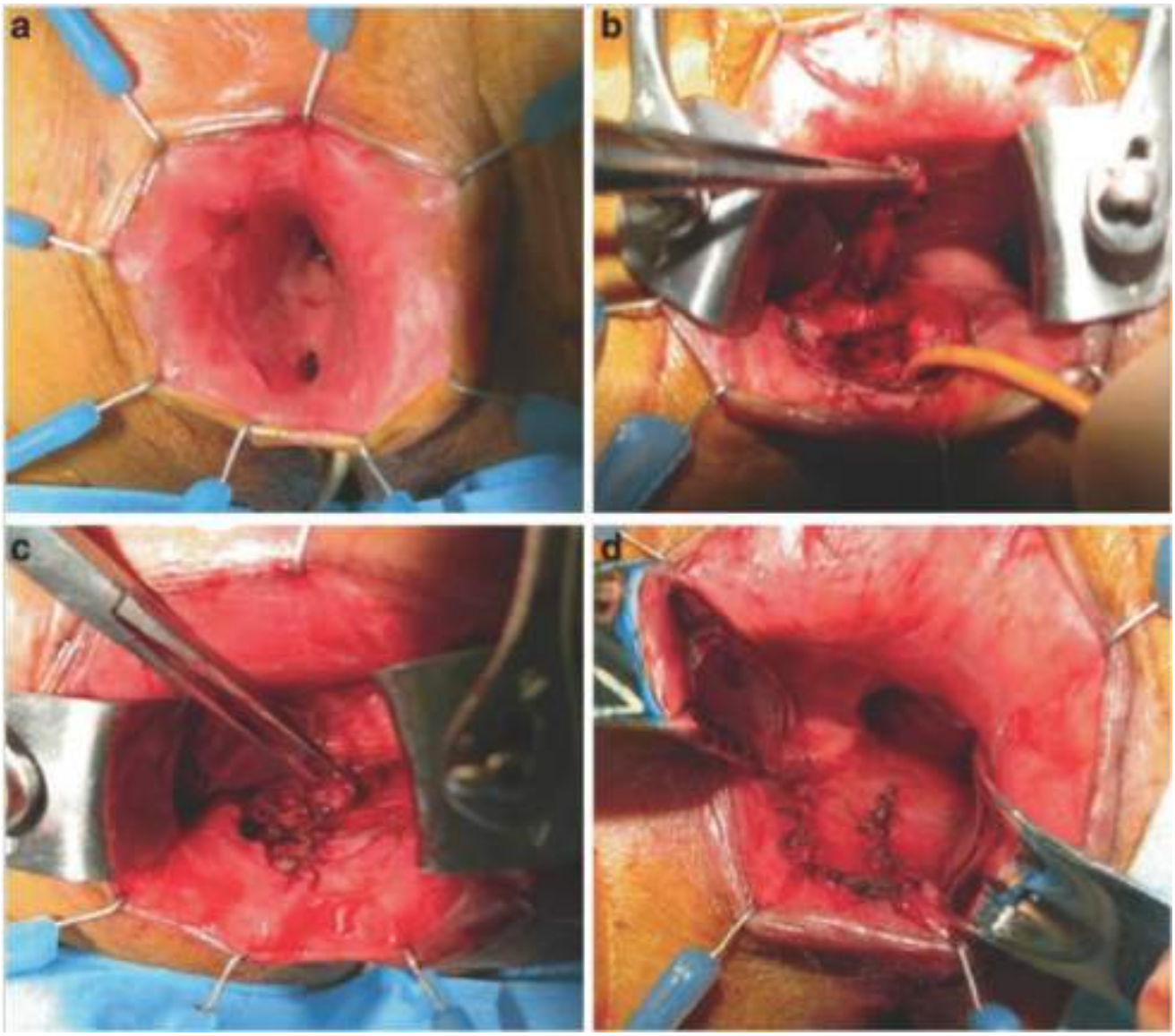

Figure 16-7. Endorectal advancement flap for rectovaginal fistula. Rectovaginal fistula is seen from the anus (**a**). The flap of mucosa, submucosa, and circular muscle is raised (**b**). Circular muscle is sutured by horizontal mattress manner (**c**). The flap is advanced over the repaired area (**d**). The flap is sutured in place at its apex and along its sides.

Table 16-2. Endorectal advancement flaps

Author	Year of publication	No. of patients	No. of successful closures (%)
Rothenberger [16]	1982	35	30 (86)
Jones [49]	1987	23	16 (70)
Lowry [17]	1988	44	56 (78)
Watson [50]	1995	12	7 (58)
Sonoda [19]	2002	37	16 (43)
Ellis [18]	2008	44	29 (66)
Hull [20]	2011	37	23 (62)

66% success rate in 44 patients [18]. Sonoda et al. reported success in 16/37 (43.2%) [19], while Hull and colleagues in 23/37 (62%) in a population that excluded Crohn's disease [20].

Athanasiadis and associates compared endorectal advancement flaps to multiple other closure techniques in a Crohn's population [6]. While the numbers are few, they reported disappointing success with this technique. Only 2/7 rectal advancement flaps were successful (29%), while the success rate for all other repair types combined was 37/49 (76%). Available data on endorectal advancement flaps is summarized in Table 16-2. There have been other modifications of the described procedure. Schwandner et al. described using a biologic graft as part of this procedure [21, 22]. Once the endorectal flap was raised, a 2 × 2 cm graft from porcine small intestine mucosa was placed in the rectovaginal space, and the flap sutured over the graft. They report successful healing in 15/21 patients (71%).

Of note, the likelihood of a successful repair with an endorectal advancement flap decreases if patients have undergone previous repairs [18, 23–26]. Halverson et al. reported only 9 successes in 30 patients who had undergone previous repairs with this technique (30%) [3]. Similarly, while Lowry had 88% success with a first repair, they found the success rate fell to 55% in those who had had two previous repairs [17].

Transperineal Repairs

A number of variations in technique exist in performing a transperineal repair, and terminology in the literature is diverse. For the purpose of this discussion, we have grouped together a variety of techniques that all share some common key points. Such techniques include episioproctotomy with layered closure, transperineal repair with levatorplasty, the LIFT procedure, and sphincteroplasty. These procedures all begin with an incision in the perineum that may be circumlinear around the anus, transverse, or vertical. Dissection continues cephalad along the rectovaginal septum. The rectum and vagina are separated from one another and the fistula tract divided, as seen in Figure 16-8. The incision is closed in layers. Ideally, some tissue, preferentially muscle, is interposed between the rectum and vagina. This may be done via levatorplasty or sphincteroplasty. The repaired areas of the rectum and vagina can also be imbricated. A rectal advancement flap can be added to the procedure.

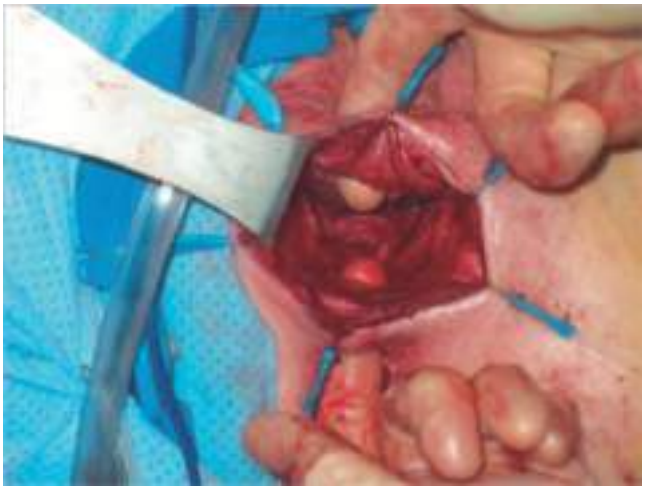

Figure 16-8. Transperineal repair where the rectum and vagina have been separated and the defects in each are visible.

Table 16-3. Transperineal repairs

Author	Year of publication	No. of patients	No. of successful closures (%)
Athanasiadis [6]	2007	20	14 (70)
Hull [20]	2011	50	39 (78)
Wiskind [51]	1992	21	21 (100)

Athanasiadis and colleagues reported good success with this technique in a Crohn's population with 14/20 (70%) undergoing successful repairs [6]. Lowry had success in 22 of 25 patients who underwent a combined sphincteroplasty and endorectal advancement flap (88%), which was an improvement over the 78% success with advancement flap alone [17]. Hull and associates reported success in 39/50 patients who underwent a transperineal repair (78%) [20]. Of note, patients with Crohn's disease were excluded. Important in this study is they found that the rate of post-repair incontinence was only 8%, as compared to 38% in those undergoing endorectal advancement flaps. A transperineal repair with sphincteroplasty is the most appropriate type of repair in women who have a sphincter defect (most often from obstetric injury), as this is addressed simultaneously.

Following repair, some authors advocate placement of a biologic graft to separate the vagina and rectum. Ellis described a transperineal repair with a graft made from porcine intestinal submucosa placed in the rectovaginal septum [18]. He reported an 81% success (22/27). The available data for transperineal repairs is summarized in Table 16-3.

Tissue Transposition Repairs

Tissue transposition repairs offer the advantage of interposing healthy, well-perfused tissue between the rectum and vagina. They add bulk to the rectovaginal septum and physically increase the distance between the rectum and vagina, and by bringing their own blood supply may aid in healing. These types of repairs have the highest success rate of all transperineal repairs; however, these repairs may be accompanied by pain, delayed healing, and unsatisfactory cosmesis at the donor site.

Patients that are appropriate candidates for transposition repairs are those who have failed less invasive techniques or who have inadequate native tissue. Due to the complexity of the operation, fecal diversion is generally performed prior to or at the time of surgery. The operation is most often conducted jointly by the colorectal surgeon and a plastic surgeon. Colorectal surgeons trained in these techniques may perform the entire operation. The labial fat pad with bulbocavernosus muscle (Martius flap) or gracilis muscle transposition are the most commonly used tissues for transposition and are reviewed here. Use of other muscles including the sartorius and gluteal muscle has also been described. The choice of a Martius flap versus gracilis muscle for the donor tissue is based on the desired bulk of tissue and individual surgeon experience.

Martius Flap

The Martius flap was initially described by Dr. Heinrich Martius in 1928 and uses the bulbocavernosus muscle and labial fat pad for transposition [27]. The technical details of the operation are well described by Kniery et al. in 2015 [28]. The initial incision is made in the vaginal introitus distal to the fistula opening in order to expose the rectovaginal septum. Dissection continues in the rectovaginal septum cephalad to the fistula (Figure 16-9). The fistula tract is curetted and closed primarily on the rectal side. The vaginal portion of the fistula is excised from the vaginal flap. In order to harvest the donor tissue, a vertical incision is made in the labia majora (Figure 16-10). The labial fat pad and underlying bulbocavernosus muscle are dissected out from the surrounding tissues. The amount of muscular tissue varies from patient to patient and may not be visible in some. The blood supply to the flap comes in inferiorly and posteriorly from the posterior labial vessels. Dissection ensues in a lateral to medial direction taking care not to injure the blood supply. The flap is transected superiorly and tunneled to the rectovaginal septum. It should be rotated carefully so as not to kink the blood supply (Figures 16-11 and 16-12). The flap is laid within the RV septum and the vaginal flap sutured over the Martius flap (Figure 16-13). Figure 16-14 shows

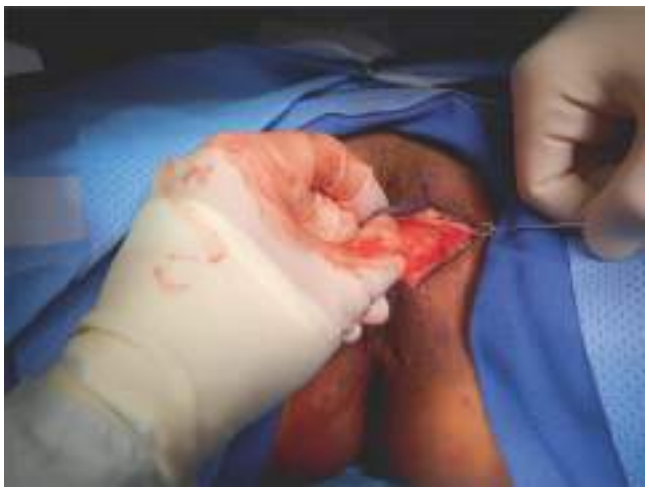

FIGURE 16-10. Martius flap repair. Incision over the left labia majora to expose the fat pad and bulbocavernosus. Courtesy of Drs. Eric Johnson and Scott Steele.

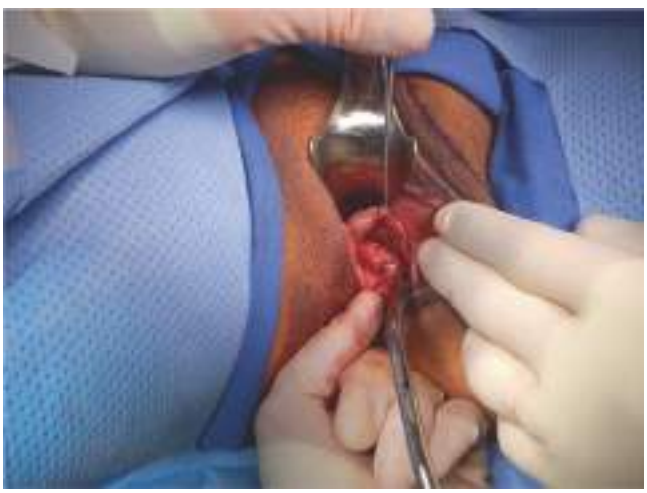

FIGURE 16-9. Martius flap repair. The vaginal flap has been raised revealing the rectovaginal fistula. Courtesy of Drs. Eric Johnson and Scott Steele.

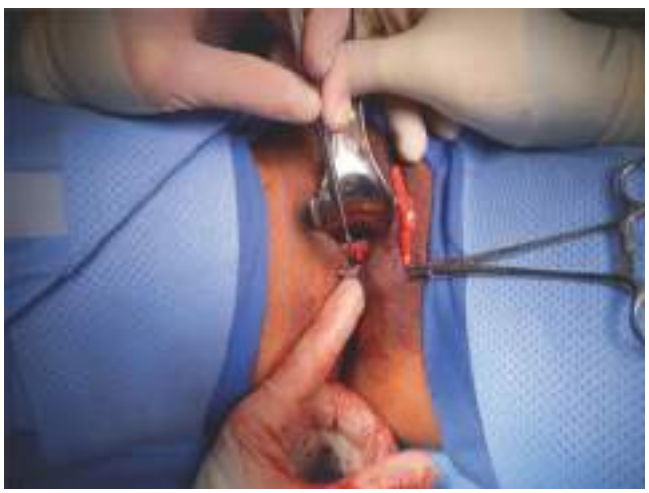

FIGURE 16-11. Martius flap. A tunnel is created from the origin of the bulbocavernosus to the vaginal incision. Courtesy of Drs. Eric Johnson and Scott Steele.

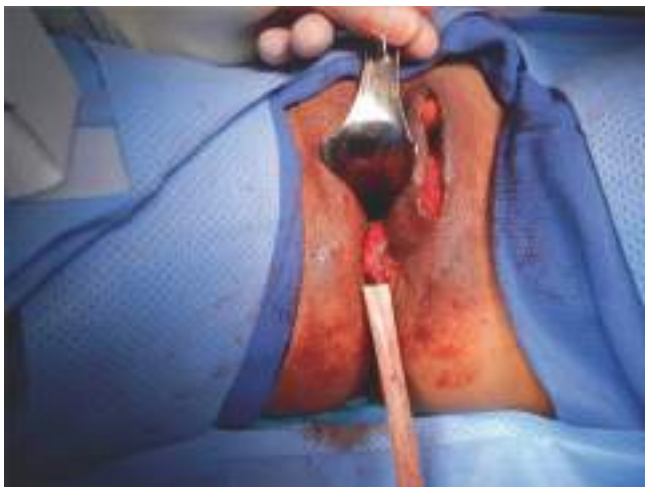

FIGURE 16-12. Martius flap. The donor tissue has been brought into the rectovaginal septum. Courtesy of Drs. Eric Johnson and Scott Steele.

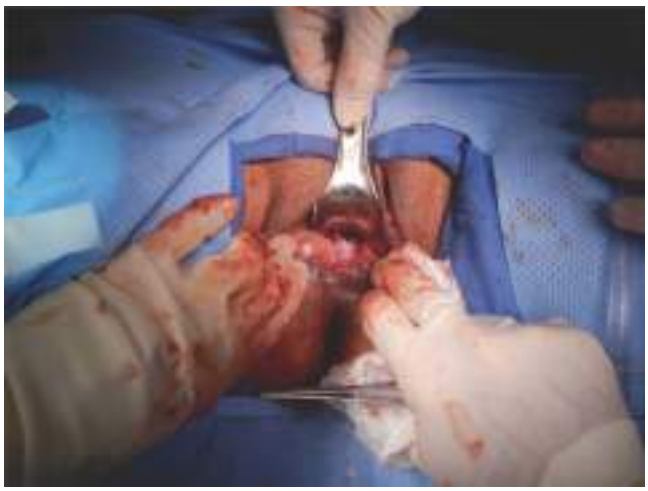

FIGURE 16-13. Martius flap. The vaginal incision has been closed over the Martius flap. Courtesy of Drs. Eric Johnson and Scott Steele.

the postoperative appearance. The authors report successful healing in 3/5 patients, all of whom had failed previous repairs. The largest case series using the Martius flap was published by Pitel et al. in 2011 [29]. They reported a 65% success rate in 23 patients. Other small case studies report success rates ranging from 92 to 100% [27, 30–34]. Complications are rare but include local wound dehiscence and dyspareunia. The available data is summarized in Table 16-4.

Gracilis Muscle Transposition

Repair using a gracilis muscle transposition offers the advantage of providing a large bulk of well-vascularized muscle to separate the vagina and rectum. Its origin is near the perineum, which makes it a convenient donor. It is, however,

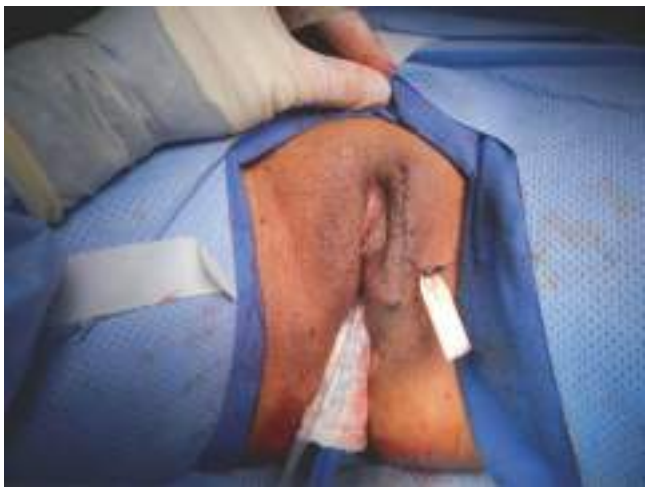

FIGURE 16-14. Appearance after the Martius flap. Courtesy of Drs. Eric Johnson and Scott Steele.

TABLE 16-4. Martius flap

Author	Year of publication	No. of patients	No. of successful closures (%)
White [27]	1982	14	13 (93)
Aartsen [30]	1988	14	13 (93)
McNevin [31]	2007	16	15 (94)
Songne [32]	2007	14	13 (93)
Pitel [29]	2011	23	15 (65)
Kniery [28]	2015	5	3 (60)

associated with higher morbidity due to the mobilization and transposition of this large muscle. Success rates are quite promising, and this repair should be considered in patients who have had multiple recurrences or poor native tissue. Fecal diversion is generally performed prior to or at the time of the procedure.

The operation involves a transperineal incision, in which the rectum and vagina are separated. The fistula is divided and both the rectum and vagina are closed primarily. Dissection should continue cephalad to the fistula until healthy tissue is reached. An endorectal advancement flap can be added to the procedure as well. The perineal incision created is seen in Figure 16-15 and does not differ from that in other transperineal approaches. The gracilis muscle is then harvested. This can be performed with a long incision the length of the gracilis, or with separate smaller incisions near the muscle's origin and insertion. The muscle is mobilized with division of the perforating vessels. It is divided just above its insertion. It is tunneled from the proximal-most portion of the incision to the perineal incision, as seen in Figure 16-16. Care must be taken that the flap is not rotated excessively and its blood supply not kinked. The muscle is secured to the apex of the rectovaginal dissection and the transperineal incision closed, as seen in Figure 16-17. Reported success rates range from 47% [35] to 92% [35, 36]. The largest

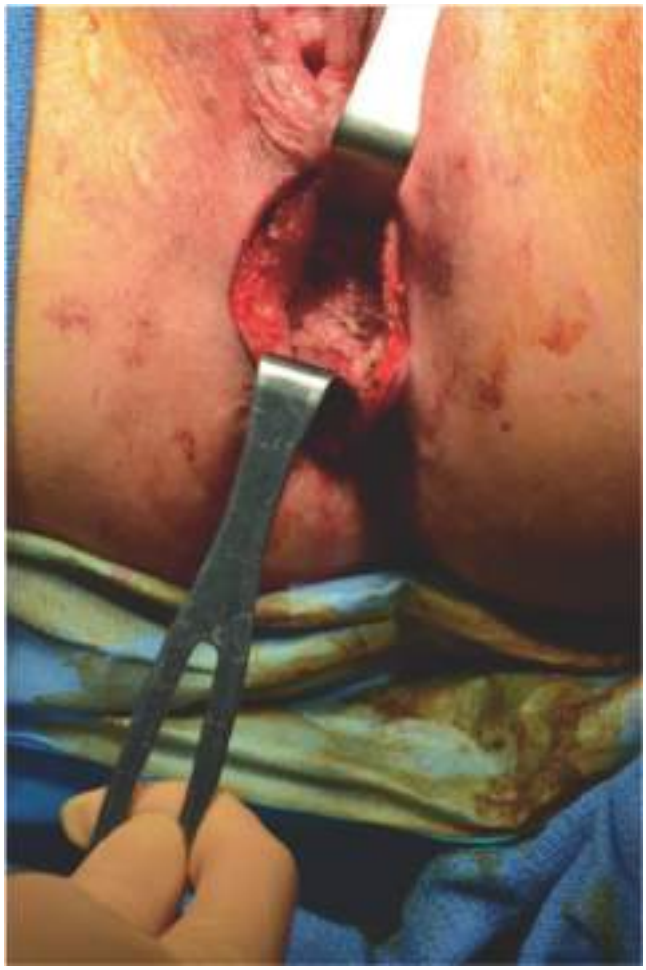

FIGURE 16-15. Gracilis transposition. A transperineal incision is made to separate the rectum and the vagina. Courtesy of Drs. Jamie Cannon, Andre Levesque, and James Long.

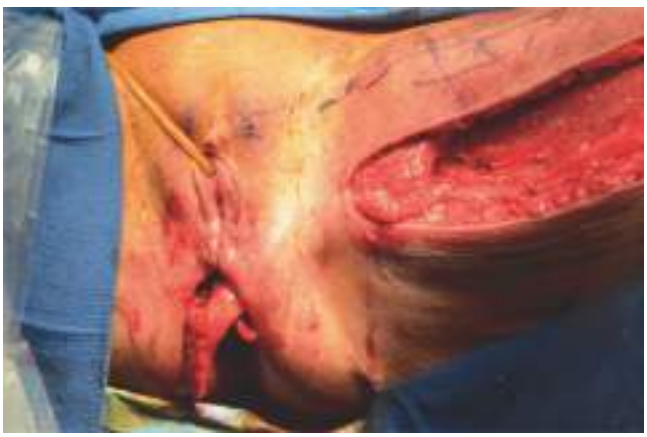

FIGURE 16-16. Gracilis transposition. The gracilis muscle has been tunneled from the left thigh to the transperineal incision. Courtesy of Drs. Jamie Cannon, Andre Levesque, and James Long.

series was published by Pinto et al. [15]. They reported a 79% success in 24 patients. Table 16-5 summarizes the available data.

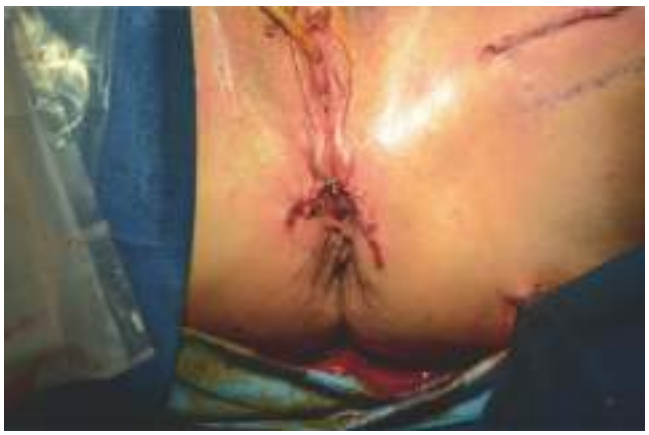

FIGURE 16-17. Gracilis transposition. Postoperative appearance. Courtesy of Drs. Jamie Cannon, Andre Levesque, and James Long.

Transvaginal Repairs

Transvaginal repairs are infrequently reported in the literature and usually found more often in the gynecologic literature than the colorectal literature; however, there is good evidence that repair through the vagina has acceptable success rates. Proponents of a transvaginal repair emphasize the relative ease and better exposure gained through the vagina as compared to the anus. The initial incision is usually made in healthy tissue, as the origin of disease is on the rectal side. However, as the rectum is the higher-pressure side of the fistula, any repair is unlikely to be successful if the rectal side is not addressed. Therefore transvaginal repairs should involve closure of the rectum and not just of the vagina.

Sher et al. report on the use of a transvaginal flap for Crohn's-related RVF [37]. They describe their technique, which is quite similar to an endorectal advancement flap. An incision is made in the vagina distal to the fistula. A flap is raised exposing the rectovaginal septum. Both the rectal and vaginal side are closed. The levators are approximated in the midline in between the repair. The fistula is then excised from the vaginal flap and the flap is sutured in place over the repair. In their study, all patients had fecal diversion and they reported that 13/14 patients healed (93%).

Transabdominal Repair

Transabdominal repairs are generally reserved for fistulas that are located in the mid-rectum with an internal opening at the fornix of the vagina, as these are difficult to access from a perineal or endoluminal approach. Transabdominal repair generally involves a low anterior resection, where the segment of rectum containing the fistula is resected and a colorectal or coloanal anastomosis performed. Depending on the height of the fistula, this may be done transabdominally only, or with a transabdominal transanal (TATA) approach and colonic pull-through. The vaginal side of the defect can be closed primarily.

Table 16-5. Gracilis muscle transposition

Author	Year of publication	No. of patients	No. of successful closures (%)
Furst [36]	2008	12	11 (92)
Wexner [35]	2008	17	9 (53)
Lefevre [52]	2009	8	6 (75)
Pinto [15]	2010	24	19 (79)

Van der Hagen and colleagues reported their experience with a transabdominal approach where a formal resection was not undertaken [38]. They laparoscopically separated the rectum and vagina and repaired each primarily. The omentum was mobilized and laid in between the rectum and the vagina. They reported successful repair in 38/40 patients. The same approach was described by Chu and associates who reported success in 6/6 patients [39]. Mukwege reported similar successful results using a laparoscopic transabdominal approach in ten patients [40]. While techniques differed from patient to patient and included traditional LAR, TATA, and fistula excision with omentum interposition, overall 9/10 repairs were successful.

Alternate Repairs

A variety of alternate techniques exist as well. The use of a fistula plug has been described but should be limited to those with a long-tract RVF. Ellis reported their protocol, which is to use a plug as first-line treatment if the length of the RVF is 1 cm or greater [18]. The plug is brought from the rectal to vaginal side, excess length on the plug is trimmed, and it is sutured in place with absorbable suture. He noted success in 6/7 patients with this technique (86%). Gajsek et al. also reported on plug use with 4/9 repairs being successful (44%) [41]. Failures were treated with repeat plug placement, but none of the repeat procedures were successful. Weerd et al. described the successful injection of fat into the tissue surrounding the fistula in a very small case series [42]. D'Ambrosio performed the repair via a transanal endoscopic microsurgical (TEMS) approach and reported success in 12/13 patients undergoing this procedure [43].

Choice of Technique for Repair

The number of types of repairs discussed above demonstrates that a one-size-fits-all approach is not practical. It is also reflective of the fact that this is a difficult condition to treat.

In deciding on a surgical approach, the surgeon should evaluate the patient for continuing inflammation or ongoing pelvic sepsis. These must be controlled prior to surgical repair or the chance of success is dismal. Ongoing pelvic sepsis should be managed with abscess drainage, antibiotics, and seton placement until resolved. The patient is reassessed 6 weeks after seton placement to confirm the sepsis has resolved. If there is evidence of residual abscess or branching fistula tracts, these must be addressed. Once a mature isolated fistula tract is present, definitive repair can be considered.

Treatment with anti-TNF agents should be considered preoperatively in all patients with Crohn's disease. If active Crohn's disease persists, the patient should undergo medical management and possible temporizing measures rather than attempting to cure the fistula. Seton placement is ideally suited. Not all patients with Crohn's disease and RVF will be candidates for repair. Repair should be considered for those who develop a mature isolated tract without branching, without other draining areas, and with healthy rectal mucosa. If this is not possible, non-cutting seton placement can be a long-term method of controlling symptoms. Proctectomy is considered for those with severe disease refractory to seton placement and maximized medical therapy. The presence of an anal stricture with quiescent disease is not a contraindication for repair, as the stricture can be addressed simultaneously with the fistula with endorectal techniques such as flap construction or sleeve advancement [44–65]. A portion of the circumference of the stricture can be removed along with the fistula when an endorectal advancement flap is performed. If this does not result in correction of the stricture, a sleeve advancement with circumferential resection of the stricture is an alternative option.

The surgeon must also decide whether preoperative diversion is indicated. As discussed above, diversion has not been shown to decrease the rate of fistula recurrence, although this may well be because the patients that undergo fecal diversion have more complicated disease. The surgeon should estimate the likelihood of success with the repair chosen, as well as the magnitude of the operation. When low rates of success are anticipated (e.g., multiple prior repairs, poor tissue compliance), preoperative fecal diversion should be considered. This is not generally necessary in the repair of simple rectovaginal fistulas. Patients undergoing major transabdominal resections, or muscle transposition procedures, should have fecal diversion.

The anatomic location of the fistula will dictate a local repair versus a transabdominal approach. Fistulas located in the mid-rectum and upper vagina will not be accessible via a local approach and should therefore be managed with a transabdominal approach.

For local repairs, the quality of the patient's tissue should be assessed. If the patient's tissues are healthy, have normal compliance, and lack scarring, an endorectal advancement flap is an appropriate first approach. If the RVF is secondary to obstetric injury, endorectal ultrasound is used to determine if a sphincter defect is also present. If a sphincter defect is identified, a transperineal repair with sphincteroplasty is performed simultaneously. The chance of success with an advancement flap decreases with each attempt at repair;

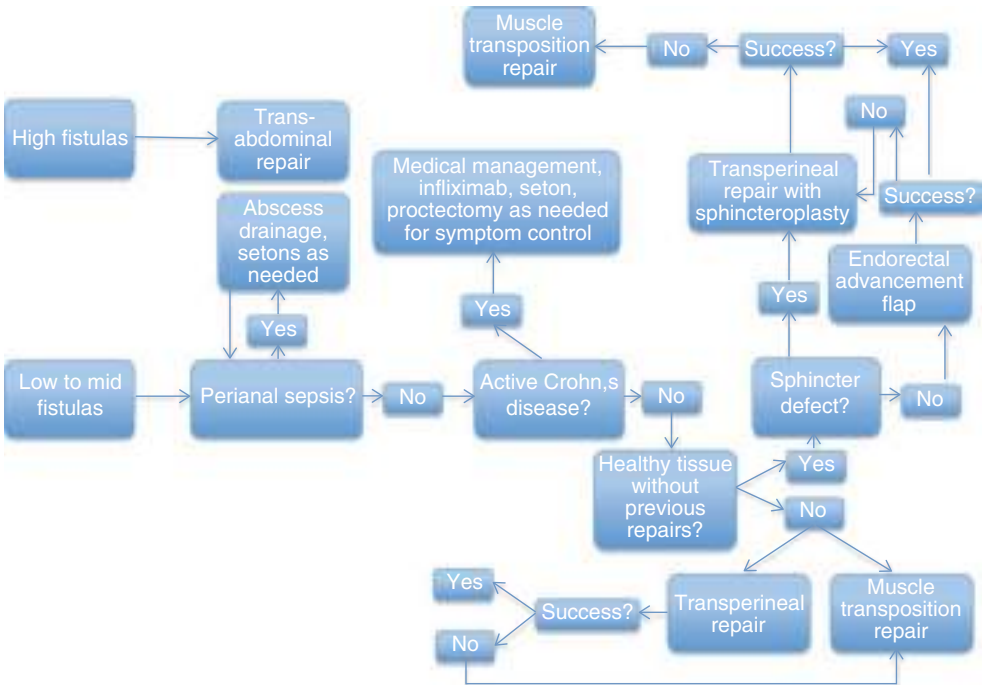

FIGURE 16-18. Algorithm for management of rectovaginal fistulas.

therefore a transperineal approach should be considered in those who have failed previous endoanal advancement flaps. For either endoanal advancement flaps or transperineal repairs, the surgeon may also consider the use of biologic grafts to reinforce the repair. If the local tissues are not adequate for repair, then transposition of healthy tissue should be considered. The most common tissues used for transposition are the Martius flap or gracilis muscle. Figure 16-18 provides an algorithm that summarizes the above recommendations.

Conclusions

Rectovaginal fistulas are distressing conditions to patients and present a therapeutic challenge to surgeons. Whether the etiology of the fistula is obstetric, Crohn's related, or cryptoglandular, a thorough evaluation of the patient's anatomy is required in order to select the right repair. While not all patients will be candidates for surgical repair, the majority of patients will eventually undergo successful treatment of their RVF. Familiarity with the various surgical techniques described and the ability to apply the appropriate surgery to the right patient will increase the chance of a successful intervention.

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17
Pilonidal Disease and Hidradenitis Suppurativa

Eric K. Johnson

Key Concepts

- Pilonidal disease presents with a wide range of symptoms and multiple treatment options exist. Treatment should be tailored to the severity of disease, anatomy of disease, and patient expectations.
- Because of the wide array of available surgical options, the surgeon treating pilonidal disease should master 3–4 approaches that are applicable to a wide range of disease presentations.
- Treatments applied to both pilonidal disease and hidradenitis suppurativa should not be more disabling for the patient than the disease itself.
- There are numerous medical options available to treat hidradenitis suppurativa. They should be investigated and attempted prior to aggressive radical surgical management.
- Radical excision of hidradenitis suppurativa with surgical reconstruction offers the best hope to avoid disease recurrence.

Background

The term "pilonidal" is derived from the root words "pilus" (a hair) and "nidus" (nest). Since 1880 when Dr. R.M. Hodges coined the term pilonidal sinus [1], the diagnoses of pilonidal cyst, sinus, and abscess have been used interchangeably and somewhat indiscriminately to mean the same thing, though they most certainly do not—in the case of abscess. It is largely for this reason that the more modern nomenclature of "pilonidal disease" (PD) is used to describe the spectrum of disorders that may be encountered. The first published description of this disease occurred in 1847 when Dr. A.W. Anderson described a case of "hair extracted from an ulcer" [2]. The first pilonidal abscess was described in 1854 [3], though there is no question that this condition was encountered earlier. It wasn't until World War II that surgeons became much more familiar with this disease entity, likely because of the large number of cases seen in members of the military. In fact, the disorder was known as "jeep disease" and was thought to be related to modern mechanized warfare, which required soldiers to ride in vehicles for extended periods of time [4].

It is clear from early publications that little has changed in terms of the issues that confront both the patient and surgeon. A 1955 publication from the Veteran's Administration health system reveals that the debate over open and closed wound management is not new [5]. In this study, patients managed with primary wound closure developed recurrence 40% of the time and required hospital stays of approximately 17 days, while those managed with open technique stayed for 30 days and had a recurrence rate of 35%! While we have seen significant reductions in both length of hospital stay and recurrence, it is clear that we still do not have the ideal answer for this condition.

Etiology

There has been considerable debate over whether PD is congenital or acquired, but most would currently agree that it is an acquired disease. It is generally believed that the initiating event is traumatization of the skin and surrounding hair follicles in the natal cleft. This occurs secondary to trapping of hairs, not necessarily those arising locally in the natal cleft. The local anatomy creates an unfavorable environment where friction, warmth, moisture, and perhaps local hypoxia lead to local trauma secondary to the barbed texture of the hair. A granulomatous foreign body-type reaction results. There is even some histological and immunohistochemical evidence that PD may represent a unilocalized type of hidradenitis suppurativa [6]. Disease typically begins as

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a small sinus that may drain fluid but then can progress to numerous sinuses with associated cystic dilation and potential abscess formation. In some cases, unless the process is interrupted, it can become more widespread leading to worsening symptoms. Disease can range from the asymptomatic single sinus found incidentally up to a severe locally destructive process associated with significant disability.

PD is not limited to the natal cleft area, and there are several reports of disease occurring in the interdigital areas in hair dressers [7], as well as in other areas such as the umbilicus [8]. The presence of disease in these atypical areas further supports the above theory. PD has been reported to affect males more commonly than females; however recent data from the armed forces suggests that the incidence rates are similar at 1.9 and 1.7 per 1000 person-years, respectively [9]. There are several risk factors that have been implicated in the development of PD including positive family history of disease, elevated body mass index (BMI > 25), poor hygiene, hirsutism, deep natal cleft anatomy, occupation that requires prolonged sitting, and excessive sweating [10–12]. It is not uncommon to see disease affect an individual who lacks many or most of these factors however. A prospective study comparing 587 patients with PD to 2780 healthy controls showed that hirsute individuals that sit down for more than 6 h per day and who bathe two or fewer times per week have a 219-fold increased risk for sacrococcygeal PD [12]. A positive family history may not only predispose to disease occurrence, but may also be associated with increased recurrence rates after surgery as well as earlier onset of disease [11].

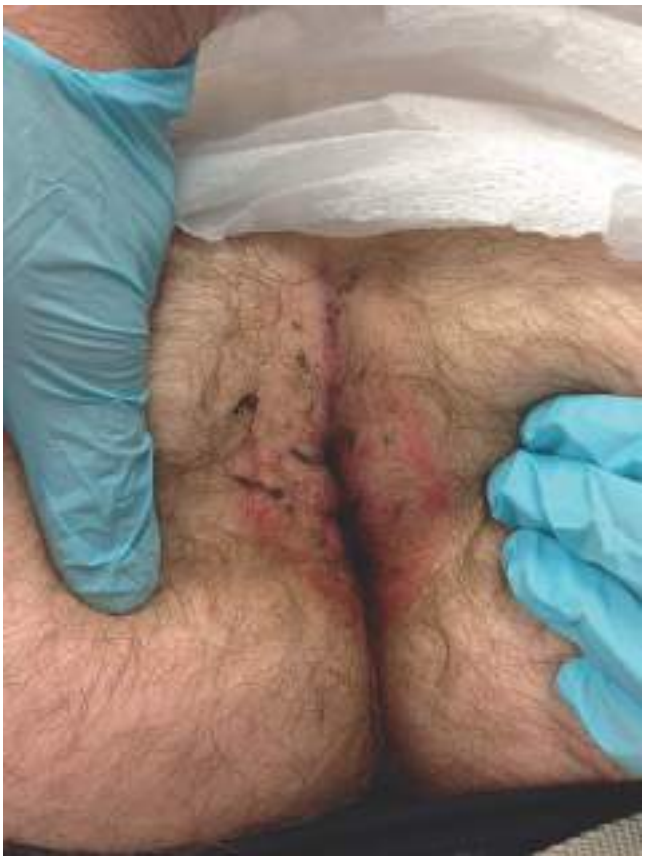


FIGURE 17-1. This image shows a hirsute individual with midline "pits" that could go unnoticed. Note the poor hygiene.

Clinical Presentation/Diagnosis

Patient presentation can range from a referral for completely asymptomatic and incidentally discovered disease to a person who is significantly disabled by locally destructive disease. Commonly encountered scenarios are the patient who has an acute pilonidal abscess that requires drainage, and the surgical office visit to discuss definitive surgical therapy after either acute abscess drainage or persistent disease of moderate severity impacting the patient's quality of life. Often, in the military setting, disease that would otherwise be ignored requires operative management secondary to its impact upon an individual's ability to perform at a high physical level or live in an austere environment.

Establishing a diagnosis is rather simple and does not require extensive testing or imaging. Simple history taking and a physical exam will in most cases solidify the diagnosis. Patients will often complain of pain over the sacrococcygeal area with drainage of clear fluid or bleeding. In the case of acute abscess, fever may also occur. Physical exam will reveal "pits" in the midline. There may be several pits, or only one small pit that could be easily overlooked if the examiner does not consider this diagnosis (Figure 17-1). Examination may also often reveal induration just lateral to midline that can be unilateral or bilateral. This may also be associated with additional draining sinuses. In more significant cases, there may be open wounds that can have a large range in size (Figure 17-2a–c). Acute abscess is typically associated with overlying erythema, fluctuance, and severe local tenderness (Figure 17-3). In a less common scenario, the examiner may mistake PD as an anorectal fistula if a sinus is present close to the anus. It is important to examine the midline overlying the sacrum for pits. If they are present, then pilonidal sinus should be included in the differential diagnosis in these individuals (Figure 17-4a, b).

Recurrent disease in the patient who has already undergone surgical excision is another commonly encountered scenario (Figure 17-5). Recurrence may occur either early (within 1 year) or late. Early recurrence is often actually persistence of an open wound that never healed after surgery. This may be thought of as PD, but in many cases is actually nothing more than a non-healing midline sacrococcygeal wound. Wounds placed in the midline often demonstrate delayed healing or non-healing. The pathophysiology related to a non-healing wound may actually be different than that related to PD; however the methods we use to treat these maladies are similar. Recurrence presents similarly to primary PD, and may be related to poor surgical technique,

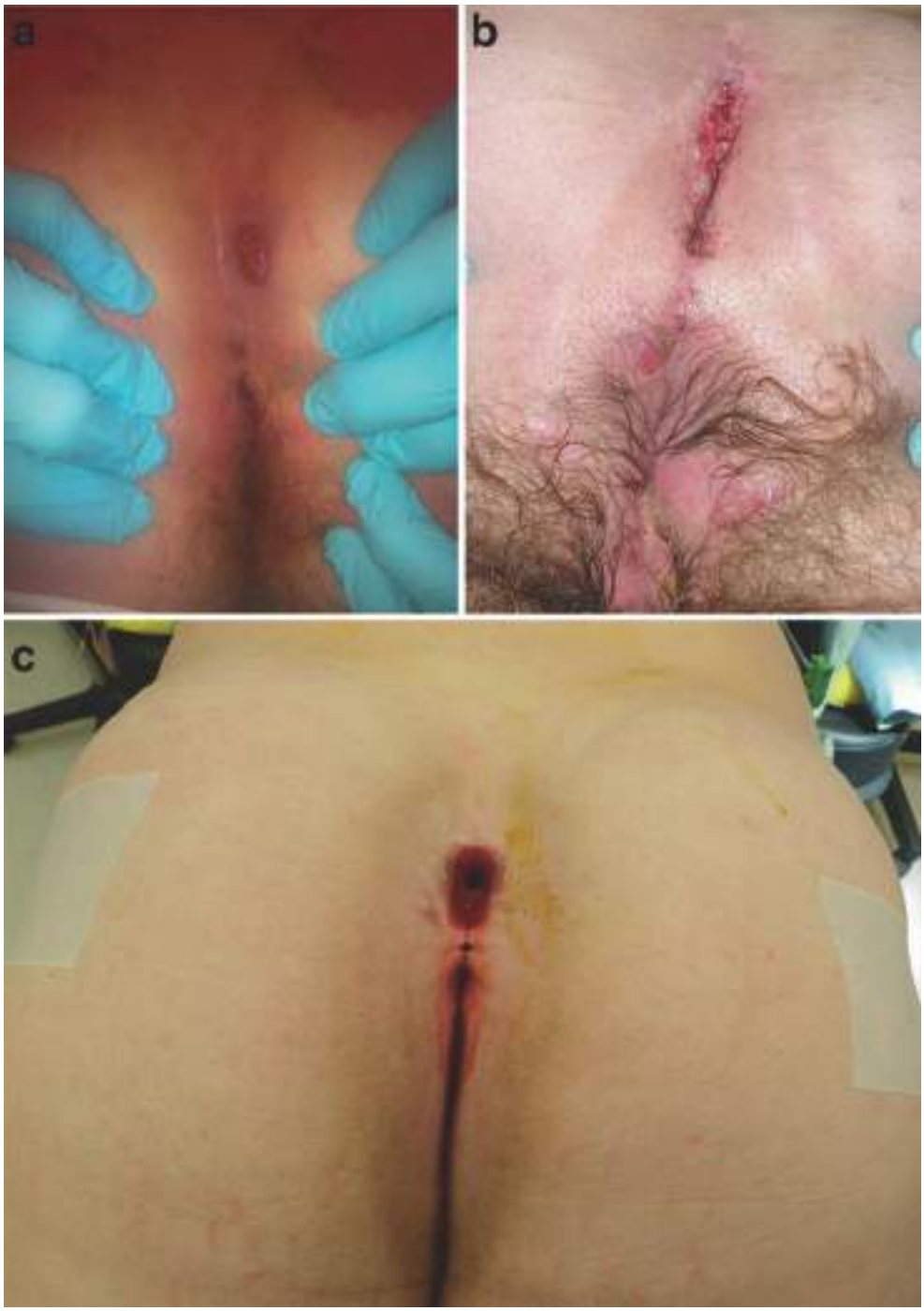


FIGURE 17-2. (**a**–**c**) These images show a range of open wounds that may be seen with pilonidal disease.

patient noncompliance, or failure to modify the pre-existing risk factors that led to disease in the first place. Recurrence may also simply be the natural history of disease.

Treatment

There are numerous treatment options available to address PD. An important overriding concept that should be completely clear is that the treatment should be tailored to the patient's expectations, disease anatomy, and disease severity. Options range from nonoperative therapies up to wide local excision with local flap reconstruction. The debate of open wound management versus closed management remains, and even when primary closure is performed, wound care and physical limitations may be required for an extended period of time. Given the large number of operative choices available, it is likely not practical to be well versed in all. A good recommendation would be to be familiar with three or four operative options that range from simple to complex and provide a solution for several different anatomic configurations of disease.

Nonoperative Management

It is first important to recognize when PD requires no invasive management at all. As stated earlier, some patients are referred based simply upon the incidental finding of midline pits in the natal cleft. If the patient is asymptomatic, and physical examination reveals no concerning findings, they require no operative management. You never want the treatment to be worse than the disease, and that is exactly what one will discover in this setting. The patient may still benefit from counseling regarding ways to reduce their risk of developing symptomatic disease. Risk factor modification such as weight loss, avoidance of prolonged sitting at work, improved hygiene, and weekly clipping of hair in and adjacent to the natal cleft may reduce the chance that a patient will develop symptoms related to PD. These are also appropriate in the setting of active and symptomatic disease. These measures may lead to either improvement in symptoms or quiescence in mild cases. A study published in 1994 showed that these measures combined with limited lateral incision and drainage in the setting of acute abscess led to fewer occupied hospital bed days when compared to excisional procedures [13]. Over a 17-year follow-up, only 23 of 101 cases went on to require excisional therapy.

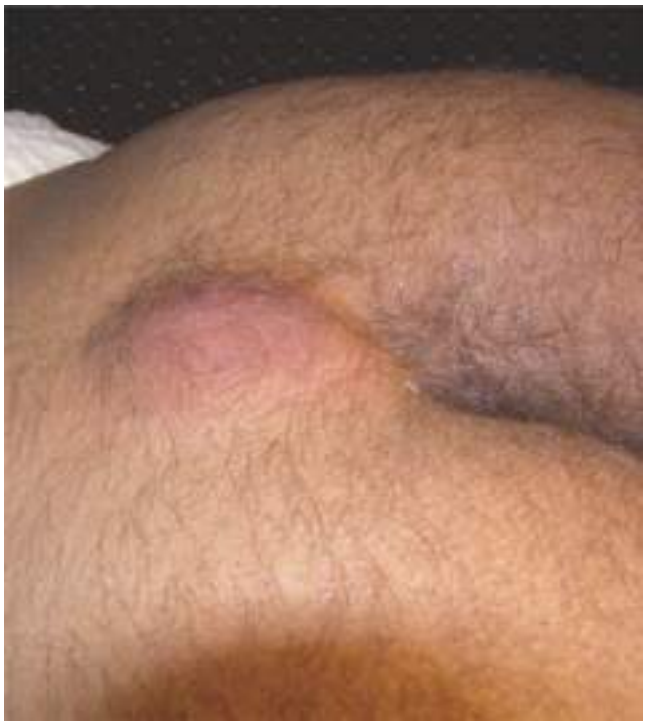


FIGURE 17-3. This image depicts an acute pilonidal abscess.

Given that weekly shaving has been associated with success, many have advocated laser hair removal as a long-lasting alternative for the conservative management of PD. Despite the interest in this mode of therapy, we lack any robust data to support its use. Small studies of 6–14 patients have shown some benefit to laser epilation in the setting of recurrent PD [14, 15]. This procedure is uncomfortable for the patient and often requires local anesthetic. Treatments are performed over 3–11 sessions at 6–8-week intervals and can be quite costly. A study of laser epilation in teenagers with PD, 25/28 of which were managed initially with surgery, showed only one recurrence over a mean follow-up of 2 years [16]. The authors concluded that use of the laser was a safe method for addressing intergluteal hair that may reduce recurrence rates.

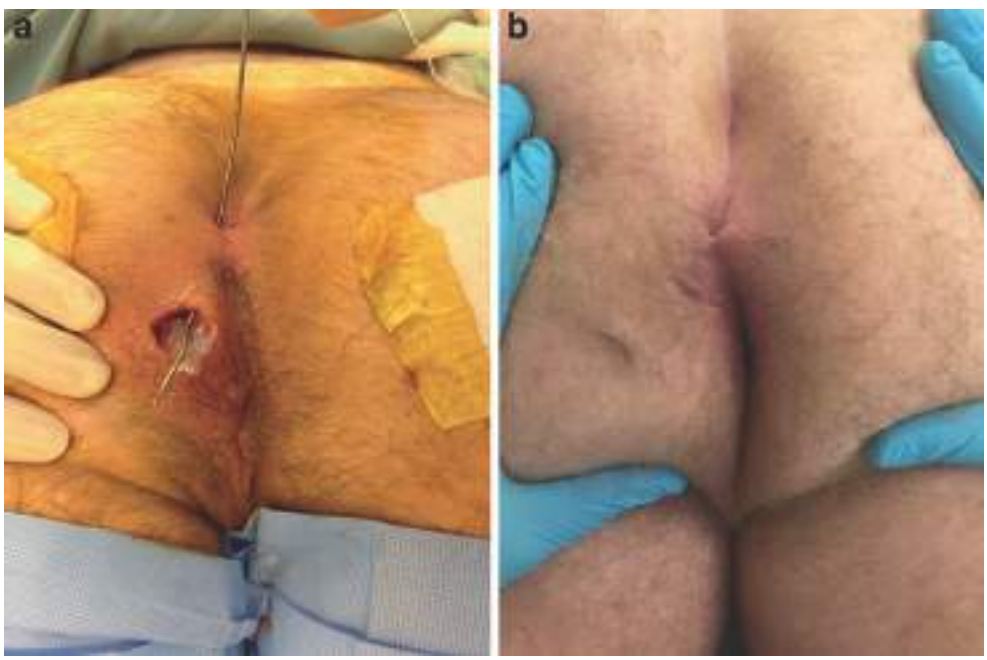


FIGURE 17-4. (**a**, **b**) These images show two different patients that presented with draining perianal sinuses. Note the midline pits over the sacrum that make one more suspicious of pilonidal disease as the cause.

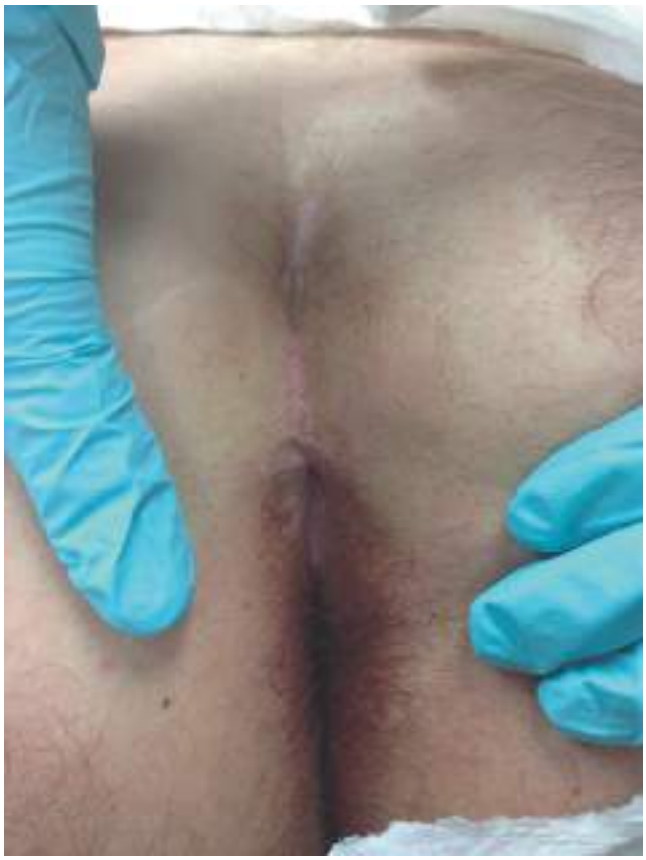


FIGURE 17-5. This image shows a patient who developed recurrence after an attempt at a cleft lift procedure. Incorrect performance of the distal portion of the procedure may have led to this recurrence.

A randomized trial comparing laser hair removal to traditional methods as an adjunctive therapy after surgery for PD demonstrated a lower recurrence rate in the laser-treated group [17]. This appeared to be related to noncompliance with traditional hair removal methods after 1 year. There is however some debate over the benefit of hair removal in the setting of PD that has been managed operatively. A retrospective analysis of patients that had undergone surgery to treat PD was performed with focus on those who performed razor hair removal vs. those that did not [18]. Recurrence was observed in 30% of those who shaved vs. 19% of those who did not shave ($p=0.01$). This would suggest a potential negative effect of postoperative razor epilation. Future studies should likely focus on a comparison between laser hair removal and no hair removal in the adjunctive setting.

While some form of hair removal may lead to reduced recurrence rates as well as reduced requirement for excisional therapy, this method alone is unlikely to lead to disease cure—especially in the setting of more significant or severe disease. Often the hair that is found inside of sinus tracts is clearly noted to be long hair from other parts of the body. It is theorized that longer hairs can fall into the natal cleft, become trapped, and result in disease. Clearly, local epilation alone will not eliminate this threat.

Although not necessarily considered nonoperative (maybe non-excisional) therapy, methods employing the use of phenol or fibrin glue injection to ablate sinus tracts have been investigated in small series by many [19–26]. These techniques often employ tract curettage, debridement, and hair removal, which contribute significantly to success. Use of phenol as an ablative agent has been associated with success rates of 60–95% [19–21]. Fibrin glue injection combined with a variety of techniques has shown success in the range of 90–100% [22–25]. A recent evaluation of individuals treated with fibrin glue revealed that 79% of patients were satisfied, 71% were back to normal activities within 2 weeks, and 74% required no further treatment [26]. A video-assisted ablative technique has also been described using a 4 mm rigid hysteroscope with a five french working channel [27]. Continuous irrigation is used, hair is removed, and the cavity and tracts are ablated using a bipolar electrode. Only one recurrence was detected over 12 months in 27 patients. This may represent a potential option for minimally invasive/non-excisional therapy. The potential advantages of these therapies over excisional methods are more rapid recovery and less post-procedural pain.

Operative/Excisional Management

There are numerous methods available for the operative management of PD. The literature is filled with a large number of publications reporting results from various procedures. The typical manuscript is a retrospective review examining the results from a small series of patients that have undergone one specific type of operative procedure. There are several randomized trials comparing one surgical method vs. another with variable results. Essentially, it is possible to find evidence to support whatever procedure one prefers to perform. Results are likely related to variations in how patients are cared for postoperatively as well as differences in surgical technique. It is best to review some of the more common methods of operative management beginning with those that are considered simple and progressing to the complex. A well-prepared surgeon will be familiar with most of these methods, and will tailor their management to disease severity, disease anatomy, and patient expectations.

Basic Procedures

Outside of incision and drainage of a pilonidal abscess, the simplest procedure to perform is laying open of the cyst and all sinus tracts. This may also be termed "unroofing" of disease. This and wide local excision of all disease down to the post-sacral fascia were the procedures performed most commonly in the early days of PD management. Often, unroofing was combined with marsupialization of the wound. Recurrence rates of 15–35% [5] led many to seek out more effective methods of surgical management. It is important to ensure that as much of the surgical wound as possible be kept

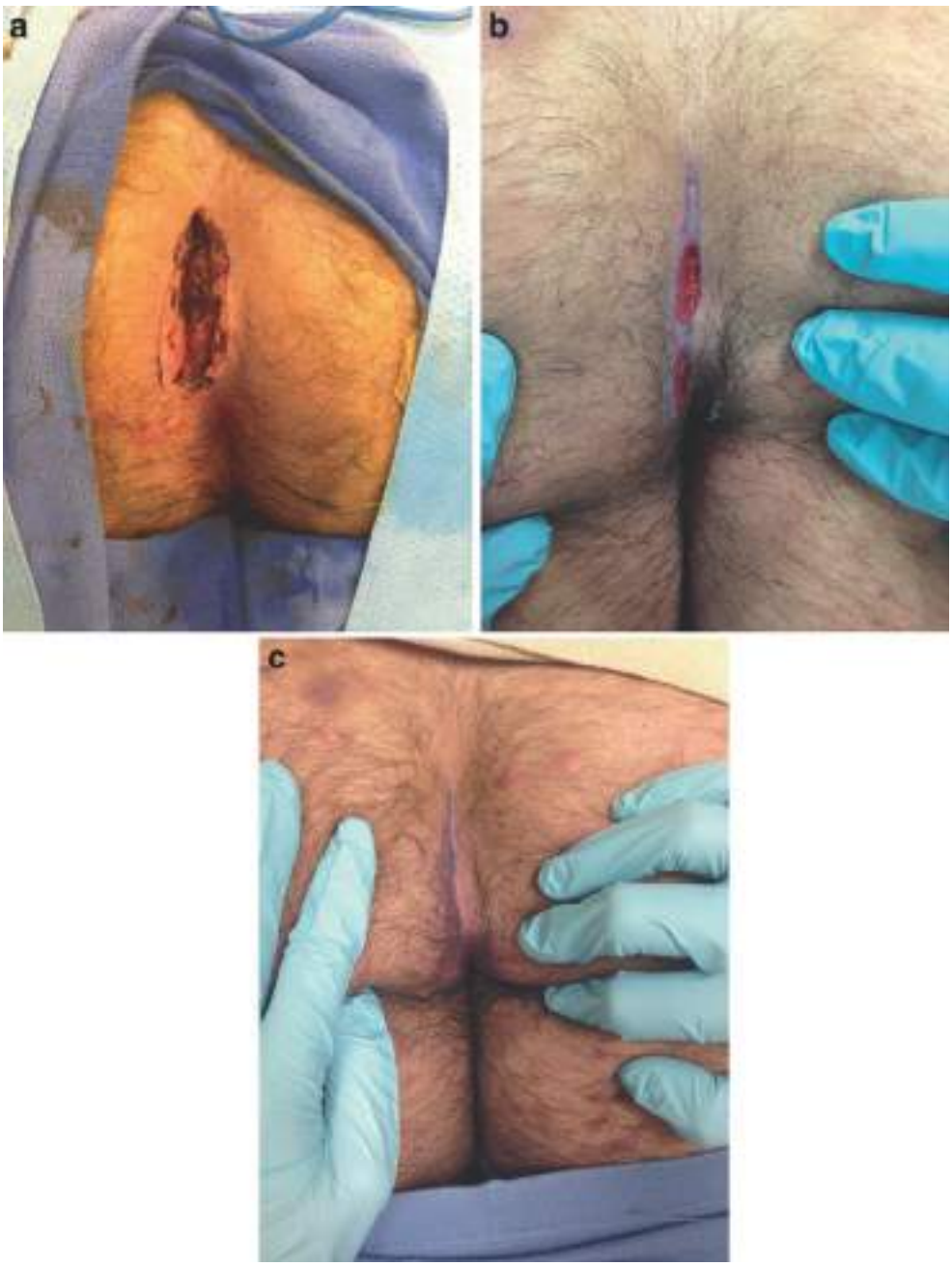


FIGURE 17-6. (**a**–**c**) These images show yet another patient who presented with what was thought to be an anal fistula. Midline pits were noted and the disease was treated with a lay-open technique, which resulted in rapid healing. Of note, this could potentially represent hidradenitis suppurativa.

off the midline, as midline wounds tend to have some difficulty with healing. Simple tract unroofing and curettage are particularly helpful in the setting of minor disease affecting the perianal area (often mistaken as an anal fistula). The bulk of this wound will lie off the midline and will heal quickly (Figure 17-6a–c). There continues to be debate over which approach is superior, though recent data would suggest that a higher volume of excised specimen is associated with a higher surgical site infection rate and likely a higher risk of recurrent disease [28]. The next logical step was to perform excision combined with primary wound closure which can often require the mobilization of minor skin flaps.

Primary closure has been combined with drainage in some settings with a wide variation in results. The use of a drain in this setting has been studied, but has not been shown to result in improved results as far as patient satisfaction, healing, or infection is concerned [29]. A meta-analysis of this subject showed that there were no statistically significant differences in outcomes with or without the use of a drain in the setting of primary wound closure [30]. A recent randomized controlled trial comparing the laying open method to wide excision with primary closure showed that healing occurred faster in the primary closure group with no differences in the groups noted at 1 year of follow-up [31]. Interestingly, this

group of investigators made no effort to keep the majority of the wound off the midline. Rao and colleagues in 2010 published a prospective randomized study comparing the lay-open technique to primary closure augmented by the placement of gentamicin-impregnated collagen [32]. The antibiotic-impregnated material was placed in the base of the wound with overlying tissue closure. The results showed improved healing at 4 weeks, improved postoperative pain, and lower cost in the primary closure group. Recurrence rates were no different at 5 years.

Another group performed a 4-arm randomized trial comparing primary closure, primary closure with hydrogen peroxide irrigation, wide local excision, and wide local excision with hydrogen peroxide irrigation [33]. The wide local excision combined with peroxide irrigation group showed the lowest recurrence rate and the fastest time to healing. The investigators attributed this to the ability to clearly delineate all tracts and disease with peroxide irrigation, allowing them to perform a more precise and low-volume excision. Similarly, another group performed a retrospective analysis of PD patients that had undergone surgery and concluded that use of methylene blue injection to delineate disease was associated with a lower recurrence rate [34].

There have been several descriptions of "pit picking" procedures over the years. These procedures are relatively minor in terms of the amount of tissue excised; they result in small wounds, and may be ideal for those suffering with mild to moderate levels of disease. These procedures are not suitable for the patient with a large open wound or in those with severe recurrent disease. The basic premise of this method is that the central pits are excised with minimal surrounding tissue, hair and debris are removed, the old adjacent abscess cavity or "cyst" is excised through a lateral incision using an undermining technique, the pit excision sites are closed primarily, and the lateral incision is closed partially to allow for drainage. This results in a good cosmetic result with minimal pain, early return to work, and rapid healing (Figure 17-7) [35]. A punch biopsy knife of appropriate size may be used to perform the pit excision and is ideal for this application. This procedure has been modified slightly by many, but the basic tenets remain in the various methods. The use of phenol as a sclerosing agent has been combined with pit excision and has resulted in good outcomes [36].

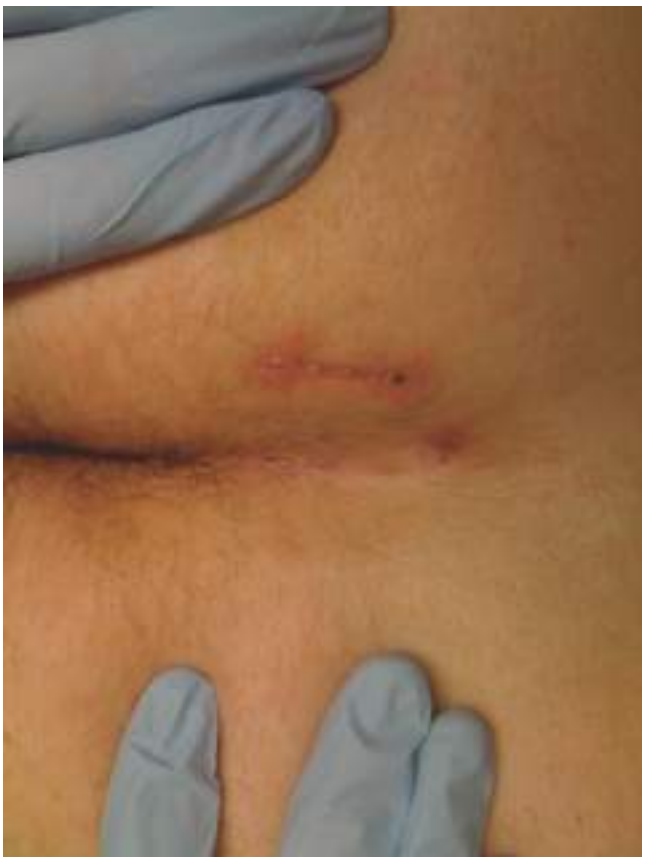


FIGURE 17-7. This image shows a patient 2 weeks after a simple Bascom, or "pit picking" operation.

Complex Procedures

The common thread among all "complex" procedures is the mobilization of adjacent tissue to achieve primary wound closure—in effect, the creation of a local flap. Some of these procedures combine wide local excision of diseased tissue with flap reconstruction, while others preserve as much local tissue as possible. These procedures also range from simple to complex. While there are numerous options, attention will be devoted to the discussion of the Karydakis flap, the Bascom cleft-lift procedure, and the rhomboid or Limberg flap procedure and its modifications. There are additional flap procedures such as the z-plasty, V-Y advancement flap, and other rotational flap techniques that will not be discussed. Many support the use of flap procedures in primary PD, while others believe that they should only be used in the setting of disease recurrence after primary surgery. It is possible that these procedures are more effective in curing disease, because they result in a modification of the natal cleft anatomy. The majority of these techniques result in a flattening of the natal cleft, which may prevent disease recurrence.

Karydakis Flap

This procedure is performed first by excising the affected tissue in the midline, typically leaving an elliptical defect. A beveled skin flap is then created and mobilized across the midline to facilitate a primary closure that is lateral of midline (Figure 17-8). A closed suction drain may be used or omitted. The purported advantages of this procedure are the tension-free closure that is out of the midline coupled with some flattening of the natal cleft. This is probably the easiest flap procedure to perform. This procedure has been shown to be superior to simple primary midline closure in terms of patient satisfaction, recurrence rate, and rate of postoperative complications [37]. It has also been reported to be comparable to other more complex flap procedures such as the modified Limberg flap [38, 39].

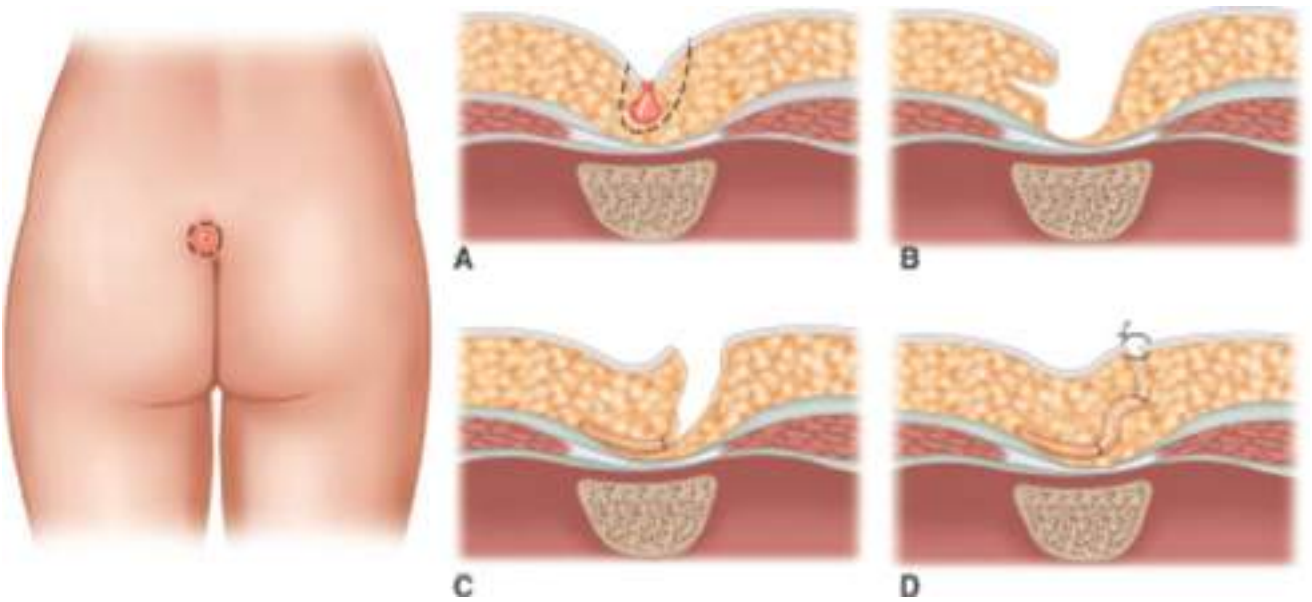


FIGURE 17-8. This drawing depicts one method of performing a Karydakis flap.

Cleft Lift Procedure (See Video 17-1)

The cleft lift procedure was originally described and popularized by Dr. John Bascom, and is often referred to as the Bascom cleft lift. This is a simple but intricate procedure that is designed to "lift" the natal cleft and result in an incision that is closed off the midline. Interestingly, wide excision is not required—in fact, the only tissue that is excised is the overlying skin on one side of the natal cleft. This procedure requires that the patient be marked prior to incision to establish a "safe zone," beyond which no dissection is performed. The patient is placed in the prone position and the buttocks are squeezed together (Figure 17-9). The area where the skin on both sides of the natal cleft touches is marked with a magic marker. This establishes the safe zone. The buttocks are then taped apart exposing the disease (Figure 17-10). After skin preparation, the area to be excised is marked with another marking pen (Figure 17-11). This proposed incision will be partially elliptical and should extend from the midline pits out to one side of the safe zone. The distal portion of this incision is scimitar shaped in order to facilitate closure near the anus without causing local deformity.

Local anesthetic is injected and the incision is made down to the level of the subcutaneous fat. The overlying skin is excised taking care to leave the subcutaneous fat in place. A flap is then raised across the midline out to the opposite safe zone border (Figure 17-12). The thickness of this flap should approximate that of a breast flap that would be created during a mastectomy. When creating the flap down toward the distal portion of the incision (near the anus), the flap should be thicker to prevent dimple formation near the anus. Any disease-related debris or granulation tissue should be gently debrided with a surgical sponge and irrigation with saline

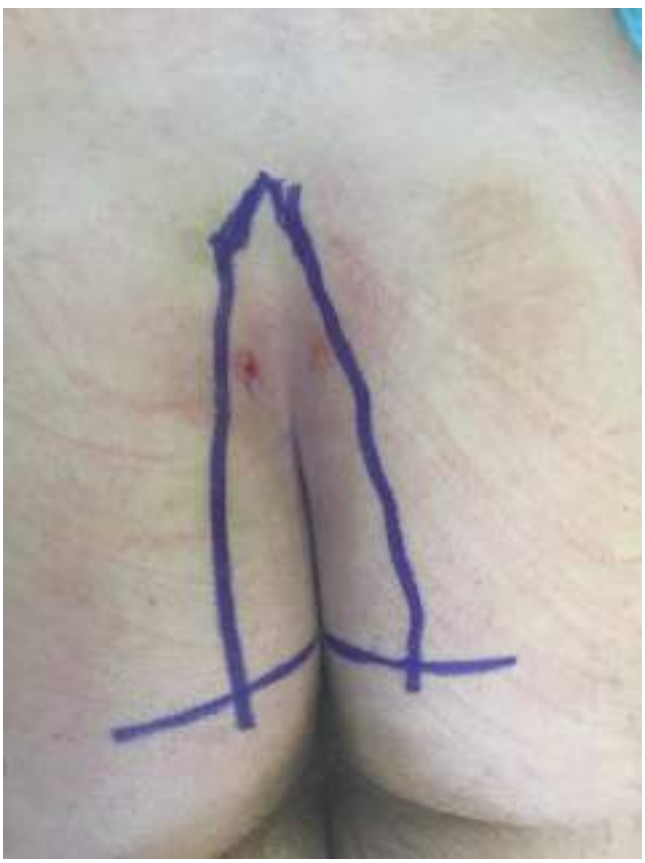


FIGURE 17-9. After squeezing the buttocks together and marking the safe zone.

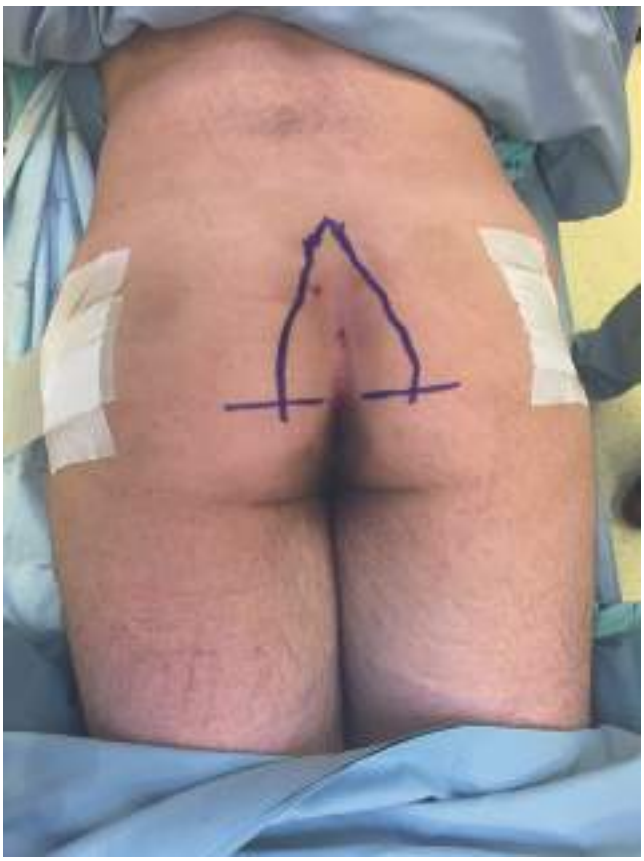
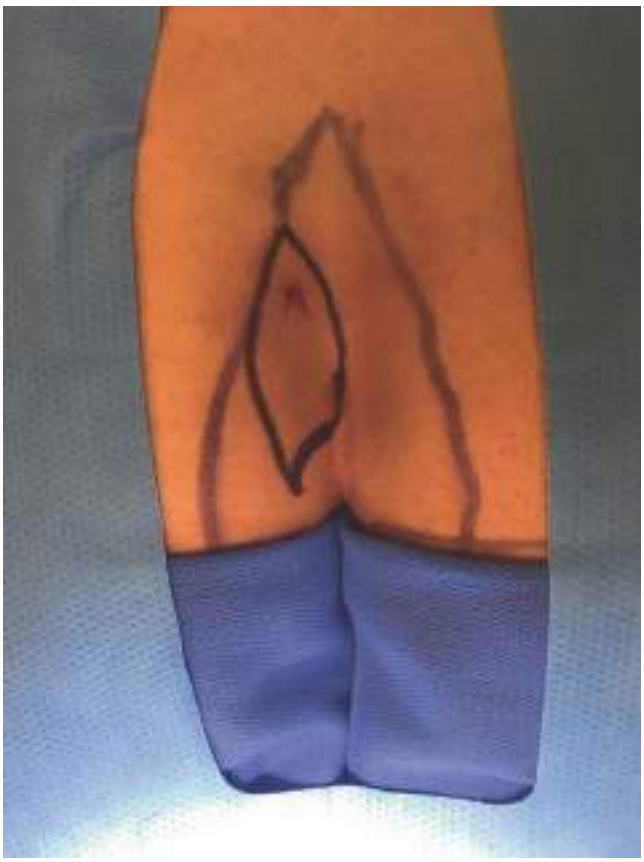


FIGURE 17-10. Image showing the buttocks taped apart under tension providing excellent operative exposure.



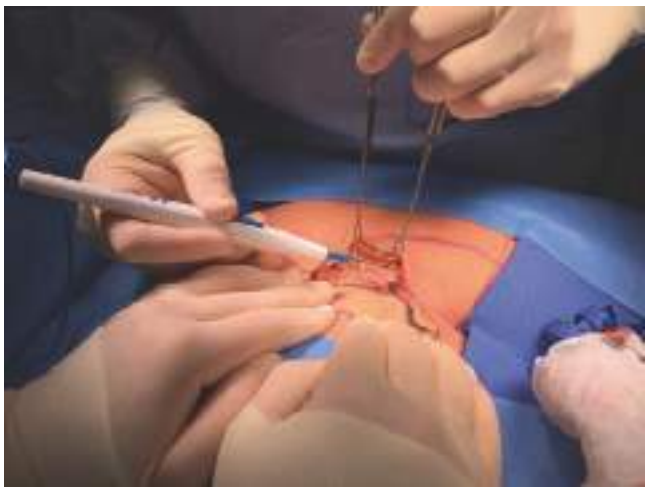


FIGURE 17-12. This image shows the operative creating the flap to be used for the cleft lift.

should be undertaken. Any remaining "cyst wall" or tissue contracture can be divided into squares with a scalpel or electrocautery device. The subcutaneous tissue is then closed in layers with an absorbable suture. The superficial layers are reapproximated in layers, lastly with a subcuticular suture (Figure 17-13a,b). Use of a drain is optional, but certainly not necessary.

A case-control study published in 2011 compared the results of the cleft lift procedure to wide excision and packing in 70 patients [40]. A total of 97% of patients undergoing cleft lift healed completely while only 73% of wide excision patients healed. Three of nine patients with chronic wounds underwent subsequent cleft lift with a 100% success rate. Recurrence was noted in 2.5% of cleft lifts and in 20% of wide excisions. Others have shown similar success in rates of healing with the cleft lift procedure as compared to wide excision and packing and excision and primary midline closure [41]. This technique has also been compared to the Limberg flap in a randomized prospective fashion [42]. Short-term outcomes of 122 patients were analyzed and revealed that those undergoing the cleft lift had shorter operative durations, less excised tissue weight, improved pain scores, and fewer physical limitations on postoperative day 10. There were no differences in healing, complications, or early recurrences.

There is little question that this technique is easier to perform, takes less time, and removes less tissue than the more complex flap procedures such as the rhomboid flap. It results in flattening of the natal cleft, which is likely desirable. Unfortunately, not every patient with PD is a candidate for this procedure. Those with complex recurrent disease and large open wounds may not be ideal candidates, and may require more extensive flap procedures. Disease that is very close to the anus may cause difficulty with this technique, though if open wounds are able to be moved off the midline, they may still heal.

FIGURE 17-11. The area to be excised is marked. Typically this excision is performed on the side where induration or a "cyst" is located.

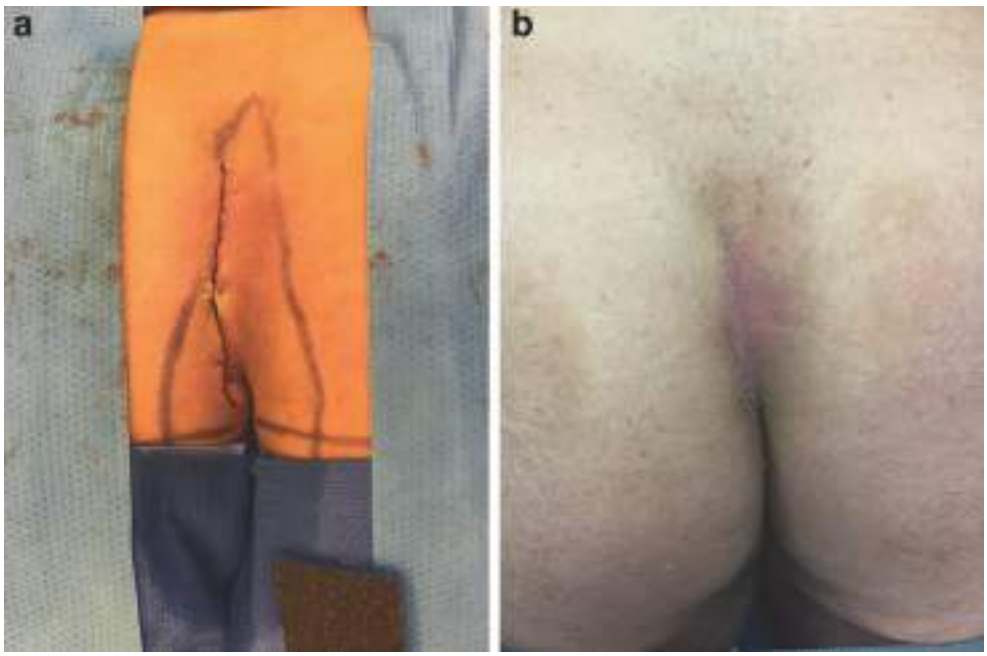


FIGURE 17-13. (**a**, **b**) These images show the procedure at the completion of the case and at 3-week follow-up with complete healing.

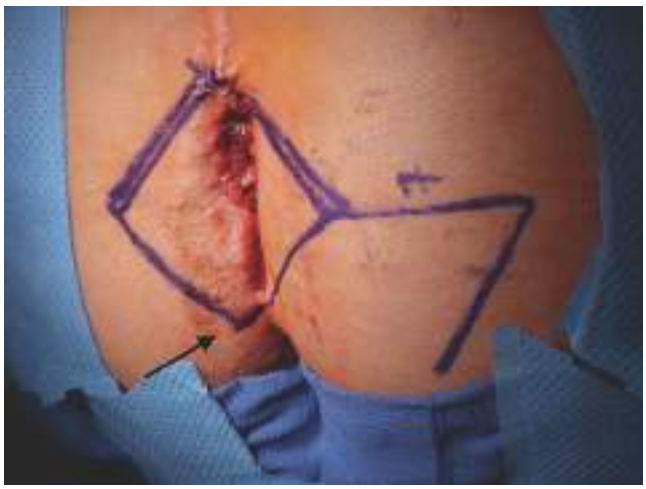


FIGURE 17-14. This image shows the planned lines of incision for the rhomboid flap. Note that the caudal tip is NOT located directly over the anus. This modification results in a wound that does not come to a point at the location of highest risk.

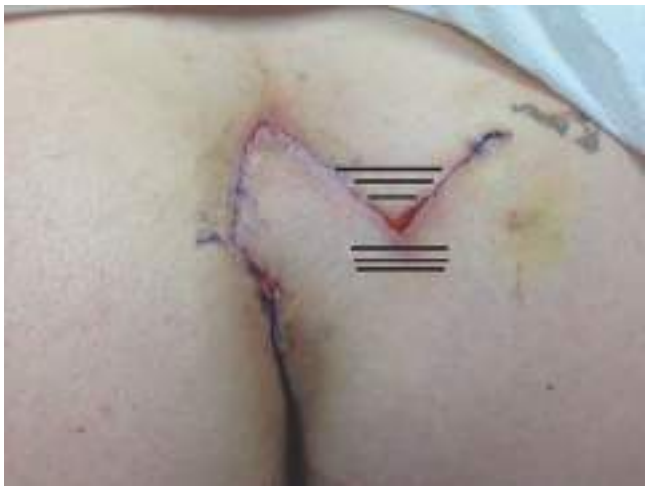


FIGURE 17-15. This image shows areas at the point of maximal tension that must be undermined to facilitate closure.

Rhomboid/Limberg Flap (See Video 17-2)

The rhomboid flap is a useful but more complex procedure that can be used in any setting of PD, but is typically reserved for more severe cases. The procedure involves a "diamond-" or rhombus-shaped area of wide excision encompassing all disease in the midline (Figure 17-14). While most will excise tissue down to the level of the post-sacral fascia, this is not entirely necessary. One must ensure however that the thickness of the mobilized lipocutaneous flap approximates the thickness of the tissue that is excised. This technique works particularly well in the setting of complex recurrent disease. The planned incision is marked, and the flap is raised with electrocautery. It is recommended to handle the flap gently during mobilization. It is important to take care to undermine the areas adjacent to the flap so that the most tension-free closure can be obtained (Figure 17-15). Once the flap is mobilized completely (Figure 17-16), it is anchored to the post-sacral tissues with an absorbable suture. A closed-suction drain is placed and a layered closure takes place using absorbable suture. The skin can be closed using a variety of techniques, none of which has proven to be superior. Some will cover the final closure with glue to create a watertight seal (Figure 17-17). A modification of this procedure was created in order to keep the caudal point of the incision away from the anus (Figure 17-14).

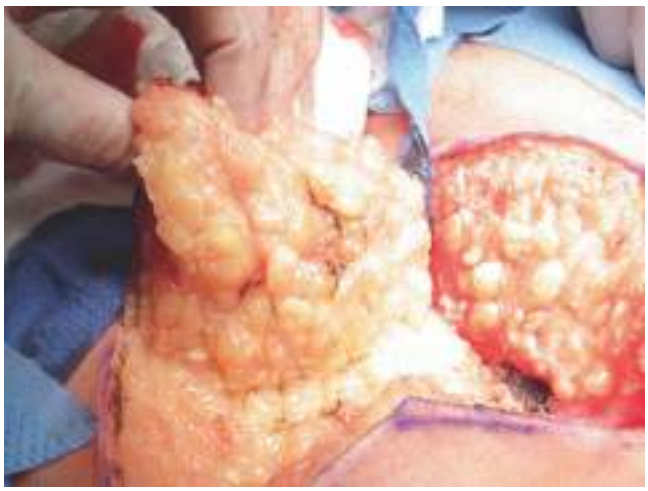


FIGURE 17-16. The Limberg flap after full mobilization, just prior to closure.

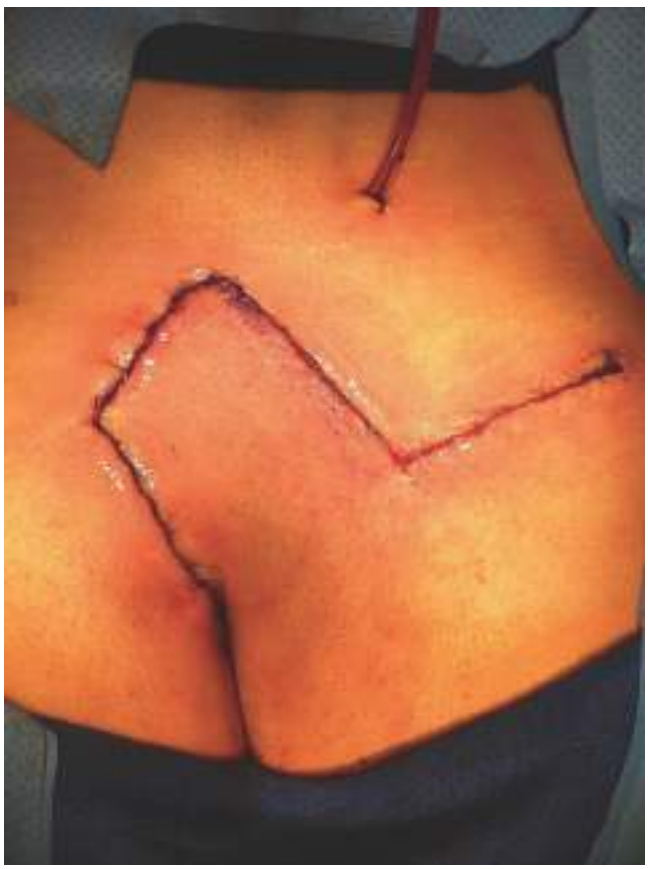


FIGURE 17-17. The appearance at the completion of the Limberg flap procedure. The wound has been covered with glue.

The drain can be left in place for 48 h or until it has produced 30 ml or less daily for 2 consecutive days. The patient should avoid any strenuous activity for 2–4 weeks. It is not uncommon for these wounds to separate slightly in one or two areas over the ensuing 2 weeks (Figure 17-18). This will require some minor wound care and is typically well

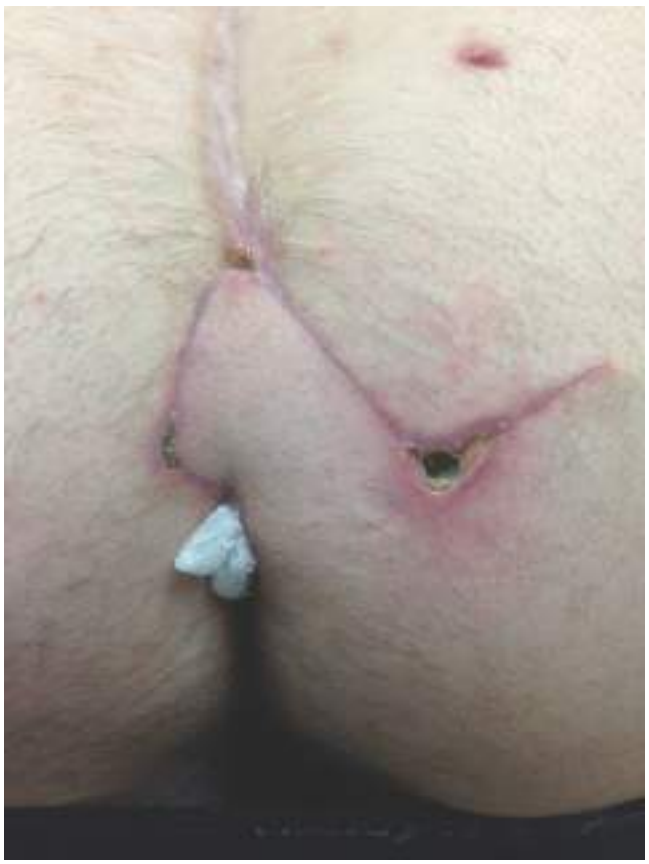


FIGURE 17-18. Follow-up will often reveal areas of minor wound separation that will require some ongoing basic wound care.

tolerated. Occasionally it will take 4–8 weeks for the wound to completely heal. In some cases, the disease spans a very large area over the sacrum extending from the perianal area for a long-distance cephalad. Many are uncomfortable creating such a large area of excision and flap in this setting. When this is the case, the technique can still be used but may be modified. The most difficult area in which to achieve healing is the caudal midline. An excision can be performed, and flap created such that the caudal midline is covered leaving an open wound cephalad (Figure 17-19). The remaining wound can be managed in a variety of ways, but the use of a negative pressure wound therapy device makes this management easy (Figure 17-20a, b). This device can be used in the standard fashion until the remaining wound is small enough to manage using standard dressings. The area will typically heal quickly, and does not impair the flap in any way.

Potential surgical site-related postoperative complications include wound dehiscence, flap necrosis, hematoma, wound infection, and seroma. These occur at rates of 4%, 0–2%, 1%, 3–5%, and 3%, respectively [43, 44]. Recurrence can be seen in approximately 4% [44]. Several series have compared outcomes associated with the Limberg flap (LF), modified Limberg flap (MLF), and excision with primary midline closure [45–48]. The evidence indicates that the LF or MLF is associated with faster return to work, lower rates of surgical

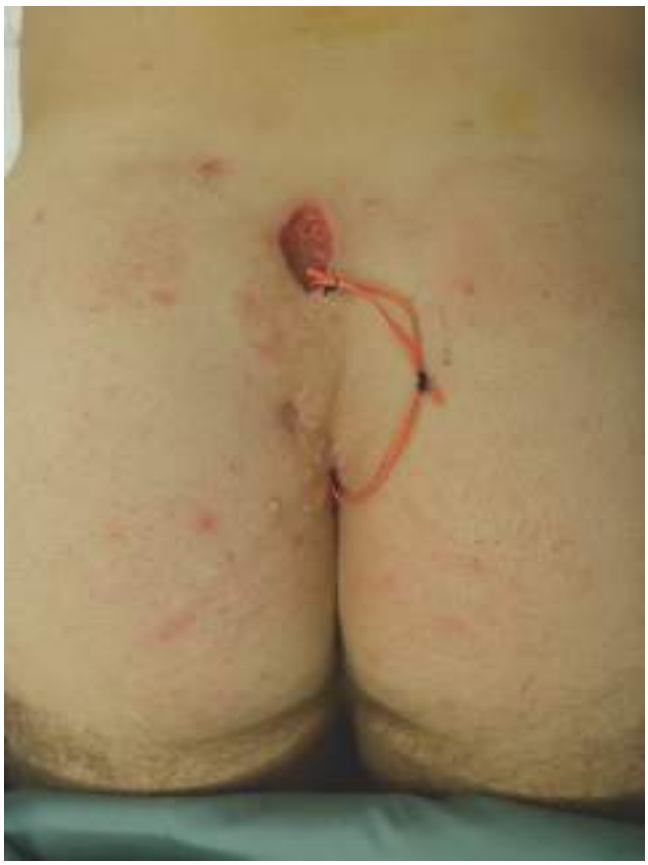


FIGURE 17-19. This image shows a patient with recurrent disease that resulted in a large abscess that was drained superiorly and required some tissue debridement. This resulted in a large area of disease to be addressed.

site infection, lower recurrence, and lower rates of wound dehiscence. Comparisons of the MLF, LF, and Karydakis flap show similar superiority for the LF and MLF [49, 50], while others have shown equivalence [51].

Disease Recurrence

Given that there are several known risk factors that predispose to the occurrence of PD, many have attempted to investigate factors that may predict disease recurrence. Familial history of disease, increased sinus number, larger cavity diameter, and primary wound closure have been shown to be associated with higher rates of recurrence [52]. Interestingly, tobacco smoking and body mass index > 25 have NOT been shown to increase recurrence [53]. Recurrence has been shown to be lower in those that undergo surgical incision and drainage prior to definitive surgery as compared to those who have spontaneous abscess rupture [54]. Along these lines, surgery performed in the "after-hours" and potentially emergent setting has been associated with higher recurrence rates [55]. Many publications that report on recurrence are criticized secondary to a lack of long-term follow-up. Doll and colleagues analyzed data from German military members and performed a telephone survey specifically investigating for recurrence [56]. They were able to demonstrate recurrence rates that were 22% higher than previously reported through collection of data over a longer period of follow-up. Recurrences up to 20 years after surgery were seen, and they recommended that studies investigating long-term outcomes should have at least 5 years of follow-up.

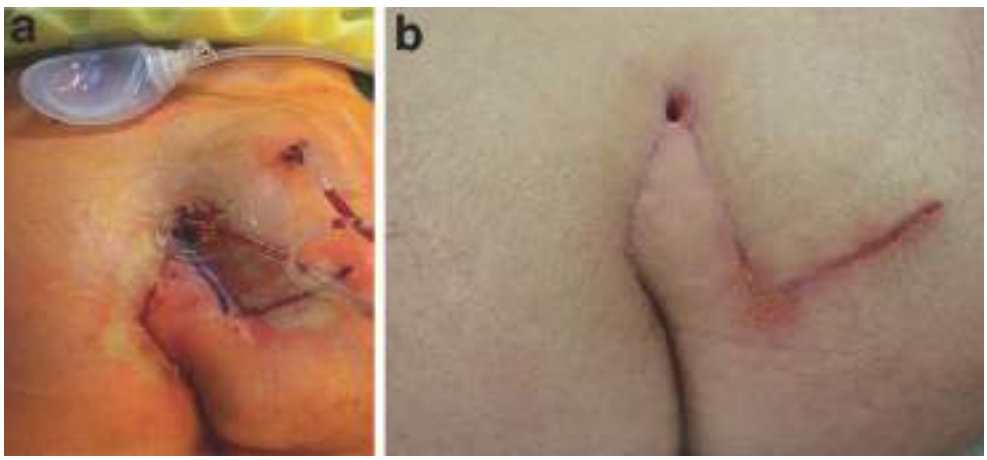


FIGURE 17-20. (**a**, **b**) This image shows a patient similar to that in Figure 17-19. The flap was created and closed leaving an open wound superiorly that was treated with negative pressure wound therapy and healed easily.

Hidradenitis Suppurativa

Background

The term hidradenitis suppurativa (HS), also known as acne inversa, was coined in 1864 by Verneuil [57] and literally refers to "sweat gland inflammation producing pus." The disease is a chronic inflammatory disorder involving the skin of apocrine gland-bearing areas, typically the perineum, inguinal, inframammary, and axillary regions. Colorectal surgeons are often consulted for assistance in managing those with perianal and perineal disease. Individuals afflicted with HS suffer a tremendous impact upon their quality of life with effects on both their physical and mental health [58, 59]. Practitioners in Europe have suggested that HS has the highest impact upon quality of life among all assessed dermatologic diseases [60].

The prevalence of HS is estimated to be 127.8 per 100,000 or 0.13%, with a higher prevalence among women, based on data from the Rochester epidemiology project [61]. This translates to fewer than 200,000 affected patients in the USA, 93% of which are between the ages of 18 and 64 years [62]. The reported mean age of onset is between 20 and 24 years of age, with less than 8% of affected individuals developing disease earlier than 13 years of age [63]. Early-onset disease seems to be correlated with family history of disease. When compared to psoriasis, another chronic skin disease, HS patients consume more health care and generate higher health care costs [64].

Etiology/Presentation/Diagnosis

Much like with pilonidal disease, the etiology of HS has been debated for quite some time. It was once thought purely to be secondary to infection of the apocrine sweat glands, but there is now general agreement that this is not true. The disease is characterized by chronic follicular occlusion resulting in secondary inflammation of the apocrine glands [65]. The initial inciting event is believed to be hyperkeratosis that leads to follicular occlusion [66, 67]. Others have proposed that the follicular occlusion occurs as a result of a defect in the follicular support system [68]. In any case, there is ultimate dysfunction in the entire folliculopilosebaceous unit (FPSU) that leads to follicular rupture and secondary bacterial infection involving the apocrine glands. Disease manifests initially as open comedones, typically with a few "heads," and tender subcutaneous papules [69]. In many this leads to a chronic and progressive worsening of symptoms in which additional nodules form, rupture, and drain a thick mucopurulent foul-smelling liquid. Over time this leads to sinus tract formation, fibrotic subcutaneous scarring, and potentially disabling contractures of the affected limb [69].

There are a number of variables that have been identified as risk factors for disease. Tobacco smoking and obesity have been associated with both the presence of disease and lower remission rates [70]. Weight loss has been shown to be temporally associated with remission [71, 72], with one report demonstrating disease quiescence with rapid weight loss after gastric bypass surgery. Sweating, shaving, deodorant use, and friction have also been implicated as potential exacerbating factors [73]. It is also believed that there may be dietary triggers that worsen disease (high carbohydrate diet, milk consumption) [74].

Diagnosis is typically made based on common physical exam findings including skin thickening, induration, abscess formation, the presence of draining sinuses, and contractures in the regions of the body considered at risk. There are several other diagnoses in the differential that should be considered (Table 17-1). The diagnosis can be confirmed histologically with a biopsy specimen. Given that disease can present with a wide range of severity, there have been two classification or staging systems proposed to grade disease, the Hurley system and the Sartorius system (Tables 17-2 and 17-3). The Hurley system is used more commonly as it seems to be better suited to clinical as opposed to research use. Because of some criticism related to the simplicity of the Hurley staging system, a French group have introduced a latent classification system, which better groups HS patients into three distinct phenotypes (Table 17-4) [75]. Despite its weaknesses however, the Hurley system seems to be most useful to physicians making treatment recommendations for affected individuals.

Several comorbid conditions have well-known association with HS. There is a well-established link between acne and HS, as well as with pilonidal disease [66]. Some other commonly

Table 17-1. A list of diagnoses that should be considered in the differential diagnosis of hidradenitis suppurative [67]

Diseases to be considered in the differential diagnosis
Acne
Actinomycosis
Anal fistula
Carbuncles
Cat scratch disease
Cellulitis
Crohn's disease
Cutaneous blastomycosis
Dermoid cyst
Granuloma inguinale
Erysipelas
Furuncles
Inflamed epidermoid cyst
Lymphadenopathy
Lymphogranuloma venereum
Nocardia infection
Noduloulcerative syphilis
Perirectal abscess
Pilonidal disease
Tuberculous abscess
Tularemia

Table 17-2. Description of the Hurley classification of hidradenitis suppurativa, likely the most useful in the clinical setting

Hurley staging system of hidradenitis suppurativa	
Stage I	Abscess formation, single or multiple, without scarring or sinus tracts
Stage II	Recurrent abscesses with tract formation and scarring, single or multiple, with widely separated lesions
Stage III	Multiple interconnected tracts and abscesses throughout an entire region

Table 17-3. The Sartorius scoring or staging system

Sartorius staging system/Sartorius score	
Involvement in specific body areas	3 points for each area involved
Nodules	2 points for each
Fistulas	4 points
Scars	1 point
Other findings	1 point
Longest distance between two lesions	2–4 points
If lesions are separated by normal skin	Yes—0 points, No—6 points

Some have modified the system by adding value to the presence of pain, drainage, or odor. This may be a more useful system in the research setting to quantify severity of disease

Table 17-4. Latent or phenotypic classification proposed by Canoui-Poitrine et al. [75]

Latent classification	Phenotype	Affected region
LC1	Axillary-mammary	Axilla, breast, perineum, inguinal
LC2	Follicular	Ears, chest, back, legs, axillary, breast
LC3	Gluteal	Gluteal fold

associated diseases include inflammatory bowel disease (particularly Crohn's disease), spondyloarthropathy, genetic keratin disorders, and squamous cell carcinoma [76]. In some cases it can be difficult to differentiate between the diseases, particularly in pilonidal disease and Crohn's disease with anal involvement. It is not entirely surprising that there can be considerable overlap in how all of these associated diseases are treated.

Treatment

As with treatment of any disease, it is important to identify the goals of therapy and patient expectations of the outcome, as well as what they will have to go through to achieve the desired end point. Medical therapy with the ultimate goal of suppression, coupled with the occasional procedure to drain an abscess, may suit a patient with Hurley stage I or II disease quite well. Conversely, the patient with Hurley stage III (Figure 17-21) disease may be so affected by their disease that they may be willing to undertake a radical surgical procedure to achieve "cure." The best way to achieve the lowest recurrence rate is to aggressively remove all apocrine gland-bearing tissue in the affected area, which will often require a complex reconstructive approach [67].

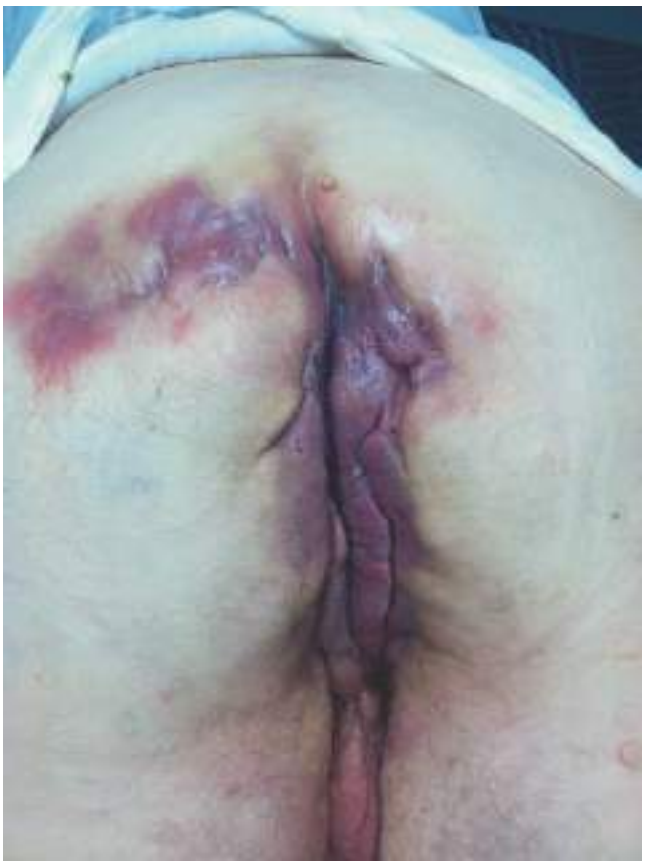


Figure 17-21. This image shows a patient with Hurley stage III hidradenitis suppurativa.

Medical Therapy

There are several different forms of medical therapy that can be considered, many of which work via different mechanisms. It appears that treatment is most successful when used in combined fashion as opposed to monotherapy [66]. Forms of medical therapy include antibacterial washes, topical antibiotics, systemic antibiotics, topical and systemic retinoids, antiandrogens, intralesional and systemic corticosteroids, and immunosuppressives [77]. Oral metformin has also been shown to be useful in treating individuals that have been unresponsive to traditional treatments [78]. Systemic antibiotics cannot be used for extended periods of time secondary to the selection of resistant strains of bacteria. While bacterial infection may be a secondary event in HS, it is clear from published research that persistence of bacterial colonization, likely in the form of biofilms, plays some role in the progression of disease [79]. Retinoids are likely beneficial secondary to their effect on normalization of epithelial cell proliferation and differentiation, which in turn may reduce the occurrence of follicular occlusion [80]. While these drugs are very effective in women of child-bearing age, their use must be cautioned due to their risk of teratogenicity. There are several reports of treatment success associated with their use [81, 82]. While antiandrogen therapy is often used (estrogen/progestin

combinations, finasteride, spironolactone), the evidence to support its use is fairly weak [83].

Given the association of HS with inflammatory bowel disease, some have suggested that HS is a systemic process and could be treated similarly [84–86]. There are several reports of the use of tumor necrosis alpha (TNF alpha) inhibitors in the treatment of HS, with infliximab supported by the majority of available data [87–94]. There is also support for the use of other TNF alpha inhibitors [95]. It may be useful to employ these newer drugs if the effect of infliximab seems to fade or if the patient develops a sensitivity to the medication. Newer reports show some success with the use of photodynamic therapy [96, 97], as well as the use of intense pulsed light therapy [98]. Lasers have been used to treat HS both superficially [99] and when used as an instrument for excision in lieu of a scalpel or other energy devices [100].

Surgical/Excisional Therapy

For patients intolerant of or unwilling to undergo medical therapy, or for those with disease of significant severity, surgical excisional therapy may present the only viable option. Excisional therapy is based on the premise that wide excision of all apocrine gland-bearing tissue in the affected region is the best method to sustain low recurrence rates. This is typically achieved through a radical approach whereby all affected skin and subcutaneous fat is excised down to the fascial level. This will often result in a very large defect that cannot be addressed through simple primary closure. Local flap closure or split-thickness skin grafting (Figure 17-22a–d) is commonly necessary to achieve adequate tissue coverage of the wound. This may require the involvement of a plastic surgeon. Attempts at simple unroofing of sinus tracts seem to be associated with higher rates of recurrence. A technique referred to as STEEP (skin tissue-sparing excision with electrosurgical peeling) has been proposed as an alternative to the above techniques [101, 102]. In this technique the sinus roof is incised with a wire-loop electrosurgical instrument, which is similar to the "unroofing" technique. Affected tissue is then tangentially excised which results in sparing of the sinus floors and surrounding subcutaneous tissue. Wounds are left to heal by secondary intention. The premise behind this technique is that it is "tissue sparing" and leads to faster healing with improved outcomes.

There are several case series reporting the outcomes associated with the use of a wide variety of radical excisional procedures employing the use of different reconstructive techniques [103–105]. Whatever technique is chosen should be based on the anatomy of disease, patient expectations, risk of recurrence, and possibility of functional limitations. Vacuum-assisted closure devices can also be helpful in wounds that are too large to close primarily, but may not require more complex reconstructive options [106]. In cases where skin grafting may be used, a two-stage approach has been described [107]. The radical excision is performed initially which is immediately followed by coverage with artificial dermis. This allows for formation of granulation tissue as well as some surrounding wound contraction which may lead to a requirement for less grafting as well as improved graft take. In almost every case, the skin graft must be placed in an area subject to high levels of motion and

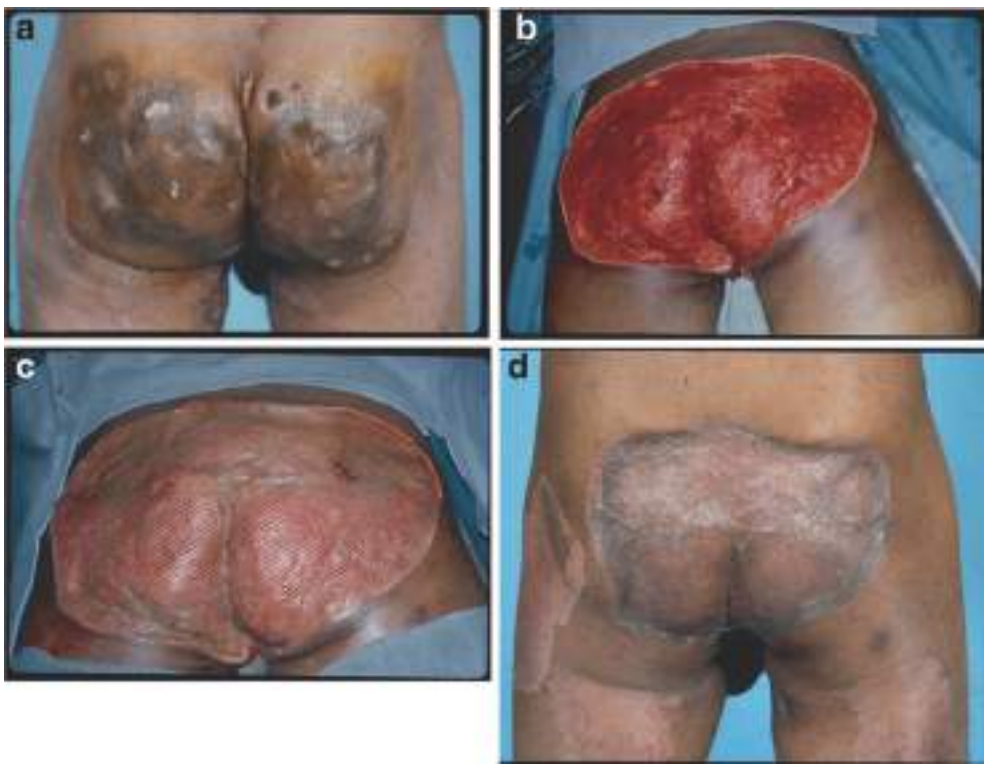


FIGURE 17-22. (**a–d**) This series of images shows a patient with Hurley stage III disease who underwent radical excision and closure with split-thickness skin grafting.

potential friction—none of which are good for a fresh skin graft. Perhaps staging the grafting approach decreases motion under the graft, which can potentially lead to improved outcomes.

Conclusion

Both pilonidal disease and hidradenitis suppurativa represent chronic inflammatory processes that can present with a wide spectrum of severity, but invariably disable those affected and result in a substantial decrease in their quality of life. While treatment of these disease processes may not seem to be surrounded in glamour, it most certainly results in a grateful patient. Pilonidal disease is quite common, while HS is much less so, but any colorectal surgeon can be expected to care for a number of individuals afflicted with these diseases. In order to ensure optimal treatment and outcomes, it is critical to tailor recommendations to the severity of disease, anatomy of disease, and our patient's expectations of risks and expected outcomes.

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18
Dermatology and Pruritus Ani

Wolfgang B. Gaertner and Genevieve B. Melton

Key Concepts

- Pruritus ani is a dermatologic condition characterized by itching or burning at the perianal area.
- Pruritus ani can be either primary (idiopathic) or secondary.
- Primary pruritus ani is the most common form of pruritus ani. The most common causes of secondary pruritus ani are local irritants and common anorectal conditions.
- All chronic perianal dermatoses require a detailed history and physical exam, including all past diagnostic tests and forms of treatment.
- The single most valuable diagnostic test in patients with recurrent or ongoing pruritus ani is skin biopsy.
- Treatment options for pruritus ani are numerous. Management should focus on the underlying or suspected etiology, following an evidenced-based stepwise diagnostic and treatment algorithm.

Introduction

Dermatologic diseases of the anus are a group of inflammatory, infectious, and neoplastic conditions that are difficult to diagnose and challenging to manage. While patients often do not openly discuss the associated symptoms with medical professionals, these conditions can often have a significant impact on their quality of life. Patients presenting with anal dermatologic disease are often seen by a diverse group of providers, including general practitioners, gastroenterologists, dermatologists, and colorectal surgeons. Some providers such as primary care physicians may encounter these conditions less commonly, thus making efficient and evidence-based treatment strategies highly important.

In 1660, Samuel Hafenreffer defined "itch" as "an unpleasant sensation that elicits the desire or reflex to scratch" [1]. More specifically, pruritus ani is defined as a dermatologic condition characterized by persistent and unpleasant itching or burning sensation in the perianal region [2]. The incidence of pruritus ani is estimated to range from 1 to 5 % in the general population, with men being affected more than women in a 4:1 ratio and most commonly diagnosed in the fourth–sixth decades of life [3–5].

Pruritus ani can be classified into primary or idiopathic (accounting for 50–90 % of cases) and secondary [6]. It may be caused by a wide spectrum of conditions, among which perianal eczema is probably the most common. Because pruritus ani often has a multifactorial etiology and high chronicity, most patients have symptoms for many years, as well as a long list of prescribed or over-the-counter treatments. Appropriate management can be difficult and requires a detailed evaluation in search for its etiology.

Pathophysiology of Perianal Signs and Symptoms

The sensation of itch is elicited as a surface phenomenon mediated by nonmyelinated C-fibers in the epidermis and subdermis and can be also classified as pruritoceptive (C-fiber mediated), neuropathic (i.e., after herpes zoster infection), and central or neurogenic. Itch has long been considered as a sub-modality of pain. The intensity hypothesis postulates that neurons are activated by both painful and pruritogenic stimuli, but weaker activation of nociceptive receptors can also result in itch [7]. Recent evidence suggests that the overall neurophysiology of itch is much more complex than initially thought. For example, when algogens are applied topically in lower concentrations, they typically result in low-intensity pain and not pruritus [8].

Microneurography experiments conducted by Schmelz et al. [9] identified afferent C-nerve fibers that were histamine sensitive but insensitive to mechanical stimuli. These findings support the labeled line theory of pruritus, which hypothesizes that discrete and mutually exclusive afferent

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fibers are able to detect either itch or pain [10]. The stimulation of these histamine-sensitive C-nerve fibers demonstrates a central response in a subset of spinothalamic tract neurons [11]. In contrast, subdermally injected histamine-induced pruritus has been shown to activate multiple sites in the brain, overall indicating that itch is a multidimensional sensation, and there is not a single neurologic itch center [12].

Biochemically, histamine, kallikrein, bradykinin, papain, and trypsin can experimentally and individually produce itching. This may explain the lack of effectiveness of antihistamine medications against itching. While multiple itch mediators have been identified, the antagonism of these mediators produces varied clinical results (Table 18-1). This strongly suggests that specific neuronal pathways are involved at both peripheral and central levels in mediating itch.

Scratching is thought to produce inadequate feedback to inhibit further itching. Persistent scratching causes skin trauma, which is an additional stimulus for itching and additional scratching; therefore, this can lead to a chronic vicious cycle. Substituting scratching for other stimuli such as heat, cold, pain, or stinging by applying alcohol or pepper extract (capsaicin) may cause inhibitory feedback and then can decrease the urge to scratch.

Table 18-1. Itch mediators and corresponding antipruritic agents

Itch mediator	Antipruritic agent
Histamine	Antihistamines
Acetylcholine	Doxepin (mainly antihistaminic mechanism)
Serotonin	Paroxetine, fluoxetine (SSRIs)
	Mirtazapine (serotonin inverse agonist)
	Ondansetron (5HT3 antagonist)
Opioids	Naloxone, naltrexone (μ-receptor antagonists)
	Nalfurafine, butorphanol (kappa-receptor agonists)
Leukotrienes	Zafirlukast, zileuton
Prostaglandins	NSAIDs
Substance P	Aprepitant
TRPV1	Capsaicin
TRPM8	Menthol
TNF-alpha	Thalidomide
GABA	Gabapentin, pregabalin

SSRI selective serotonin reuptake inhibitor, *TRPV1* transient receptor potential vanilloid 1, *TRPM8* transient receptor potential melastatin 8, *TNF* tumor necrosis factor, *GABA* gamma-aminobutyric acid, *NSAIDs* nonsteroidal anti-inflammatory drugs, *5HT* 5-hydroxytryptamine

Itching associated with healing is also common after the inflammatory response caused by common anorectal conditions (i.e., fissure and hemorrhoids), as well as after anorectal operations and trauma. The release of histamine and various kinins and prostaglandins is a contributing factor in this situation; therefore, antihistamines, topical anti-inflammatory agents (steroids), and topical anesthetics have shown beneficial effects in these patients [13].

The complexity of the neurophysiological mechanisms causing pruritus as well as the extensive range of peripheral as well as central mediators of pruritus suggests that an effective antipruritic strategy would require a diverse approach.

Etiology and Contributing Factors

Although the overall differential diagnosis of anal dermatoses includes a long list of inflammatory, infectious, sexually transmitted, and neoplastic diseases, in this section, we will focus on the most common primary and secondary etiologies. Proposed etiologies of primary or idiopathic pruritus ani include a variety of associated factors, including anatomic, dietary, hygienic, psychogenic, local irritants and medications (Table 18-2). In many cases, both primary and secondary etiologies coincide, but a careful history and full physical examination will help elucidate the most significant contributing factor. For example, a patient with pruritus ani may present with irritable bowel syndrome, diarrhea, and fecal incontinence. Both primary and secondary etiologies in this patient may include fecal contamination, anal leakage, anxiety, dietary, and hygiene; and some of these may be directly related to one another. One must therefore individualize each case and focus on the most significant contributing factor for that patient taking into consideration the overlap of different etiologies. The causes of secondary pruritus ani can be divided into several broad categories: infectious, dermatologic, systemic disease and anorectal causes (Table 18-3) [3, 4].

In the absence of a primary cutaneous disorder, pruritus ani is thought to have two probable causes: (1) irritation from mucus, fecal material, or other perineal moisture (such as urine in an elderly patient with urinary incontinence) and (2) nerve impingement in the sacral region that causes a neuropathic itch or notalgia paresthetica. While there is good

Table 18-2. Proposed etiologies of primary or idiopathic pruritus ani

Anatomic factors	Obesity, deep clefts, hirsutism, tight clothing
Diet	Coffee (including decaffeinated), chocolate, spicy and heavily condimented foods, citrus fruits, tomatoes, beer, dairy products, vitamin A and D deficiencies, fat substitutes, consumption of large volumes of liquids
Personal hygiene	Poor cleansing habits, excessive perianal hygiene causing trauma
Local irritants	Fecal contamination, moisture, soaps, perfumes, topical medications, toilet paper, wet wipes, alcohol, witch hazel
Drugs	Quinidine, colchicine, IV steroids
Psychogenic	Anxiety, neurosis, psychosis, neurodermatitis, neuropathy, "itch syndromes"

Modified from Stamos MJ, Hicks TC, Pruritus ani: diagnosis and treatment. In: Perspectives in Colon and Rectal Surgery, 1998;11(1):1–20. Thieme Medical Publishers [17]

Table 18-3. Causes of secondary pruritus ani

Infectious
Bacterial
Fungal/yeast
Viral
Parasitic
Dermatologic
Psoriasis
Lichen planus, lichen simplex chronicus
Lichen sclerosus
Contact dermatitis
Atopic dermatitis
Local malignancy (squamous cell carcinoma, Paget's and Bowen's disease)
Systemic disease
Diabetes mellitus
Leukemia, lymphoma, polycythemia vera
Liver disease (jaundice)
Chronic renal failure
Thyroid disorders
Colorectal and anal causes
Hemorrhoids (internal and external)
Rectal prolapse (mucosal and full thickness)
Fissure
Fistula-in-ano
Diarrhea (infectious, inflammatory bowel disease, irritable bowel syndrome)
Secreting villous tumors
Other
Radiation dermatitis
Fecal incontinence and anal leakage
Gynecologic conditions (pruritus vulvae, vaginosis, vaginal discharge)

evidence supporting fecal contamination as a cause of anal pruritus, this seems to produce more of an irritant effect rather than an allergic effect [14]. The perianal skin also seems to be more susceptible to fecal contamination as a cause of perianal skin irritation compared to other sites of the body [14]. Anal leakage alone is frequently associated with anal pruritus, and this has been correlated with a pronounced anal inhibitory reflex in patients with pruritus ani [15]. Anxiety, stress, and fatigue, as well as personality, coping skills, and obsessive-compulsive disorders, probably play a role in the exacerbation of pruritus ani [16].

Irritants

Pruritus ani can result from several products including lanolin, neomycin, parabens, topical anesthetics from the "caine" family, and certain toilet papers [18]. Bowyer and McColl [19] studied 200 consecutive patients with pruritus ani and found that topical local anesthetics were the most commonly found causative factor. The enzymes responsible for perianal skin irritation from fecal contamination include lipase, elastase, and chymotrypsin [20]. Further skin irritation is often exacerbated by multiple and diverse treatment attempts and excessive hygiene measures. This allows for sensitization of the perianal area, which may then be followed by allergic contact dermatitis or perianal eczema.

There are six common foods that often are associated with and thought to cause perianal irritation and pruritus: coffee, tea, cola, beer, chocolate, and tomato (ketchup). In some cases, total elimination will result in remission of itching in 2 weeks [21]. After a 2-week elimination period, foods may be reintroduced to determine the association and potentially the threshold exposure with the appearance of symptoms.

Steroid-Inducing Itching

Although anogenital itching has been reported with both topical and systemic steroids, it commonly occurs as a rebound phenomenon after withdrawal of steroids [22, 23]. Application of topical steroids for as little as 2 weeks can produce acute dermatitis resembling that seen with a blister that has been unroofed and exposed to air [24]. Steroids should only be used to achieve specific effects to the anogenital area. The potency and dosing of steroids should be tapered in a planned fashion with the goal of eliminating steroids altogether from a maintenance regimen. Allergic contact dermatitis to topically applied steroids has been well documented and is class specific. Switching to desoximetasone (a less commonly used agent in steroid class) may be a solution, but the ideal solution would be elimination of all steroids. Calcineurin inhibitors (tacrolimus and pimecrolimus) offer excellent anti-inflammatory effect without many of these steroidal side effects.

Infectious

Perianal infections associated with pruritus can be bacterial, viral, fungal, or parasitic in origin. Overall, infections have been commonly described as rare causes of pruritus ani [25]. However, emerging data demonstrates that fungal infections may be more prevalent in patients with pruritus ani than once thought [26].

Common bacterial causes include beta-hemolytic *streptococci*, *Staphylococcus aureus*, and *Corynebacterium minutissimum* [27], with beta-hemolytic *streptococcus* being the leading cause of perianal dermatitis in children [28]. *Staphylococcus aureus* perianal infections are more commonly reported in the adult population and typically present as a refractory and prolong dermatitis [29]. Erythrasma, a superficial infection of the intertriginous skin caused by *Corynebacterium minutissimum*, has been reported to cause up to 18 % of cases of pruritus ani in warm climates [27].

Fungal infections may account for 10–43 % of secondary infectious pruritus ani cases [4, 26, 27]. *Candida albicans* is the most common fungi identified in patients with pruritus ani [26, 30]. *Candida*, however, often colonizes the skin and

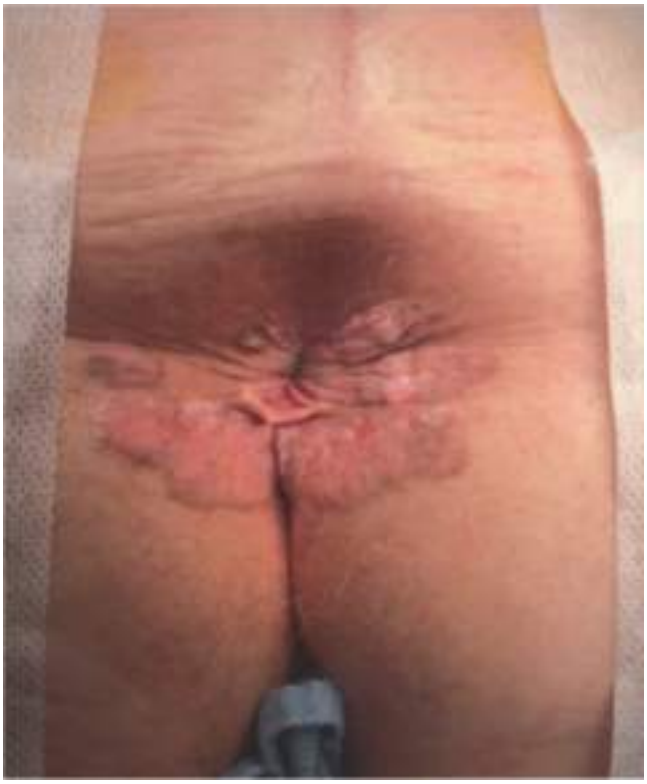

Figure 18-1. Patient with external anal condyloma acuminata and perianal fungal infection that presented with anal pruritus. Condyloma fulguration and antifungal treatment were effective at resolving pruritus.

can also be cultured from the perianal skin in normal subjects. *Dermatophytes* can cause pruritus ani less frequently but should be considered pathogenic and treated appropriately when found in patients with pruritus ani [27].

Several viral and sexually transmitted diseases (STD) can present as pruritus ani. These include herpes syndromes, syphilis, gonorrhea, molluscum contagiosum, and condyloma accuminata. Condyloma accuminata, which is associated with human papillomavirus infection (see section of "Neoplasm"), is a common cause of itching (Figure. 18-1). The diagnosis of condyloma accuminata is easy to recognize and should not be confused with primary or idiopathic causes. Herpes syndromes are typically characterized by pain and burning with red macules that progress to vesicles that rupture, ulcerate, and may become secondarily infected. Although parasite infections are a rare infectious cause of pruritus ani, they should be considered when clinically appropriate. Common perianal parasites include *Enterobius vermicularis* (pinworms), *Sarcoptes scabiei*, and pediculosis pubis [3]. Pinworms, in particular, are a common cause of nocturnal and post-defecation pruritus ani, especially in children.

Dermatologic

Several dermatologic conditions may present as pruritus ani. These conditions include psoriasis, seborrheic dermatitis, atopic dermatitis, contact dermatitis, lichen planus, lichen sclerosus, lichen simplex chronicus, and local malignancies. Accurate diagnosis largely depends on a thorough history and physical examination of the perianal skin as well as the skin of the entire body [18].

Anal eczema, probably the most common dermatologic cause of pruritus ani, is generally considered to primarily represent contact dermatitis to chemicals and medications that are applied to the anal area. These substances are used by up to 57 % of patients with anogenital complaints and include popular hemorrhoid ointments that contain potent sensitizers (local anesthetics, *Myroxylon pereirae*, bufexamac), dyes, and perfumes used in scented toilet paper and soaps, feminine hygiene sprays and deodorants, and medicated talcum powders and skin cleansers [31–33]. Patients with anal eczema are also more likely to have asthma and hay fever. Most studies evaluating the role of specific allergens causing anal eczema have identified local anesthetics, aminoglycoside antibiotics, and thimerosal as the most common causative agents [26, 31, 34]. It is also important to test the patients' own products, as some studies have found these to be common and clinically relevant allergens. Although the role of dry, moist, or recycled toilet paper has been looked at, well-designed studies have not shown toxic effects of its components [33, 35, 36].

For example, Kranke et al. [26] prospectively studied 126 patients with a presumptive diagnosis of anal eczema over a 4-year period. All patients followed a diagnostic algorithm that involved medical history, physical examination, biochemical and microbiology testing, patch tests, proctoscopy, and biopsy if appropriate. The majority of patients had symptoms for over 1 year. Fifty-eight patients (46 %) were confirmed to have contact eczema, and the leading noneczematous etiology was intertrigo dermatitis with *Candida* spp. in 54 patients (43 %). The most common positive contact allergen identified was thimerosal.

Atopic dermatitis may be the most common hereditary cause of pruritus ani, with a frequency of 15–20 % of the population. Atopic dermatitis is caused by disruption of the epidermal barrier function. Filaggrin, the cement of the epidermis, is defective or absent in patients with atopic dermatitis because of mutations of the filaggrin gene [37]. Complete loss of the filaggrin gene is seen in ichthyosis vulgaris, a common keratinizing disorder frequently associated with atopic dermatitis and seen at the buttocks and perianal skin [38]. Psoriasis affects 1–3 % of the general population and is an important etiology of secondary pruritus ani, with reports varying from 5.5 to 55 % [19, 39–41].

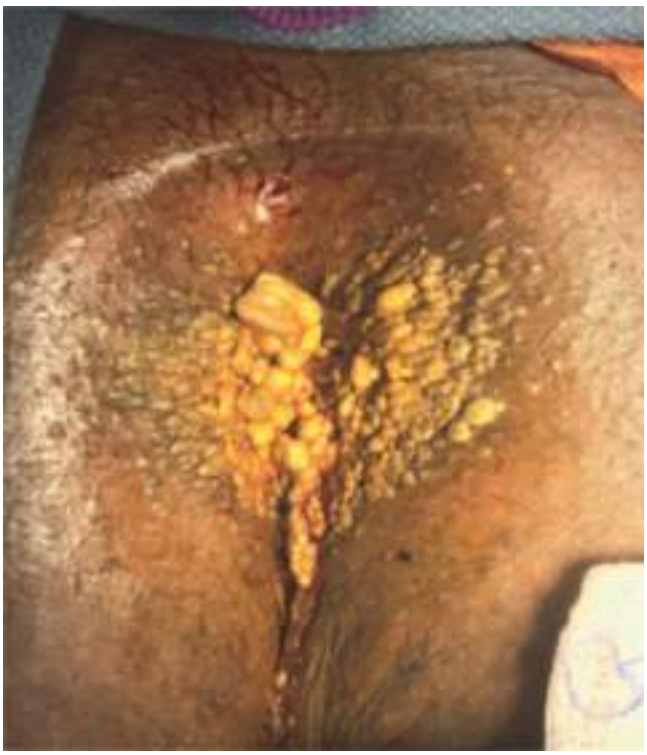

Figure 18-2. External anal condylomata acuminata presenting with perianal pruritus. Condyloma fulguration was effective at resolving pruritus.

Other less common dermatologic causes of pruritus ani include seborrheic dermatitis, lichen planus, lichen sclerosus, and lichen simplex chronicus. Seborrheic dermatitis is an uncommon cause of pruritus ani, characterized by extensive, moist erythema in the perineum [4]. Lichen planus is a relatively common inflammatory disease that affects the skin and mucous membranes and is thought to be caused by an altered, cell-mediated immune response. It is commonly seen in patients with other disease processes, such as ulcerative colitis, primary biliary cirrhosis, hepatitis C infection, and myasthenia gravis [42]. It is typically self-limited, resolving after 8–12 months.

Lichen sclerosus is a disease of unknown cause, seen more frequently in women, and involves the vulva extending posteriorly to the perianal region [4, 18, 43]. When it occurs on the penis, it is termed balanitis xerotica obliterans. Lichen simplex chronicus, also known as neurodermatitis, is a secondary skin manifestation that develops in an area of repetitive trauma from scratching or rubbing. A primary etiology may not be found in many cases, and the pruritus is typically intermittent and worsens at night or when a patient is quiet or still [44].

Neoplasms

Although uncommon, pruritus ani can be a presenting symptom of dermatologic neoplasms, such as condylomata, Paget's disease, and Bowen's disease. Condyloma acuminata with anal intraepithelial neoplasia is the sequel to human papillomavirus infection and refers to premalignant changes in the area of the dentate line and anal transitional zone. Although pruritus has not been well studied in large studies evaluating patients with AIN [45, 46], it is commonly identified in patients with a history of anal warts (Figure 18-2). Extra-mammary Paget's disease (cutaneous adenocarcinoma in situ) is rare and occurs more often during the sixth decade of life, in white patients, and in women compared to men (3–4:1 ratio) [47]. The perianal region is the most commonly involved extra-mammary site, and pruritus is a common presenting symptom [48]. When diagnosed, it may be indicative of and associated with an underlying apocrine or eccrine carcinoma. In particular, the rate of anorectal malignancy associated with perianal Paget's disease ranges from 33 to 86 % [48, 49]. Therefore, investigations of the gastrointestinal, urinary, and gynecologic systems should be performed for a potential associated malignancy. Intraepithelial squamous cell carcinoma in situ, also known as Bowen's disease, of the anus is also rare but frequently presents with pruritus as the main symptom [50].

Anorectal Conditions

Hemorrhoidal disease, skin tags, and chronic anal fissure in ano are commonly seen pathologies in patients with pruritus ani [51, 52]. These conditions alone can cause pruritus but also are often associated with varying degrees of leakage, prolapse, and soiling. Correcting these disorders in patients with pruritus ani is typically warranted. However, the response to treatment and the impact of correcting these conditions on pruritus ani symptoms are unclear and have only been reported in small retrospective studies [39, 40, 52]. Treatment modalities have included both office-based and operative strategies with varying degrees of success.

For example, Murie et al. [52] found that pruritus was more common in 82 patients with hemorrhoids than in age- and sex-matched controls without hemorrhoids and that correction (with banding or hemorrhoidectomy) usually eliminated itching. Bowyer and McColl [19] reported that hemorrhoids were the sole cause of itching in 16 of 200 patients and contributory in 27 others. Correction of fissure was required in five patients before symptoms were relieved. Five others had skin tags which when removed, eliminated symptoms. In general it is difficult to know whether anorectal conditions are the cause or a contributing factor of pruritus ani. Operative management that avoids further scaring or corrects fecal incontinence or leakage should be offered to pruritus patients in most cases.

Systemic Diseases

Several systemic diseases have been associated with pruritus ani; however, the precise causative factors remain unknown. Diabetes mellitus is the most commonly reported systemic

disease. Other frequently reported associated conditions include liver disease, lymphoma, leukemia, pellagra, vitamin A and D deficiencies, renal failure, iron-deficiency anemia, and hyperthyroidism [3, 4, 27].

Diagnoses of Perianal Disease

Establishing an exact diagnosis may be difficult mainly because the clinical presentation is frequently nonspecific. This often results in dissatisfied patients, who may be seen multiple times and by several doctors in different specialties. Consequently patients can have symptoms for many years, as well as a long list of prescribed and over-the-counter medications [53].

To pinpoint the cause of dermatologic diseases of the anus, it is recommended that patients be asked about their current diet, current and previous medications, personal history of atopy, information about bowel habits, and perianal hygiene regimen, including how they routinely clean the anal area after a bowel movement. A review of the patient's medical history, including any history of anorectal conditions or operations, is essential. Other pertinent history includes previous skin infections, especially mycotic infections of the genitalia, STDs, anal seepage, and symptoms of fecal and urinary incontinence.

A diagnostic algorithm, including a full history and physical examination, biochemical and microbiology testing, proctoscopy, and patch tests (including the patient's own products), is strongly recommended (Figure 18-3).

Physical Examination

The morphology of a lesion is a starting point for diagnosis, but may not be specific, and some diseases may present with a number of different appearances. Physical examination should also include evaluation of other related sites of skin manifestations including the groins, axillae, buttock cleft, and other intertriginous areas or skin folds. Response to treatment at these areas should also be documented at follow-up examinations. Washington Hospital classifies pruritus ani based on physical exam findings: stage 0 is normal skin, stage 1 is red and inflamed skin, stage 2 has lichenified skin, and stage 3 has lichenified skin, coarse ridges, and ulcerations [18]. This classification system is practical and useful for communicating with other providers.

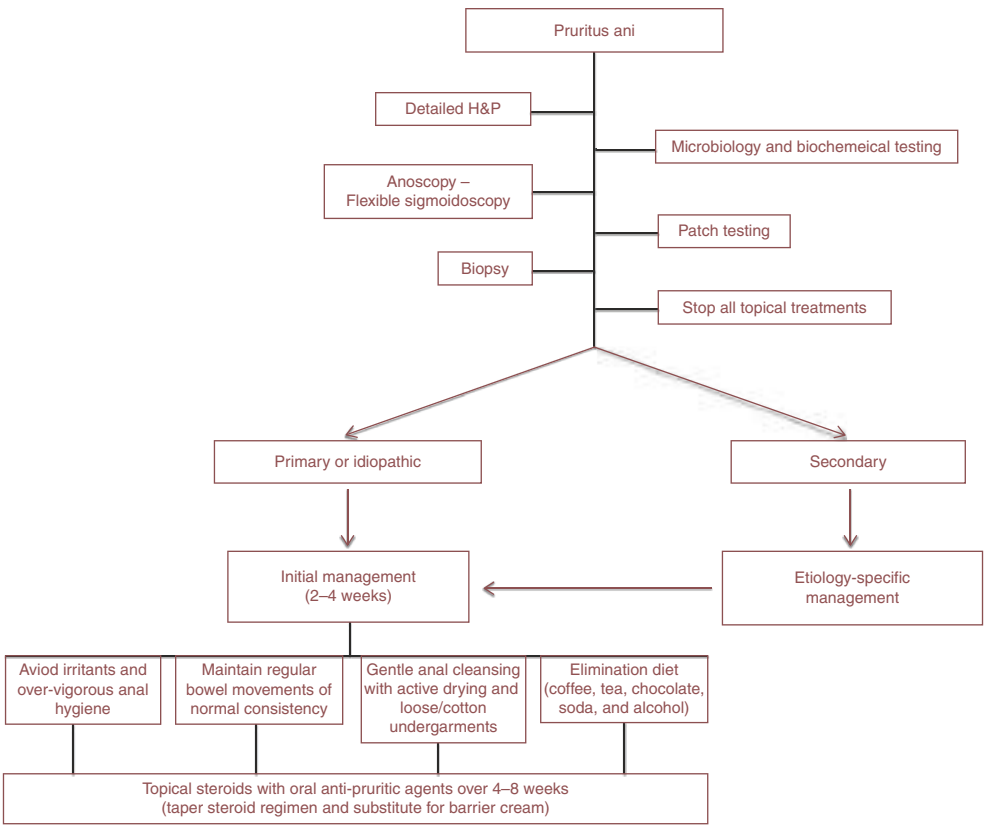

FIGURE 18-3. Diagnostic and treatment algorithm for patients presenting with pruritus ani.

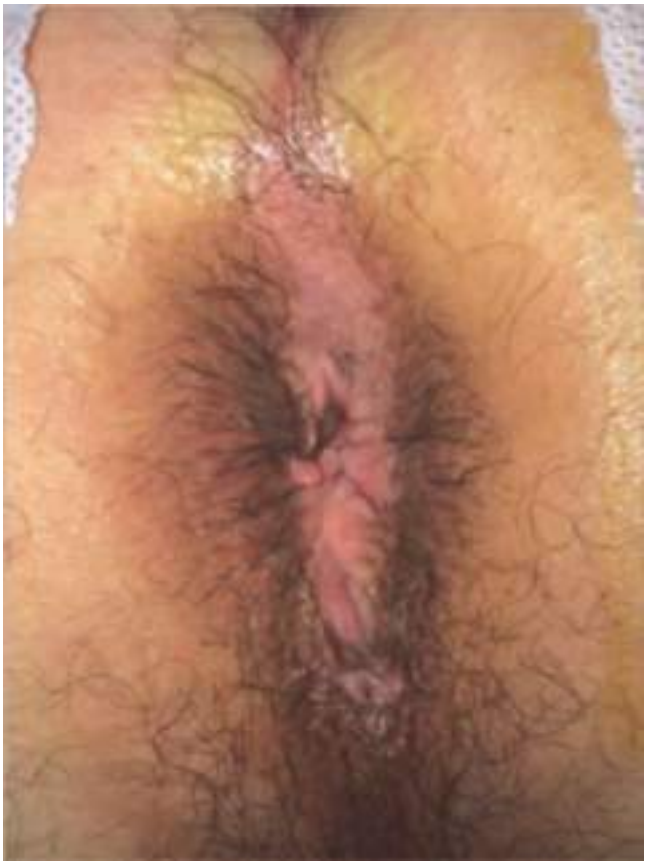

FIGURE 18-4. Hyperpigmentation and perianal skin lichenification seen in a patient with erythrasma.

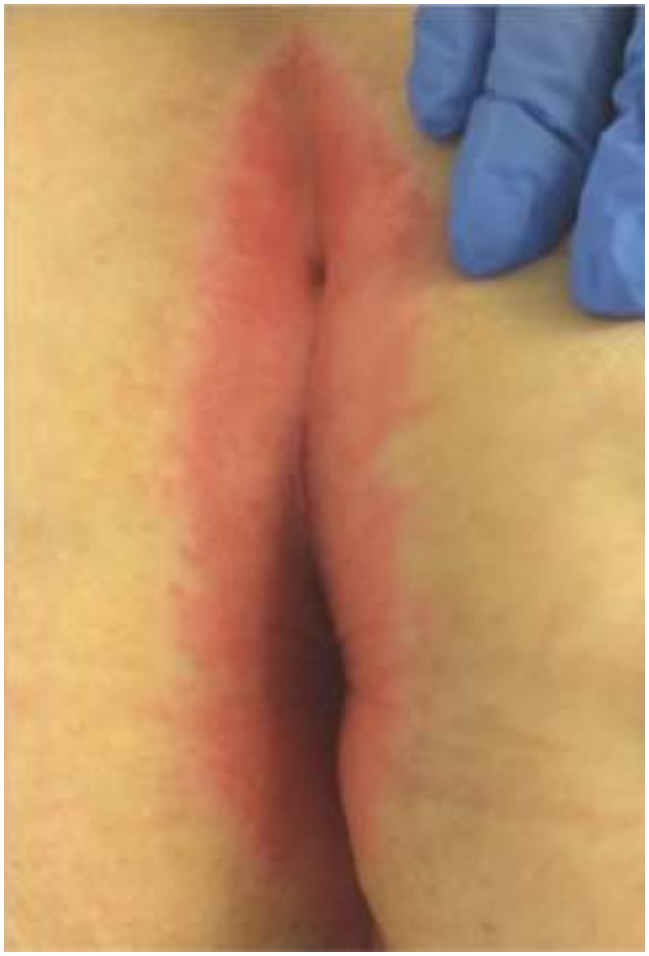

FIGURE 18.5. Perianal fungal infection in a patient with anal seepage and fecal incontinence. This infection is characterized by a bright red rash at the perianal area and intergluteal fold in a "butterfly" distribution.

Infectious

In the setting of bacterial perianal dermatitis, the perianal skin typically shows a moist, bright, and erythematous eruption with distinct borders and no satellite lesions. Patients usually do not have upper respiratory symptoms [28]. Chronic infected discharge from the anus may lead to hyperpigmentation of the anorectal cleft. This finding is commonly seen in patients with long-standing anorectal conditions, including pilonidal disease, anorectal fistulas, and hidradenitis suppurativa. Erythrasma is often associated with scaly, well-defined patches of initially reddish and then brownish-colored lesions at other intertriginous areas (Figure 18-4) [54, 55]. When caused by *Corynebacterium minutissimum*, these lesions show a characteristic coral-red fluorescence when examined with a Wood's lamp. *C. minutissimum* is commonly present and pathogenic at other body folds (axillae, groin, inframammary) and toe webs [54].

Molluscum contagiosum has a distinct presentation with clusters of small, palpable, flesh-colored papules with central umbilication. In general, human immunodeficiency virus (HIV)-associated lesions rarely present with itching except for secondary fungal infections. Perianal fungal infections are characterized by a bright red rash without the cheesy exudate sometimes seen in other parts of the body (Figure. 18-5). These infections may present following treatment with systemic antibiotics and topical or systemic steroids [56]. *Candida* is commonly found in patients with pruritus secondary to common anorectal conditions (i.e., hemorrhoids, fissure) and is typically eliminated with adequate treatment of the underlying condition [57]. Infections where *dermatophytes* are cultured almost always present with pruritus and are considered pathogenic, as compared to infections caused by *C. albicans* [30]. Topical steroids may render direct scrapings negative for hyphae but frequently facilitate *dermatophyte* growth.

Dermatologic

Anal eczema or contact dermatitis is characterized by erythema, scaling, and vesicles. Similar findings may be located on the face, neck, dorsum of the hands, as well as popliteal and antecubital fossas. Atopic dermatitis presents as nonspecific and diffuse erythema, often seen with signs of

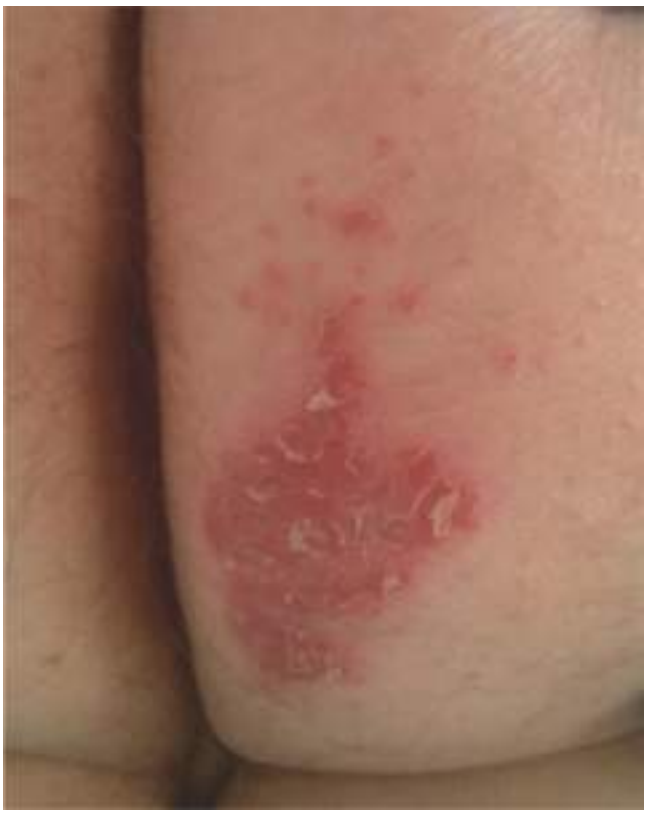

FIGURE 18-6. Perianal psoriasis or psoriasis inversa showing a well-demarcated, scaly, bright red, plaque-like lesion.

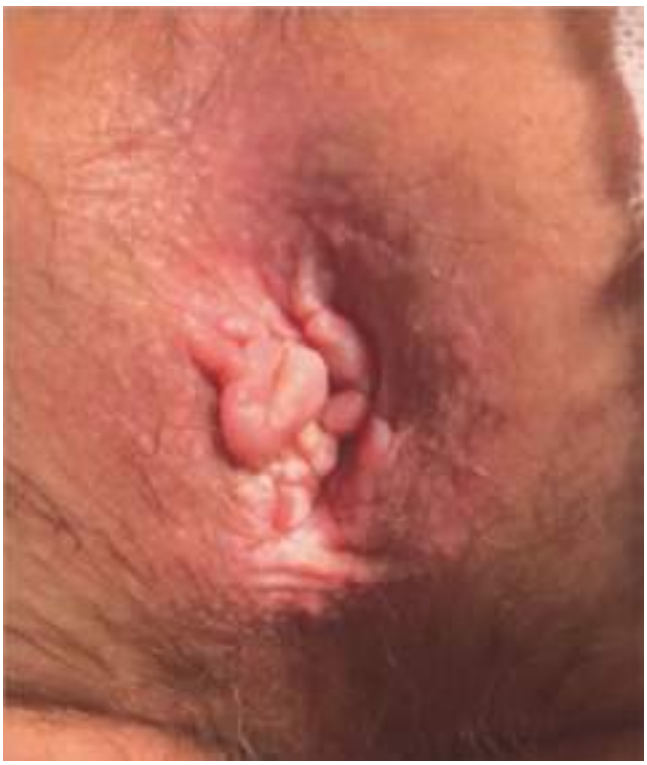

FIGURE 18-7. Lichen sclerosus of the anus with chronic healing showing replacement by chronic inflammation, sclerosis, and atrophy of the affected area.

skin excoriation. Associated findings include: keratosis pilaris (rough sandpaper-like texture over the posterior biceps and thighs), Morgan's folds or Morgan–Dennie lines (redundant creases beneath the eyes), "sniffers" lines (a subtle transverse crease across mid-nose), urticaria, and white dermatographism. With the loss of an adequate epidermal barrier, secondary infections and irritation by contact agents are common in patients with atopic dermatitis.

Psoriasis typically appears as well-demarcated, scaly, plaque-like lesions that are bright red in color (Figure 18-6). Typical lesions are commonly found on the scalp, elbows, knees, knuckles, and penis [18], but perianal psoriasis may also present as an isolated lesion. In the perianal region, lesions tend to be poorly demarcated, pale, and non-scaling because of persistent maceration, hence the term inverse psoriasis [4, 18]. With seborrheic dermatitis, excessive perianal moisture is the common denominator, and special attention should be directed to the scalp, chest, ears, beard, and suprapubic areas since these regions are commonly affected as well.

Lichen planus presents as shiny, flat-topped papules that are darker than the surrounding skin and begin on the volar aspects of the wrists and forearms. Genital and mucous membrane involvement are common [18]. Wickham striae are intersecting gray lines that can be seen if mineral oil is applied to the plaques and help to establish the diagnosis. Lichen sclerosus mainly involves the vulva but typically extends posteriorly toward the perianal region. The first phase of this condition begins as ivory-colored, atrophic papules that break down and expose underlying erythematous raw tissue. This process is severely pruritic and painful. As this heals, the area is replaced by chronic inflammation, sclerosis, and atrophy of the affected area (Figure 18-7). The classical finding is white patches around the vulva and anus [4, 18]. Histologically, these lesions are consistent with a chronic scar, lacking a lymphocytic interface (Figure 18-8) [41, 58–61]. Because of a reported 4–6 % risk of developing squamous cell carcinoma, all nonresponders or those with recurrent sclerosis should have a skin biopsy to rule out malignancy [27, 62]. Treatment of the disease does not appear to modify this risk [63].

Lichenification is the characteristic finding seen in patients with lichen simplex chronicus or neurodermatitis. The perianal skin appears thickened and is commonly described as cracking and scaling. Patients frequently have a history of an anorectal operation that involved a chronic wound or delayed healing.

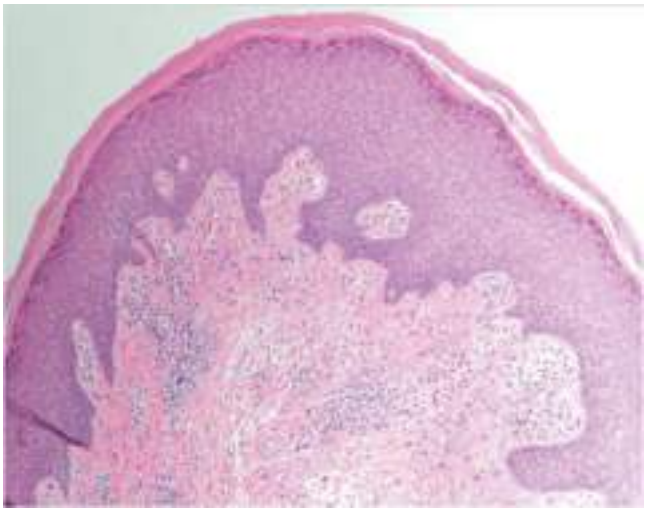

FIGURE 18-8. Photomicrograph of lichen sclerosus showing signs of chronic scaring and lack of lymphocytic interface dermatitis.

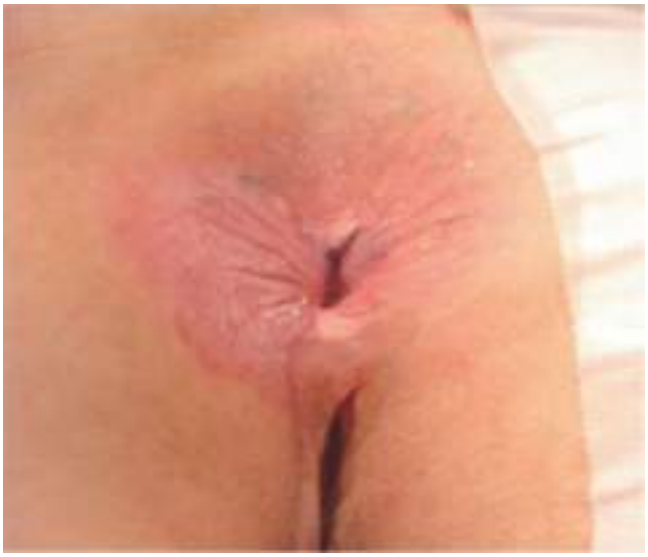

FIGURE 18-9. Perianal Paget's disease presenting with anal pruritus.

Neoplasms

The presentation of dermatologic malignancies, such as Paget's and Bowen's disease, may vary from a mild rash to a florid type of eczema at times associated with indurated skin. The classic presentation is an erythematous and eczematoid perianal plaque (Figure 18-9). Infiltrative processes may be less well defined in Paget's disease with the same caveat about margins. Pruritus and bleeding are the most common complaints [48]. Other symptoms include pain, mucous seepage, lump, and difficulty with defecation [64].

Biochemical Testing

After failed topical management and if systemic disease is suspected, biochemical testing is warranted. Common laboratory tests to rule out systemic and infectious causes include liver and kidney function tests, blood glucose level, white blood cell count with differential, C-reactive protein, and erythrocyte sedimentation rate. These tests are most useful in patients with decompensated chronic systemic disease like hepatic and renal failure and severe perianal infections.

Microbiology Testing

Cultures of perianal skin exudates and infectious material are simple and straightforward but can be misleading if not performed adequately. Infected material should be aspirated with a syringe and expelled into a sterile container. Alternatively, a swab may be used to collect a specimen but this is less than ideal. Culture specimens should be placed in appropriate media (anaerobic, bacterial, fungal, and viral) and refrigerated without delay. Viral cultures should be kept on ice. Fluid from vesicular lesions should be aspirated or taken with a swab from the base of an unroofed lesion and placed on a cell culture media or a microscopic slide for Tzanck smears if herpes zoster is suspected [65]. Swabs should be lubricated with saline if lubricated at all because conventional water-soluble lubricant is bactericidal for some organisms including *Neisseria gonorrhoeae*. Skin scrapings may be submitted for fungus culture. Scrapings can also be examined for hyphae with KOH prep, but this test is rarely available because of the lack of trained and experienced personnel. It is essential to have discussed the proper arrangements with the laboratory and nursing personnel (clinic and operating room) to assure adequate specimen handling and testing well before obtaining a specimen.

In patients with diarrhea, bacterial stool cultures as well as ova and parasites on three different stool samples can be useful. In patients with suspected or confirmed streptococcal or staphylococcal perianal infections, nasal or throat swabs rarely detect the offending bacteria and therefore are unnecessary [42]. If pinworms are suspected, a cellophane or scotch tape test in the early morning identifies adult worms and their eggs and confirms the diagnosis [4].

Patch Testing

Patients with an extensive list of allergies, both dietary and drug related, are good candidates for patch testing. This usually involves a dermatologic consultation, which can be very helpful when the staff has a particular interest in perianal dermatology. As part of a diagnostic algorithm in a prospective study of patients with clinical suspicion of anal eczema, Kranke and colleagues [26] found that patch testing was confirmatory in 33 of 58 patients (57 %), with at least one positive

Table 18-4. Patch test findings in 58 consecutive patients suspected of having allergic contact anal eczema [26]

Contact allergen	*N* (%)
Thimerosal	11 (19)
Patients own products	6 (10)
Balsam of Peru (*Myroxylon pereirae*)	5 (9)
Amerchol	3 (5)
Lanolin alcohol	3 (5)
Nickel sulfate	3 (5)
Fragrances/perfumes	3 (5)
Lidocaine, benzocaine	2 (3)
Propolis	1 (2)
Neomycin	1 (2)

allergic reaction (Table 18-4). It is important to also test the patient's own products as these have been shown to be a significant etiology in pruritus ani [1, 26].

Endoscopic Evaluation

All patients with pruritus ani should undergo anoscopy and flexible sigmoidoscopy. These exams are especially useful in patients with anorectal pathology and inflammatory bowel disease. Full colonoscopy is indicated for patients who are age-appropriate for colorectal cancer screening and those with hematochezia, iron-deficiency anemia, and positive family history of colorectal cancer.

Biopsy

Skin lesions not responding to treatment or suspicious for malignancy require biopsy. This is the single most valuable test in patients with primary pruritus ani and should include an area of the lesion with adjacent normal skin. Specific query should be made to a pathologist with expertise in dermatologic pathology with clinically suspected diagnoses. Biopsy may conveniently be done with either an 11 blade or skin punch blades (Keyes dermal punches) that come in numerous sizes in separate sterile packages. Bleeding is readily controlled with silver nitrate or topical thrombin-based hemostatic agents.

Evidence-Based Management

The management of dermatologic diseases of the anus in practice is particularly challenging for several reasons. These conditions are hidden on a part of the body often associated with embarrassment, and therefore patients may have advanced disease before they present to a doctor for help. Additionally, there is limited class A data regarding the management of pruritus ani.

Aims of Treatment

The aims of treatment for any form of anal dermatitis are rapid relief of symptoms, healing of dermatitis, and prevention of recurrence. Long-term recurrence can be prevented in many patients by avoiding contact with allergens and irritants, as well as curing the underlying anorectal disease or condition. The choice of treatment must take into account the different causative factors: irritation from contact, allergic contact, infection, primary inflammatory disease, and neoplasia. Treatment of underlying anorectal conditions (hemorrhoids, fistula, incontinence, etc.) should be initiated from the first patient visit.

Primary Pruritus Ani

Because primary or idiopathic pruritus ani is more common, a therapeutic trial of generic management is recommended. This will be effective in more than 90 % of patients [6]. This management strategy focuses on reestablishing ideal anal hygiene and providing reassurance that there is no underlying condition causing the symptoms. Treatment begins with avoiding known irritants such as soaps, lotions, creams, perfumed powders, medicated baby wipes, and any product with witch hazel. The patient must also know to avoid further trauma to the perianal skin, which may be caused by scratching, dry toilet paper, and vigorous scrubbing with bathing. Gently blotting the skin clean with moist toilet paper, a cotton ball, or a soft, unscented, and non-medicated baby wipe is recommended. Generally, baby wipes of all types should be avoided, especially when contact and atopic dermatitis is suspected. An important part of the initial management of primary pruritus ani is to avoid moisture and keep the perianal area dry. Patients should avoid tight-fitting, synthetic undergarments and may also use a small piece of cotton or makeup removal pad to help soak up any excess moisture. The brief use of a hair dryer with cool air is an excellent way to keep the perianal skin dry after cleansing. Unscented Dove® (Unilever, London, UK) is free of conventional soap and is the preferred bathing agent. It is also important for patients to maintain regular bowel movements of normal consistency. This is especially useful to avoid seepage and fecal contamination of the perianal skin. A high-fiber diet without excessive fluid intake and the judicious use of loperamide or cholestyramine is recommended, as needed. As mentioned earlier in this chapter, an elimination diet excluding "high-risk" dietary components such as coffee, tea, chocolate, soda, and alcohol for 2 weeks can be strongly considered in most patients with primary pruritus ani. Smith et al. [39] showed that an elimination diet gave partial or complete relief in 27 of 56 (48 %) of their patients.

In those patients in whom the initial management strategy is not effective after 4–6 weeks, attention is directed toward excluding the multiple potential causes of secondary pruritus

Table 18-5. Marketed topical products most commonly prescribed for the treatment of perianal dermatitis [66]

Active ingredients	Brand name(s)
Single active agents	
Hydrocortisone	Procto-Kit, DermoPosterisan
Tribenoside	Borraza-G
Cinchocaine	Dolapostern
Glyceryl trinitrate	Rectogesic
Corticosteroids + local anesthetics	
Hydrocortisone + pramocaine or cinchocaine or lidocaine or benzocaine + amylocaine + esculin	Pramosone, Proctofoam, Proctocream-HC, Proctosedyl, Xyloproct
Prednisolone + cinchocaine or + desonide + lidocaine + heparin + vitamins A and E	Scheriproct, Cirkan
Diflucortolone + lidocaine	Neriproct
Fluocinonide + lidocaine	Jelliproct
Fluocortolone + lidocaine or cinchocaine	Doloproct, Ultraproct
Fluocinolone + lidocaine (+ menthol + bismuth)	Synalar Rectal
Corticosteroids + antimicrobials/antiseptics	
Hydrocortisone + benzyl benzoate + Peru balsam + bismuth + zinc with or without resorcinol	Anusol-HC
Corticosteroids + local anesthetics + antimicrobials/antiseptics	
Hydrocortisone + cinchocaine with neomycin + esculin or framycetin	Proctosedyl
Local anesthetics + antimicrobials/antiseptics	
Cinchocaine + policresulen	Faktu
Other combinations	
Trimebutine + ruscogenin	Proctolog
Peru balsam + bismuth + zinc	Anusol
Hydrocortisone + *Escherichia coli* suspension	Posterisan
Hydrocortisone + phenylephrine + paraffin oil + fish oil	Preparation H
Lidocaine + carraginates + zinc	Titanoreine

Products with >10,000 prescriptions in 2011 according to IMS data for Brazil, France, Germany, Japan, the UK, and the USA [66]

ani. If no secondary cause can be found, topical therapy is recommended (Table 18-5). After generic management and proper anal hygiene are assured, topical steroids are an effective and safe treatment option. First-line topical treatment includes preparations with a low-potency topical steroid such as 1 % hydrocortisone, which should not be given for more than 8 weeks. In a double-blinded, randomized trial, 11 patients with primary pruritus ani received 1 % hydrocortisone or placebo for 2 weeks followed by the opposite treatment for another 2 weeks [67]. There was a washout period of 2 weeks between treatments. Treatment with 1 % hydrocortisone resulted in a 68 % reduction of itch using a visual analogue score, and 75 % showed significant improvements in quality of life. Potent or extended use of topical steroids should be avoided as they can lead to skin atrophy, infections, and worsened pruritus ani (Figure 18-10) [18, 27]. Capsaicin has also been studied in a randomized fashion in 44 patients with primary pruritus ani [68]. This topical agent decreases levels of substance P, a neuropeptide that triggers itching and burning pain. Topical capsaicin (0.006 %) showed relief of symptoms in 70 % of patients as compared to 2 % patients who received placebo (1 % menthol).

The majority of patients with moderate symptoms and minimal skin changes will respond well to low-dose topical steroids or topical capsaicin. These preparations are applied at night and in the morning after bathing. If topical steroids are used, a tapering regimen should be set in place ending with substitution of a barrier cream such as Calmoseptine® (Calmoseptine, Inc., Huntington Beach, CA). Patients with chronic perianal skin changes should be managed with a medium- or high-potency steroid (Table 18-6). It is important to emphasize to patients that a high-potency steroid should be used for a limited period of time, generally 4–8 weeks. Once normalization of the skin has occurred, patients are switched to a mild steroid that can be further tapered down to bi-weekly applications until total elimination.

Non-irritating cleansers are highly recommended during the initial therapeutic trial, especially when patients do not have a bath or shower directly available. Dilute white vinegar (one tablespoon in an 8-oz glass of water) on a cotton ball is a cheap and effective non-soapy cleanser. It is our personal preference to use tea tree oil, a volatile oil with antibacterial and antifungal properties, in patients with moist perianal skin and pruritus. Patients who come to the office with acute moderate to severe changes of the perianal skin may be treated with Berwick's dye (crystal violet 1 % + brilliant green 1 % + 95 % ethanol 50 % + distilled H2O q.s.ad. 100 %), which is dried with a hair dryer, and subsequently covered with benzoin tincture as a barrier and dried similarly. This topical treatment will stay in place for several days if only water is used to cleanse, relieves symptoms rapidly, and allows for re-epithelialization of broken-down skin. Application of Berwick's dye to the perianal skin is especially useful for pruritus ani occurring after anorectal operations.

FIGURE 18-10. Chronic skin changes of atrophy and ulcerations secondary to pruritus ani with associated left buttock infection in a patient who had been taking steroids for 8 years.

TABLE 18-6. Relative potency of topical steroids

Group 1 (most potent)
Betamethasone dipropionate 0.05 % (Diprolene®)
Clobetasol propionate 0.05 % (Temovate®)
Group 2
Desoximetasone 0.25 % (Topicort®)
Fluocinonide 0.05 % (Lidex®)
Group 3
Betamethasone valerate ointment 0.1 % (Valisone®)
Triamcinolone acetonide 0.5 % (Aristocort®)
Group 4
Desoximetasone 0.05 % (Topicort LP®)
Flurandrenolide 0.05 % (Cordran®)
Group 5
Betamethasone valerate cream 0.1 % (Valisone®)
Hydrocortisone butyrate 0.1 % (Locoid®)
Triamcinolone acetonide 0.1 % (Kenalog®)
Group 6 (least potent)
Alclometasone dipropionate 0.05 % (Aclovate®)
Hydrocortisone 1 %

Finne CO, Fenyk JR, Dermatology and pruritus ani. In: Fleshman JW, Wolff BG, editors. The ASCRS textbook of colon and rectal surgery. New York: Springer; 2007. p. 277–294) [69]. © Springer

Skin breakdown or maceration caused by scratching or over vigorous cleansing efforts must be avoided. A combination of topical and systemic medications has shown the best results compared to either alone. Doxepin (both topical and oral) and hydroxyzine are effective adjuncts to reduce or eliminate itching. Doxepin, a tricyclic antidepressant, possesses both anti-H1 and anti-H2 activity. Hydroxyzine, a potent H1 receptor inverse agonist, has shown to have equal antipruritic efficacy compared to oral doxepin but with higher sedation effects [70]. Although centrally acting agents such as gabapentin and paroxetine have shown to be effective antipruritic agents in uremic and cholestatic patients [71], their efficacy in patients with pruritus ani has not been studied. Our experience with gabapentin in severe refractory pruritus ani has been quite rewarding. Patients may not be aware of nocturnal scratching and this can be a serious contributing factor in many cases of primary pruritus ani. Patients who are awakened by the urge to scratch should gently cleanse the perianal skin and reapply their barrier ointment.

For intractable cases or primary pruritus ani, intradermal injection of methylene blue has been described with some efficacy (Figure 18-11) [27, 72]. The presumed mechanism of symptomatic improvement is through the destruction of nerve endings. This treatment modality was initially

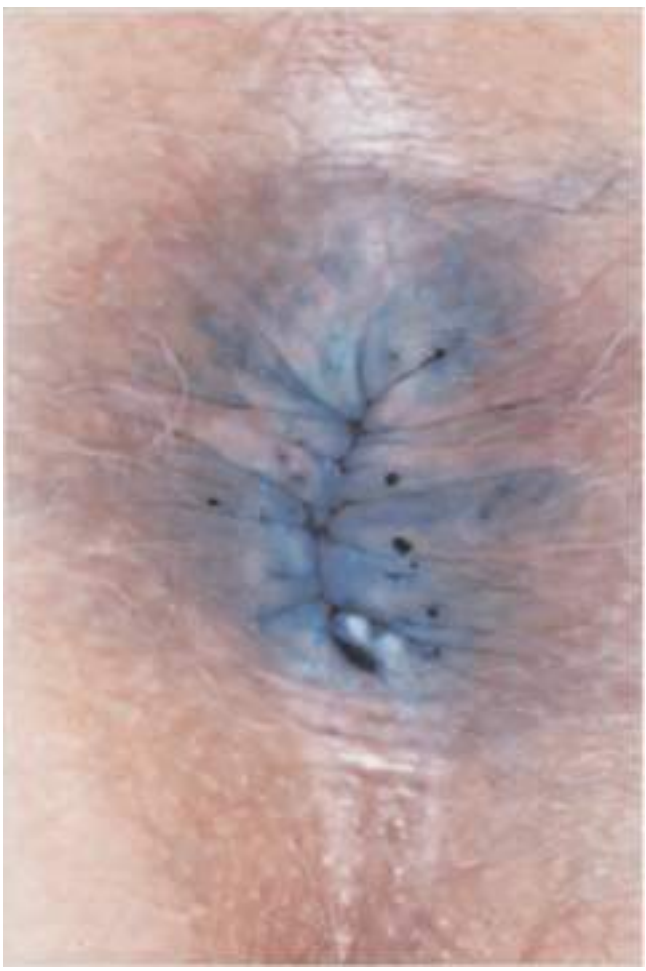

FIGURE 18-11. Tattooing with methylene blue for severe refractory idiopathic pruritus ani. Courtesy of C.O. Finne, St. Paul, MN.

described by Eusebio and colleagues [72] and involved the intracutaneous and subcutaneous injection of 30 mL of 0.25 % bupivacaine with 1:200,000 epinephrine mixed with equal volumes of 0.5 % lidocaine at the anoderm and perianal areas, with the patient under deep sedation in the operating room. After this, 20–30 mL of 0.5 % methylene blue was injected at the same sites using a 25-G spinal needle. Twenty-one of 23 patients reported good short- and long-term results. However, the authors also reported full-thickness skin necrosis in three patients. Mentes et al. [73] used a slightly different technique in 30 patients with intractable primary pruritus ani. Patients underwent intradermal and subcutaneous injection of a mixture of 7–8 mL of 2 % methylene blue with equal volumes of 0.5 % lidocaine without previous local anesthesia or sedation. For patients who had a partial response at 1-month follow-up, a "rescue treatment" was offered. At 1 month, 80 % of patients were free of symptoms. Five patients underwent an additional "rescue" injection and four of five had complete relief of symptoms. No major complications or cases of skin necrosis were reported. The authors attributed this to a smaller injected volume.

Secondary Pruritus Ani

Infectious

Bacterial infections of the perianal region should be treated with systemic antibiotics. If a specific agent has not been identified, antibiotic coverage should include Gram-positive and Gram-negative cocci. Parenteral antibiotics have been reported to be especially useful with *Staphylococcus aureus* infections [74]. When refractory pruritus ani is associated with cultures that show growth of *Candida albicans*, antifungals should be given, especially in patients who are immunosuppressed, who are diabetic, or who were recently treated with systemic steroids or antibiotics [27]. We have seen good results with a combination of oral fluconazole and topical luliconazole 1 %, given for 2–3 weeks. Again, when *dermatophytes* are found in the setting of pruritus ani, this associated fungal infection should also be treated appropriately [27]. The treatment of erythrasma involves systemic antibiotics, typically erythromycin 250 mg *qid* for 10 days. Tetracycline may be used as a second alternative [54, 55]. Silver sulfadiazine is an effective topical adjunct in patients with bacterial perianal dermatitis, especially in patients with ulcerations and fissuring skin as it sooths and promotes re-epithelialization. It should be noted that when topical therapy is given with systemic antibiotics and antifungals, it should be for symptom relief but not as the primary antibacterial or antifungal agent.

Dermatologic

With regard to anal eczema, both the European and American Academy of Allergy, Asthma, and Immunology guidelines recommend starting treatment with basic skin care. Keys to success include avoiding allergens, irritants, and tight constricting undergarments, liberal use of warm sitz baths for comfort, and keeping the affected area dry at all other times. As mentioned above, gentle but thorough cleansing of the perianal area with soap substitutes (i.e., Dove) is recommended during bathing [75]. When these methods fail, mild-to-moderately potent topical corticosteroids for 2–3 weeks periods are recommended. The efficacy of topical steroids compared to placebo has been studied in a small, double-blinded, randomized controlled trial, favoring topical steroid treatment [66]. Topical calcineurin inhibitors such as tacrolimus and pimecrolimus are also effective for reducing inflammation and itch in patients with anal eczema and also avoid skin atrophy. Two randomized controlled trials comparing topical tacrolimus 0.1 % to placebo in a total of 53 patients with chronic idiopathic pruritus ani showed significant symptomatic improvement up to 6 weeks follow-up [76, 77]. One of these studies failed to show significant differences in quality of life as assessed by the Dermatology Life Quality Index questionnaire [77]. Although systemic gamma interferon and narrowband UVB therapy have shown promising results in patients with atopic dermatitis as well as cholestatic and uremic pruritus [78, 79], no evidence in patients with pruritus ani exists. Of importance, bacterial and fungal infections should be suspected after multiple or prolonged unsuccessful treatments.

Treatment of atopic dermatitis begins with providing a barrier such as Vaseline® (white petrolatum USP) or Calmoseptine® (Calmoseptine, Inc., Huntington Beach, CA), the use of anti-inflammatory agents (systemic and topical) and antipruritic agents. Psoriasis is not a curable condition, but symptoms can be well controlled with mild topical steroid preparations (i.e., 1 % hydrocortisone cream). Seborrheic dermatitis responds well to 2 % sulfur with 1 % hydrocortisone or miconazole lotion [80]. Keeping the perianal area clean and dry is essential for treatment success.

Lichen sclerosus is initially managed with topical steroids. Potent topical steroid creams, such as clobetasol 0.05 %, for a short course (4–6 weeks) followed by less potent hydrocortisone cream are the mainstay of treatment. Systemic steroids are given only for very severe cases [18, 42]. Topical calcineurin inhibitors are effective alternatives in the treatment of lichen sclerosus in patients who have failed therapy with potent corticosteroids or who have a contraindication for the use of corticosteroids [81]. Treatment with retinoid and testosterone creams may be useful in selective cases [28, 43]. Patients should be followed periodically for raised lesions or ulcers that fail to heal, and it is important to explain to patients that the appearance of the vulvar and perianal lesions may never change even if the symptoms are relieved [43]. The treatment of lichen simplex chronicus or neurodermatitis begins with topical steroids to decrease the inflammation and break the itch-scratch-itch cycle. Antihistamines, doxepin, or capsaicin creams are effective adjuncts to topical steroids. For patients who have a poor response to topical steroids, topical

acetylsalicylic acid/dichloromethane or immunomodulators, such as tacrolimus, have shown positive results [44].

Treatment of perianal Paget's disease requires wide local excision. Adequate microscopically clear margins and ruling out invasive disease are important to avoid clinical recurrence [82]. Positive skin margins are a common occurrence after excision; therefore, preoperative and intraoperative planning should involve a detailed discussion with an experienced pathologist regarding specimen location and orientation. Invasive disease is treated with abdominoperineal resection and delayed margin positivity requires re-excision. Soft-tissue and skin reconstruction frequently requires V–Y gluteal flaps or skin grafting, with the assistance of plastic surgery. It is important for the patient to be aware of the possibility of radical resection, delayed re-excision of margins, and stoma. Recurrence of disease is common and may occur up to a decade after initial excision [18]; therefore, regular and long-term follow-up is imperative.

Systemic Diseases

Effective treatment of pruritus ani in patients with poorly controlled or exacerbated systemic disease involves appropriate management of the underlying disease. Occasionally, pruritus will be the presenting symptom in patients with liver failure and diabetes mellitus. Appropriate skin cleansing, application of a topical barrier, and antipruritic agents are the mainstay of treatment. Cimetidine has been reported to eliminate itching induced by lymphoma and polycythemia vera. In our experience, doxepin and gabapentin are also effective antipruritic agents in patients with systemically induced pruritus ani. Chronic itching in these patients may also lead to lichenification and secondary infections. Appropriate systemic antibiotic or antifungal therapy is warranted.

In summary, perianal dermatologic conditions include a wide variety of diagnoses that require comprehensive and stepwise diagnostic and management algorithms. These conditions are likely to be much more common than estimated in the current literature, mainly because of the embarrassment associated with seeking medical attention as well as the relapsing and chronic nature of idiopathic etiologies. Patients with primary pruritus ani refractory to treatment should be aware of this chronicity and focus on symptom control instead of symptom eradication and also understand the potential need for treatment strategies for relapsing disease or flares.

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19
Sexually Transmitted Infections

Cindy Kin and Mark Lane Welton

Key Concepts

- Nucleic acid amplification tests are superior to culture to screen for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* infections. The best specimens are vaginal or endocervical swabs from women and first catch urine samples from men.
- Nucleic acid amplification tests for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* can be used for rectal and oropharyngeal specimens in addition to genital sites to increase the sensitivity of testing.
- If one suspects failure of standard antibiotic treatment for gonococcal infection then a culture needs to be performed to evaluate antibiotic susceptibility.
- Male and female patients with infections causing rectal or genital ulcerations are at increased risk for HIV infection, compared to patients with non-ulcerative STIs.
- Patients diagnosed with syphilis should be tested for HIV. Patients with HIV should be regularly screened for syphilis.
- Empiric treatment for proctitis in populations at high risk for STIs should be given at the time of evaluation rather than waiting for test results, and should consist of treatment for gonorrhea, chlamydia/lymphogranuloma venereum, and genital herpes.
- Herpes simplex virus is a common cause of proctitis in men who have sex with men and often present without visible external ulcerations.

Introduction

This chapter discusses sexually transmitted infections (STIs) that are likely to be encountered by colorectal surgeons. Clinicians must maintain a high level of suspicion for STIs to avoid delays or errors in diagnosis. A frank discussion of the patient's sexual history should direct STI testing and empiric therapy.

A substantial proportion of patients with STIs are completely asymptomatic. Overall, 7 % of men who have sex with men (MSM) undergoing screening for STI test will be positive for at least one infection. Asymptomatic MSM who report an STI exposure have a 17 % chance of testing positive for at least one STI. An HIV-positive MSM with an STI is twice as likely to be asymptomatic from the STI than an HIV-negative MSM with an STI [1].

"Sexually transmitted diseases" and "sexually transmitted infections" are interchangeably used terms, but the latter has been increasingly adopted to emphasize that infections may not cause symptoms of disease, nor may they result in development of disease. For example, infection with the human papillomavirus may not develop into the diseases of cervical cancer or anal cancer. This term is also regarded as less stigmatizing and thus may result in improved testing rates.

This chapter will discuss the diagnosis and management of STIs, as well as the risk factors for infection and public health concerns related to the infections.

Screening Guidelines for Asymptomatic High-Risk Patients

The predominant risk factor for contracting STIs is high-risk sexual behavior. Other risk factors include current infection with ulcerative STIs and HIV seropositivity. MSM, especially those who engage in unprotected receptive anal intercourse, represent the demographic group at greatest risk for STIs and should undergo regular universal testing for STIs. People in high-risk sexual networks such as swingers are also at very high risk for STIs and should also undergo universal testing for STIs. A policy of universal testing can help to stop the cycle of ongoing transmission of STIs within these networks [2].

Furthermore, MSM and other high-risk populations including prostitutes and swingers should undergo testing for STIs (mainly, chlamydia and gonorrhea) at anorectal,

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TABLE 19-1. Initial sexually transmitted infections (STI) testing and empiric therapy by symptom

Symptom	Suspected etiology	Testing	Empiric therapy
Genital, anal, perianal ulcers	Herpes Syphilis Chancroid Donovanosis	Syphilis serology HSV culture or PCR HIV *H. ducreyi* testing in settings where chancroid is prevalent	Treatment for HSV or syphilis depending on clinical suspicion
Proctitis	Gonorrhea Chlamydia Syphilis Herpes	Intra-anal swabs for chlamydia and gonorrhea and HSV culture or PCR	Treatment for gonorrhea, chlamydia/LGV, and herpes depending on clinical suspicion and risk factors
Proctocolitis	*Campylobacter*, *Shigella*, and *Entamoeba histolytica* LGV	Stool studies NAAT for chlamydia	
Enteritis	*Giardia*	Stool studies	

HSV herpes simplex virus, *LGV* lymphogranuloma venereum, *PCR* polymerase chain reaction, *NAAT* nucleic acid amplification tests

oropharyngeal, and urogenital sites, as isolated non-urogenital infections represent the majority of infections in both MSM and high-risk women. With testing at multiple anatomic sites, over 10 % of MSM had chlamydia and 6 % had gonorrhea, while 7 % of female prostitutes and swingers had chlamydia and 3 % had gonorrhea. Given that most of these infections were isolated non-urogenital infections, the practice of coincidental treatment is an inadequate strategy for controlling transmission of these infections [3].

Screening Guidelines for Symptomatic Patients

Symptoms of STIs may include painful or painless perianal or genital lesions; rectal, vaginal, or urethral discharge; or proctitis. Table 19-1 details the suspected etiologies, recommended testing, and empiric therapy by symptom class.

Perianal or Genital Lesions

Lesions or other symptoms involving the anus and perianal skin may be easily mistaken for other diagnoses, such as fissure or hemorrhoid disease, delaying appropriate treatment. Lesions in the perianal skin may also be misdiagnosed as a perianal fistula or abscess, folliculitis, hidradenitis, or pruritus ani. Patients (and sometimes their physicians) are likely to assume that any discomfort in the anal region can be attributed to hemorrhoids and will start empiric treatment for hemorrhoids without confirming the diagnosis. Thus, it is imperative to perform at least a visual inspection of the perianal skin and anal canal when evaluating any anorectal complaint. Digital exam with anoscopy should also be performed if the patient can tolerate it.

Genital lesions in young sexually active patients are most likely to be genital herpes or syphilis. Less commonly, chancroid and donovanosis may also be the cause of genital ulcers.

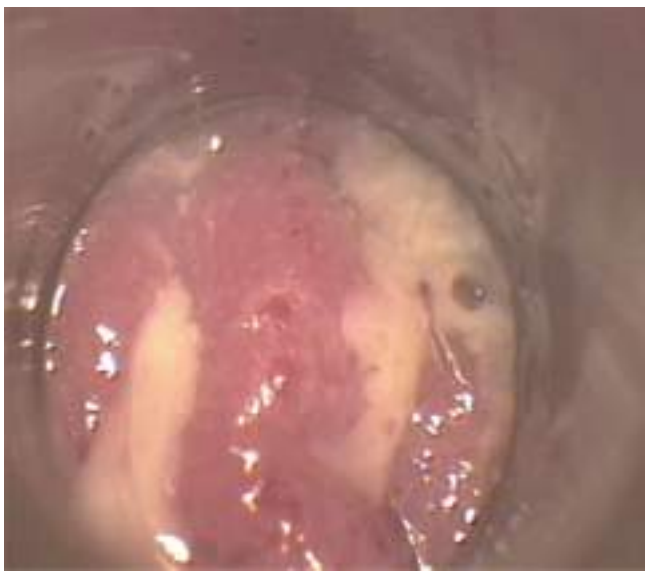

FIGURE 19-1. Patients with STIs may present with proctitis, characterized by anorectal pain, tenesmus, and mucopurulent discharge. Proctoscopy may not be possible due to pain.

Patients should undergo serologic testing for syphilis and HSV culture or PCR, as well as HIV testing. Empiric treatment of the most likely pathogen should be started. Painless lesions may be condyloma or other HPV-related dysplasia. The genital lesions of molluscum contagiosum may cause pruritus.

Proctitis

Proctitis is inflammation of the rectum, causing symptoms of anorectal pain, tenesmus, and discharge (Figure 19-1). The suspected etiologic agents are *N. gonorrhea*, *C. trachomatis*, *T. pallidum*, and HSV. Patient discomfort may preclude a proctoscopic examination, but intra-anal swabs for chlamydia and gonorrhea and HSV can and should be performed. Swabs should be taken before doing a rectal

exam with lubricant given its bacteriostatic properties. Infectious proctitis is often misdiagnosed as inflammatory bowel disease so it is important to elicit a clear sexual history to help distinguish between the two. Anorectal pain and bleeding may also signal the presence of a malignancy such as anal or rectal cancer.

Patients who present with both symptoms of proctitis as well as anal ulceration are very likely to have HSV (83 %) or gonorrhea [4]. However, as over two-thirds of MSM with HSV proctitis do not have a concomitant external ulceration, it is important to test for HSV in these patients without the classic herpetic ulcer [4].

HIV-positive MSM presenting with proctitis are more likely than their HIV-negative counterparts with proctitis to be infected with HSV-1 (14 % vs. 7 %) or HSV-2 (22 % vs. 12 %), lymphogranuloma venereum (8 % vs. 0.7 %), or multiple STIs (18 % vs. 9 %). They are equally likely to have chlamydia or gonorrhea [4]. Empiric treatment for proctitis should be given at the time of evaluation rather than waiting for test results and should consist of treatment for gonorrhea (ceftriaxone 250 mg intramuscular × 1 day), chlamydia/LGV (doxycycline 100 mg bid × 21 days), and HSV (valacyclovir 1 g bid × 10 days). Symptom management with topical anesthetics and stool softeners will also be helpful. When test results come back, the medication regimen can be adjusted.

Proctocolitis

Proctocolitis causes symptoms of proctitis (anorectal pain, tenesmus, and discharge) along with diarrhea and abdominal cramps. Lower endoscopy reveals inflammation of the rectal and distal colonic mucosa. Stool studies may reveal fecal leukocytes. The suspected etiologic agents include *Campylobacter*, *Shigella*, and *Entamoeba histolytica*. LGV serovars of *C. trachomatis* may also cause proctocolitis. The route of transmission may be oral or oral-anal.

Enteritis

Symptoms of enteritis include diarrhea and abdominal cramping; since the rectum is not involved, patients will not present with proctitis symptoms. Enteritis acquired as an STI can be attributed to oral-anal contact. The most common etiologic agent is *Giardia lamblia*.

Diagnosis and Management of Sexually Transmitted Bacterial Infections

Testing for Chlamydia and Gonorrhea

Nucleic acid amplification tests (NAATs) are 86 % sensitive and 97 % specific for detecting gonorrhea and chlamydia, regardless of the specimen type used [5]. NAATs are also superior to other forms of testing due to the increased ease of specimen transport. The Centers for Disease Control (CDC) recommends that NAATs be used in all circumstances to detect chlamydia and gonorrhea, except for special circumstances involving prepubescent patients, and potential treatment failures in which cultures are indicated [6].

Gonorrhea

Epidemiology

Neisseria gonorrhoeae is the causative agent in gonococcal infections and represent the second most common notifiable communicable disease in the US with over 300,000 cases reported to the CDC in 2011. This is likely a gross underestimation of the actual disease burden due to underdiagnosis and underreporting. While US public health efforts have made great strides in controlling gonococcal infection, there are still groups within the population suffering from particularly high rates of gonorrhea, including MSM, HIV-positive patients, African Americans, adolescents, and young adults [7].

Clinical Presentation

Most men infected with gonorrhea experience urethritis manifesting as painful urination. They may also experience epididymitis or disseminated infection. Proctitis can also occur in those who engage in anal receptive intercourse. Gonococcal infections in women tend to be asymptomatic although they can cause cervicitis, urethritis, proctitis, and, later, pelvic inflammatory disease.

*Screening and Testing for **N. gonorrhoeae***

MSM with high-risk sexual practices such as multiple anonymous partners and unprotected oral and anal intercourse are at higher risk for gonococcal infections affecting the oropharynx and rectum. For this reason, the CDC recommends routine screening of oropharyngeal, anorectal, and urogenital sites for all MSM who are sexually active and at risk for STI.

NAATs are the recommended testing method given their high sensitivity and specificity [5]. First catch urine or urethral swab is the recommended sample type for men. In women, the recommended sample types are vaginal swabs that can be either self- or clinician-collected or endocervical swab if a pelvic examination is also indicated. First catch urine in women may miss 10 % of infections compared to the other sample types [6]. Rectal and oropharyngeal specimens can also be tested with NAATs. The CDC recommends testing extragenital sites to increase the sensitivity of screening. Patients who test positive by NAAT do not need to undergo routine repeat testing as this does not improve the positive predictive value of the test [6].

Treatment and Management of Gonorrhea

For uncomplicated gonococcal infections, the CDC recommends combination therapy with ceftriaxone 250 mg intramuscular injection plus a single dose of oral azithromycin 1 g, or a 7-day course of oral doxycycline 100 mg twice daily [8]. Azithromycin is preferred due to the high prevalence of tetracycline resistance. Patients with allergies to cephalosporins can be treated with a single oral dose of azithromycin 2 g, but *N. gonorrhoeae* isolates have demonstrated resistance to azithromycin (Figure 19-2).

N. gonorrhoeae culture testing to evaluate for antibiotic susceptibility with rectal or oropharyngeal swab, endocervical swab for women, or urethral swab for men should be performed if treatment failure is clinically suspected, or NAAT positivity persists [6].

Patients who have undergone treatment for gonorrhea should be referred to programs to reduce STI risk and also undergo retesting for gonorrhea at 3 months. Sexual partners of infected patients in the preceding 2 months should also undergo treatment with ceftriaxone and azithromycin [9].

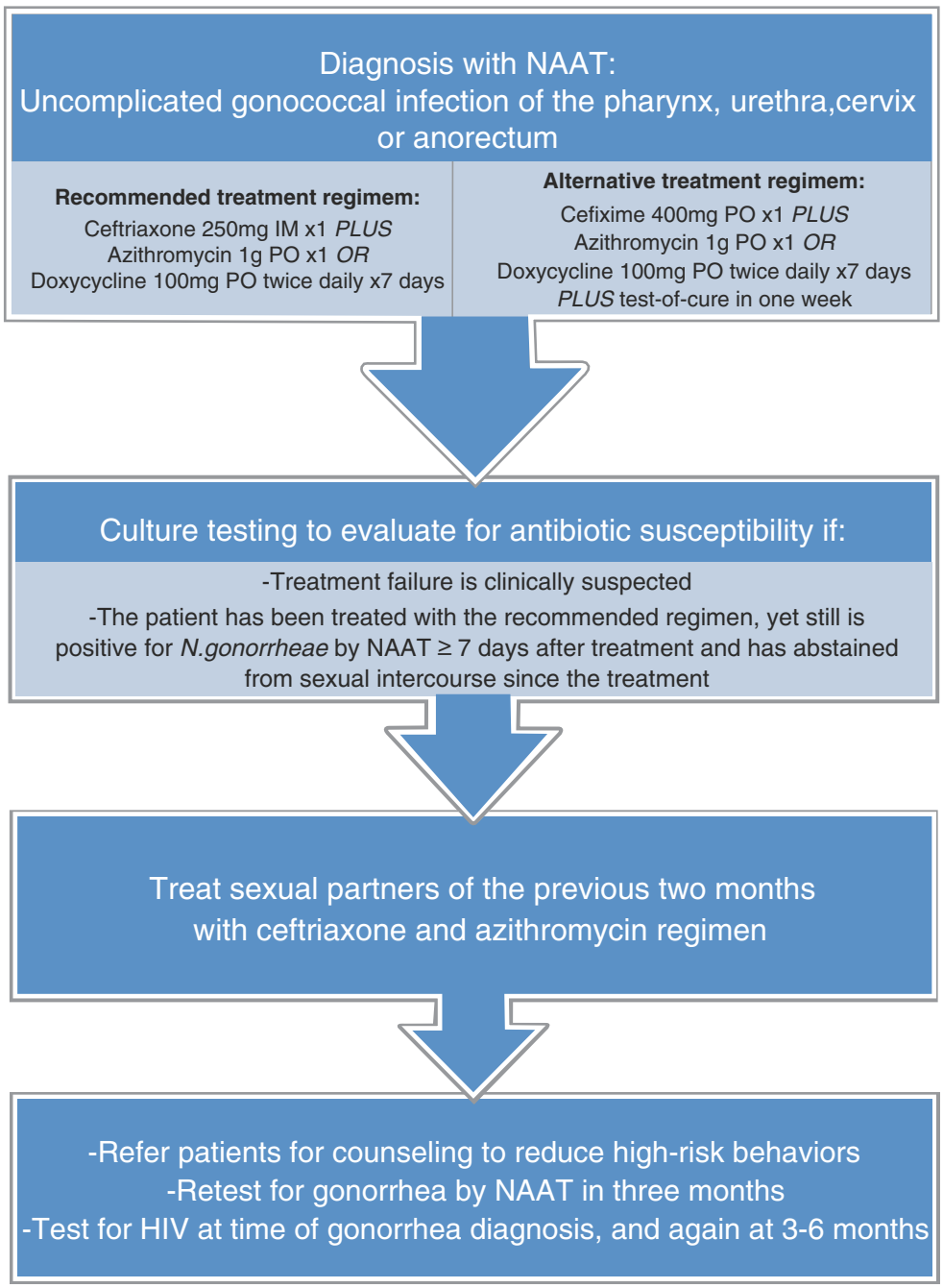

FIGURE 19-2. Treatment algorithm for patients with *N. gonorrhoeae* infection.

As patients with gonococcal infection have a higher risk of HIV infection, they should also undergo testing for HIV at the time of gonorrhea detection and 3–6 months later.

Emerging Antibiotic Resistance

N. gonorrhoeae has a record of developing antibiotic resistance—to penicillins and tetracyclines in the 1980s and then to fluoroquinolones in the 2000s [7]. Resistance to cephalosporins is developing as well, limiting treatment options to third-generation cephalosporins [9, 10]. MSM are more likely than heterosexual men to be infected with resistant strains of *N. gonorrhoeae* [11]. As antimicrobial susceptibility testing is not routinely performed, clinicians need to maintain a high suspicion for treatment failure and must report treatment failures [12].

Chlamydia

Epidemiology

Infection with *Chlamydia trachomatis* is the most common notifiable disease in the USA with over 1.3 million cases reported to the CDC in 2010. The prevalence of urogenital chlamydia is over 11 % and anorectal chlamydia is over 8 % among women undergoing STI evaluation [13].

Clinical Presentation

Most patients with chlamydia are asymptomatic or have such mild nonspecific symptoms that a visit to a physician never occurs, and they never become aware that they are infected. Therefore, screening is crucial to controlling this disease and preventing the severe potential sequelae of pelvic inflammatory disease that increases the risk of infertility (20 %), chronic pelvic pain (18 %), and ectopic pregnancy (9 %). Men with chlamydia infection most commonly have symptoms of urethritis; a smaller proportion has epididymitis and an even smaller proportion experiences infertility as a result of the infection. Infections affecting the rectum are usually asymptomatic and can be attributed to unprotected anal receptive intercourse (Figure 19-3). However, some patients may develop proctocolitis. Ocular infection and reactive arthritis can also occur.

*Screening and Testing for **C. trachomatis***

As for gonorrhea, the recommended testing method for *C. trachomatis* is the NAAT. The recommended sample type for men is a first catch urine or urethral swab. For women, vaginal swab is recommended and if a pelvic examination is indicated then endocervical swab is also an acceptable sample type. Urine samples from women are less sensitive. Rectal and oropharyngeal specimens should also be used for screening to increase the sensitivity of the test. Positive NAATs do not need to be routinely repeated [5, 6].

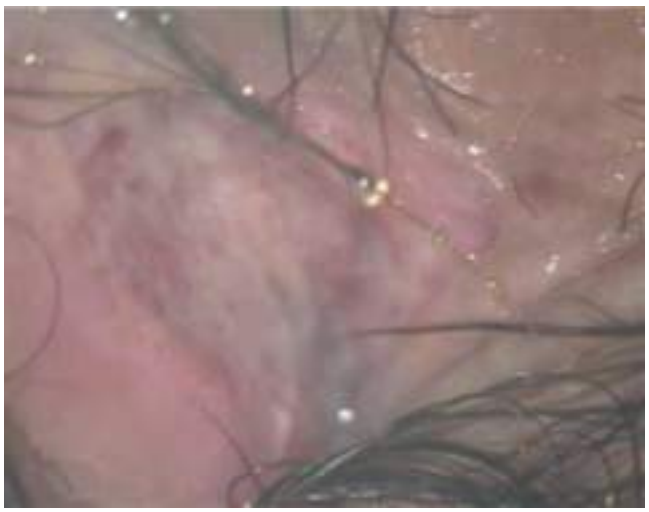

FIGURE 19-3. Chlamydia infection may present with no symptoms, mild symptoms, urethritis, ulcerations, or proctitis. Pictured is an ulcer due to chlamydia infection. Photograph courtesy of Stephen Goldstone, MD.

There is a high incidence of co-occurrence of anorectal and urogenital chlamydia in women—over 94 % of women with anorectal infection also have urogenital chlamydia, and over 71 % of women with urogenital infection also have anorectal infection [13].

Due to its high prevalence and serious sequelae and the potential to reduce the incidence of pelvic inflammatory disease, the CDC and the US Preventive Services Task Force recommend screening sexually active women aged 24 and younger for chlamydia, as well as older women at increased risk for infection [5, 14]. Selective testing based on symptoms and sexual history is an inadequate strategy for identifying most cases of chlamydia infection [13].

Routine universal screening for men is not recommended, as complications from chlamydia infection in men is rare. Chlamydia screening is recommended for certain high-risk male populations based on prevalence data. These populations include men in STI clinics, National Job Training Programs, and juvenile detention facilities, as well as men under 30 years old who are in the military or in jail, and men whose partners have been diagnosed with chlamydia [15]. For all MSM reporting receptive anorectal intercourse, rectal chlamydia screening is recommended [16].

Treatment and Repeat Testing

A single oral dose of 1 g of azithromycin is the recommended treatment for *C. trachomatis* infection and should be given empirically for acute nongonococcal urethritis or for suspected or proven infection in women. A 7-day course of twice daily doxycycline 100 mg is equally effective [17].

TABLE 19-2. Centers for Disease Control recommended antibiotic regimens for bacterial sexually transmitted infections (STIs) [18]

Infection	Recommended regimens	Alternative regimens
Chlamydia trachomatis	Azithromycin 1 g PO × 1 dose or doxycycline 100 mg PO twice daily × 7 days	Erythromycin base 500 mg PO four times daily × 7 days or erythromycin ethylsuccinate 800 mg PO four times daily × 7 days or levofloxacin 500 mg PO once daily × 7 days or ofloxacin 300 mg PO twice daily × 7 days
Neisseria gonorrhoeae	Ceftriaxone 250 mg IM injection × 1 dose *plus* azithromycin 1 g PO × 1 dose *or* doxycycline 100 mg PO twice daily × 7 days	Cefixime 400 mg PO × 1 *plus* azithromycin 1 g PO × 1 *or* doxycycline 100 mg PO twice daily × 7 days plus test-of-cure in 1 week
Acute proctitis in patient with recent receptive anal intercourse, with anorectal exudate or WBCs on gram-stained smear	Treat empirically with: ceftriaxone 250 mg IM × 1 dose plus doxycycline 100 mg PO twice daily × 7 days	
LGV proctitis/proctocolitis (MSM with anorectal chlamydia and proctitis or HIV)	Doxycycline 100 mg PO twice daily × 3 weeks	Erythromycin base 500 mg orally four times daily for 3 weeks
Primary, secondary, or early latent syphilis	Penicillin G benzathine 2.4 million units IM × 1 dose	Doxycycline 100 mg orally twice daily for 2 weeks or tetracycline 500 mg four times daily for 2 weeks (Penicillin-allergic pregnant women with syphilis should undergo desensitization and be treated with penicillin regimen)
Tertiary or late latent syphilis or syphilis of unknown duration	Penicillin G benzathine 2.4 million units IM once per week × 3 weeks	
Neurosyphilis	Aqueous crystalline penicillin G 18–24 million units per day, administered as 3–4 million units IV every 4 h or as a continuous infusion, × 10–14 days	
Chancroid	Ceftriaxone 250 mg IM × 1 dose or azithromycin 1 g PO × 1 dose or ciprofloxacin 500 mg PO twice daily × 3 days or erythromycin base 500 mg PO three times daily × 7 days	
Granuloma inguinale (Donovanosis)	Doxycycline 100 mg PO twice daily[a]	Azithromycin 1 g PO once per week[a] or ciprofloxacin 750 mg PO twice daily[a] or erythromycin base 500 mg PO four times daily[a] or trimethoprim/sulfamethoxazole 800 mg/160 mg PO twice daily[a]

WBC white blood count, *HIV* human immunodeficiency virus, *MSM* men who have sex with men, *LGV* lymphogranuloma venereum

[a]All regimens are for at least 3 weeks duration and should be continued until all lesions have healed

Alternative regimens include 7-day courses of erythromycin, levofloxacin, or ofloxacin (Table 19-2) [18]. Azithromycin is also effective treatment for the other infectious causes of nongonococcal urethritis aside from *C. trachomatis*, including *Mycoplasma genitalium* and *Ureaplasma urealyticum* [19]. The single dose of azithromycin is preferred as it can be given directly to the patient at the time of testing to maximize compliance. Patients should be instructed not to engage in sexual intercourse for 7 days after the single dose of azithromycin (or until they complete the full 7-day course of the other antibiotic regimens), and they should also avoid having sexual intercourse until their partners are treated as well to avoid reinfection [18]. Patients should be counseled to refer anyone with whom they have had sexual contact in the 60 days prior to chlamydia diagnosis or symptom onset for testing and treatment.

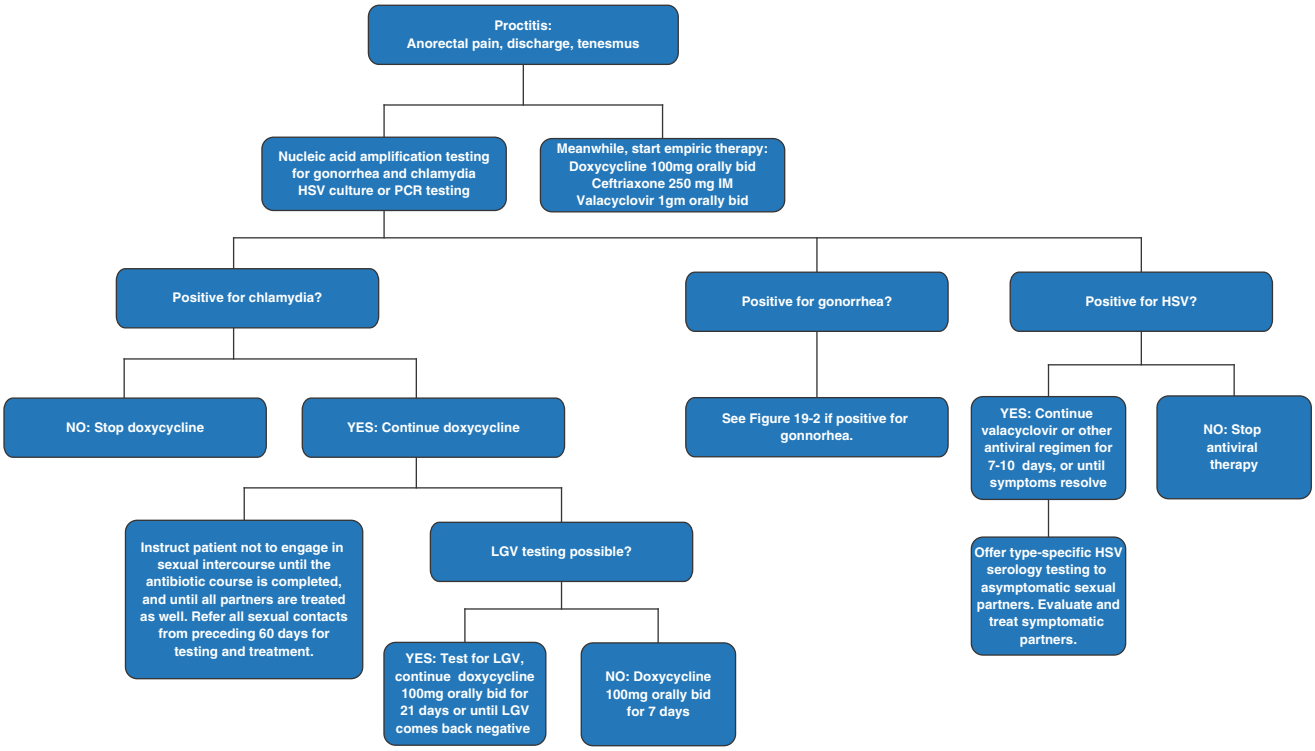

FIGURE 19-4. Management algorithm for MSM with proctitis reporting receptive anal intercourse.

Routine test-of-cure several weeks after treatment for chlamydia is not recommended by the CDC if the patient has undergone appropriate treatment and is asymptomatic with no suspicion of reinfection. However, as recurrent chlamydial infections are common in both men and women after treatment due to reinfection, repeat testing should be performed three months after treatment [15, 18].

Lymphogranuloma Venereum

Epidemiology

C. trachomatis serovars L1, L2, and L3 cause lymphogranuloma venereum. L2b has been identified as the main causative agent of the recent epidemic [20]. While anorectal infection with non-LGV *C. trachomatis* serovars A-K is mild and often asymptomatic, the LGV serovars cause severe inflammation and invasive infection. LGV has reemerged recently in its anorectal form due to outbreaks within MSM sexual networks. Infection has been associated with attendance at sex parties as well as HIV seropositivity. Hemorrhagic proctitis due to LGV has only been reported in MSM [21–24]. Risk factors for LGV proctitis include HIV seropositivity and chlamydia with concurrent ulcerative disease, previously diagnosed STI, unprotected receptive anal intercourse with casual partners, MSM, having sex at sex parties, and having sex with HIV-positive partners [16, 25]. MSM with anorectal chlamydia should undergo LGV testing; if it is not available, then MSM with anorectal chlamydia and either proctitis, >10 white blood cells per high-power field on anorectal smear, or HIV seropositivity should be treated empirically for LGV [16]. A recommended algorithm for testing and treatment of chlamydia and LGV for MSM reporting anal intercourse is detailed in Figure 19-4.

Clinical Presentation

Depending on the site of primary inoculation (genital vs. anorectal), patients will manifest different syndromes. Patients with the inguinal syndrome (genital inoculation) experience unilateral painful inguinal or femoral lymphadenopathy (buboes), possibly with a genital ulcer. Patients with the anorectal syndrome experience ulcerative proctocolitis or proctitis characterized by mucopurulent discharge and tenesmus, along with systemic constitutional symptoms (Figures 19-5 and 19-6) [20]. Untreated LGV infection can result in severe complications including colorectal fistulas and strictures, elephantiasis, infertility, and pelvic fibrosis [21].

The proper diagnosis of LGV is frequently delayed because symptoms can be misleading, physicians may be unfamiliar with the disease, and there is no routine diagnostic

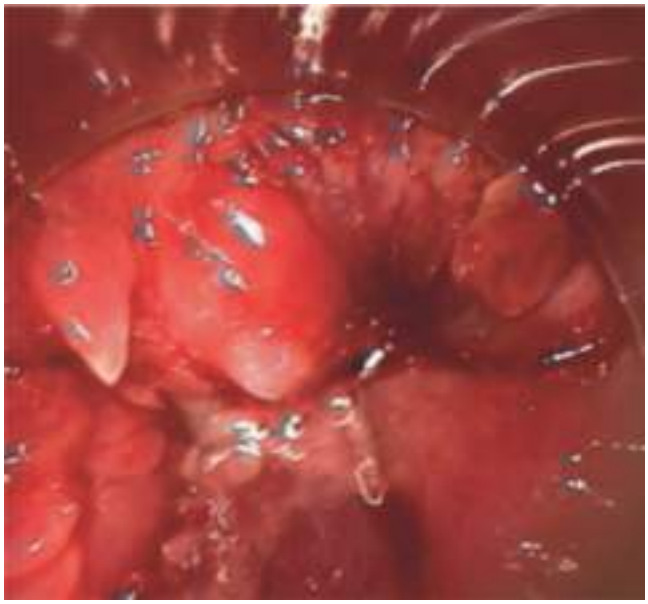

FIGURE 19-5. Proctitis due to lymphogranuloma venereum, demonstrating marked inflammation one week after treatment started. Photograph courtesy of Stephen Goldstone, MD.

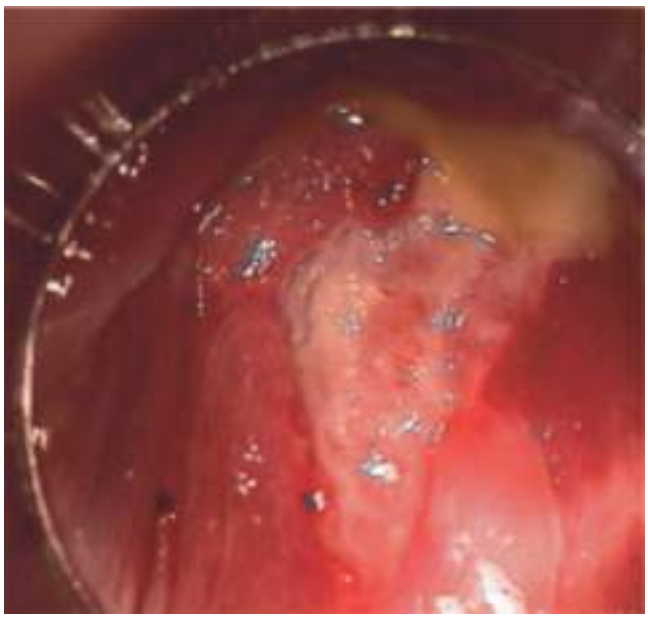

FIGURE 19-6. After two months of treatment for lymphogranuloma venereum, proctitis has resolved and ulcerations are healing. Photograph courtesy of Stephen Goldstone, MD.

test for LGV serovars [20]. Since LGV proctocolitis presents with bleeding, pain, and tenesmus, it can be mistaken as inflammatory bowel disease [21, 22]. Even pathologic specimens from endoscopic examination can be confusing, as mucosal ulcers, cryptitis, crypt abscesses, and granulomas are common histological findings that can also be attributed to inflammatory bowel disease [22, 23].

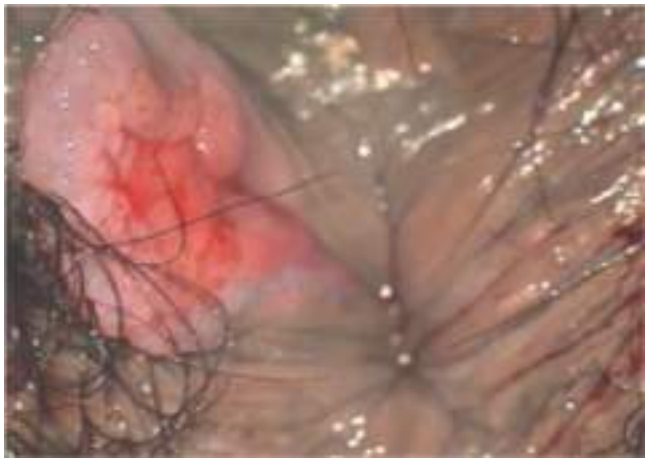

FIGURE 19-7. Chancre due to primary syphilis. Photograph courtesy of Stephen Goldstone, MD.

Treatment

The recommended treatment for LGV proctitis is twice daily doxycycline 100 mg orally for 3 weeks or for as long as anorectal symptoms persist. Buboes may require aspiration or incision and drainage to prevent ulcerations. Clinical follow-up should be continued until signs and symptoms have resolved. Sex partners from the preceding 60 days should undergo testing for chlamydia and be treated for chlamydia (one oral dose of azithromycin 1 g or one week of doxycycline) (Table 19-2) [20].

Syphilis

Epidemiology

Rates of primary and secondary syphilis, after declining for many years to a nadir of 2.1 cases per 100,000 in the year 2000, have experienced a concerning resurgence to over double that rate to 5.3 per 100,000 in 2013. Over 90 % of cases of primary and secondary syphilis occur in men, and the rise in syphilis rates is attributable to increases in men [26, 27]. Men in their 20s, MSM, black men, and Hispanic men have had the greatest increases. Rates of syphilis among women increased in the mid 2000s but have since decreased again. Similar to their male counterparts, the rate among black and Hispanic women is higher than in white women [27]. Half to a third of MSM infected with syphilis are coinfected with HIV, and the rates of HIV seroconversion following syphilis infection are high [27].

Clinical Presentation

Syphilis, caused by the spirochete *Treponema pallidum*, presents classically in its primary form as a solitary nontender genital chancre, but it can also present with multiple chancres or proctitis with bleeding, pain, and tenesmus (Figures 19-7, 19-8, and 19-9). Only a third of patients are

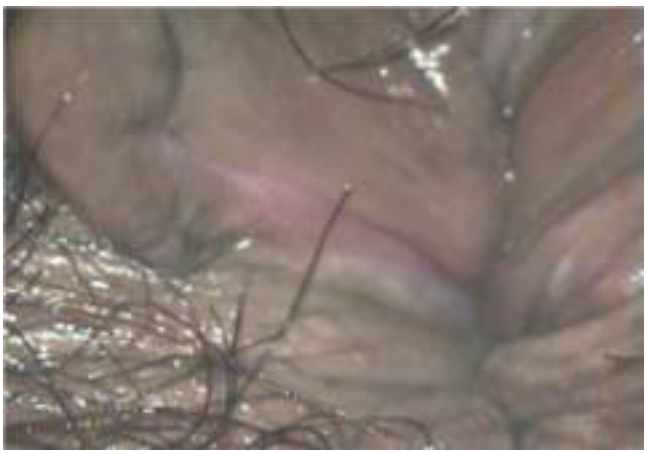

FIGURE 19-8. Healed chancre after resolution of primary syphilis. Photograph courtesy of Stephen Goldstone, MD.

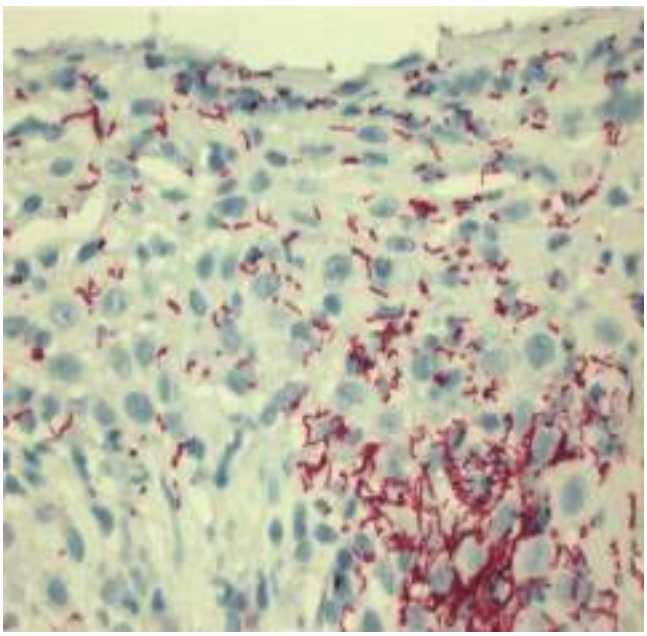

FIGURE 19-9. Immunohistochemistry staining for spirochetes, indicative of syphilis infection. Photograph courtesy of Stephen Goldstone, MD.

diagnosed during the primary infection as the primary chancre can be quite small and unnoticeable. HIV-positive patients have a higher rate of asymptomatic primary syphilis, may experience more aggressive secondary infection, and are at increased risk of developing neurosyphilis [28].

Testing Recommendations

Two types of serologic tests are used to make a presumptive diagnosis of syphilis. The nontreponemal tests include the Venereal Disease Research Laboratory (VDRL) and RPR tests and are used for screening as they become positive within 3 weeks of the primary chancre. Dark field examination to detect *T. pallidum* in lesion exudate or tissue may be successful in diagnosing early syphilis, as the nontreponemal tests may be negative in these early stages. Some patients may manifest a serofast reaction, causing the nontreponemal test to be elevated for a long period of time [26]. Treponemal tests include the fluorescent treponemal antibody absorbed tests, *T. pallidum* passive particle agglutination assay, and other immunoassays. These tests usually remain reactive for life in patients who have had a reactive test at one point. Patients with a positive nontreponemal test should undergo a confirmatory treponemal test. Patients with a negative VDRL or RPR but with strong clinical indicators of primary syphilis should undergo repeat nontreponemal testing two weeks later [18, 26]. Confirmed cases of syphilis must be reported to local and state health departments.

Due to the rebound in syphilis rates disproportionately affecting MSM, all sexually active MSM should be screened at least annually for syphilis, more frequently if they engage in high-risk sexual practices such as having multiple or anonymous sex partners [18, 27]. Due to the high rate of coinfection with HIV, patients with syphilis should undergo HIV testing, and all patients with HIV should undergo regular syphilis screening [18, 28].

Treatment

The CDC recommends a single intramuscular dose of 2.4 million units of penicillin G benzathine for primary, secondary, and early latent syphilis [18, 26]. Patients coinfected with HIV should be treated with the regimen recommended for the treatment of neurosyphilis and should be closely monitored due to increased rates of relapse [28]. The Jarisch-Herxheimer reaction, an acute febrile reaction characterized by headache, myalgia, and fever, may develop within 24 h of treatment and occurs most commonly in patients with early syphilis. Patients with penicillin allergy should be treated with doxycycline, tetracycline, ceftriaxone, or azithromycin. Pregnant women with syphilis and a penicillin allergy should undergo desensitization and treated with penicillin. Sexual contacts of patients with primary, secondary, or early latent syphilis should undergo presumptive treatment.

Treatment of primary and secondary syphilis should result in a decline of the nontreponemal test titers over the ensuing months. Repeat testing with nontreponemal tests should be performed at 6 and 12 months after treatment [18]. Retreatment for relapse should consist of 2.4 million units of intramuscular penicillin G benzathine weekly for three weeks (Table 19.2) [18].

Chancroid

Chancroid, caused by *Haemophilus ducreyi*, has declined worldwide but is a common cause of genital ulcer disease, a risk factor for HIV transmission. It usually presents with

multiple painful purulent genital ulcers that progress through pustular and ulcerative stages, as well as painful regional lymphadenopathy with bubo formation. Perianal chancroid is less common than genital chancroid but can occur in MSM. Diagnosis can be difficult due to its rarity. There are no FDA-approved tests for it in the USA. Thus, diagnosis of chancroid is made based on symptoms of painful genital ulceration and regional lymphadenopathy in the absence of syphilis and HSV [18].

First-line treatment of chancroid includes azithromycin, erythromycin, ceftriaxone, and ciprofloxacin, detailed in Table 19.2 [29]. HIV-positive patients may have a higher risk of treatment failure with single-dose regimens. Inguinal bubo formation requires at least a two-week course of antibiotic therapy and may also require aspiration or incision and drainage to prevent spontaneous rupture [30, 31].

Granuloma Inguinale (aka Donovanosis)

Granuloma inguinale is a rare tropical genitoulcerative disease caused by *Klebsiella granulomatis* (formerly *Calymmatobacterium granulomatis*), endemic in Papua New Guinea, South Africa, India, Brazil, and Australia. The mode of transmission is via sexual contact, fecal contamination, and autoinoculation [32]. Clinical presentation includes papules or nodules that progress into a painless ulcer, usually in the genital area. Disseminated disease may cause cervical ulceration, pelvic lymphadenopathy, and septic arthritis and can be mistaken for cervical and ovarian cancer [32, 33]. Coinfection with HIV may worsen the course of the disease with more ulceration and tissue damage and thus the need for prolonged antibiotic therapy. Malignant transformation can also occur in HIV-positive patients [34, 35]. Testing is performed using tissue smears from the lesions and microscopic identification of characteristic intracytoplasmic inclusion bodies (Donovan bodies). PCR has recently become available as well. Treatment regimens include three-week courses of doxycycline, ciprofloxacin, erythromycin base, or trimethoprim/sulfamethoxazole [32].

Diagnosis and Management of Sexually Transmitted Viral Infections

Herpes

Epidemiology

Herpes simplex virus types 1 and 2 (HSV-1 and HSV-2) are common in the population with a seroprevalence of 54 % and 15.7 %, respectively [36]. Both may cause anogenital herpes infection. While most cases are caused by HSV-2, HSV-1 is an increasing etiologic agent in anogenital herpes, especially among heterosexual women and young MSM [37, 38]. The overall seroprevalence of HSV-2 has decreased among the 14–49-year-old population in the USA over the last two decades—from 21.2 % in the late 1980s and early 1990s to 15.5 % in the late 2000s. However, this decrease is due mainly to decreases among whites while the rates in black men and women have not changed, thus representing increased racial disparity. Over 90 % of patients with genital herpes are unaware that they have it [39]. Primary prevention of genital herpes is difficult due to the high rates of unrecognized infection [40]. HSV has been found to be frequently reactivated for short periods of time (less than 12 h) and then rapidly cleared without causing clinical symptoms, likely by the peripheral mucosal immune system. These subclinical reactivations may also contribute to increased transmission [41, 42]. Men with HSV infection, even when asymptomatic, also have higher rates of HIV shedding which has implications for increased HIV transmission.

Clinical Presentation

HSV infections classically present with multiple painful vesicular ulcers, although not all infected patients have these symptoms (Figure 19-10). HSV is the most common cause of proctitis among HIV-positive men, occurring in more than a third of HIV-positive MSM with proctitis. HSV is the cause of proctitis in 20 % of HIV-negative men with proctitis [4]. Only a third of patients with HSV proctitis have external ulcers as well, thus underscoring the need to test and treat for herpes in MSM with proctitis, regardless of the presence of ulcers [4]. HSV-2 infection is more likely to cause recurrences than HSV-1 infection. Patients who also have HIV are more likely to have more severe and painful lesions, and increased HSV shedding, even when they are asymptomatic.

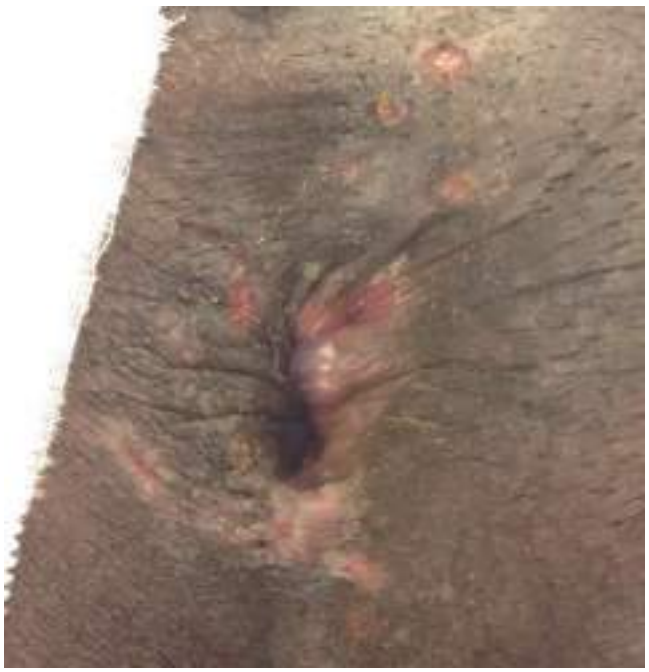

FIGURE 19-10. Perianal herpes lesions that have started to resolve.

Testing and Screening

HSV testing can be performed with cell culture or PCR, although a negative result may be attributed to intermittent viral shedding. Type-specific HSV serologic assays are also available and can be used to evaluate patients with symptoms of genital herpes but with negative HSV cultures, patients who have a partner with genital herpes, patients seeking an STI evaluation, HIV-positive patients, and MSM at high risk for being infected with HIV. Routine screening of the general population is not recommended.

Treatment

The first clinical episode of genital herpes can cause severe ulcerations as well as systemic symptoms. Therefore, treatment with antiviral therapy—acyclovir, famciclovir, or valacyclovir—is recommended to shorten the course of the episode. Suppressive antiviral therapy can decrease the number of recurrences in patients with frequent recurrences (at least four per year) [43]. Suppressive therapy may also be indicated to decrease the risk for transmission to sexual partners, especially when the patient's sexual partner is not positive for HSV, or if the patient has multiple partners [44]. Condom use and avoidance of sexual activity during recurrences offer additional protection against transmission to HSV-negative partners [45]. Another option for recurrent genital herpes is the use of episodic treatment. Recommended regimens for treatment of the first clinical episode, suppressive therapy, and episodic therapy are detailed in Table 19-3. Rarely, HSV can cause severe complicated disease requiring hospitalization and intravenous acyclovir therapy. For patients coinfected with HIV, suppressive herpes treatment with valacyclovir has also been shown to decrease rectal, seminal, and plasma HIV levels [46–51]. HSV resistance to acyclovir, valacyclovir, and famciclovir may result in persistent infections, which will need to be treated with alternative regimens such as foscarnet or cidofovir. Asymptomatic sex partners should be offered type-specific serologic testing for HSV infection, and symptomatic sex partners should be evaluated and treated accordingly.

Human Papillomavirus

Epidemiology

Over 40 different HPV types can cause genital infection, and most infections are asymptomatic and self-limited. Sexually active people have at least a 50 % risk of becoming infected at least once in their lifetime, if they are not vaccinated. Low-risk HPV types include HPV types 6 and 11, and these are the most common etiologic agents for genital warts, while the high-risk HPV types 16 and 18 are associated with cancers of the anus, cervix, penis, vulva, and vagina. Genital warts may also harbor more high-risk HPV types 16, 18, 31, 33, and 35 and may contain areas of high-grade dysplasia. These precursor lesions are common among high-risk populations such as MSM- and HIV-positive patients, occurring in over half of HIV-positive MSM and over a third of HIV-negative MSM [52].

Clinical Presentation

While the majority of infections with HPV are asymptomatic and self-limited, some patients may develop genital warts, dysplastic lesions, or cancer depending on the virus type. Genital warts, or condyloma, present as growths on the genital mucosa, anal mucosa, and perianal skin (Figure 19-11). Patients with warts within the anal canal may have a history of receptive anal intercourse but not necessarily. Symptoms may include pain, pruritus, discomfort, or bleeding, depending on the location and size of the warts. Patients with HIV infection or another source of immunosuppression are more likely to develop genital warts, and these warts are less likely to respond to treatment and more likely to recur.

The high-risk HPV types can cause invasive squamous cell cancers of the anus. Squamous cell carcinoma occurs more frequently in patients who are immunosuppressed, especially in patients who are coinfected with HIV. Disturbances in the peripheral immune function in the anal mucosa may explain this increased risk to progress to invasive anal cancer [53–56].

Testing

HPV testing can be used to screen women for cervical cancer, but screening for HPV is not indicated for men, sex partners of women with known HPV, adolescent women, or for other HPV-related malignancies such as anal cancer [18].

As certain high-risk populations such as HIV-positive MSM have seen a rise in incidence of invasive anal squamous cell carcinoma, screening programs to detect precursor lesions have been developed to prevent progression to invasive cancer [52]. Liquid-based anorectal cytology specimens are the preferred specimen type to screen for high-grade anal dysplasia [57]. Self-collected samples are less sensitive than clinician-collected samples [52]. Patient with positive findings should be referred to a specialist for high-resolution anoscopy or routine anoscopy and monitoring.

Treatment

The indication to treat anogenital warts is to relieve symptoms. Untreated genital warts may self-resolve or worsen. Treatment does not affect the risk of transmission of HPV. External genital warts can be treated in a variety of ways (Table 19-3). Patients may apply their own treatment at home

TABLE 19-3. Centers for Disease Control recommended treatment regimens for viral STIs [18]

Infection	Recommended regimens
Genital herpes (HSV-1 or HSV-2): first clinical episode	Acyclovir 400 mg PO three times daily for 7–10 days or acyclovir 200 mg PO five times daily for 7–10 days or famciclovir 250 mg PO three times daily for 7–10 days or valacyclovir 1 g PO twice daily for 7–10 days
Suppressive therapy for recurrent genital herpes (frequent recurrences)	Acyclovir 400 mg PO twice daily or famciclovir 250 mg PO twice daily or valacyclovir 500 mg PO once daily[a] or valacyclovir 1 g PO once daily
Suppressive therapy for patients coinfected with HSV and HIV	Acyclovir 400–800 mg PO twice to three times per day or famciclovir 500 mg PO twice day or valacyclovir 500 mg PO twice daily
Episodic therapy for recurrent genital herpes	Acyclovir 400 mg PO three times daily for 5 days or acyclovir 800 mg PO twice daily for 5 days or acyclovir 800 mg PO three times daily for 2 days or famciclovir 125 mg PO twice daily for 5 days or famciclovir 1000 mg PO twice daily for 1 day or famciclovir 500 mg once, then 250 mg PO twice daily for 2 more days or valacyclovir 500 mg PO twice daily for 3 days or valacyclovir 1 g PO once daily for 5 days
Episodic therapy for patients coinfected with HSV and HIV	Acyclovir 400 mg PO three times daily for 5–10 days or famciclovir 500 mg PO twice daily for 5–10 days or valacyclovir 1 g PO twice daily for 5–10 days
External genital warts (HPV) Patient applied	Podofilox 0.5 % solution or gel: application with cotton swab twice daily for 3 days, then 4 days without therapy; can repeat cycle up to four times (max 0.5 mL per day) or imiquimod 5 % cream: apply three times per week up to 16 weeks, washing treated area with soap and water 6–10 h afterward or sinecatechins 15 % ointment: apply three times daily for up to 16 weeks
External genital warts (HPV) Provider administered	Cryotherapy with liquid nitrogen or cryoprobe or podophyllin resin 10–25 % in a compound tincture of benzoin or trichloroacetic acid (TCA) or Bichloroacetic acid (BCA) 80–90 % or surgical removal
Anal warts (HPV) Provider administered	Cryotherapy with liquid nitrogen or trichloroacetic acid (TCA) or bichloroacetic acid (BCA) 80–90 %: can be applied weekly as needed or surgical removal

HIV human immunodeficiency virus, *HSV* herpes simplex virus, *HPV* human papillomavirus

[a]This regimen may be less effective than the others for patients with over ten recurrences per year

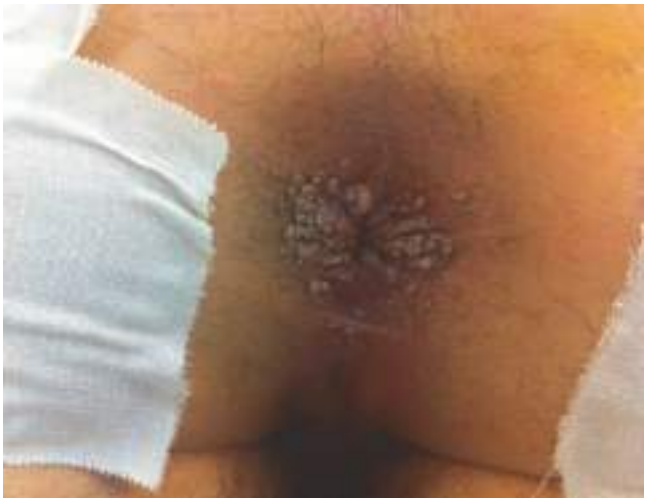

FIGURE 19-11. Perianal condyloma due to HPV infection.

using podofilox solution or gel, imiquimod cream, or sinecatechins ointment. Provider-administered options include cryotherapy, podophyllin resin, or trichloroacetic or bichloroacetic acid. The latter compounds should be applied sparingly to avoid adjacent tissue damage, and if the treatment causes pain or if too much acid is accidentally applied, soap, talc, or sodium bicarbonate (baking soda) can be used to neutralize the acid. Patients with extensive genital warts may warrant surgical management.

Anal condyloma—including warts in the anal canal and the distal rectum—can be treated with cryotherapy, TCA or BCA, or surgical therapy. High-resolution anoscopy may be indicated to inspect for high-grade dysplasia as well.

The management of high-grade anal dysplasia, the precursor to invasive squamous cell carcinoma, remains a controversial topic. While some clinicians view ablation or destruction of high-grade dysplasia as an important strategy to prevent progression to invasive cancer, others disagree with this approach. Patients with high-grade intra-anal dysplasia who undergo ablation have recurrence rates of about 50 % overall (higher in HIV-positive patients) but a low risk of developing anal cancer [58–62]. This controversy is discussed more thoroughly in the chapter on Anal Malignancies.

Vaccine

The two HPV vaccines available are the bivalent vaccine, which protects against high-risk oncogenic HPV types 16 and 18, and the quadrivalent vaccine which protects against HPV types 6, 11, 16, and 18 and should be given before one become sexually active. Both are approved for girls and boys aged 9–26 years old [18]. The quadrivalent vaccine has been shown to reduce the rates of high-grade anal dysplasia among MSM and may help to reduce the risk of anal cancer [63].

HIV and AIDS

Epidemiology

Over one million people in the USA have HIV, and over half of those infected are MSM. A quarter of those patients reported high-risk sexual practices such as unprotected sexual intercourse with a casual partner, or sex in exchange for money or drugs, and almost half of those patients reported using noninjection drugs over the past year [64].

Testing

HIV screening is recommended for all patients who present for STI testing. Positive screening tests for HIV antibody require confirmatory testing before a diagnosis can be made. If patient is suspected of having acute HIV infection, then a nucleic acid test should be performed in addition to the antibody test, and the patient should be referred immediately to an infectious disease specialist [18]. The FDA has recently approved combination tests detecting both HIV antigen and antibody, as well as tests that differentiate HIV-1 from HIV-2 [65].

Anorectal Issues

Anorectal complaints such as pain due to fissures may be the presenting symptom of patients with HIV infection. Fissures in HIV-positive patients may be a manifestation of HIV but could also represent coinfection with other STIs such as HSV or syphilis. Treatment of fissures in patients with HIV should consist of the same treatment undertaken for fissures in the general population. Special attention should be given to controlling diarrhea symptoms as well as avoidance of anal receptive intercourse.

Anal ulcers are another source of anal pain in patients with HIV and are located in a more proximal location within the anal canal—often above the dentate line—and are broader and more ulcerative than fissures. There may be evidence of destruction of the underlying sphincter muscle.

Perianal abscesses and fistulas are common in patients with HIV or AIDS. Patients with well-controlled HIV and normal CD4 counts who develop abscesses and fistulas can be treated with the same surgical techniques as one would do for patients without HIV. However, abscesses in patients with AIDS should be treated with smaller incisions, favoring drain placement over larger incisions. Fistulas in patients with advanced or poorly controlled AIDS should be treated with placement of draining setons rather than fistulotomy to avoid the creation of a nonhealing wound.

External thrombosed hemorrhoids in patients with HIV or AIDS should be treated in the same manner as those occurring in patients without HIV. Symptomatic internal hemorrhoids should be treated with first-line therapy with fiber and improvement of bowel habits. A more proximal source of

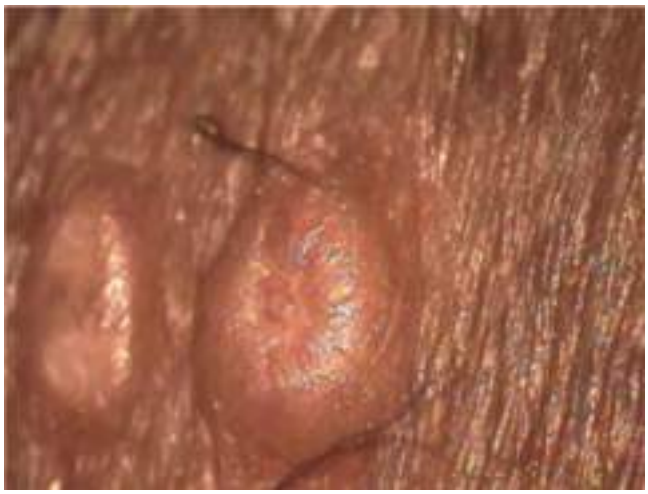

FIGURE 19-12. Molluscum contagiosum lesions present as waxy dome-shaped umbilicated papules.

bleeding should be ruled out with lower endoscopy. Patients who fail nonoperative management may safely undergo rubber band ligation of internal hemorrhoids. Hemorrhoidectomy is safe in HIV-positive patients without AIDS; patients with advanced or poorly controlled AIDS and severe hemorrhoids not amenable to banding may have wound healing problems.

Molluscum Contagiosum

Molluscum contagiosum is a common cutaneous viral infection caused by the *Molluscipoxvirus*, causing small, waxy, dome-shaped umbilicated papules (Figure 19-12). It is second only to genital warts as the most common nonulcerative STI, affecting up to 5 % of the population, 18 % of patients with immunosuppression, and 30 % of patients with advanced AIDS [66]. Secondary bacterial infection may occur especially if patients tend to scratch the lesions. Mollusca contagiosa occur frequently in young children, but their occurrence in adults is usually considered an STI and involves the pubic area. Risk factors include shaving. Transmission occurs through skin-to-skin contact, and autoinoculation can also occur to spread to other sites, especially in the 30 % of patients who develop an eczematous reaction around the lesions, which cause pruritus. Sexual contact can lead to transmission from the genitalia to the oral mucosa, conjunctiva, and cornea [67]. Diagnosis can be made by visual inspection although if there is difficulty then dermatoscopy revealing orifices, vessels, and specific vascular patterns can help confirm the diagnosis [68]. A recent PCR test has been developed as well for the molluscum contagiosum virus [69].

Immunocompetent patients will self-resolve these lesions over a period of months to years, so most patients prefer treatment. Treatment consists of removal of the lesions, similar to the treatment of genital warts. Curettage excision and cryotherapy are the most common methods of treatment [70, 71]. These treatments should not be performed in patients with immunosuppression due to the risk of nonhealing wounds and superinfection with other bacterial, viral, or fungal organisms. For these patients topical treatments such as imiquimod 5 % cream may be helpful without incurring the risk of open surgical wounds [72].

FIGURE 19-13. Pubic lice infestation causes severe pruritus and can be treated with permethrin 1 % cream. Photograph courtesy of Stephen Goldstone, MD.

Pubic Lice: *Phthirus pubis*

Pubic lice are obligate blood-sucking parasites and infestation is diagnosed by finding lice on pubic hair (Figure 19-13). As lice can neither jump nor fly, transmission is due to close contact. Therefore, the diagnosis of pubic lice should prompt testing for other STIs. Pubic lice infestation affects 2–10 % of the population worldwide [73]. The increased incidence of pubic hair removal has been associated with a lower incidence of pubic lice infections due to destruction of their natural habitat [74].

The CDC recommends permethrin 1 % cream or pyrethrins 0.3 %/piperonyl butoxide 4 % cream as the first-line therapy for pubic lice. Alternative regimens include malathion 0.5 % lotion or oral ivermectin. Permethrin should be used on the day of diagnosis and again 7–10 days later to completely

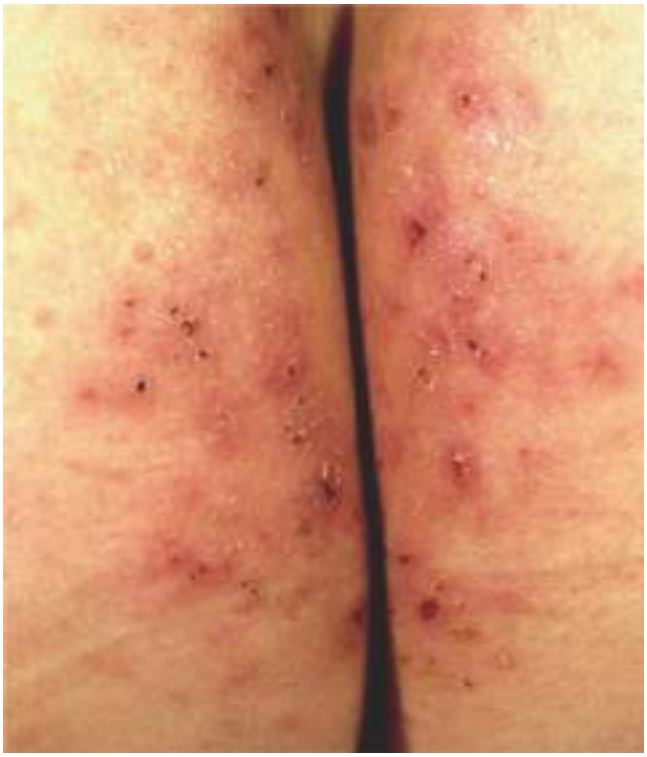

FIGURE 19-14. Scabies infestation causing an intensely pruritic rash can be treated with permethrin 5 % cream. Photograph courtesy of Stephen Goldstone, MD.

eradicate the infestation as the treatment does not kill the eggs. Laundering clothes and bedding in hot water should be done as well to prevent reinfection and transmission [18, 75].

Scabies

Scabies is caused by the mite *Sarcoptes scabiei* var. *hominis*. Scabies transmission is via skin-to-skin contact, as the mites neither jump nor fly. Scabies most commonly occurs in young children but can also occur in patients subject to overcrowded conditions, poor hygiene, homelessness, and via sexual contact. The mites burrow into the skin, creating wavy scaly lines on the skin surface, usually located on the hands and feet, typically in finger webs. The infestation causes an intense pruritic rash localized in a characteristic distribution in the armpits, elbow creases, wrists, and groin areas (Figure 19-14). Infants, children, and immunosuppressed patients may develop a more severe vesicular and pustular rash. Diagnosis can be made by visual inspection and history. Skin scrapings of the burrows, papules, and vesicles can be performed by applying mineral oil to the skin and scraping laterally across the lesion with a scalpel and examining the scraping microscopically for mites, eggs, and fecal pellets.

First-line treatment of scabies is with topical permethrin 5 % cream, which is rather effective as there is not much resistance [76]. The cream should be applied to all areas of the body from the neck down, and then washed off 8–14 h later. Reapplication of the cream should be performed 1 week later to ensure eradication. The pruritus may persist for up to 2 weeks after treatment. Oral ivermectin can also be used as first-line therapy or second-line therapy if the permethrin cream does not work [18]. Clothing and bedding should be washed in hot water and dried in a hot dryer to prevent re-infestation and transmission. Crusted scabies results when uncomplicated scabies goes untreated. Treatment involves both ivermectin orally on days 1, 2, 8, 9, and 15, as well as permethrin 5 % cream daily for 1 week, then twice a week until the disease is cured [77].

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20
Anal Intraepithelial Neoplasia

Rocco Ricciardi

Key Concepts

- Anal intraepithelial neoplasia is a dysplastic condition of squamous tissue and is considered to be a premalignant stage of anal cancer.
- The histological findings and cellular abnormalities mirror cervical dysplasia.
- Anal cytology is a useful method to identify anal neoplasia in high-risk groups.
- When cytology is concerning, the evaluation of anal neoplasia can proceed with anal cytology and high-resolution microscopy, a technique similar to colposcopy.
- A targeted approach to dysplasia ablation through microscopy is more sparing than historically practiced wide local excisions and flap advancements.
- Treatment should be tailored to the patient's degree of dysplasia, risk factors, immune status, continence, symptoms, and likelihood of progression.

Introduction

Anal intraepithelial neoplasia is a dysplastic condition of the squamous tissue and is considered to be a premalignant stage of anal cancer. Anal intraepithelial neoplasia (AIN) is further stratified into three grades: AIN I, AIN II, and AIN III, defined as low-, moderate-, and high-grade dysplasia, respectively (Figure 20-1). The histological findings, including the cytologic changes, mitotic activity, nuclear membrane changes, and cellular abnormalities [1, 2], mirror cervical dysplasia grading. Terminology can be confusing as anal intraepithelial neoplasia is referred to by many names including anal dysplasia, intraepithelial carcinoma, intramucosal carcinoma, squamous cell carcinoma in situ, and Bowen's disease. In addition, recently the terms high-grade anal intraepithelial neoplasia (HGAIN) and low-grade anal intraepithelial neoplasia (LGAIN) have been proposed that correspond to AIN III/II and AIN I, respectively [1]. In this chapter we will use the terms anal intraepithelial neoplasia which parallel the pathophysiology of cervical intraepithelial neoplasia, vulvar intraepithelial neoplasia, and perineal intraepithelial neoplasia.

Symptoms

The vast majority of individuals will experience no outward manifestation of human papillomavirus (HPV) infection, and similarly most patients with AIN have no clear symptoms. A small subset of patients will describe occasional rectal bleeding, and an even smaller group will experience pain with bowel movements. As AIN progresses to anal cancer, symptoms become more frequently reported. In fact, 50 % of patients with invasive cancer describe pain and bleeding [3, 4]. A minority of patients with anal intraepithelial neoplasia describe a palpable lesion on the non-hair-bearing portion of the anal skin, but the majority have no outward sign of disease. However, those patients with signs of external genital warts and immunosuppression have a very high risk of AIN.

Epidemiology

Anal intraepithelial neoplasia develops from HPV contact generally through direct exposure [1, 5, 6]. It is estimated that there are more than 100 subtypes of HPV but not all have been implicated as disease causing. In fact, as stated in the prior section, most patients who come into contact with HPV have no actual symptoms and experience no untoward effects. For those who come into contact with the virus, about 90 % of all patients remain asymptomatic and those that have infection resolve without any treatment within 2 years [7]. A small number develop persistent asymptomatic infections, while a smaller number of patients will develop condyloma. It is unclear why a fraction of patients develop neoplasia in the form of AIN that then may progress to squamous cell cancer.

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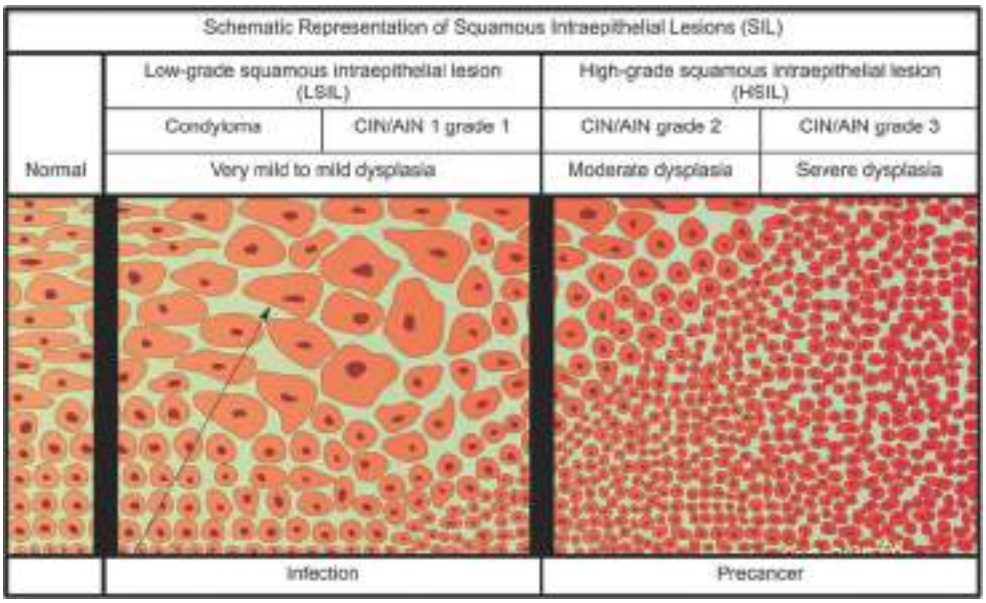

FIGURE 20-1. Schematic representation of squamous intraepithelial lesions (SIL). As shown in this illustration, with increasing severity of SIL of the anus, the proportion of the epithelium replaced by immature cells with large nuclear-cytoplasmic ratios increases. Invasive cancer probably arises from the one or more foci of high-grade SIL (HSIL) as depicted in the drawing by epithelial cells crossing the basement membrane below the region of HSIL. With permission from Brickman C, Palefsky JM Human papillomavirus in the HIV-infected host: epidemiology and pathogenesis in the antiretroviral era Curr HIV/AIDS Rep 2015;12:6–15. Copyright Springer [73].

Explanations for why the virus causes condyloma or neoplasia in some patients but not in others are speculative. It is likely related to patient immune function, subtype of HPV, repetitive inoculation, and/or potentially concomitant infections such as other sexually transmitted infections. For example, among HPV subtypes, types 6 and 11 cause 90 % of genital warts [8] as compared to those subtypes that are associated with cancer (i.e., types 16, 18). We do know that almost all patients with anal squamous cell cancer, and presumably AIN, have been exposed to HPV at some time in their life. The HPV exposure was likely years prior to the development of actual squamous tissue changes.

HPV, the causative exposure to AIN, is quite prevalent in both the developed and developing world. Estimates indicate that at any point in time, one in ten women worldwide harbors the HPV virus [9]. Prior to the introduction of the HPV vaccine, there had been a steady rise in the rate of HPV infections across the nation and the globe. However, with the introduction of the HPV vaccine, the prevalence of HPV types 6, 11, 16, and 18 identified by cytology specimens decreased by over 50 % among teens and young women. In addition and as expected, HPV prevalence has not been declining in older women who would not have received the vaccine [10]. Data from the National Disease and Therapeutic Index suggest that although cases of genital warts as measured by initial visits to physicians' offices increased during the late 1990s through 2011, genital wart cases appear to have decreased since 2011 [11], presumably because of increased vaccination (Figure 20-2).

Incidence data characterizing trends of HPV infection and condyloma are easily obtainable, yet it is unclear whether the rate of AIN has changed in the last several years. There are no public records and cancer surveillance data do not record incidence or treatment of dysplastic lesions. National cancer incidence data do reveal that the rate of anal cancer has been increasing for several years. Using statistical models for analysis, rates for new anal cancer cases have been rising on average 2.2 % each year over the last 10 years [12]. The number of new cases of anal cancer was 1.8 per 100,000 people per year based on 2007–2011 cases, and the cancer is still slightly more common in women than in men [12].

Much of what is known regarding the transformation of AIN to squamous cell cancer has been extracted from the cervical cancer literature. A recent review of medical records of men who developed anal cancer revealed a common history of precursor high-grade squamous intraepithelial lesions, i.e., anal intraepithelial neoplasia [13]. Because the virus has been detected in many asymptomatic patients, it is likely that viral persistence after integration of the viral genome into the host [14] occurs in order to produce genetic change. Viral oncogenes are then ultimately responsible for directly coupling to oncogenic enhancers and promoters permitting continued expression through integration and immortalization [14]. A number of genetic changes are proposed to

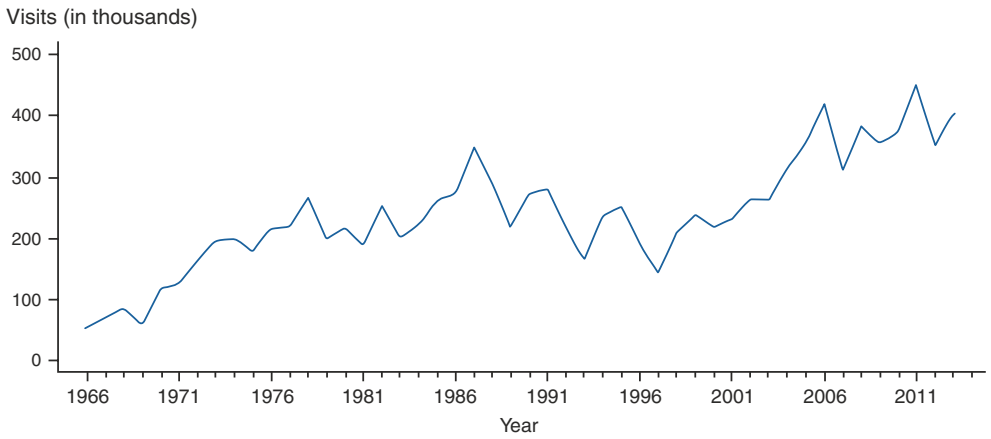

FIGURE 20-2. Genital warts. Initial visits to Physicians' Offices, United States, 1966–2013 http://www.cdc.gov/std/stats13/figures/49.htm. *Source*: IMS Health, Integrated Promotional Services™. IMS Health Report, 1966–2013.

occur after viral integration leading to phenotypic changes of the squamous epithelium. Abnormalities to chromosomes 1, 3, 7, 8, 11, 15, and 20 have all been reported with varying frequency [15, 16]. One of the most frequently reported changes in chromosomal structure is a gain in the long arm of chromosome 3q [17], which is also reported to occur in the transition from low-grade to severe cervical dysplasia and/or cervical cancer [15]. Although it is unclear which gene mediates this transformation, the mechanism may be through phosphatidylinositol 3-kinase, an oncogene on chromosome 3 that phosphorylates other proteins involved in cellular growth. This oncogene has been similarly implicated in the tumorigenesis of ovarian [18] and cervical [19] cancer but not in anal cancer at this time.

Following incorporation of the viral genome into host DNA, cellular changes and atypia of squamous tissues occur [1, 13, 20]. Ultimately these changes correspond to AIN I which then can progress to AIN II and AIN III and ultimately dedifferentiate into squamous cell cancer. It is unclear whether the development of anal neoplasia must traverse all these steps or if squamous cell cancer can skip one or more phases, i.e., from AIN I directly to AIN III. The degree of cellular abnormality and the level of cellular changes correspond to each phase; AIN I has minor changes to the epithelial cells and AIN III corresponds to full-thickness changes to the epithelium with aberrant structure and cellular atypia (Figure 20-1). Ultimately, the oncogenetic pathway is similar to the pathway described in cervical cancer, which degenerates from cervical intraepithelial neoplasia.

Screening/Surveillance

Most patients at risk for anal neoplasia undergo screening with digital rectal examination, anal cytology, and anoscopy. Anal cytology is akin to cervical cytology, providing cellular material for review of intraepithelial lesions. The technique is performed as part of a full physical examination and generally includes a digital rectal examination and anoscopic examination. The cytology must be performed before any instrumentation of the anus and before lubrication is used. The procedure is performed with a moist swab in the anal canal and without any preparation. Following completion, a digital rectal examination and anoscopy can be performed. Obvious condylomatous lesions are concerning if found, particularly in immunosuppressed patients, and should be removed or treated topically with close follow-up.

The anal cytology smear is graded by a cytologist with the same classification used in gynecologic samples. Anal cytology may return as insufficient, normal, atypical squamous cells of undetermined significance, low-grade squamous intraepithelial lesion, high-grade squamous intraepithelial lesion, or anal cancer. Based on these results and prior medical history, the recommendation is either continued surveillance or more detailed evaluation with high-resolution anoscopy. Lesions classified as atypical squamous cells of undetermined significance or higher are generally referred for high-resolution anoscopy. However, a large number of patients have abnormal cytology results leading to a considerably large population of patients to evaluate in microscopy. In addition, given that the sensitivity of anal cytology ranges from 69 to 93 % and specificity ranges from 32 to 59 % [21–23], results can be difficult to interpret. It is important to remember that anal cytology in high-risk cohorts such as men who have sex with men has false-negative rates of up to 23 % in HIV-negative patient and 45 % if HIV positive [24]. Therefore, close follow-up of all high-risk patients is likely to be the best strategy (see Figure 20-3).

Defining the population that is high risk and requiring evaluation is challenging because of societal and other behavioral concerns. Overall, the risk of anal neoplasia is highest in immunosuppressed individuals as they appear to have great difficulty in clearing the virus from their body. Rates of anal dysplasia in HIV-infected patients of all sexual

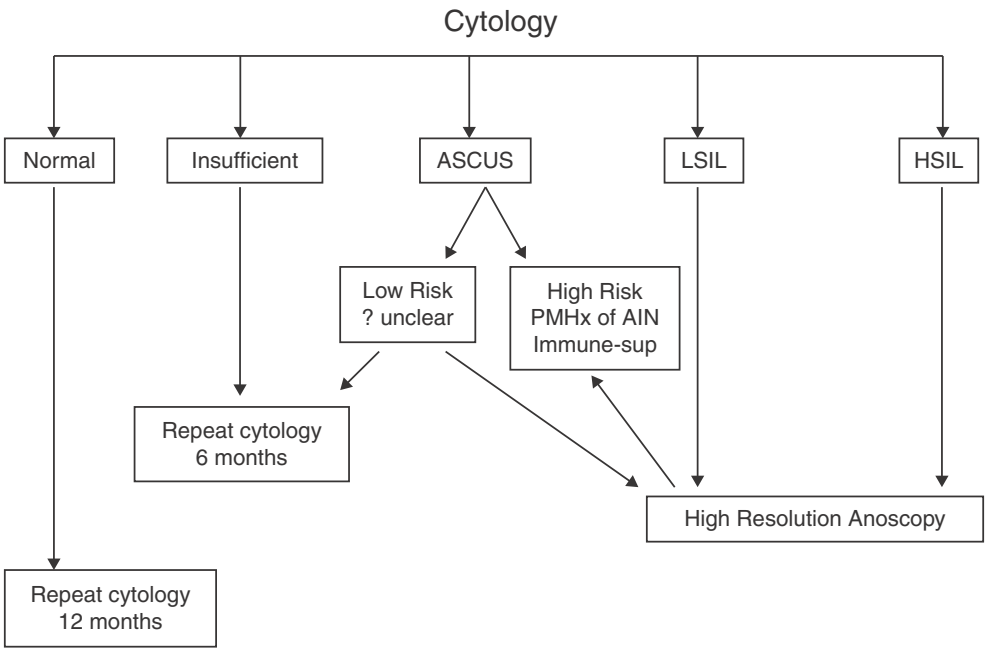

FIGURE 20-3. Management algorithm for anal cytology results. General guidelines provided. Individual case management is based on many factors, which may increase or decrease the interval of evaluation.

risk groups are substantial indicating some value for anal cancer screening in all HIV-infected patients regardless of sexual practices [25, 26]. The immunosuppressed group should also include those with organ transplants [27, 28], as well as other medically induced suppressive conditions. Men who have sex with men and a concomitant diagnosis of HIV pose the greatest risk of HPV-related illnesses and thus anal neoplasia [29]. Patients with prior history of HPV infection are also likely to be at high risk for anal dysplasia and cancer as well as those patients who practice anal receptive intercourse or persons with a high lifetime number of sexual partners [30].

One of the highest-risk groups is women with a past history of cervical, vulvar, or perineal neoplasia. A number of population-based studies report an increase in anal neoplasia risk among women with a history of invasive cervical cancer [31, 32]. In addition to invasive cervical cancer, a recent review of Surveillance, Epidemiology, and End Results data identified a significant association between gynecologic neoplasm and anal cancer for both in situ and invasive cancers of the cervix and vulva and in situ neoplasm of the vagina. In that study, the highest risk for anal cancer was identified in those women with evidence of either in situ or invasive squamous cell cancer of the vulva [33]. The proximity of the anus to the vulva may explain why patients with vulvar neoplasia were at highest risk for anal cancer, yet the increased risk with in situ neoplasia was also remarkable. Thus, patients with gynecologic neoplasia, and especially vulvar neoplasia, should be followed closely for potential anal cancer development.

Individuals with a past history of sexually transmitted infections may also represent an important screening population. A past history of condyloma is generally a sign of prior contact with human papillomavirus. At this time, it is unclear whether those individuals who tend to develop condyloma (without any sign of dysplasia) have a tendency to develop benign warts rather than cancer. Further studies are needed to investigate the link between prior history of condyloma and anal neoplasia. In addition, it is difficult to prove any synergy between human papillomavirus and other sexually transmitted infections that might act in an additive way to speed up transformation to AIN. However, the presence of HIV with anal coinfection with syphilis, gonococci, Epstein-Barr virus, cytomegalovirus, or herpes simplex was identified as an independent risk factor for dysplasia and cancer [34]. These data point to association between the herpes virus and HPV, yet the effect of these infections on anal neoplasia pathogenesis is certainly unclear.

The value of anal cancer screening is difficult to quantify. There are several studies using computer models to determine the benefit of these tests. Screening HIV-positive homosexual and bisexual men for anal dysplasia with anal cytology offers quality-adjusted life expectancy benefits at a cost comparable with other accepted clinical preventive interventions [35]. Others have not come to the same conclusion indicating that many of the criteria for assessing the

need for a screening program were not met for anal neoplasia screening and that cost-effectiveness remained unacceptable [36]. The lack of concordance for these models may be related to the lack of agreement with uncertainties in modeling clinical scenarios in the face of poor evidence. For those patients with a past history of high-grade dysplasia and immunosuppression, a role for surveillance is likely to be of some benefit given the high rate of recurrent disease in this population [17]. It is thought that a combination of surveillance high-resolution anoscopy and anal cytology at 6 and 12 months is cost-effective after treatment of anal neoplasia in HIV-infected men who have sex with men [37].

At this time, a review of 30 regional and national guidelines for screening in HIV patients revealed that only two societies recommended digital and anorectal examination [38]. The "European AIDS Clinical Society Guidelines" recommends digital examination every 1–3 years for HIV-positive men who have sex with men. In New York State, the Department of Health has recommended annual anal cancer screening for HIV-positive men who have sex with men, HIV-positive patients with history of condyloma, and HIV-positive women with a history of gynecologic neoplasia. However, the US Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents recommended only an annual digital examination for the HIV-positive population in general [38].

Diagnosis

Most patients are diagnosed with anal neoplasia through investigation with digital rectal examination, anal cytology, anoscopy, and/or endoscopy. The sensitivity of digital rectal examination in identifying anal neoplasia is fairly low as many AIN lesions are not palpable. Anoscopy is routinely performed by colon and rectal surgeons and can be used to identify macroscopic areas of AIN, which often appear to be benign condylomata, but may return with AIN on biopsy (Figure 20-4). In addition, endoscopic identification of AIN occurs quite commonly particularly during the retroflexed view of the anus. A biopsy of the lesion should lead to a consult with a surgeon who has experience with these lesions. Last, a large number of patients are identified with anal dysplasia on cytologic evaluation during routine screening. These patients are best evaluated with microscopic examination and referred to a facility with appropriate knowledge and capacity.

During diagnostic evaluation, it is imperative to remember that patients with AIN should have a complete and thorough history and physical examination. It is important to remember the link between anal dysplasia and other HPV-related diseases such as oral cancer, gynecologic neoplasia [33], and other genital lesions. In our practice, we refer all female patients for gynecologic evaluation and inquire about dental examinations. The physical exam should include a head to toe evaluation for squamous cell lesions, considering the mouth and all lymph node basins. Referral to gynecology or a urologic service should also be considered when applicable based on findings and history.

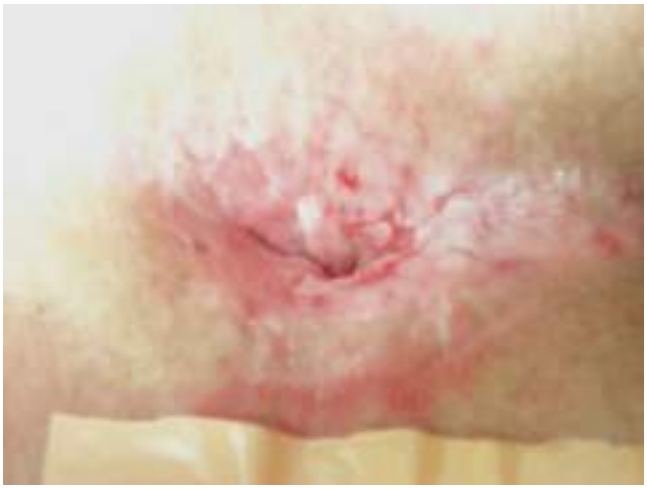

FIGURE 20.4. AIN 3. Courtesy of Richard Billingham, MD.

Following examination of the entire body, the evaluation of AIN can proceed with anal cytology and high-resolution microscopy, a technique similar to colposcopy of gynecologic neoplasia. In fact, the colposcopic appearance of variable grades of anal squamous intraepithelial lesions is similar to those described for the cervix [39]. In high-resolution anoscopy, a colposcope or another microscope is used to examine the anal verge and anal canal in close detail. The procedure can be performed in any position, but left or right lateral positioning provides greater visualization of difficult areas, such as under the prostate in men. No bowel or anorectal preparation is necessary and the procedure is most commonly performed without analgesia. After positioning, the tissues to be examined are swabbed with a 3–5 % acetic acid solution for 2–5 min. Some colposcopists choose to add an iodine-based Lugol's solution to further assist with detection of dysplastic tissue. The mechanism for Lugol's utility is that only healthy epithelial tissue absorbs the compound which causes normal tissue to appear wood-like. However, dysplastic tissues do not absorb the solution leaving these tissues with a yellowish hue. Although used by many colposcopists, our protocol is to avoid Lugol's solution as it interferes with proper dysplasia differentiation (i.e., AIN I versus AIN II or III).

For those who do not use Lugol's solution, the acetowhitening from acetic acid with microscopic assistance is sufficient to identify dysplastic tissues. The entire anal canal and anal verge should be examined, but we find that dysplastic tissues are most commonly found within the transition zone, as this area has the greatest area of susceptible and immature squamous tissues. The acetowhitening is particularly helpful in characterizing the degree of dysplasia. Dysplastic epithelium will absorb acetic acid and appear scaly white as

compared to columnar tissues. The characterization of dysplastic tissue and differentiation of AIN I, II, or III can then be performed without biopsies and in real time under high magnification. Dysplastic tissues are characterized by scaly white plaques and with greater disarray of vascular patterns, the higher the grade of dysplasia. We also find that high-grade dysplasia tends to be quite friable when in contact with the anoscope or a swab (Figure 20-5).

The equipment used for the evaluation of AIN is expensive and the high-resolution microscopy procedure is time intensive and difficult to learn. Others have taken to diagnose AIN with simple anoscopy or endoscopic methods. At this time, data have not demonstrated that high-resolution anoscopy is superior to other methods. However, a multicenter randomized trial is underway to demonstrate the value of close surveillance. Interestingly, a recent study from Ohio revealed no difference in anal cancer progression with simple observation versus high-resolution anoscopy [40]. However, the length of follow-up, diagnostic accuracy, and follow-up protocols were unclear as the study was underpowered to detect smaller outcome differences. Others have demonstrated a very low rate of anal cancer progression with an intense surveillance strategy involving anal cytology, digital anorectal examination, and oncogenic HPV testing in men who have sex with men. Abnormalities on screening lead to high-resolution anoscopy and ablation as indicated [41].

Treatment

It should be clear that there is no proven treatment for HPV infection. As stated earlier, the infection is self limited such that treatment is directed only to the macroscopic (i.e., genital warts) or pathologic (i.e., precancerous) lesions caused by infection [42, 43]. It is thought that all subclinical HPV infections resolve without treatment, and thus, any attempt at antiviral therapies is not indicated [43, 44]. When dysplasia is present, whether in the anus, vulva, or cervix, there are a number of methods to manage or treat these neoplastic tissues ranging from no intervention to very aggressive care. At this time there is no clear best treatment option for all types of patients and all degrees of anal dysplasia. Ultimately the best method of treatment must be efficacious in preventing the progression of anal intraepithelial neoplasia to cancer while reducing the morbidity of treatment and preserving function. In addition, one other consideration in treatment should be reducing the rate of virus transmission to others (Table 20-1).

Observation may be the best option for patients with low-grade dysplasia. In particular, this may be the least difficult technique for patients with no symptoms and with low likelihood of conversion to anal cancer. Management would consist of surveillance every 4–12 months [45]. Supporters of this "watch and wait" strategy cite overall low rates of disease progression and malignant potential (especially for low-grade disease) and the increased morbidity associated with excision and repeated focal destruction [1]. Certainly, the risk of progression is fairly low in patients with low-grade dysplasia with evidence indicating that some proportion of patients will exhibit regression of disease without treatment [45, 46]. It is our practice to recommend observation in select cases depending on risk factors, comorbidities, and available resources. In a recent review of cases observed for anal neoplasia, patients followed with expectant management or high-resolution anoscopy rarely develop squamous cell cancer if they were compliant with treatment protocols [40].

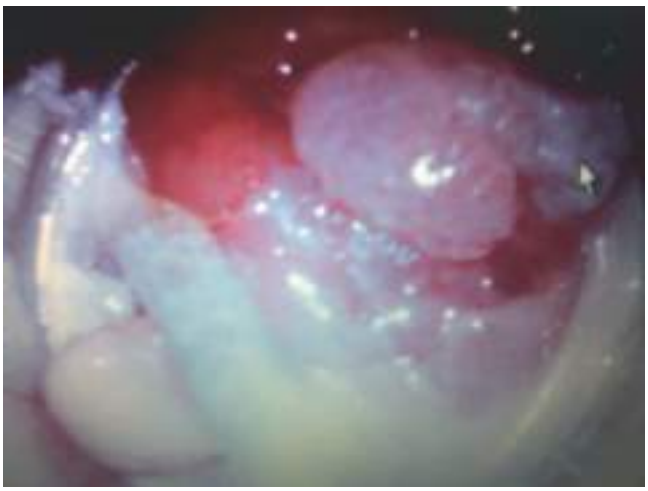

FIGURE 20.5. AIN on high-resolution anoscopy. The *pointer* denotes area of high-grade dysplasia. Courtesy of Rocco Ricciardi, MD.

Topical treatments have demonstrated effectiveness for both high- and low-grade dysplasia. These agents include imiquimod and 5-FU. Imiquimod is one of the most tested agents [47–49] and is considered to be efficacious by those who use it regularly. Despite its effectiveness in both immunosuppressed [47] and immunocompetent patients, there is a high rate of recurrence when treatment is discontinued [47, 48]. Many of the recurrent lesions are unrelated to the primary dysplastic lesion but rather due to undetected HPV types [48]. Interestingly a recent meta-analysis failed to demonstrate any statistically significant effect of imiquimod in the management of anal intraepithelial neoplasia, but there was a trend for imiquimod to downgrade high-grade AIN to a lower-risk stage [50]. As compared to imiquimod, 5-FU has fewer trials but is similarly effective in reducing dysplasia with complete response in 39 % [50]. Unfortunately, patients treated with 5-FU similarly had high rates of recurrence (50 %) and even higher rates of side effects [50, 51]. There are a smattering of reports demonstrating efficacy for other topical agents such as trichloroacetic acid [52], cidofovir [53], as well as photodynamic therapy [54].

Surgery is an effective option to treat anal neoplasia. Data reveal that electrocautery is highly effective in inducing complete response of AIN especially in immunocompetent

Table 20-1. Common options used in treatment of anal dysplasia

Treatment	Advantages	Disadvantages	Cure	Recurrence
Observation	Cost cheap No side effects	Low cure rate Time intense	Poor	High
Imiquimod	Minimal pain Easy to use	Burning Moderate cost	Poor	High with DC
5-FU	Easy to use	Burning Moderate cost	Poor	High with DC
Infrared coagulation	Clinic use	Need equipment	Good	Moderate in immunosuppressed
Ablation	One application	Painful Costly	Good	Moderate in immunosuppressed
Wide local excision	Removes all tissue	Disfiguring Painful	Good	Low

individuals (72 %) as compared to immunosuppressed individuals (51 %) [55]. Ablation is generally performed in the operating room with electrocautery in conjunction with high-resolution anoscopy; yet, others perform the procedure in the clinic with local anesthesia. The technique is highly selective with targeting of only those areas with evidence of dysplasia. The operating surgeon should remember that the disease is limited to the epidermis and does not require destruction of deeper dermal tissues. In addition, margins are unnecessary with ablation, so the electrocautery can be highly targeted without damage of healthy neighboring tissues. In fact, healthy skin bridges should be preserved as much as possible. During ablation, the surgeon should be mindful of potential scarring, stricture formation, and the need to preserve as much healthy tissue as possible. The preservation of the patients' gastrointestinal function and continence is critical. In addition, the patient will likely require further observation, and limiting electrocautery burns will lead to reduced scarring and ease of further examination in microscopy clinic.

In addition to ablation or excision, infrared coagulation can also be used to destroy lesions. Infrared devices use a beam of infrared light delivered through a light guide covered with a disposable plastic sheath to ablate tissue and coagulate blood in the immediate surface area in contact with the tip [56]. The infrared beam can be pulsed at varying intervals to prevent trauma to deeper tissues. A 1 s pulse penetrates the tissue to a depth of approximately 1 mm targeting the epithelium and destroying dysplastic tissue [56]. The other advantage of infrared coagulation is the ability to perform the technique within the clinic setting and without general anesthesia [57]. The technique is reportedly as effective as electrocautery and considered to be associated with less pain [1].

In the past, mapping biopsies with wide local excision was recommended for patients with anal intraepithelial neoplasia. Unfortunately, much healthy and uninvolved tissue was removed with the dysplastic tissues, and this treatment option was associated with high rates of recurrence between 13 and 63 % [58–60]. In addition, because of the extensive tissue destruction, wide local excision was associated with high rates of local wound complications such as stenosis and incontinence [59]. Although anal mapping with wide local excision was once routinely performed [61], it is generally not required to treat even the most challenging and diffuse disease.

When selecting which of the above options is best for an individual patient, the physician should consider patient treatment goals, symptoms, history of immunosuppression, past history of dysplasia, and bowel function. At this time, it is unclear what role HPV subtype, concurrent sexually transmitted infections, and other concerns should play in selecting treatment options. There is one trial comparing imiquimod, topical fluorouracil, and electrocautery in HIV-positive men that revealed higher rates of complete response and fewer side effects in the electrocautery group [62]. However, an attempt at Cochrane review failed to provide guidelines for treatment in anal intraepithelial neoplasia because of lack of high-quality randomized controlled trials [50].

Management Strategies

For AIN I, a minimalist approach may be the most effective strategy. Again, in the cervical literature, a large number of patients will regress to normal epithelium but similar data are unavailable in the anus. Given the lack of data regarding progression of low-grade dysplasia in healthy immunocompetent patients, most clinicians would advocate observation. However, the high likelihood of cure after ablation or other interventions makes a surgical approach attractive, particularly if the patient does not wish to return to a microscopy clinic on a regular basis. Low-grade dysplasia in an immunosuppressed patient presumably has a higher likelihood of progression but a high likelihood of recurrence as well. Thus, repeated ablative attempts to the anus with the potential development of scarring, stenosis, bleeding, and chronic pain render an aggressive approach difficult for patients. For immunocompetent patients with high-grade dysplasia, the simplest method of treatment is ablation. There are some who would attempt topical therapy, but surgical ablation is efficient, is effective, and can be targeted with high-resolution

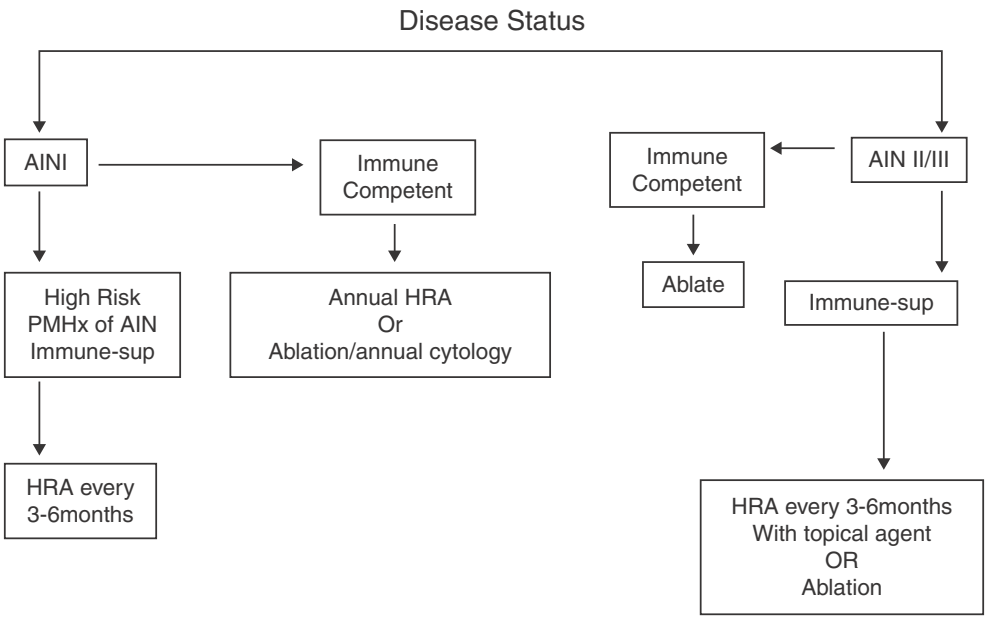

FIGURE 20.6. Algorithm for the treatment of AIN based on immune status and biopsy results.

anoscopy in the right hands. For immunosuppressed individuals with high-grade dysplasia, the best treatment is unclear (Figure 20-6). These patients have high likelihood of recurrence, multifocal disease, other comorbidities and health concerns, and other difficulties. Our approach is to combine therapies with topical therapy, close observation with high-resolution anoscopy, and ablation when the disease appears to be worsening or when patient follow-up is questionable. Our office chooses to limit the ablative interventions for these high-risk patients but follow closely and ablate only those areas that appear most ominous. In addition, the role of wide local excision in the surgical armamentarium is unclear.

Progression

Progression of anal intraepithelial neoplasia to squamous cell cancer of the anus parallels the pathway of cervical dysplasia to cervical cancer [63]. Once established in the anal epithelium, dysplasia of the anus rarely regresses [64] causing substantial concern for patients and their caregivers. The persistence of disease is particularly troubling for those with symptoms, but data proving persistence is incomplete as not all cases with anal dysplasia present for workup. In addition, it is unclear why anal dysplasia is thought to be more persistent than equivalent degrees of cervical dysplasia given the common pathogenic cause of these two conditions. In fact, it is estimated that approximately 60 % of low-grade cervical lesions will spontaneously regress in the cervix [45, 46]. Despite the favorable results in the cervix, similar anal disease is seen as prognostically worse. There are no natural history studies of untreated anal dysplasia, although case reports do detail a high rate of progression of the precursor lesions to anal cancer with lack of follow-up [65, 66]. The high rate of progression is particularly true for immunosuppressed patients as compared to immunocompetent patients [65].

Prevention

As with all infectious diseases that are transmissible by sexual contact, the best method of prevention is safe sexual practices or limiting sexual contact [67]. In addition to monogamy, proper and consistent use of prophylactic condoms has been shown to reduce the transmission of HPV [68]. Although latex condoms can prevent infection most of the time, the virus can still cause infection by infecting areas that are not covered by a condom. In addition to condoms, educational interventions targeting socially and economically disadvantaged women in which information provision is complemented by sexual negotiation skill development can encourage at least short-term sexual risk reduction behavior [69]. Thus, educational interventions do have the potential to reduce the transmission of HPV and possibly reduce the incidence of squamous carcinoma [69].

In addition to primary prevention techniques, vaccines have also been efficacious in reducing the incidence of HPV infection. In the general screening population, HPV vaccine efficacy was almost 100 % for cervical intraepithelial neoplasia, vulvar and vaginal intraepithelial neoplasia, and anogenital condyloma [70]. In men who have sex with men, the use of quadrivalent HPV vaccine significantly reduced the

rates of moderate and high-grade anal intraepithelial neoplasia [42]. Although the vaccinated populations were HPV naïve, there are some data indicating effectiveness of HPV vaccines in preventing reinfection or reactivation of disease [71]. Along the same reasoning, a nonconcurrent cohort study of HPV-vaccinated men who had been previously treated with high-grade anal intraepithelial neoplasia was noted to have a reduction in anal intraepithelial neoplasia recurrence [72].

Conclusions

Anal cancer incidence is rising in the United States indicating increased prevalence of AIN; therefore, screening programs are under development to identify disease earlier. There is a growing body of data indicating that high-resolution anoscopy with ablation leads to a low rate of anal cancer development [41]. However, optimal therapy of anal intraepithelial neoplasia is unclear. Multiple modalities exist and the clinician should balance factors such as symptoms, disease severity, dysplasia multifocality, immunosuppression, and past history of disease into account. Ultimately, the condition should be treated with the intent to preserve continence and reduce postoperative scarring and strictures while reducing the potential for disease progression to invasive cancer.

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Part III
Malignant Disease

21
Anal Cancer

Tushar Samdani and Garrett M. Nash

Key Concepts

- Chemoradiotherapy (CRT) is the primary treatment for patient with anal squamous cell carcinoma (mitomycin + 5-FU + radiotherapy). The dosage of radiotherapy varies based on the size of the tumor and presence of lymph node involvement.
- Surgery (local excision) can be used to remove some small squamous cell carcinomas (usually measuring <1 cm or ½ in.) that do not involve the anal sphincter musculature.
- Following primary treatment with chemoradiotherapy, patients are evaluated with repeat physical examination of the anal area at approximately 8–12 weeks after completion of treatment, and then at 6- to 8-week intervals until resolution of any suspicious findings. Patients with persistent but nonprogressive disease may be followed up to 6 months after chemoradiotherapy for assessment of complete remission.
- Patients with progressive disease or recurrence after chemoradiotherapy are considered for salvage abdominoperineal resection (APR).
- Dosage of radiotherapy and chemotherapy may be modified based on CD4 count and blood count in immunocompromised patients.
- Anal melanoma is very aggressive, and is generally treated with local excision (LE).
- Anal adenocarcinoma is treated with APR and usually with neoadjuvant chemoradiotherapy, as in treatment for distal rectal adenocarcinoma.

Introduction

Anal cancer accounts for only a small percentage (4 %) of all cancers of the lower alimentary tract [1]. Approximately 0.2 % of men and women will be diagnosed with anal cancer at some point during their lifetime, based on 2009–2011 data. As per the American Cancer Society: Cancer Facts and Figures 2015, estimated new cases of anal cancer in the USA will be approximately 7270 in 2015; the estimated deaths from anal cancer in 2015 will be approximately 1010 (Tables 21-1 and 21-2) [2].

Risk Factors

The incidence of anal cancer appears to have risen over the last few years. This may be due to a higher incidence in persons engaging in receptive anal intercourse, or having multiple sexual partners. These practices increase the likelihood of infection with human papillomavirus (HPV), which is strongly associated with premalignant anal squamous intraepithelial lesions and the development of anal squamous cell cancer [3].

Risk factors associated with anal cancer:

- Sexually transmitted disease.
- Anal receptive intercourse.
- More than ten sexual partners.
- The presence of precancerous anal lesions such as condylomas or high-grade anal intraepithelial neoplasia, and cervical, vulvar, or vaginal cancers.
- Immunosuppression secondary to solid organ transplantation or chronic glucocorticoid therapy.
- HIV seropositivity, low CD4 count.
- Smoking.

Anatomy of the Anal Canal

Complete knowledge of anatomical landmarks and histological features of the anal canal is crucial in order to understand the origins of different types of anal neoplasms and determine their management (see Chap. 1). The surgical anal canal extends from the puborectal sling to the intersphincteric groove (the white line of Hilton). It is histologically divided into two unequal

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sections (the upper two-thirds and lower one-third) by the dentate line (pectinate line), which is the site of fusion of the proctodeum below and the post-allantoic gut above (Fig. 21-1).

Table 21-1. WHO histological classification of malignant tumors of the anal canal

- Carcinoma
  - Squamous cell carcinoma
  - Adenocarcinoma
    - Rectal type
    - Of anal glands
    - Within anorectal fistula
  - Mucinous adenocarcinoma
  - Small-cell carcinoma
  - Undifferentiated carcinoma
  - Others
- Carcinoid tumor
- Malignant melanoma
- Nonepithelial tumors
- Secondary tumors

WHO World Health Organization
Source: AJCC Cancer Staging Manual plus EZTNM, 6th edition

- The anal canal just above the dentate line (for about 1–2 cm) is known as the anal transition zone (ATZ). Beyond this transition zone, the [surgical] anal canal is lined with columnar epithelium. Its lower ends are joined together by folds of mucus membranes known as anal valves. The upper two-thirds of the anal canal are supplied by the superior rectal artery, which is a branch of the inferior mesenteric artery.
- The lower one-third of the anal canal is lined by stratified squamous epithelium that blends with the skin. The lower one-third is supplied by the inferior rectal artery, which is a branch of the internal pudendal artery.

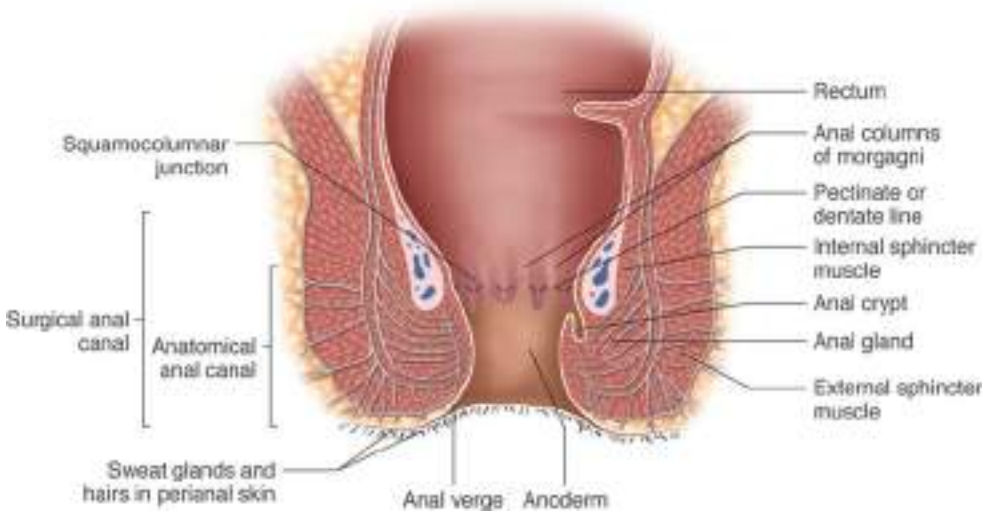
The anal margin extends laterally from the intersphincteric groove to a radius of approximately 5 cm, and is characterized by keratinized stratified squamous epithelium. The intersphincteric groove indicates the junction between keratinized

Table 21-2. TNM classification for anal cancer

	Primary tumor (T)
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ (Bowen's disease, high-grade squamous intraepithelial lesion HISL), AIN II–III
T1	Tumor 2 cm or less in greatest dimension
T2	Tumor more than 2 cm but not more than 5 cm in greatest dimension
T3	Tumor more than 5 cm in greatest dimension
T4	Tumor of any size invades adjacent organ(s), e.g., vagina, urethra, bladder (direct invasion of rectal wall, perirectal skin, subcutaneous tissue, or sphincter muscle is not classified as T4)
	Regional lymph node (N)
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in perirectal lymph nodes(s)
N2	Metastasis in unilateral internal iliac and/or unilateral inguinal lymph node(s)
N3	Metastasis in perirectal and inguinal lymph nodes and/or bilateral internal iliac and/or inguinal lymph nodes
	Distant metastases (M)
M0	No distant metastasis
M1	Distant metastasis

Source: AJCC Cancer Staging Manual plus EZTNM, 6th edition

Figure 21-1. Anal canal anatomy.



stratified squamous epithelium and the non-keratinized stratified squamous epithelium [4, 5]. Anal squamous cell carcinoma commonly arises from either squamous epithelium of the lower part of the anal canal. Rarely does it arise from the ATZ. On the other hand, histological variants of SCC, such as transitional, basaloid, and cloacogenic variants, arise from ATZ. Adenocarcinoma of the anal canal originates from the colorectal zone in the upper portion of the anal canal or from the glandular cells of the ATZ mucosa whereas anal margin squamous cell carcinoma arises lateral to intersphincteric groove. Of note, histological features of anal melanoma are similar to cutaneous melanoma arising from basal cell layer of stratified squamous epithelium.

Some authors have simplified classification of the anal region, dividing it into three easily identifiable regions based on visual examination [6].

Intra-anal lesions are lesions that cannot be visualized on perianal examination until gentle traction is applied on the buttocks.

Perianal lesions are completely visible, without traction on the buttocks, extending within 5 cm of the anal margin.

Skin lesions fall outside the 5 cm radius from the anal opening. Hence, some have classified this into three distinct regions: intra-anal (visualized with gentle traction on the buttocks), perianal, and skin tumors (beyond a 5 cm radius from the anal opening).

Squamous Cell Carcinoma of the Anal Canal

In the USA, the median age at diagnosis of squamous cell carcinoma of the anal canal (SCAC) is 60–65 years, and there is slightly higher incidence in women [3, 7].

Symptoms

Approximately one-third of patients with SCAC are asymptomatic, or have nonspecific symptoms on presentation. Clinical manifestations of anal canal tumors are mainly related to tumor size and extent of infiltration. The most common symptom is rectal bleeding, which is seen in approximately 45 % of cases, followed by anal pain or sensation of anal mass, seen in 30 % [8, 9]. Other symptoms include anal pruritus, discomfort in sitting, a change in bowel habits, incontinence (due to tumor infiltration into the sphincter), discharge, bleeding, fissure, or fistula. Diagnosis may be delayed because initial symptoms are nonspecific, and the anal canal is often a difficult location for examination. Moreover, because anal cancer is rare, many primary care practitioners have little experience in diagnosing it.

The clinical diagnosis of an anal tumor should be confirmed by histologic examination. A forceps or needle biopsy may be done to establish the diagnosis. It is very important to document an exact description of location and appearance of the biopsy site, as this will help in planning radiation fields and posttreatment surveillance. If the lesion is large or involves the sphincter, an excisional biopsy is inadvisable because the subsequent wound healing may delay optimal chemoradiation treatment (CRT). Enlarged lymph nodes may be excised or biopsied with needle aspiration, under radiological guidance [3, 10].

Examination

Detailed physical examination is very important, as a lesion in the anal canal may be easily missed on cursory exam. Physical examination includes inspection to assess for tumor location, size, and extent, and direct visualization of the mass via anoscopy, rigid proctoscopy, or flexible sigmoidoscopy, which may be retroflexed in the rectum. Digital rectal exam should be done to assess sphincter function, and relation of tumor to the sphincter (Figs. 21-2 and 21-3a, b). The tumor may present as a small ulcer or fissure with slightly exophytic and indurated margins, and irregular thickening of the anal canal. If a thorough anal canal examination is not possible due to significant perianal pain or spasm, examination under anesthesia may be done to assess the tumor. Along with local examination of the anal canal, groin lymph nodes (LNs) should be examined to rule out involvement. It has been traditionally recommended that patients with an anal cancer should undergo colonoscopy to evaluate for synchronous colorectal lesions [3, 10]; however, it should be noted that there are no definitive data demonstrating an association between SCAC and adenomatous neoplasia of the colon or rectum. In women

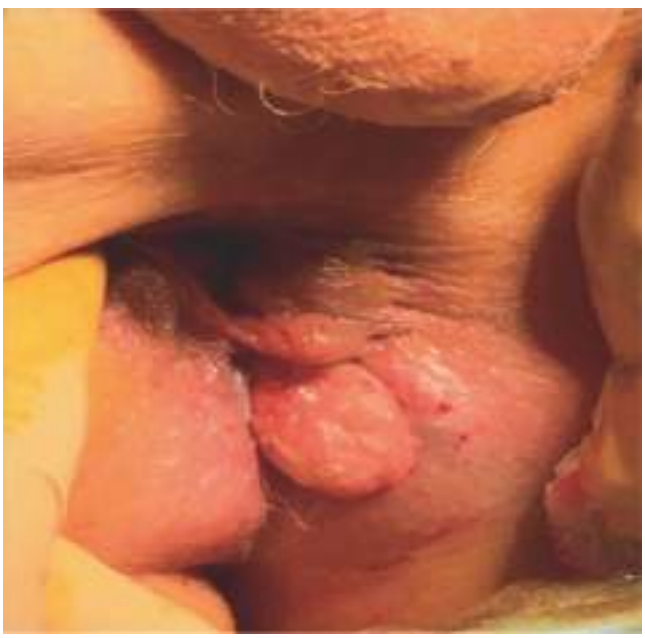


FIGURE 21-2. Anal cancer.

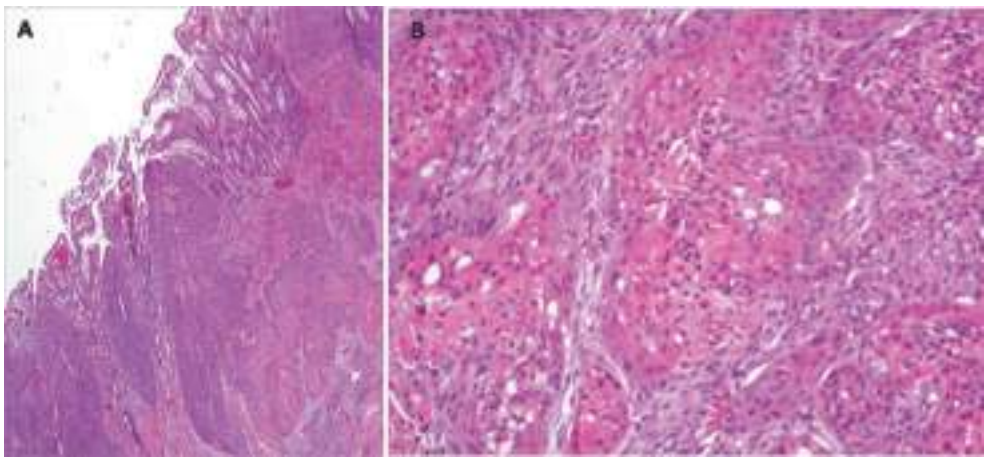


FIGURE 21-3. Anal squamous cell carcinoma invading rectal mucosa. (**a**) Low power view; (**b**) higher power view.

with anal cancer, a pelvic examination may be performed to determine the extent of invasion of an anterior lesion into the posterior vagina. Female patients should have routine gynecologic evaluations, given the risk of other HPV-associated diseases such as cervical dysplasia (Fig. 21-4) [11].

Investigation

Treatment of anal cancer is based on the stage of the tumor. Therefore, a comprehensive physical exam should be complemented with imaging, to determine the possibility of locoregional or systemic spread.

Investigation of Choice

- Locoregional staging: MRI of the rectum/pelvis, with or without endoscopic ultrasound.
- Distant metastasis: CT scan of the chest, abdomen, or pelvis; or FDG PET/CT.

MRI of the Rectum/Pelvis

MRI provides high-resolution, multiplanar information regarding the location, size, circumferential and craniocaudal extent of the primary tumor, and involvement of adjacent structures, including the sphincter (Fig. 21-5). The sensitivity of MRI in identifying SCAC has been reported to approach 90–100 % [12]. Along with evaluation of the primary tumor, MRI can be used to assess involvement of the pelvis and inguinal LNs. MRI determines LN involvement based on various criteria such as LN size, loss of the normal bean-shaped morphology and fatty hilum, internal T1 and T2 signal heterogeneity with central necrosis, and inhomogeneous enhancement. Short-axis threshold values of 8 mm, 5 mm, and 10 mm have been suggested for pelvic, perirectal, and inguinal LNs, respectively [13, 14].

Transanal Endoscopic Ultrasound

Transanal endoscopic ultrasound may be used to assess local staging of anal cancer (Fig. 21-6). This modality may be

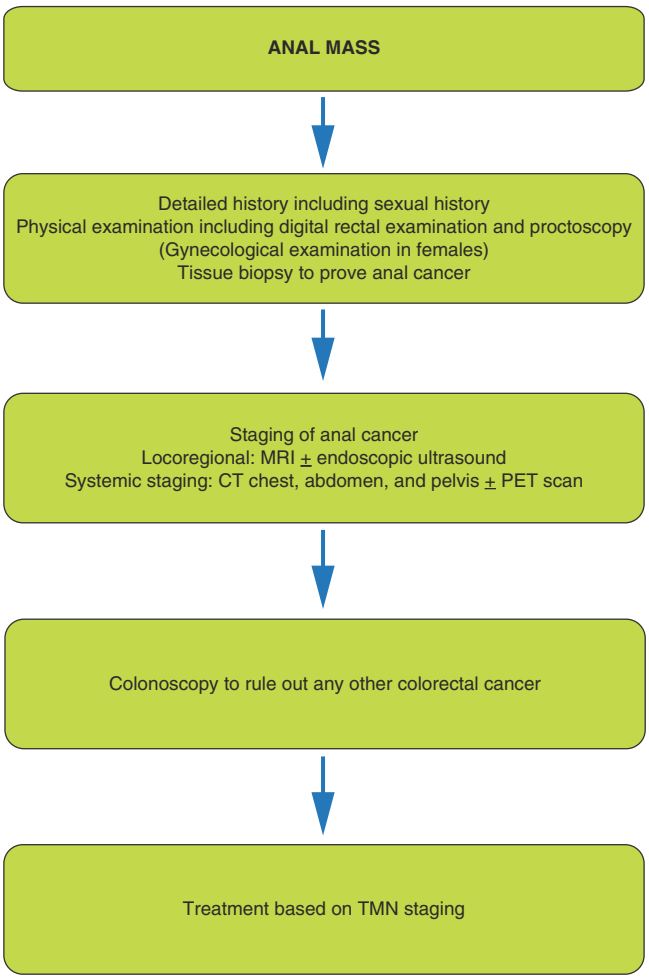


FIGURE 21-4. Algorithm for anal mass evaluation and work-up.

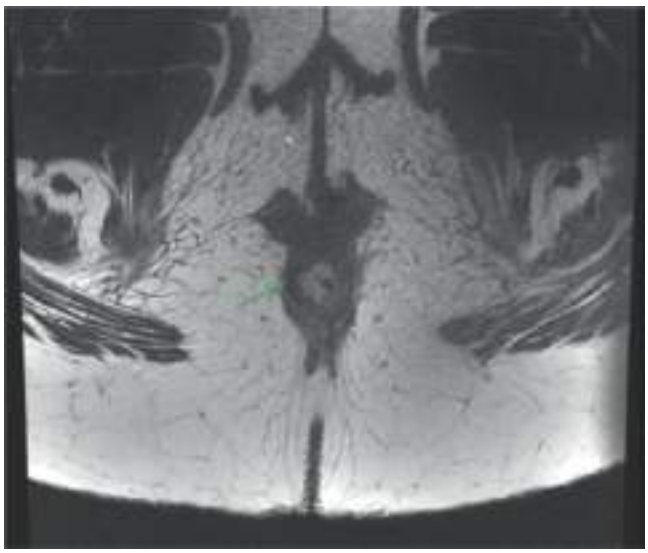


FIGURE 21-5. Anal cancer: pretreatment MRI T2 oblique, suspicion for focal tumor invasion into the right lateral internal anal sphincter (green arrow).

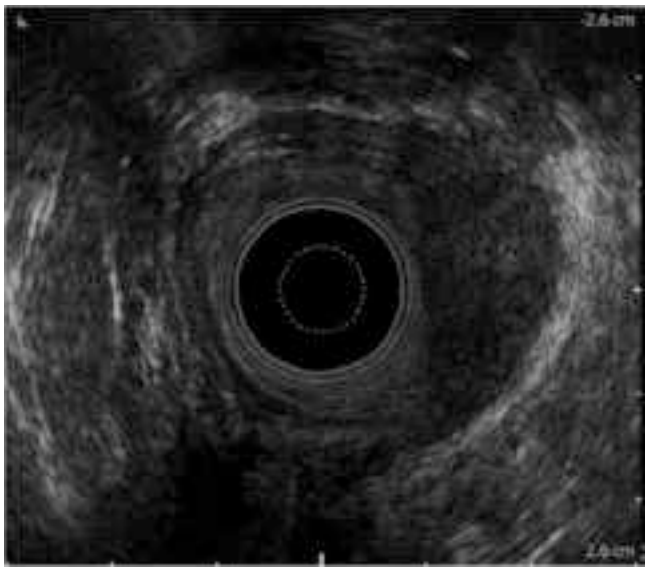


FIGURE 21-6. Transanal endoscopic ultrasound can be used to assess local staging of anal cancer.

superior to MRI in evaluating small superficial tumors [15]. However, the limitations of transanal endoscopic ultrasound include an inability to ascertain involvement of the proximal pelvis or groin LNs, and it may be difficult to use in assessing a stenotic or painful anal lesion. Lastly, its accuracy is highly operator dependent.

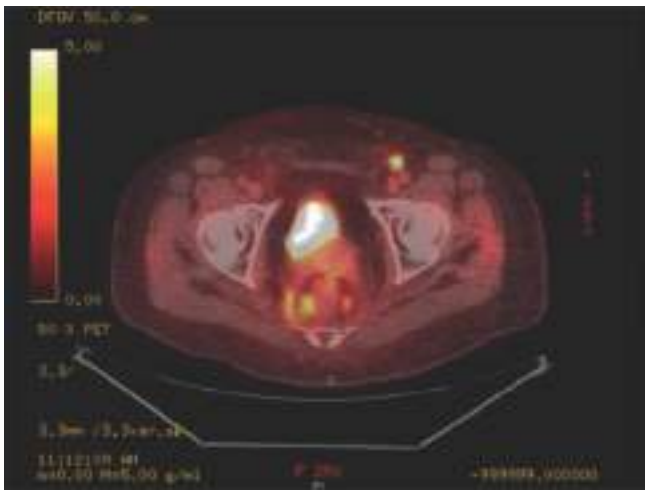


FIGURE 21-7. Anal cancer: left inguinal adenopathy and mesorectal adenopathy seen on PET/CT.

CT Scan of Chest, Abdomen, and Pelvis with IV Contrast

CT scanning of the chest, abdomen, and pelvis is used to identify possible metastatic disease [16].

FDG PET/CT

Approximately 98 % of anal tumors are FDG avid. Hence, FDG PET/CT has assumed an increasing role in the staging and assessment of treatment response [17]. PET/CT may be used to evaluate primary tumor size, LN status, and distant metastasis, and may help in planning radiation therapy by clearly defining the site of metabolically active tumor. It may also be useful in posttreatment surveillance (Fig. 21-7). PET/CT is indicated for node-positive and T2–T4 anal canal and anal margin cancer to verify staging before treatment. PET/CT has become part of the standard work-up, particularly for evaluating LNs that appear ambiguous on CT, to aid in management, and to serve as a pretreatment baseline. PET/CT has demonstrated a sensitivity of >90 % and a specificity of 80 %. PET/CT has been shown to alter the staging of anal carcinoma in approximately 20 % of cases, and treatment intent in approximately 3–5 %. The main impact of PET/CT on therapy stems from its superiority in detecting involved pelvic or inguinal nodes, prompting the radiation oncologist to include these in the RT field [18, 19, 20]. PET/CT has also impacted posttreatment management in 18 % of anal cancer patients (Fig. 21-8). It may confirm persistence of disease or local recurrence, and influence decision making regarding the use of chemotherapy in patients with metastatic disease [3, 21]. The high negative predictive value of PET-CT may dictate avoidance of unnecessary biopsy after chemoradiotherapy.

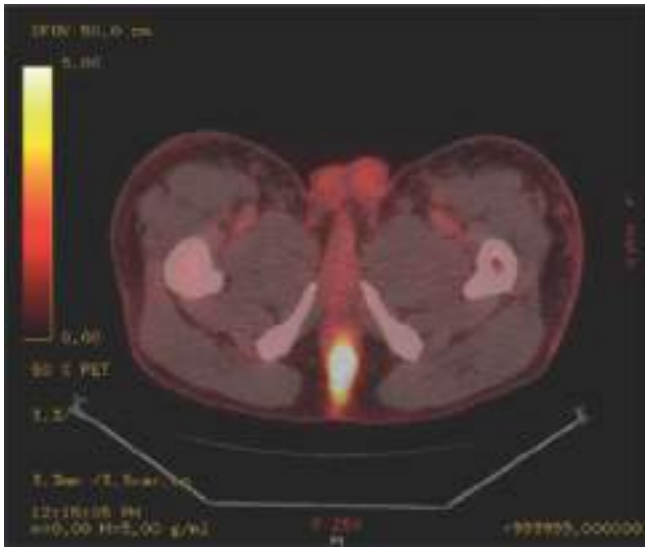


FIGURE 21-8. Anal cancer: pretreatment SUV = 18.1.

Summary of the Initial Work-Up of Anal Cancer

1. In the setting of a T1 tumor, after a thorough physical exam, MRI of the rectum/pelvis or transanal endoscopic ultrasound may be used for additional local staging. In the absence of nodal disease, a CT scan of the chest and abdomen may be used for distant staging.
2. In the setting of a T2–T4 tumor or node-positive anal cancer, PET/CT may be used in addition to MRI or transanal endoscopic ultrasound to screen for distant metastases, to assess response to CRT, and as a tool in subsequent cancer surveillance.

Treatment of Anal Cancer

Until three decades ago, abdominoperineal resection (APR) of the rectosigmoid and anus was the preferred surgical procedure for most cancers of the anal canal. This radical operation was performed in order to achieve adequate margins of resection [8]. Local resection was done for smaller lesions. Surgical treatment alone was associated with local failure in 27–47 % of cases [22]. Early tumors could be cured by APR, with 5-year survival rates of 50–70 %. However, APR entails a permanent intestinal stoma and is associated with substantial morbidity. Over the last three decades, there has been significant change in the management of epidermoid anal carcinomas, with more patients undergoing nonsurgical treatment.

Evolution in the Management of Anal Cancer (Fig. 21-9)

Radiotherapy

Dosage

Dosage of RT varies based on the size of the tumor and presence of suspected LN involvement. In general, larger cancers require higher doses of radiation. The database of the RTOG 9811 trial suggests that size >5 cm is a poor prognostic factor [29]. Doses in the range of 30 Gy, with concurrent mitomycin C and 5-FU, have been shown to control small tumors (CCR rate of 86 %) and subclinical disease effectively. The preliminary results of the ACCORD-03 trial compared 45 Gy in 25 patients plus a 15 Gy boost with a higher dose, but found no benefit in CFS, and higher toxicity, at >59 Gy [30]. Similar results were reported in the RTOG 92-08 trial [31].

Patients with SCAC receive a minimum RT dose of 45 Gy to the primary cancer. The recommended initial dose is 30.6 Gy to the pelvis, anus, perineum, and inguinal nodes. Following initial dose of 30.6 Gy, field of radiation should be reduced from L5–S1 junction to bottom of sacroiliac joints. In patients without nodal metastasis, inguinal nodes are not included in radiation field after 36 Gy. Patients with disease clinically staged as node positive or T3–T4 or with T2 residual disease after 45 Gy should receive an additional boost of 9–14 Gy [28].

Field of Radiotherapy

Multi-field techniques with supervoltage radiation (photon energy >6 mV) are used to deliver a minimum dose of 45 Gy in 1.8 Gy fractions (25 fractions over 5 weeks) to the primary cancer. The RTOG panel established three elective clinical target volume (CTV) areas: CTVa targets the perirectal, presacral, and internal iliac regions; CTVb targets the iliac LNs; and CTVc targets the inguinal LNs; inclusion of all is recommended in RT for anal cancer. The superior field border includes the rectosigmoid junction (L5–S1 junction); the inferior border includes the anus, with a minimum 2.5 cm margin around the anus and tumor; the lateral border includes the lateral inguinal nodes, based on imaging or body landmarks. An attempt should be made to reduce the dose to the femoral heads [32, 33] (Fig. 21-10).

Side Effects [34–36]

The short-term side effects of RT include:

- Dermatitis.
- Temporary anal swelling and pain.
- Frequency and urgency in defecation.
- Nausea, weakness.
- Vaginal discomfort and discharge.

These side effects often improve after radiation stops. Long-term side effects include:

- Anal stenosis.
- Pelvic fracture.
- Chronic radiation proctitis.
- Vaginal stenosis (female patients should be encouraged to use a vaginal dilator).

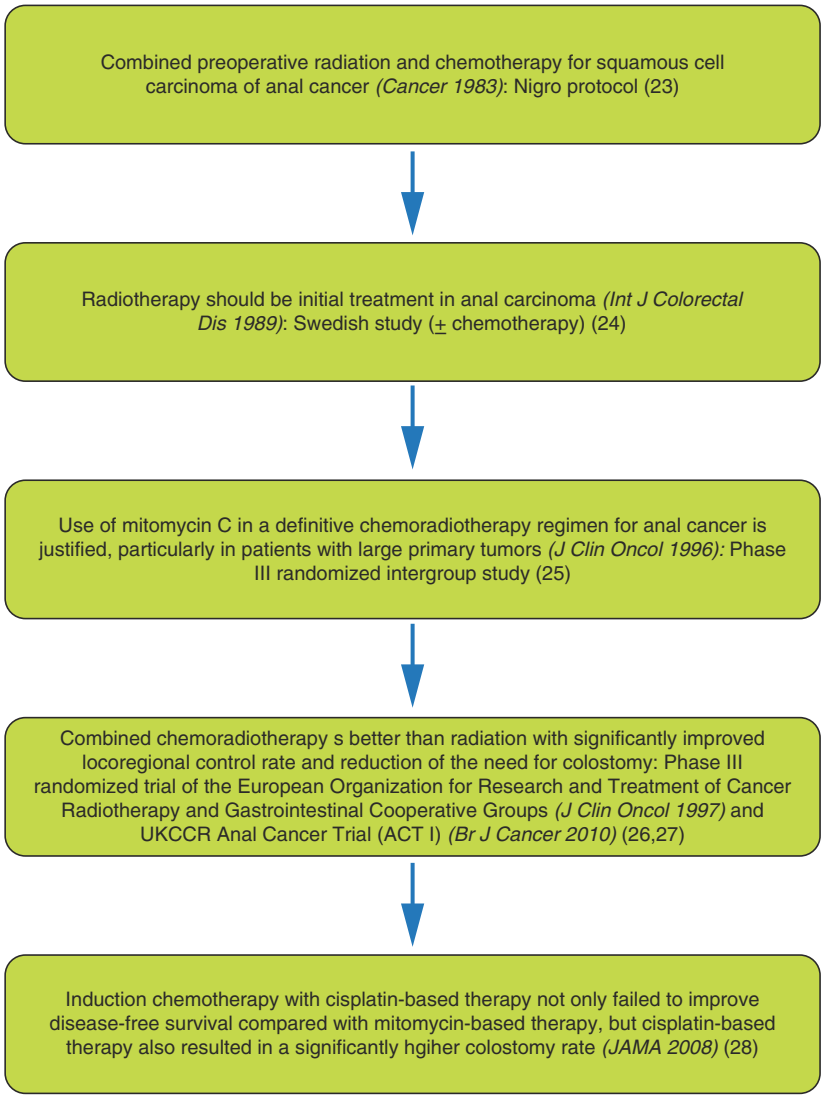


FIGURE 21-9. Evolution of management of anal cancer (algorithm).

- Radiation may affect fertility in both women and men (patients should be informed about sperm and ovarian tissue banking).
- Dyspareunia.
- Lymphedema.

Special Considerations

Intensity-Modulated Radiation Therapy

Intensity-modulated radiation therapy (IMRT) utilizes detailed beam shaping, enabling precision in targeting tumor and sparing normal tissue. Compared with conventional three-dimensional (3D) CRT (Figs. 21-11 and 21-12), IMRT may spare the perineal skin, external genitalia, and bladder, reducing toxicity to surrounding anatomic structures, and preventing toxicity-related delay in completion of treatment—thereby improving treatment outcomes [3, 72, 73]. In a retrospective study from Memorial Sloan Kettering Cancer Center of 221 patients with anal SCC treated with CRT between 1991 and 2007, 44 patients received IMRT and 177 received 3DCRT. The 2-year local recurrence-free survival, distant metastasis-free survival, colostomy-free survival, and overall survival were 88 %, 83 %, 96 %, and 92 %, respectively, in the IMRT group, and 81 %, 88 %, 91 %, and 89 %, respectively, in the 3DCRT group, demonstrating no significant difference between the groups [74].

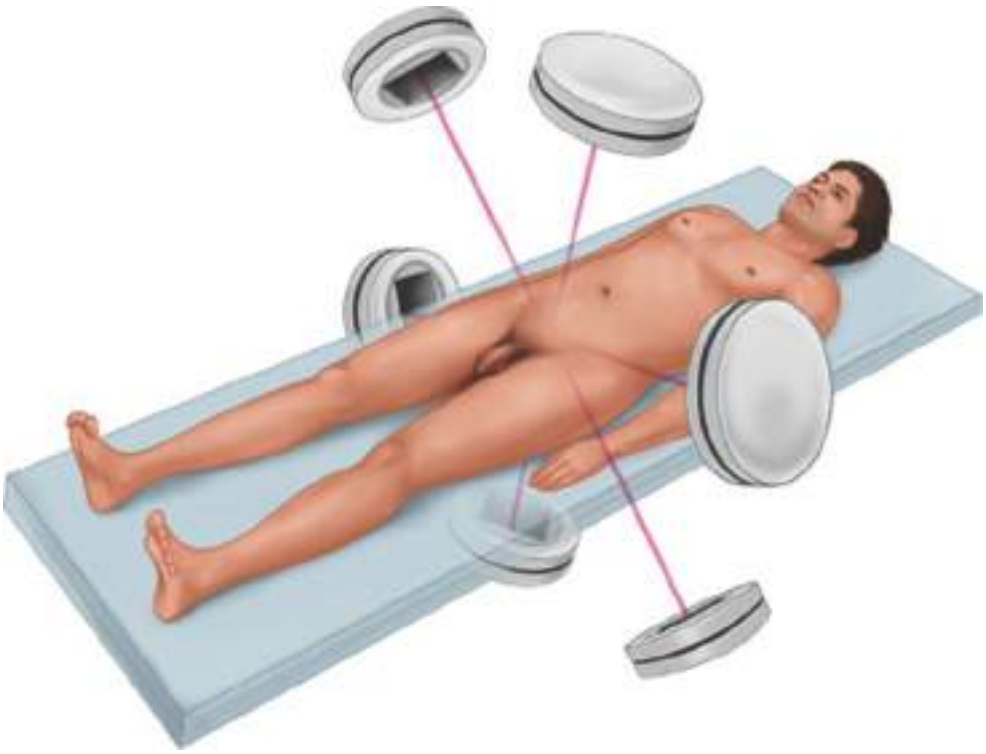


FIGURE 21-10. External beam radiotherapy.

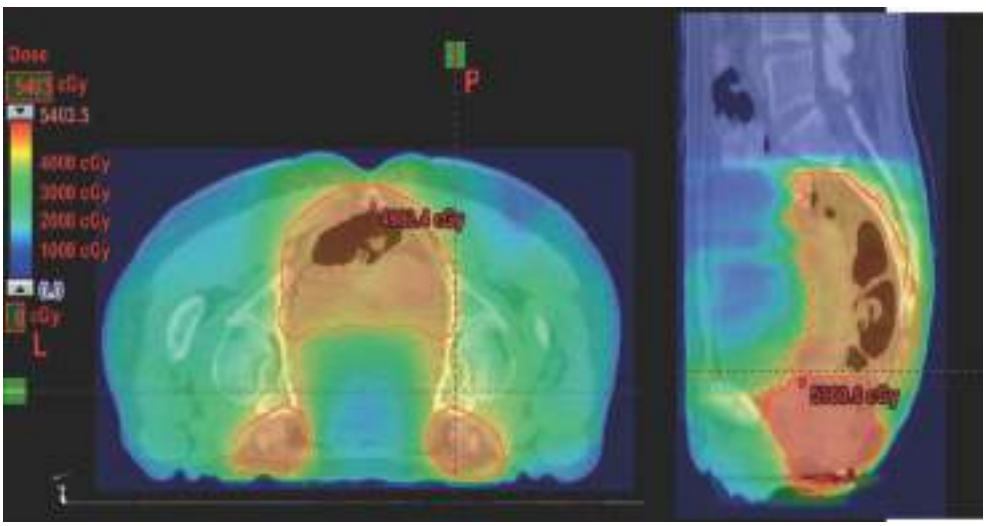


FIGURE 21-11. T1N0 anal SCC—IMRT: 4500cGy in 180cGy fractions to pelvic nodes (*orange*); 5000cGy in 200cGy fractions to primary tumor (*red*).

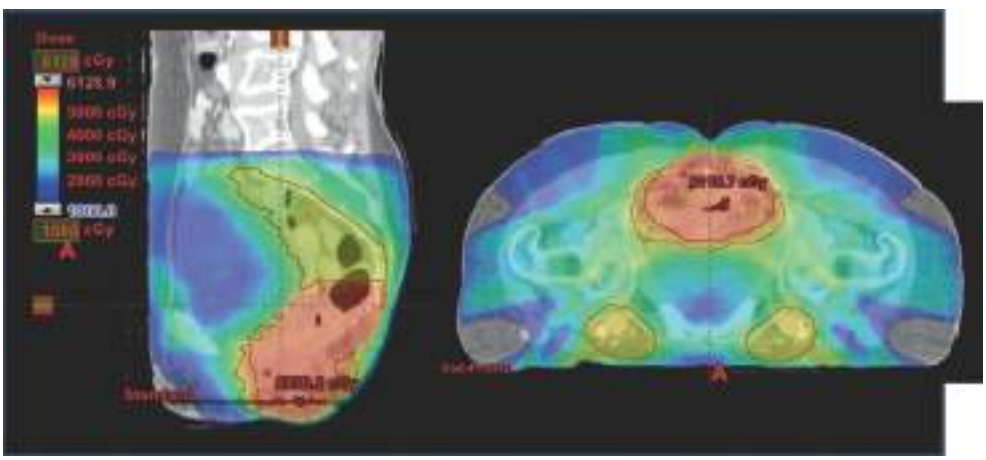


FIGURE 21-12. T3N1 anal SCC—IMRT: 4500cGy in 180cGy fractions to pelvic nodes (*brown*); 5000cGy in 200cGy fractions to primary tumor (*red*); additional boost of 600cGy in 200cGy fractions to the primary tumor (*red*).

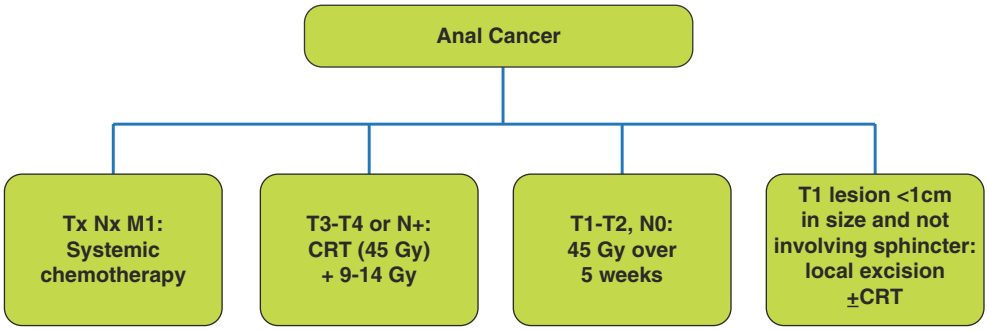


FIGURE 21-13. Anal cancer treatment.

Current Management Protocol (Fig. 21-13)

Limited Localized Disease: Stages I–III (Any T, Any N, M0)

LE can be used to remove some small tumors (usually measuring <1 cm or ½ in.) that do not involve the sphincter. In some cases, this may be followed with chemotherapy and RT, which is especially recommended in the setting of a positive margin. The standard treatment for anal cancers that cannot be removed without harming the anal sphincter is RT combined with chemotherapy (CRT).

Current primary recommendations for the treatment of non-metastatic anal cancer include CRT; commonly used therapeutic drugs include 5-FU and mitomycin.

Mitomycin + 5-FU + RT

This regimen consists of 5-FU 1000 mg/m^2/day delivered via IV continuous infusion on days 1–4 and 29–32 (maximum daily dose of 5-FU = 2000 mg/day), plus mitomycin 10 mg/m^2 via IV bolus on days 1 and 29 (maximum = 20 mg per dose) [28]. RT may be included in all stages of disease, with a minimum 45 Gy delivered over 5 weeks. Additional RT of 9–14 Gy may be considered for patients with T3, T4, or node-positive disease, or those with residual disease after an initial dose of 45 Gy [37, 38].

Metastatic Disease (Stage IV): Any T, Any N, M1

Metastatic disease is commonly treated with cisplatin-based (5-FU + cisplatin) chemotherapy.

Cisplatin + 5-FU

The regimen consists of 5-FU 1000 mg/m^2/day via IV continuous infusion on days 1–5, plus cisplatin 100 mg/m^2 via IV on day 2, repeated every 28 days [39]. Patients with metastatic disease receiving systemic chemotherapy have approximate survival rates of 60 % at 1 year and 32 % at 5 years, respectively [8, 39].

In some patients with metastatic disease, surgical intervention may be required for relief of symptoms such as pain, bleeding, or fecal incontinence.

Prognostic Factors

The size of the primary tumor and the presence of nodal or distant metastases are the principal determinates of outcome. Patients with de novo tumors >5 cm are at significantly increased risk of requiring an APR with permanent colostomy, and such tumors are associated with inferior disease-free and overall survival. Male gender and HIV-positive status may portend an unfavorable long-term outcome [8, 40, 41].

Evaluation of Treatment Response

The mainstay in assessment of tumor response is clinical follow-up. Patients are evaluated by repeat physical examination of the anal area at approximately 8–12 weeks after completion of chemoradiotherapy, and at 6- to 8-week intervals until resolution of any suspicious findings. Based on evaluation, patients are classified with respect to remission, as follows:

- *Persistent disease*: Patients with persistent disease but no progression are followed closely to see if further regression occurs. Based on the ACT II study, patients with persistent but nonprogressive disease may be followed up to 6 months after chemoradiotherapy, until determination of complete remission.
- *Complete remission*: Patients with complete remission should undergo evaluation every 3–6 months for 5 years. This should include digital rectal examination, endoscopic examination, and examination of the groin. CT

scan of the chest, abdomen, and pelvis, or PET/CT, is performed annually for 3 years in patients with slow disease regression, and those who initially had locally advanced disease (T3/T4) or node-positive cancer.

- *Progressive or persistent disease at 6 months*: If the patient has persistent disease at 6 months, or progressive disease develops in the meantime, biopsy may be done to confirm cancer. Biopsy is recommended earlier in the setting of tumor mass progression or unsatisfactory response to treatment [3, 8, 10, 36]. However, unnecessary biopsy should be avoided to minimize the risk of soft tissue infections, tissue necrosis, or impairment of anal function.

Salvage Treatment

Approximately 10–30 % of patients have persistent or recurrent disease after initial CRT. Risk factors associated with failure of initial treatment include:

- HIV-positive status.
- High T and N stage at original presentation.
- Interruption of treatment during CRT.

Progressive disease is biopsied and restaged before salvage treatment [42–44]. Some studies recommend an additional RT of 9 Gy, rather than resorting to APR immediately. However, salvage surgery is generally recommended for persistent anal cancer. Surgical treatment is based on the extent of the persisting tumor. Patients with very limited residual tumor may be able to undergo LE. Others with larger residual disease should undergo salvage APR. Salvage APR is associated with 5-year locoregional control in 30–77 % of patients [43, 45, 46]; overall survival at 5 years ranges from 30 to 60 %. Wound complications are common, and may be seen in as many as 80 % of patients who undergo salvage APR after CRT. In order to reduce wound complications, muscle flap reconstruction of the perineum may be considered [47].

Treatment of Recurrent Anal Cancer

If anal cancer recurs locally after initial treatment, restaging is performed to rule out systemic metastasis; this includes CT chest, abdomen, and pelvis or PET/CT based on institutional preference. Local recurrence after CRT is commonly managed with salvage APR. Isolated recurrence in an inguinal node may be treated with RT to the groin, with or without chemotherapy, if there is no history of previous RT to the groin. If isolated recurrence develops in an inguinal node despite previous RT, inguinal node dissection may be performed without an APR [25, 48] (Table 21-3).

Treatment of HIV-Positive Patients

HIV is associated with a markedly increased incidence of anal cancer, most likely due to immunosuppression, and HPV infection secondary to anal-receptive intercourse [49, 50]. Initial treatment of anal cancer is CRT; however, certain factors such as a patient's CD4 count play a role in modifying the dose of RT; doses range from 32 to 63 Gy; chemotherapy may be delivered in conventional dose regimens, including 5-FU combined with mitomycin or cisplatin. Studies have shown that patients with CD4 >200 have acceptable treatment-related toxicity and may achieve very good disease control. On the other hand, patients with CD4 <200 have a markedly higher incidence of treatment-related morbidities. However, this is not associated with decreased overall survival. The chemotherapy dose may need to be altered, based on the patient's blood counts.

Mitomycin + 5-FU: If nadir WBC count is <2400 but >1000, or if nadir platelet count is >50,000 but <85,000, the second dose of mitomycin is reduced to 7.5 mg/m^2, from 10 mg/m^2.

If nadir WBC count is <1000 or if platelet count is <50,000, the second dose of mitomycin is reduced to 5 mg/m^2, from 10 mg/m^2.

On day 28, if the WBC count is <2400 or the platelet count is <85,000, chemotherapy is delayed for 1 week [25].

There is a higher incidence of in situ anal cancer among homosexual and bisexual men, irrespective of their HIV status. Data suggest that anal cytology screening in these men every 2–3 years may be cost effective and yield benefits in life expectancy [51].

Anal Melanoma

Anal melanoma represents 1–4 % of all anorectal malignancies. It is the third most common site of melanoma, after the skin and retina, accounting for less than 1 % of all melanomas [52, 53]. It is most commonly seen in females, and the mean age of presentation is 60 years [54]. These tumors arise from the transitional epithelium of the anal canal, the anoderm, or the mucocutaneous junction.

Symptoms

The most common symptom of anal melanoma is bleeding per rectum. However, as in the setting of any other anal lesion the patient may present with pain, change in bowel habits, or tenesmus. Early lesions may be mistaken as thrombosed hemorrhoids [53].

Physical Examination

A thorough physical exam, including assessment of the groin, should be done. Anal melanoma may be pigmented, and either polypoid or ulcerated, with raised edges. Satellite lesions may also be present.

Histopathological Diagnosis

The features of anal melanoma resemble those of cutaneous melanomas. The majority shows a junctional component adjacent to the invasive tumor, which proves that the lesion is primary in nature. The tumor cell expresses S-100, HMB-45, and Melan A. Perineural invasion is an important prognostic factor (Figs. 21-14 and 21-15) [5, 55].

Treatment

The overall prognosis of anal melanoma is dismal, with a 10- to 19-month survival after diagnosis [56, 57]. Melanoma does not respond well to chemotherapy or RT; thus, surgery is the principal treatment when disease is localized. The extent of surgical resection is a matter of debate. Anal melanoma is very aggressive, and up to 35 % of patients initially present with metastatic disease. Patients with tumor >1 cm are unlikely to be cured by any type of treatment. Some authors claim that APR is the first choice of treatment, particularly for patients with small tumors and no evidence of nodal metastasis. However, as most patients with anal melanoma die of distant metastasis, major operative intervention like abdominoperineal resection may not offer a survival advantage; hence some author prefer local excision as initial treatment for melanoma. Melanoma of anal canal is sometimes detected as an incidental tumor when local excision is done for hemorrhoids. If R0 resection is achieved during local excision for hemorrhoids, patients do not need further intervention and have shown acceptable cure rates. Palliative local excision should be considered for patients with local symptoms due to anal melanoma (Table 21-3) [53, 54, 58–62].

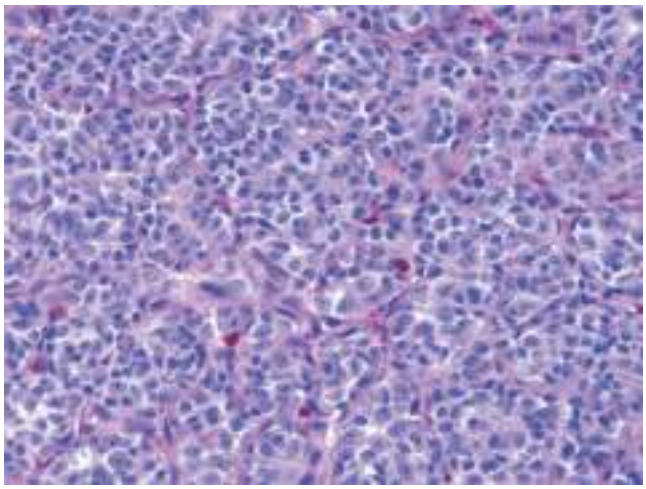


FIGURE 21-14. Anal melanoma with epithelioid morphology.

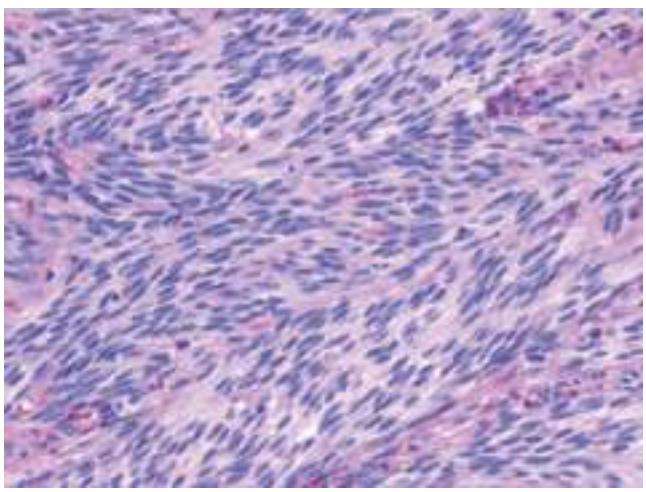


FIGURE 21-15. Anal melanoma with spindle cell morphology.

Anal Margin Squamous Cell Carcinoma (Fig. 21-16)

The anal margin begins at the margin of hair-bearing perianal skin, extending onto the perianal skin for a 5 cm radius. SCC at the anal margin behaves like any other SCC of the skin, and drains into regional LNs such as the inguinal nodes. Anal margin SCC accounts for one-fourth to one-third of all anal SCC [63–65].

Epidemiology

SCC of the anal margin generally presents in patients between 65 and 75 years of age. There is no gender predilection [63, 64].

Symptoms

Like other anal canal tumors, diagnosis of SCC of the anal margin is delayed because of nonspecific symptoms, and difficult location. The most common presentation is a symptomatic mass in the perianal region, or persistent pruritus. Any person with persistent pruritus in the perianal region should be thoroughly examined for a perianal mass; suspicious lesions should be biopsied.

Examination

A thorough exam including assessment of the groins should be performed in patients with anal canal tumors. The relationship of tumor to the anal sphincter must be ascertained [68].

Staging

A CT of the chest, abdomen, and pelvis should be performed to rule out distant metastasis.

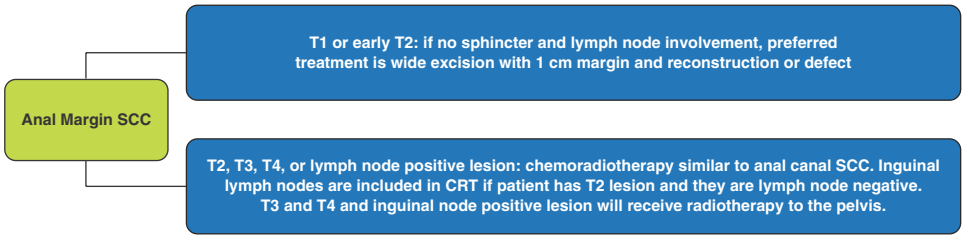


FIGURE 21-16. Algorithm for management of anal margin cancer.

Lymph node involvement: Studies have shown that the chance of LN involvement in a T1 lesion is extremely low. However, the chance of LN involvement in a T2 lesion is 24 %, and as high as 67 % in a T3 lesion [63].

Management (Fig. 21-6)

Management depends upon:

- Size of tumor.
- LN involvement.
- Sphincter involvement.

T1 N0 lesions: If there is no sphincter or LN involvement, the preferred treatment is wide excision with a 1 cm margin, when possible. The defect may be closed primarily; however, a large defect may require a V-Y advancement flap or skin graft. If the defect cannot be closed with an advancement flap, a pedicle flap may be necessary.

T2 N0 lesions: Early T2 lesions may be treated with surgery if no LN involvement is present; however, advanced lesions may be treated with CRT, as the chance of occult LN involvement is higher. Surgery to achieve a clear margin may result in an unacceptably large defect.

T3, T4, or LN-positive lesions: CRT protocols similar to those given for anal canal SCC are used. Inguinal LNs are included in CRT. T3 and T4 and inguinal node-positive lesions should receive radiotherapy (RT) to the pelvis [63–69].

Anal Adenocarcinoma

Primary mucinous adenocarcinoma of the anus is a rare malignancy, accounting for approximately 3 % of anal cancers. Most anal adenocarcinomas originate from the colorectal zone in the upper portion of the anal canal, or from the glandular cells of the ATZ mucosa.

Adenocarcinoma of the anal canal can be categorized based on origin (Fig. 21-17).

- Colorectal-type adenocarcinoma: Macroscopically and histologically, these lesions are indistinguishable from ordinary colorectal adenocarcinoma. However, they carry a higher risk of nodal disease along the inguinal and femoral nodal chains. Immunohistology shows positivity for cytokeratin (CK) 20 and CDX2, and negativity for CK7, which is compatible with colorectal subtype anal adenocarcinoma.
- Adenocarcinoma within an anorectal fistula: Anorectal fistulae can be developmental or acquired due to inflammatory conditions such as Crohn's disease.
- Adenocarcinoma of the anal glands: This diagnosis is given if the tumor is primary to the anal canal and centered within the wall of the anorectal area, without a preexisting fistula and without surface mucosa dysplasia, irrespective of the extent of mucin production. Anal gland adenocarcinoma is CK7 positive [5].

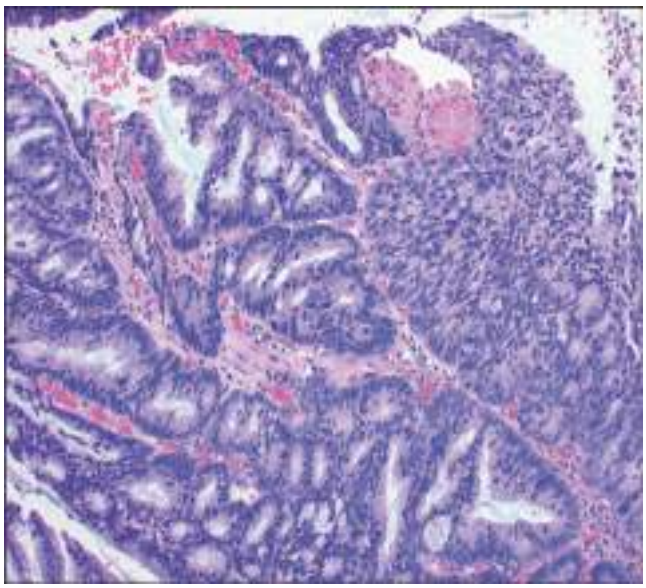


FIGURE 21-17 Superficial portion of an anal adenocarcinoma showing a low-grade gland forming component and a high-grade component with more solid growth.

Clinical Features and Diagnosis

Anal adenocarcinoma presents with symptoms similar to those of any other anal mass. Thorough physical examination and biopsy are required to confirm the diagnosis.

Table 21-3. Types of anal cancer and preferred treatment

Type of anal cancer	Preferred treatment
Recurrent SCC	Local recurrences after treatment with radiation therapy and chemotherapy are treated with salvage APR
Anal melanoma	Local excision
Anal adenocarcinoma	Combined modality treatment including APR with adjuvant CRT to be optimal treatment

Staging

Staging is similar to that done for anal canal SCC.

Prognostic Factors

Prognostic factors in anal adenocarcinoma are [70]:

- T stage.
- N stage.
- Histologic grade.
- Treatment modality.

Management (Table 21-3)

Due to the rarity of this disease, very few studies have been published reporting on management of anal adenocarcinoma. Management options include LE, radical surgery (APR) with or without chemotherapy, or CRT. Historically, APR was the preferred treatment; however, with recent advances in CRT, a combined modality treatment including APR plus adjuvant CRT is considered optimal [70–77].

Biologicals

SCC of the anus commonly overexpresses EGFR. EGFR and KRAS mutations appear rare (76, 77). In a study by Lukan et al. the potential role of EGFR inhibition was supported by partial remission, minor remission, or no progression in five patients with wild-type KRAS anal cancer treated with either cetuximab as a single agent or cetuximab with irinotecan. Two patients with KRAS mutation did not respond to cetuximab, and had progression of disease. The authors concluded that cetuximab-based treatment can be used in patients with metastatic KRAS wild-type anal cancer after failure of, or as an alternative to, cisplatin/5-fluorouracil (FU)-based therapy [77].

Conclusions

Anal cancer is an uncommon gastrointestinal cancer. A thorough clinical examination and high index of suspicion are needed for diagnosis. Chemoradiotherapy, using 5-FU/mitomycin C with RT, is the mainstay of treatment for patients with anal SCC; early T1 tumors may be treated surgically, if excision does not compromise sphincter function. Patients with metastatic anal SCC are most commonly treated with cisplatin-based chemotherapy. Improvements in current treatment modalities including IMRT, and biologics such as cetuximab, may provide more refined and successful treatments for patients with anal cancer.

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22
Presacral Tumors

John Migaly and Christopher R. Mantyh

Key Concepts

- Unless contraindicated, presacral tumors should be surgically excised because of the risk of malignancy.
- MRI should be performed to characterize the lesions and to plan surgery.
- Lesions that are below sacral level S4 can be excised through a posterior/perineal approach.
- Complete, non-piecemeal excision is critical to avoiding recurrence or infection.

Introduction

Retrorectal masses are a group of lesions that encompass a wide spectrum of disease processes, ranging from congenital lesions (with varied malignant potential) to inflammatory disease processes and overt malignancy [1, 2]. In general, retrorectal tumors are extremely rare, with the incidence of the tumors varying in the reported literature [1–3]. The Mayo Clinic has reported that retrorectal tumors represent 1 in 40,000 hospital admissions [4]. Diagnosis of these lesions is usually incidental on physical exam or on imaging studies, as symptomatology is usually vague [4]. Imaging remains the key to preoperative characterization of these lesions in addition to preoperative planning. Although the majority of patients will have undergone computed tomography (CT scan), magnetic resonance imaging (MRI) is an essential element in the preoperative evaluation. Although the role of preoperative biopsy has been a source of debate, because of the fear of recurrence at or seeding of biopsy tracts, there is a good single institutional data to support its selective use [5].

Anatomic Considerations

The presacral or retrorectal space is not a true space but rather a potential space (see Chap. 1). It is a unique area in that it represents a developmentally critical location where several types of embryological distinct cell lines converge for the final steps prior to the completion of ontogeny. It is these changes that produce the variety of benign and malignant and solid and cystic growths that can occur in this space [1]. The retrorectal space is the area posterior to the rectum, but, more specifically, its superior extent is the pelvic peritoneal reflection, its lateral limits are the ureters and iliac vessels, posteriorly it is defined by the sacrum, and anteriorly it is defined as the posterior wall of the rectum. The inferior border is the levator complex and the coccygeal muscles (Figure 22-1) [3].

The retrorectal space presents a multitude of challenges to the surgeon, and this subset of procedures is not recommended for those uninitiated in pelvic surgery. The sacral nerve rootlets are located in this retrorectal space, and thus injury to and sacrifice of these structures can have substantial implications on rectoanal and sexual function. In cases requiring the unilateral sacrifice of all of the sacral nerve rootlets, the patient will likely retain normal anorectal and sexual function. Bilateral sacrifice of the third sacral nerve rootlet will usually result in fecal incontinence [6, 7].

Classification

Histology/Pathology

The classification of presacral masses encompasses a wide variety of etiologies and tissue types (Table 22-1). The classification of these retrorectal lesions, first elaborated by Uhlig and Johnson in 1975, divides these lesions broadly into congenital, acquired, neurogenic, osseous, and “others” [3]. Understanding the various subtypes, disease behavior, and malignant potential is essential to tailor treatment regimens.

Congenital Lesions

Congenital lesions represent two-thirds of all retrorectal lesions, which are thought to arise from various combinations of the three embryonic cell layers. These congenital

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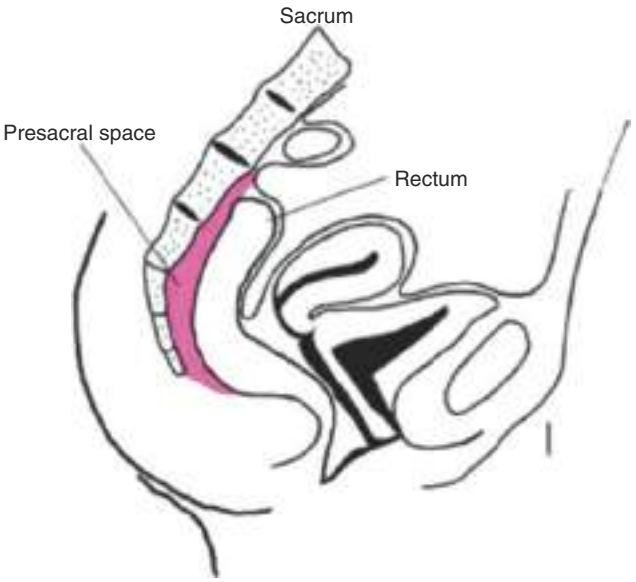

FIGURE 22-1. Location of the presacral space (Reprinted with permission from Ghosh J, Eglinton T, Frizelle FA, Watson AJ. Presacral tumours in adults. Surgeon. 2007 Feb;5(1):31–8 © 2007, Elsevier Ltd. [30]).

lesions can be cystic or solid [8]. In general, these lesions are more common in females than males [4, 8].

Dermoid and Epidermoid Cysts

Dermoid and epidermoid cysts are lined with squamous epithelial cells and may contain various skin appendages such as hair or nails (Figure 22-2). These lesions are thought to arise from the ectodermal layer in embryonic development. Patients can have a postanal dimple or sinus that can be mistaken for an abscess and errantly drained [9, 10]. This also accounts for the high rate of infection of these cysts.

Enterogenous

Unlike dermoid and epidermoid cysts, enterogenous cysts are multilocular. Enterogenous cysts arise from the endoderm of the primitive hindgut. These lesions can also undergo malignant degeneration.

Tailgut Cysts

Tailgut cysts are also referred to as retrorectal cystic hamartomas which arise from the persistence of the hindgut. Rectal duplication cysts contain all of the layers of the intestinal tract (Figure 22-3). Rectal duplication cysts can also undergo malignant change [11].

TABLE 22-1. Classification of retrorectal tumors

Congenital
Developmental cyst
Epidermoid cyst
Dermoid cyst
Teratoma
Teratocarcinoma
Chordoma
Anterior meningocele
Rectal duplication
Adrenal rest tumors
Neurogenic tumors
Neurofibroma
Neurilemmoma
Ependymoma
Ganglioneuroma
Neurofibrosarcoma
Malignant peripheral nerve sheath tumors
Osseous
Osteoma
Osteogenic sarcoma
Sacral bone cyst
Ewing's tumor
Giant-cell tumor
Chondrosarcoma
Chondromyxosarcoma
Miscellaneous
Metastatic or recurrent disease
Lipoma
Fibroma
Leiomyoma
Hemangioma
Desmoid
Liposarcoma
Leiomyosarcoma
Fibrosarcoma
Endothelioma
Granuloma
Perineal abscess
Fistula

Teratomas

Teratomas also contain cells from all three germ layers, but, more importantly, these lesions are true neoplasms. They can contain both solid and cystic components. Up to 10 % of these lesions contain cancer, and thus aggressive extirpation should be pursued. Because of the diverse germ cell layers, these lesions can become squamous cell carcinomas, rhabdomyosarcomas, or anaplastic tumors [1]. These tumors can contain tissues from almost any organ system including digestive and respiratory or bony tissue. Similar to other congenital lesions, teratomas are more common in females. They are also more common in children than adults. Factors that are associated with malignant degeneration and/or recurrence are incomplete resection and resections where the coccyx is not removed [1, 12].

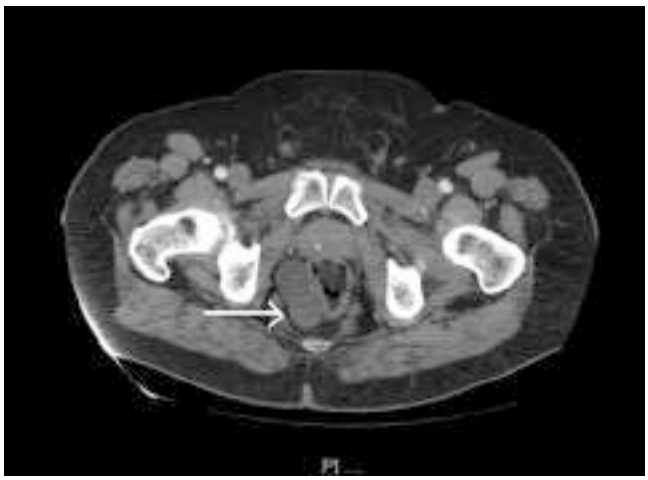

FIGURE 22-2. CT image of an epidermoid cyst.

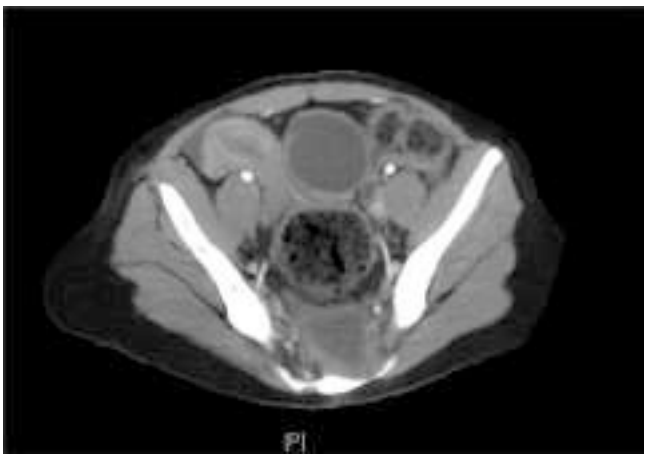

FIGURE 22-3. CT image of rectal duplication cyst.

Chordomas

The most common malignant tumor of the presacral space is the sacrococcygeal chordoma. These tumors arise from what is believed to be vestigial notochord tissue. These lesions are more common in male patients under 40 with an incidence of about 0.08 per 100,000. These lesions can occur almost anywhere on the spinal cord but are most commonly found in the presacral area. The patients present with vague symptomatology including low back pain. The 5- and 10-year survival rates are 67 and 40 %, respectively, and though surgery remains a mainstay of treatment, it is associated with a high recurrence rate [13].

Anterior Sacral Meningocele

These lesions arise from protrusions of the dural sac through a defect in the sacrum. The classic radiologic finding of the "scimitar sign" can often be seen on plain films. Patients often have vague symptomatology including headaches related to postural changes and Valsalva [4, 14]. Magnetic resonance imaging usually easily characterizes these lesions, and percutaneous biopsy should be avoided for fear of bacterial contamination of the cerebrospinal fluid and iatrogenic meningitis.

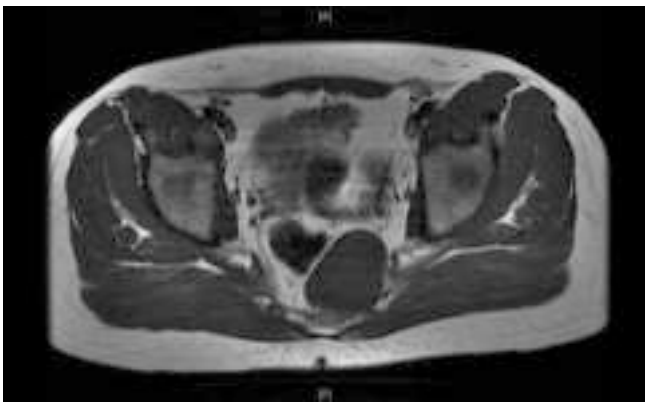

FIGURE 22-4. MRI image of a ganglioneuroblastoma.

Neurogenic Tumors

Neurogenic tumors represent about 10 % of all retrorectal tumors (Figure 22-4). They arise from peripheral nerves and include neurofibromas, schwannoma, ganglioneuroma, neuroblastomas, ganglioneuroblastoma, and ependymoma. Ependymomas are the most common of these tumors [4, 15]. Differentiation between benign and malignant variants can be difficult, and these tumors can produce significant neuropathy as a presenting symptom.

Osseous Lesions

Osseous lesions include giant-cell tumors, osteoblastoma, aneurysmal bone cysts, osteogenic sarcoma, Ewing's sarcoma, myeloma, and chondrosarcomas. These lesions represent 10 % of all retrorectal tumors. These may be the most aggressive of all the retrorectal tumors and can be very locally destructive and have pronounced metastatic potential [1, 16].

Diagnosis

History and Physical

Because of the location of these tumors in the presacral space, the symptomatology tends to be vague and nonspecific. Many of these tumors are diagnosed incidentally on rectal examination, and in fact 97 % of presacral lesions are palpable on digital rectal examination [4]. Many patients will have lower back pain or pelvic pain; however, in general,

there is not a plethora of common findings. Patients with congenital cysts/tumors may have a postanal sinus; however, the most likely etiology of a postanal sinus is perianal fistulous disease. Therefore the lesions may be diagnosed after several unsuccessful attempts at treatment of a perianal fistula that usually culminates in cross-sectional imaging as the true manner of identification. Patients with advanced tumors can have constipation, sexual dysfunction, urinary incontinence, and other leg and gluteal symptoms related to local extension and mass effect. Neurologic exams with attention to these symptoms in addition to gluteal and lower extremity dysfunction allow for preoperative documentation of these defects and aid in assessing the locally invasive nature of the lesion.

Imaging Studies

The preoperative assessment of a retrorectal tumor should include intraluminal evaluation of the rectum via flexible sigmoidoscopy. Understanding the extent of the mass of the tumor on the rectum and the ability to assess the mucosal integrity of the rectum are both important elements of the preoperative preparation. Flexible sigmoidoscopy allows for a better assessment of the upper and lower extents of these tumors, in addition to the relationship of the lesion to the sphincter complex. Endorectal ultrasound (ERUS) can be utilized to assess the relationship of tumors to the muscular layers of the rectum and the anal sphincters; despite the fact that majority of the lesions are well circumscribed, the subset of tumors that are not can be quite locally advanced and destructive. ERUS can also allow a very preliminary assessment of sacral bony destruction by tumors.

Plain films have limited utility but can sometimes demonstrate osseous destruction of the sacrum or calcifications within the tumor itself. In patients with anterior sacral meningocele, the classic "scimitar sign" can often be seen on plain films, but usually cross-sectional imaging is a requirement for confirmation. Magnetic resonance imaging (MRI) with gadolinium is the imaging modality of choice for retrorectal tumors. MRI is critical in the management of these tumors by facilitating accurate diagnosis, determining the anatomic extent of the lesion, and selecting the optimal surgical approach. Information that can be extracted from an MRI is much more granular in comparison to other modalities, including key elements such as location, size, morphology, margins, and interface [17]. MRI determination of the location of lesions in relation to the sacral vertebral bodies allows for planning of abdominal versus posterior versus combined surgical approaches. Characterization of the lesion as solid or cystic is easily achievable via MRI, but subtle nodularity or septation of these lesions allows for further characterization of these lesions into their various subtypes (Figure 22-5). Threatened margins can be more easily identified via MRI

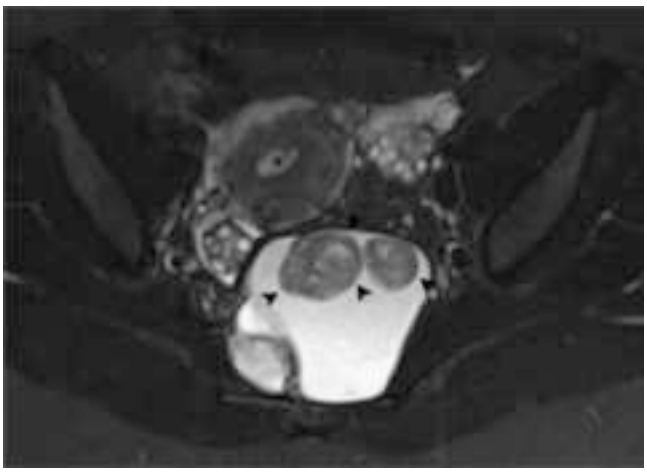

FIGURE 22-5. MRI of presacral cyst. T2-weighted imaging of an epidermoid cyst shows a bilobulated cystic lesion with pools of keratin debris (*arrows*) inside the larger cyst (Reprinted Loock MT, Fornès P, Soyer P, Rousset P, Azizi L, Hoeffel C. MR imaging features of nongynaecologic cystic lesions of the pelvis. Clin Imaging 2013;37(2):211–8 © 2013 Elsevier Ltd, with Permission from Elsevier. [31]).

such as bony erosion, or invasion of tumors and pelvic side wall invasion are more clearly definable. Arterial and venous anatomy is seen in much greater detail. What MRI excels at in comparison to CT scan is defining invasion of the muscular walls of the rectum, particularly in cases of sacrococcygeal chordoma [18]. These details, in total, make multimodality and multispecialty planning for operative interventions requiring en bloc resection of the rectum, partial sacrectomy, and arterial reconstruction or endovascular techniques much easier.

Preoperative Biopsy

Biopsy of presacral tumors presents a twofold question. First, is biopsy associated with a higher rate of local recurrence? Second, does biopsy have proven utility in the management of presacral tumors, i.e., does it changes the management? In general, biopsy of cystic lesions should only be undertaken in situations where there is some question of the characterization of the lesion *after* a high-quality MRI interpreted by an experienced radiologist. To be clear, it is universally acknowledged that biopsy of presacral lesions via the transrectal or transvaginal route is strongly discouraged, as it is possible to infect a sterile cystic lesion. In addition, biopsy via these routes necessitates either partial or complete proctectomy or vaginectomy to remove the biopsy tract in continuity with the presacral tumor in order to prevent recurrence. Biopsy of a meningocele via any route should be avoided for fear of an infection of the cerebrospinal fluid and resultant meningitis.

Early work from several authors discouraged biopsy of these tumors for fear of local recurrence [19–21]. More recent data suggests that percutaneous biopsy of retrorectal tumors can be performed without an increased risk of recurrence. In a single institutional series of 87 patients, Messick et al. performed biopsy of 24 patients (28 %) prior to surgical extirpation with no postoperative tumor recurrences. In this same series, only 4 of the 24 patients underwent excision of their biopsy site, also without any reported recurrences [5]. In our current practice, we do not biopsy all solid presacral lesion and even fewer mixed solid or cystic lesions. There is a role for biopsy in unresectable, sizeable, or aggressive tumors such as Ewing's sarcoma or osteogenic sarcoma where preoperative radiation or chemotherapy could be of value for systemic or local control or to improve the likelihood of resectability. It is our current practice to excise the biopsy tract and site at the time of definitive surgery.

Management

Role of Preoperative Neoadjuvant Therapy

Retrorectal tumors can exhibit a diverse set of behaviors and can be quite large and locally advanced by the time they are diagnosed. In addition, the subset of pelvic sarcomas has fairly significant systemic metastatic potential. With this in mind, there is a definite role for neoadjuvant chemotherapy for some of these tumors. In cases of large locally advanced presacral tumors, where resectability is at issue, neoadjuvant radiotherapy may render some benefit in decreasing tumor size and increasing resectability.

Surgical Treatment

Unless the lesion is unresectable or there is evidence of systemic metastasis, presacral tumors should be resected, as 30–40 % of the lesions will be malignant and benign lesions can undergo malignant change. Furthermore, approximately up to 10 % of cystic lesions will become chronically infected and can complicate any planned operative intervention [2–5].

Preoperative Planning

The key to preoperative planning is understanding the extent of the resection field. In patients that have direct invasion of the muscular wall of the rectum, proctectomy must be anticipated. In cases of bony invasion, partial sacrectomy is planned. Pelvic sidewall involvement may necessitate intraoperative radiotherapy and vascular or ureteric reconstruction. The assembly of a multispecialty team of colorectal, urologic, neurosurgical, orthopedic, vascular, and plastic surgeon is a prerequisite for many of these undertakings.

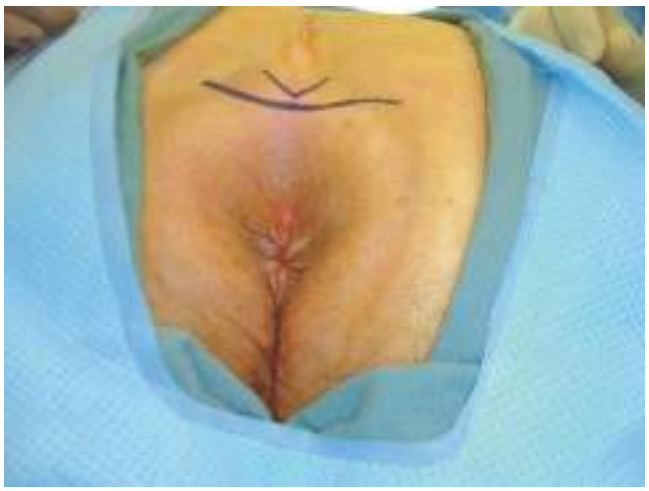

FIGURE 22-6. Transverse incision marked, as well as the sacrum and coccyx, for a posterior approach.

Surgical Approach

The location, the morphology, and the impingement or involvement of other pelvic structures dictate the operative approach. In general, a well-circumscribed presacral lesion whose uppermost extent can be palpated on digital rectal examination can usually be approached via a posterior approach. Several single institutional series also seem to share consensus where the S4 level is the line of division between abdominal and posterior approaches [3, 5, 22–25]. In lesions above the S4 level of the spine, a purely abdominal approach can be considered, while lesions below S4 can be approached posteriorly. Lesions spanning both above and below are best approached via a combined abdominal and posterior approach.

Posterior Approach

Patients are given a mechanical, cathartic bowel preparation the night before in preparation for this procedure. After intubation, the patient is placed in the prone jackknife position atop a large bolster. The rectum is irrigated with a dilute solution of betadine and saline; after this the buttocks are taped apart. While the incision for this procedure is usually described as a midline incision from the lower portion of the sacrum down to the anus, while yet others describe a transverse incision (Figure 22-6), our practice is different. The technique used by our group involves making a curvilinear incision; the incision is placed just to the left of the lower portion of the sacrum and carried in a curvilinear caudad direction around the lateral aspect of the coccyx toward the midline and the intergluteal fold just below the tip of the coccyx. Once the intergluteal fold is reached (below the tip of the coccyx), the incision is extended downward in the midline to a point approximately 2–3 cm short of the anal orifice (Figure 22-7). The reason for this type of incision is that the

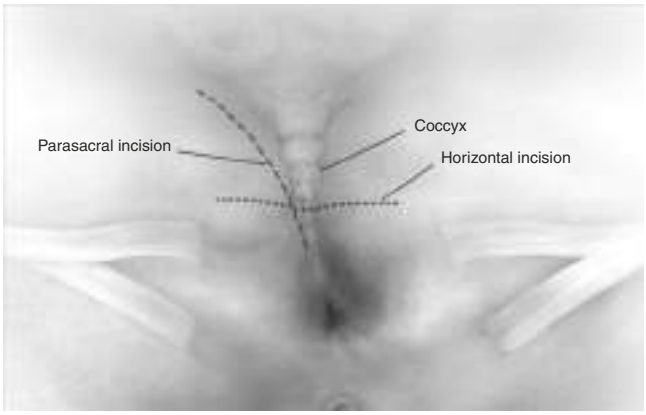

FIGURE 22-7. Posterior approach for the removal of a presacral tumor and placement of incision. The patient is in prone jackknife position, and the incision can either be horizontal on the anococcygeal ligament or curvilinear to the left of the lower sacrum/coccyx and into the intergluteal fold (With permission from Ludwig KA, Kalady MF. Transsacral approaches for presacral cyst: rectal tumor. Operative Techniques in General Surgery 2005;7:3-126-136 © 2005 Elsevier Ltd. [32]).

curvilinear incision allows for easier access to the lateral aspect of the coccyx, which is routinely removed.

Once the skin incision is completed, the dissection is deepened until the coccyx and the anococcygeal ligament are visualized. The anococcygeal ligament is divided, and extreme care is taken to identify the posterior aspect of the sphincter complex in order to preserve it. After this, the coccyx is freed along both sides of its lateral aspects and then the coccyx is removed (Figures 22-8 and 22-9). It is our practice to routinely remove the coccyx for two reasons. The first is that many of the congenital cysts are tethered to and originate at the coccyx, and it is thought that preserving the coccyx results in a higher recurrence rate [3, 26]. The second reason we routinely remove the coccyx is that removal allows for better visualization of the retrorectum and the mass, which creates a somewhat wider operative field, which facilitates removal of these tumors. This technique allows for intact removal of the lesion and reduces the likelihood of inadvertent perforation of the lesion, which is linked to a higher rate of recurrence and infection.

The lesion can be usually "shelled out" by dissecting it off of the sacrum and then slowly rolling the most proximal aspect of the tumor toward the incision from a cephalad to a caudad direction and then slowly dissecting it off the rectum (Figures 22-10, 22-11, and 22-12). There is quite often a feeding vessel that is encountered on the proximal aspect of many of these lesions that needs to be controlled; this can be safely and easily accomplished with a long handled bipolar energy source. After the removal of the tumor (Figure 22-13), the operative field is submerged beneath irrigant, and a proctoscope is used to insufflate the rectum to check for an air leak and assure that the rectum has not been violated. The soft tissue and the incision are closed in multiple layers over a closed suction drain (Figure 22-14).

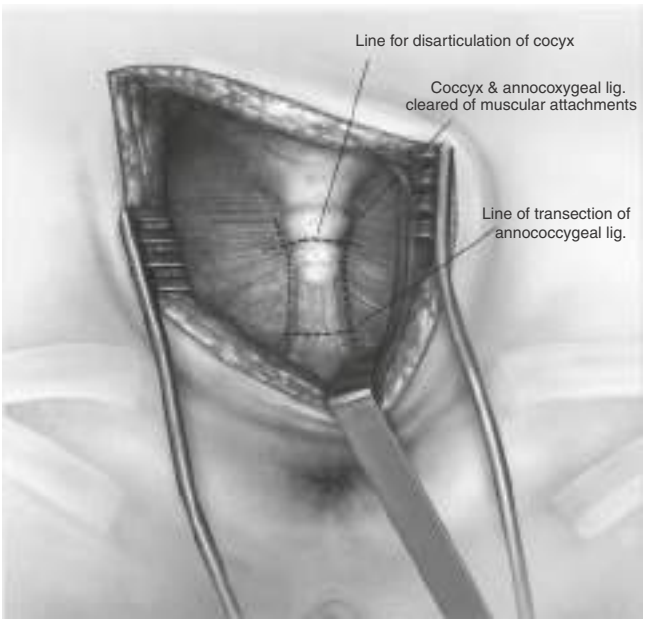

FIGURE 22-8. The anococcygeal ligament is divided, and the coccyx is subsequently cleared of its lateral attachments and removed; this facilitates dissection along the sacrum (With permission from Ludwig KA, Kalady MF. Transsacral approaches for presacral cyst: rectal tumor. Operative Techniques in General Surgery 2005;7:3-126-136 © 2005 Elsevier Ltd. [32]).

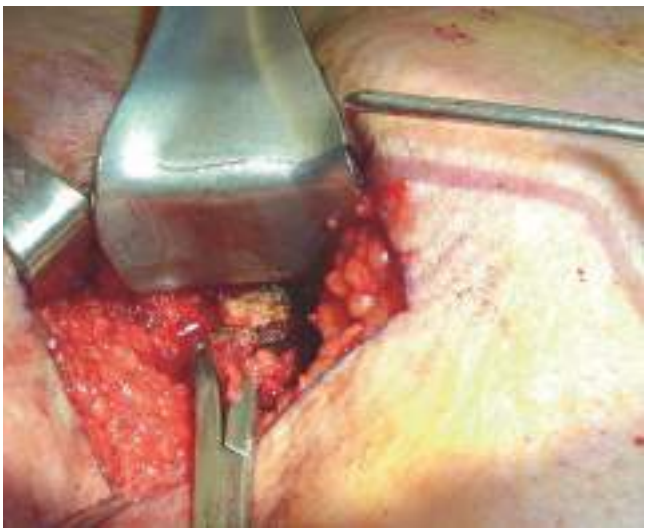

FIGURE 22-9. The tip of the coccyx is removed en bloc with the specimen.

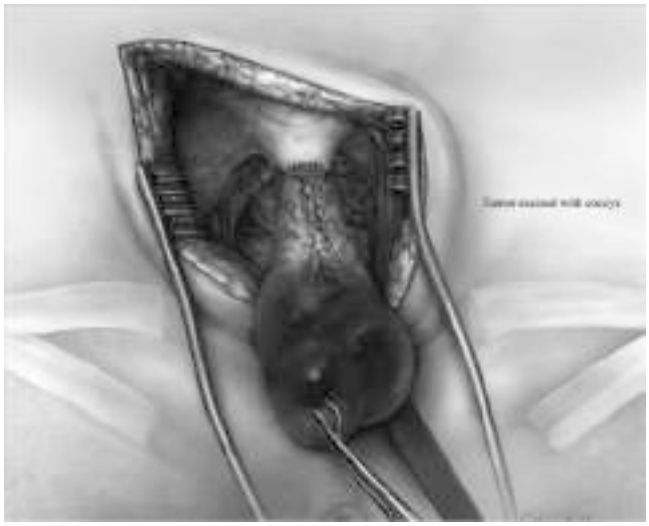

FIGURE 22-10. Now with access to the presacral space, the surgeon can carefully dissect the cyst off of the sacrum and "roll" it toward himself from cephalad to caudad (With permission from Ludwig KA, Kalady MF. Transsacral approaches for presacral cyst: rectal tumor. Operative Techniques in General Surgery 2005;7:3-126-136 © 2005 Elsevier Ltd. [32]).

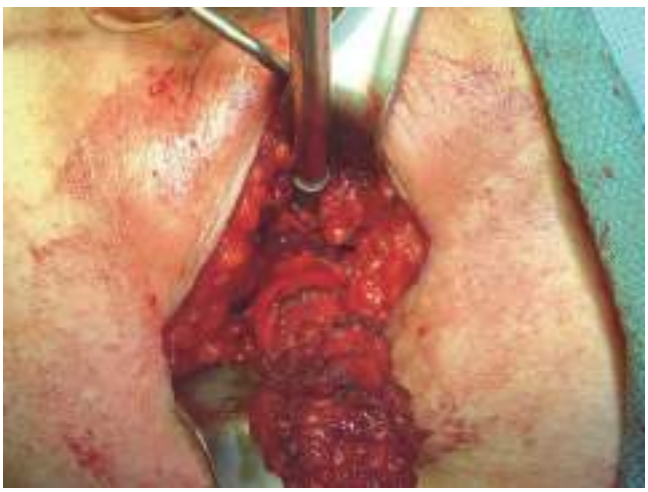

FIGURE 22-11. The presacral mass is mobilized off the rectal wall.

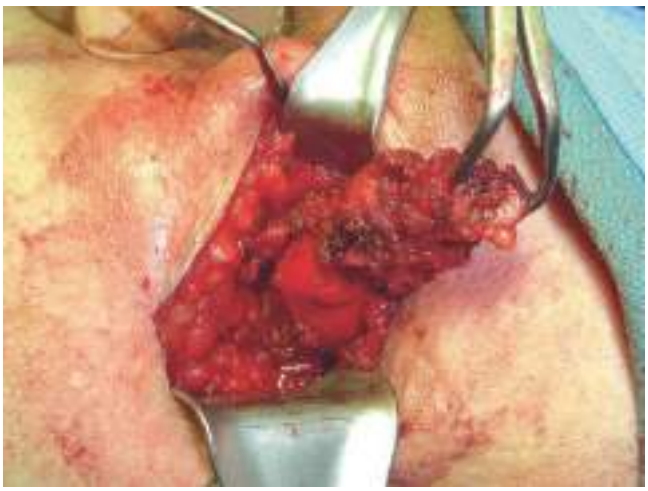

FIGURE 22-12. Side view of the coccyx tip and mass en bloc dissection from the rectal wall.

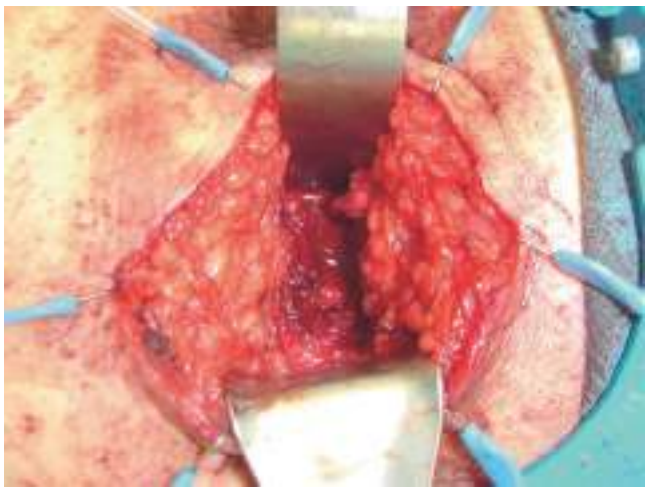

FIGURE 22-13. With the specimen out, a large cavity is present, and the posterior rectal wall can be visualized.

Combined Abdominal and Perineal Approach

Although there are subsets of tumors that are appropriate for a purely abdominal approach, it is advisable to prepare the patient as if a combined abdominal approach is planned to allow for all contingencies. The patients should be placed in lithotomy so that if a perineal or posterior approach is needed, access to the area has been anticipated and facilitated. Ureteric stents can be placed in bulky, high tumors.

A standard midline incision is utilized, and a thorough examination of all quadrants of the abdomen should be performed to assure that there are no metastases. The sigmoid colon is mobilized along the white line of Toldt, and the presacral space is entered at the level of the sacral promontory in the same fashion as a total mesorectal excision. The left and right hypogastric nerves are identified and preserved. The rectum is pulled forward. The lesion can then be dissected away from the mesorectum with preservation of the rectum.

When the lesion is large (Figure 22-15) and the space is small or visualization posteriorly is less than ideal, there are several maneuvers that can aid with visualization and facilitate posterior dissection. The lateral stalks can be taken down to the level of the levators, and the rectum can be mobilized anteriorly to the pelvic floor; in addition the superior rectal artery can be divided at the level of the sacral promontory to take tension of the mesentery, and the root of sigmoid and left colon mesentery can be detached from the retroperitoneum and aorta all the way to the root of the inferior mesenteric

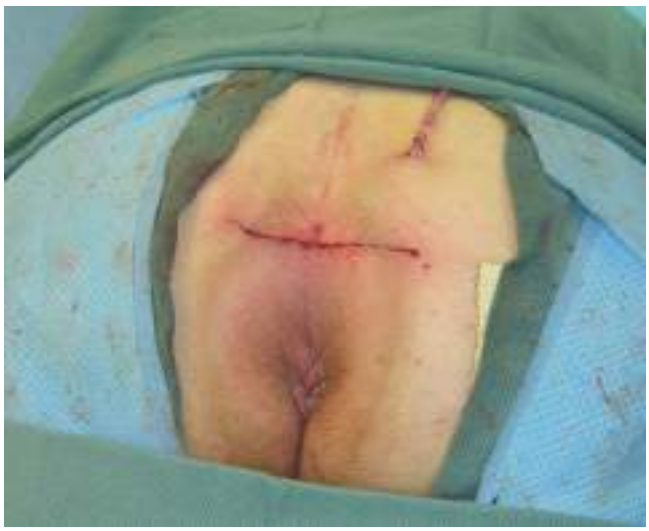

FIGURE 22-14. The incision is closed in multiple layers over a suction drain.

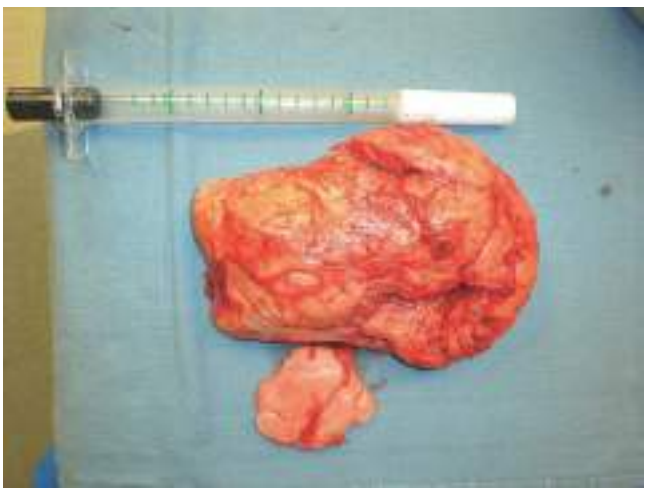

FIGURE 22-15. A large presacral mass.

artery. These maneuvers, in combination, allow the rectum to be pulled up and out of the pelvis to allow easier visualization of the dissection planes and better retraction. There is often a feeding vessel to the tumor in the midline, and ligating the middle sacral vessels can often help stem potential blood loss. The tumor is then dissected anteriorly off of the rectum and posteriorly off of the sacrum and laterally off of the sidewalls. In situations where tumor is densely adherent to the posterior rectum, a proctectomy should be performed for en bloc removal with the tumor. Most of the time, a stapled low colorectal anastomosis can be performed, but on occasion a hand-sewn coloanal anastomosis may be necessary.

If the internal iliac artery or vein needs to be sacrificed, communication with the anesthesiologist in advance of ligation is ideal, as the sacrifice of these vessels can sometimes be associated with large-volume bleeding misadventures and blood products should be on hand. If the involvement of these vessels is identified preoperatively, catheter-based venous or arterial embolization can be considered in advance of surgery.

In situations where the lowermost portion of the tumor cannot be reached from the abdominal approach, there are two options: the first is to place the patient in high lithotomy and proceed via a posterior approach, and the second is to close the abdomen and place the patient in prone jackknife position. The visualization and performance of the posterior approach with the patient placed in high lithotomy are challenging, and it is our preference to close the abdomen and subsequently flip the patient to the prone jackknife position. The visualization is superior, and the incidence of cyst perforation is much lower. In addition, partial sacrectomy of the lower sacrum including nerve rootlets can be accomplished via this approach when necessary.

In patients where the tumor is quite large and the anticipated pelvic or perineal defect is quite large, there are several options for tissue interposition or reconstruction. A transabdominal rectus abdominis myocutaneous (TRAM) flap can be transposed into the pelvis to fill fairly impressive defects. For more modest defects, less morbid options may be V-Y fasciocutaneous flap closure and unilateral or bilateral gracilis transposition.

Closed suction drainage of the pelvis and the perineum should be performed in these patients.

Outcomes

Malignant Lesions

In a single institutional report, Messick et al. reported on 87 patients who had excision of retrorectal tumors; the overall recurrence rate was 16 %, with the recurrence rate of malignant tumors being 30 %. In this particular series, all of the recurrences in the malignant cohort were distant, and the median survival was 47.5 months [5]. In series where the tumors are extracted piecemeal or the tumors are violated, the recurrence rate can be as high as 65 % or higher [21, 27].

Although retrorectal sarcomas tend to be locally advanced, half of all patients have reasonable long-term survival. Dozois et al. reported a median survival of 4.7 years with survival at 2 and 5 years reported at 75 and 55 %, respectively [24]. In other data acquired from the Surveillance, Epidemiology, and End Results (SEER) program, McMaster and colleagues reported on sacral chordomas, which represent 29 % of all chordomas. In this study, the 5- and 10-year survival rates for sacral chordomas were 74 and 32 %, respectively [13]. Another series of 39 patients with malignant retrorectal tumors by Cody and associates reported a 5- and 10-year survival of 50 and 37 %, respectively. In this series, 38 % of these tumors were chordomas and 15 % were neurogenic tumors [2].

Finally, Wang and colleagues reported a series of 45 patients with presacral tumors, in which 48 % of the patient had malignant tumors. Incomplete resections were associated with inferior outcomes. The 5-year survival rate for malignant tumors was 41 % [28].

Benign/Cystic Lesions

The Cleveland Clinic series of tumors located strictly below S4 reported that 95 % were approached via a posterior approach only, and the local recurrence rate for the benign cohort was 11 %. Coccygectomy was performed in 51 % of patients; however, there was no difference in the recurrence rates between patients that underwent coccygectomy and those that did not [5]. Glasgow et al. published a series of 34 patients with retrorectal tumors where 26 patients had benign tumors. At a mean follow-up of 22 months, none of the patients in the benign group had recurred [29]. Another series by Jao and associates reported on a series of presacral lesions, of which 66 were benign retrorectal tumors. Of note, there was a 15:1 ratio of females to males. The overwhelming majority of the lesions were resected through a posterior approach, with 10 of 66 patients experiencing a recurrence [4].

Conclusion

Presacral tumors represent a diverse set of tumors with a strong predominance of the congenital cysts. The symptomatology of these tumors is often vague, and early diagnosis is an unusual event. Many of these tumors are found on digital rectal examination, and many are found incidentally on imaging or in the workup of nonspecific symptomatology. The tumors can have solid, cystic, or mixed features. Surgical extirpation is recommended for almost all tumors, as they a third can contain a malignancy and they can undergo malignant degeneration. MRI is essential in preoperative planning, as in a multidisciplinary team. Biopsy of lesions should only be reserved for lesions that are thought to be unresectable or metastatic. The majority of lesions that are below the S4 level can be approached via a posterior approach. Larger or more locally advanced lesions may require both an abdominal and perineal approach with en bloc resections of a portion of the sacrum or rectum. Lesions that are resected completely without disruption have a better prognosis than those that are not.

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23
Molecular Basis of Colorectal Cancer and Overview of Inherited Colorectal Cancer Syndromes

Matthew F. Kalady and Y. Nancy You

Key Concepts

- Colorectal cancer is a genetically heterogeneous disease that arises via at least three main oncogenic pathways: chromosomal instability, microsatellite instability, and the methylator phenotype. Each pathway produces distinct but overlapping clinical phenotypes. These pathways are represented in sporadic colorectal cancer as well as in hereditary colorectal cancer syndromes.
- Identification and diagnosis of a hereditary colorectal cancer syndrome require a high level of suspicion and appropriate knowledge to evaluate the patient and at-risk family members. These syndromes have distinct genetic and clinical traits and are broadly classified into polyposis (adenomatous, hamartomatous, serrated polyps) and non-polyposis (HNPCC and Lynch syndrome).
- Familial adenomatous polyposis is a multisystem disease that confers a near 100 % colorectal cancer malignancy risk. Close endoscopic surveillance and timely prophylactic surgery are required to limit colorectal cancer formation. Desmoid disease and duodenal adenocarcinoma are other leading causes of morbidity and mortality.
- *MutYH*-associated polyposis (MAP) is a recessively inherited syndrome that carries an approximately 75 % lifetime risk of colorectal cancer. Annual colonoscopic surveillance is necessary, and surgery is indicated for uncontrolled polyp burden or the development of adenocarcinoma. Extended colectomy should be offered in healthy patients.
- The hamartomatous syndromes (Peutz-Jeghers syndrome, juvenile polyposis syndrome, and PTEN hamartoma syndrome) are rare but are associated with significant colorectal cancer and extracolonic multisystem malignancy. Early recognition and extensive screening and surveillance protocols are required.
- Serrated polyposis syndrome is characterized by numerous and/or large serrated polyps. Although no genetic etiology has been identified, it carries an approximately 25 % risk of developing colorectal cancer. Annual colonoscopic surveillance is necessary and surgery is indicated for uncontrolled polyp burden or the development of adenocarcinoma. Extended colectomy should be offered in healthy patients.
- Lynch syndrome is the most common of the hereditary syndromes and is responsible for about 3 % of all colorectal cancers. Universal screening and systematic molecular analysis of newly diagnosed colorectal cancer for DNA mismatch repair deficiency provide an effective approach to identifying patients at risk for Lynch syndrome.
- Patients with Lynch syndrome face significantly elevated risks for colorectal and extracolonic cancers in multiple organs. Lynch syndrome patients benefit from colonoscopic screening and participation in a hereditary registry.
- After the development of an initial colorectal cancer, patients with Lynch syndrome have high risk for metachronous colorectal neoplasia. Extended resection (total abdominal colectomy for colon cancer and total proctocolectomy for rectal cancer) should be considered weighing risks of future malignancy and quality of life.

Introduction

Our understanding of the genetic and molecular changes leading to colorectal cancer (CRC) development continues to evolve. A complex system of checks and balances maintains normal colorectal mucosa homeostasis and integrity during cell division and replication. Alterations in these mechanisms can lead to malignant change. In general, CRC is a multistep process that entails the accumulation of genetic and epigenetic changes over time. Mutations in oncogenes may result in overexpression of a gene or pathway, leading to constitutive cellular signaling or proliferation. Conversely, mutations or loss of tumor suppressor genes may remove an inhibitory signal that produces uncontrolled cell growth.

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Furthermore, mutations in caretaker genes may result in oncogenesis by losing the ability to induce apoptosis or repair damaged DNA. The underlying genetic and epigenetic changes leading to CRC influence the disease course including clinical phenotype, prognosis, and response to therapy.

Clinical management and research must be executed with the knowledge that CRC is not a single entity but rather a heterogeneous disease, different in each person. Understanding CRC in this context and classifying tumors based on their molecular underpinnings are needed to truly study the disease and meaningfully stratify clinical management. This applies to both sporadic CRC as well as CRC arising within a hereditary syndrome. There are at least three major molecular pathways that have been described for the development of CRC: chromosomal instability, microsatellite instability, and the methylator phenotype. Each pathway has unique characteristics, but there is some overlap between the pathways and two or more pathways may exist in the same patient. This chapter is not a comprehensive review of cancer genetics or even CRC genetics but provides an overview of the current understanding of both sporadic and hereditary CRC for the practicing surgeon.

Chromosomal Instability

Chromosomal instability is the most common form of genomic instability in CRC, accounting for about 75 % of all CRC [1]. Chromosomal instability refers to an alteration in the chromosome copy number or structure. Physical loss of a chromosome segment may delete entire genes and produce loss of heterozygosity for those genes. That is, as one allele is lost, only one functional copy of the gene exists and there is no longer redundancy for that gene. Loss of the second allele results in complete loss of that gene function. *APC* and *p53* are examples of tumor suppressor genes, whose loss via this mechanism results in chromosomal unstable CRC.

The traditional adenoma-to-carcinoma sequence as described by Vogelstein and Fearon is characterized by the accumulation of genetic changes over time and the prototype chromosomal instability CRC [2]. An overview of this pathway is given in Figure 23-1. Clinically, CRCs arising via chromosomal instability tend to be located in the left colon, have male predominance, and develop later in life. Genetically, key genes mutated in this pathway include *APC*, *KRAS*, and *p53*.

APC

The adenomatous polyposis coli (*APC*) gene, a tumor suppressor, has been called the gatekeeper gene because it is the key initiating step to malignant transformation for many colorectal adenocarcinomas. The APC protein regulates the WNT signaling pathway via intracellular binding of β-catenin. Mutations in *APC* lead to transcription of no protein or a protein without normal function. Decreased quantity or function of APC protein allows for intracellular accumulation of β-catenin and thus increased translocation into the nucleus where it serves as a transcription factor responsible for proteins involved in cell signaling, proliferation, and cell-to-cell adhesion. Inherited *APC* mutations are the cause of familial adenomatous polyposis (FAP), which is discussed elsewhere in this chapter.

KRAS

KRAS is an oncogene involved in the mitogen-activated protein kinase (MAPK) pathway whose upstream signaling receptor is the epidermal growth factor receptor (EGFR). This pathway drives nuclear transcription of cellular proliferation. Oncogenic mutations turn on the KRAS signal and drive uncontrolled cell growth, regardless of upstream signaling. Thus, KRAS mutation status is an important factor when deciding to use monoclonal antibodies that target the EGFR signaling pathway to treat CRC. Mutant KRAS provides constitutive MAPK signaling and upstream blockage of EGFR is not effective in blocking MAPK [3]. RAS mutations are present in nearly 40 % of CRC [4]. In practical terms, the tumor should be tested for the KRAS mutation if the patient is being considered for anti-EGFR therapy

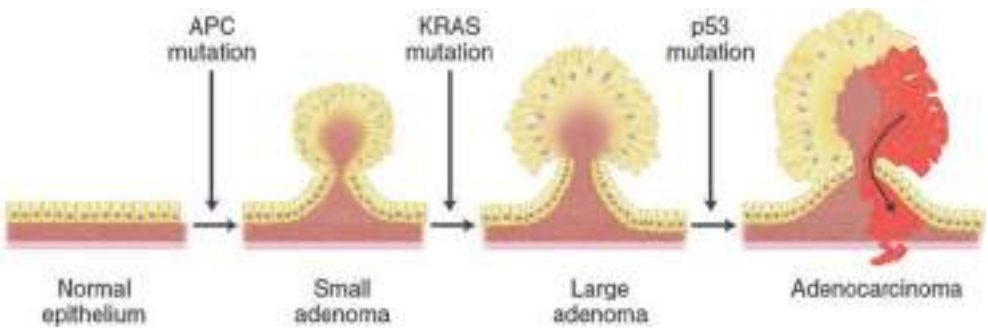

FIGURE 23-1. Schematic representation of the traditional adenoma-to-carcinoma sequence resulting in chromosomal instability.

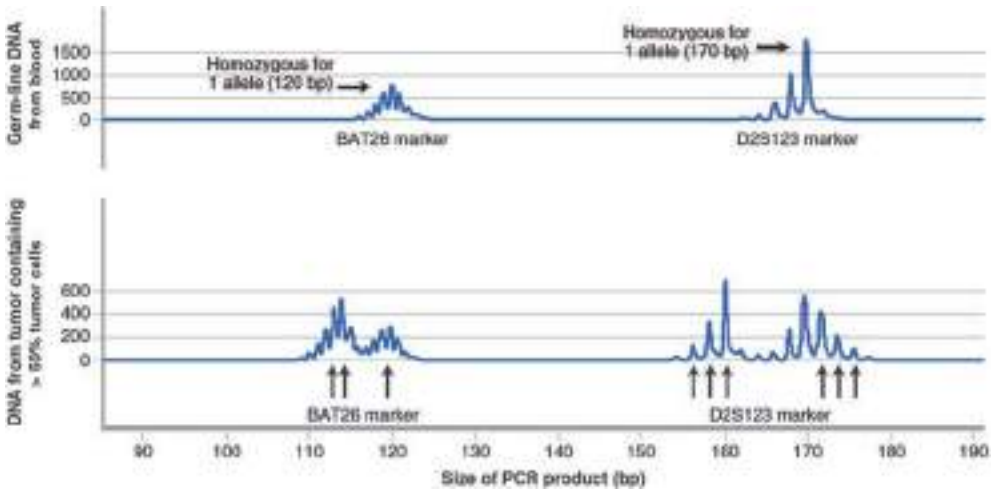

FIGURE 23-2. Example of DNA fragment lengths from polymerase chain reaction (PCR) products used to determine microsatellite instability. Two markers, BAT26 and D2S123, are shown here. The upper track readout is from germline DNA derived from patient blood. The lower track readout is from a portion of the patient's tumor that was histologically confirmed to contain at least 50 % cancer cells. In the germline track, BAT26 displays a single peak (*arrow*), indicating that the patient is homozygous for this marker. In the tumor DNA, there are two peaks for the BAT26 marker. The second peak represents a new allele (*double arrows*) in the tumor that is approximately five nucleotides smaller than the normal allele. This constitutes microsatellite instability for that marker. Marker D2S123 is homozygous in the germline (*arrow*), but two different new alleles exist in the tumor DNA (*triple arrows*). The allele on the left has lost approximately ten nucleotides and the allele on the right has gained two nucleotides. Thus, this marker also demonstrates microsatellite instability.

(e.g., cetuximab), and such therapy should not be instituted if the patient is found to have mutated KRAS CRC, as anti-EGFR therapy has been shown to be no more effective than supportive care in this situation.

p53

p53 is encoded by the gene *TP53* and preserves the cell cycle and genomic stability. As a tumor suppressor, p53 stops the cell cycle in G1/S phase to allow mutations or replications errors to be repaired. If the damage cannot be repaired, p53 may induce apoptosis. p53 is thought to be necessary to drive invasiveness of the lesion. It is rarely found in adenomas (5 %) and increased in malignant polyps (50 %) and is present in 75 % of invasive CRC [5].

Microsatellite Instability

Microsatellite instability results from faulty DNA mismatch repair (MMR) function. Routine DNA replication is associated with high infidelity, with specific sites along the DNA strand that are prone to errors. These sites are areas of repetitive DNA sequences, called microsatellites. Microsatellites are noncoding segments of DNA that contain repetitive sequences of one to four nucleotides. There are hundreds of thousands of microsatellites in the genome, and microsatellite patterns provide a unique DNA fingerprint. When these errors are not repaired due to MMR deficiency, the length of the microsatellite regions are altered and the fingerprint changes; i.e., there are different lengths of the DNA fragments. Thus, the pattern of fragments detected by PCR techniques produces a different pattern of microsatellites and thus the term microsatellite unstable or microsatellite instability high (MSI-H). An example of a DNA fragment length fingerprint is shown in Figure 23-2.

Functionally, loss of MMR function leads to an accumulation of unrepaired errors. Several key tumor suppressor genes have multiple short repetitive sequences that make them prone to DNA mismatch. Loss of MMR function allows the accumulation of mutations in these genes that subsequently lead to adenoma and cancer formation. Examples include TGF-β receptor II, BAX, and IGF2R. Cancers arising through this molecular pathway are termed the mutator phenotype as these tumors tend to be hypermutated and account for approximately 15 % of CRC [4]. Inherited mutations in one of the DNA mismatch repair genes result in Lynch syndrome, which is discussed elsewhere in this chapter.

CpG Island Methylator Phenotype (CIMP)

Epigenetic mechanisms such as hypermethylation of DNA promoter regions can affect gene expression and protein translation without changing the inherent DNA sequence.

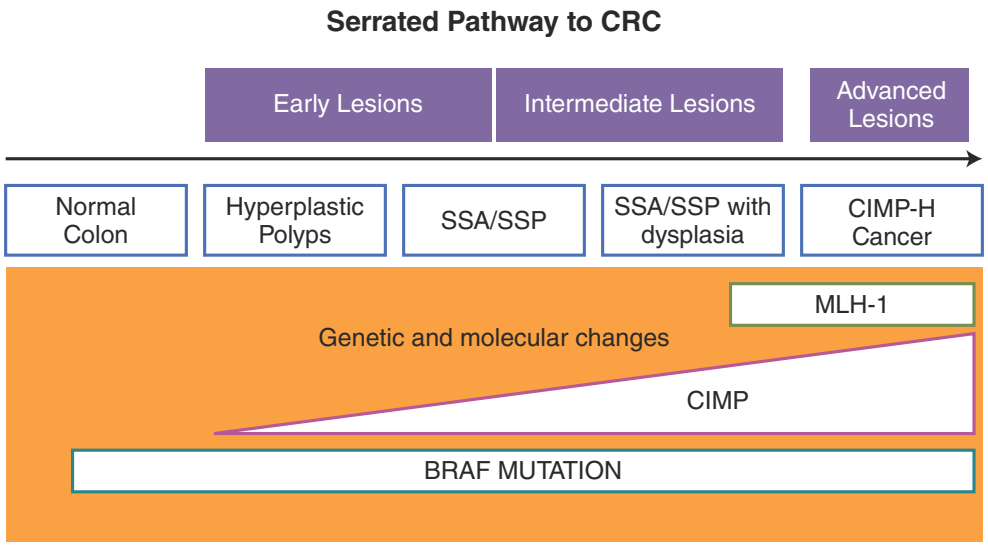

FIGURE 23-3. Schematic representation of proposed serrated pathway to colorectal cancer.

Methylation of cytosine is a common biological phenomenon that occurs throughout the genome and controls multiple processes. Several key tumor suppressor genes contain cytosine-guanine (CpG) repetitive sequences, which are prone to hypermethylation in the promoter region. Hypermethylation in the promoter region silences transcription of that gene, and thus no functional protein is made. As the areas prone to hypermethylation contain regions rich in cytosine and guanine dinucleotide repeats or CpG islands, they have been termed CpG island methylator phenotype (CIMP or CIMP high). The exact definition of CIMP is still debated, but it is characterized by the hypermethylation of a panel of markers [6]. This pattern is reproducible in approximately 20 % of CRCs and is associated with aberrant methylation of the mismatch repair gene, *MLH1*. Approximately 85 % of MSI-H CRCs develop via loss of the expression of the MMR gene, *hMLH1* caused by DNA hypermethylation. Methylation of other key genes and their contribution to CRC initiation are an area of intense study and research.

In contrast to CRC arising via chromosomal instability in which the precursor lesions are adenomatous polyps, the precursor lesions in CIMP cancers are serrated polyps. The sequence of mutations and contributions of specific mutations as initiators and drivers of oncogenic change continue to be defined. The most common initial mutation occurs in the *BRAF* oncogene [7]. *BRAF* mutations support the transformation of normal mucosa to aberrant crypt foci or a hyperplastic polyp or sessile serrated polyp (SSP). These altered cells become senescent as a protective mechanism so as not to propagate mutated cells. Senescence is controlled by p16. As methylation becomes more prevalent, loss of p16 via promoter methylation which keeps the cells senescent allows progression to more advanced polyps [8]. Increasing methylation gives rise to CIMP and eventual methylation of *MLH1*, which in turn silences transcription. Loss of MLH1 results in MMR deficiency and thus the development of an MSI-H CRC. As CIMP CRCs develop through serrated polyp intermediates, this pathway is called the serrated pathway. An overview of this process is shown in Figure 23-3. Clinically, CIMP CRC tends to develop in the right colon, at advanced age, and is more common in females [9].

General Approach and Classification of Suspected Hereditary Syndromes

Awareness and suspicion are the keys to identifying hereditary CRC syndromes. Although only about 5–10 % of all CRCs arise with a known hereditary syndrome, recognizing these cases and making the correct diagnosis impact care of that particular patient and their family including future generations. Clinical evaluation should include a personal and family history, physical examination, documentation of gastrointestinal polyps or cancers, and identification of extracolonic manifestations. If the patient or family members have colorectal polyps, note should be made of the histology, size, location, and age at diagnosis. Family history can provide clues to the inheritance patterns and thus also the syndrome. This information can be used to broadly characterize the syndrome into polyposis or nonpolyposis. The histologic types of polyps (adenomas, hamartomas, or serrated polyps) further refine the possible syndromes. The main adenomatous polyposis syndromes are familial adenomatous polyposis (FAP) and *MUTYH*-associated polyposis (MAP). The more common of the extremely rare hamartomatous polyp syndromes include Peutz-Jeghers syndrome (PJS), juvenile polyposis syndrome (JPS), and PTEN hamartoma syndrome. A predominance of serrated polyps or large serrated polyps

Table 23-1. Classification and overview of hereditary colorectal cancer syndromes

Syndrome	Gene(s)	Main polyp type	Inheritance	Predominant clinical findings	Approximate CRC risk
Polyposis syndromes					
FAP					
Classical	*APC*	Adenoma	AD	100–1000 adenomas; duodenal adenomas and carcinomas; gastric fundic gland polyps, desmoid tumors, epidermoid cysts, extra teeth, osteomas	100 %
Profuse	*APC*	Adenoma	AD	>1000 adenomas; duodenal adenomas and carcinomas; gastric fundic gland polyps, desmoid tumors, epidermoid cysts, extra teeth, osteomas	100 %
Attenuated	*APC*	Adenoma	AD	<100 adenomas; gastric fundic gland polyps, desmoid tumors, epidermoid cysts, extra teeth, osteomas	80 %
MAP	*MYH*	Adenoma	AR	0–1000 adenomas, CRC <50 years; gastric fundic gland polyps, duodenal adenomas, and carcinomas	80 %
JPS	*BMPR1A* *SMAD4*	Hamartoma	AD	≥5 juvenile polyps; any juvenile polyp and JPS family history; HHT	40 %
PJS	*STK11*	Hamartoma	AD	Peutz-Jeghers polyps Orocutaneous pigmentation Family history of PJP; cancer of small bowel, colon, stomach, pancreas, breast, ovary, testis	40 %
PHTS	*PTEN*	Hamartoma	AD	Colorectal adenomas, lipomas, fibromas, ganglioneuromas, juvenile hamartomas; colorectal cancer; macrocephaly, trichilemmomas	10 % (Cowden)
SPS	Unknown	Serrated polyps	Unknown	>20 serrated polyps Any serrated polyp and family history of SPS >5 serrated polyps proximal to the sigmoid, 2 are >1 cm diameter	25–40 %
Nonpolyposis syndromes					
Lynch syndrome	*MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*	Adenoma	AD	Microsatellite-unstable CRC, advanced adenomas; gastric, duodenal, small bowel, transitional cell, gall bladder, pancreas, endometrial, ovarian	60–80 %
Familial CRC type X	Unknown	Adenoma	AD	Amsterdam criteria positive, microsatellite stable tumors	12 %

FAP familial adenomatous polyposis, *MAP MUTYH*-associated polyposis, *JPS* juvenile polyposis syndrome, *PJP* Peutz-Jeghers polyposis, *PHTS* PTEN hamartoma tumor syndromes, *SPS* serrated polyposis syndrome, *CRC* colorectal cancer, *HHT* hereditary hemorrhagic telangiectasia, *AD* autosomal dominant, *AR* autosomal recessive

should raise suspicion for serrated polyposis syndrome (SPS), which is defined by clinical criteria. Nonpolyposis syndromes are generically referred to as hereditary nonpolyposis colorectal cancer (HNPCC) and are defined by patterns of cancer within the family. HNPCC is defined clinically by Amsterdam criteria, while Lynch syndrome is characterized by a genetic proclivity to colorectal and extracolonic cancers [10, 11].

A specific diagnosis is warranted to assign risk for cancer development and guide surveillance and prophylactic interventions. Information gained from the initial evaluation can guide the specific diagnostic tests required to make a diagnosis. Genetic counseling is a critical component to this evaluation and is recommended before genetic testing to discuss potential implications of the results. An overview of the classification of hereditary CRC syndromes is given in Table 23-1. Key distinguishing points about each of these syndromes are discussed in the remainder of this chapter.

Adenomatous Polyposis Syndromes

Familial Adenomatous Polyposis

Clinical Presentation

FAP is an autosomal dominant inherited disease that occurs in approximately 1:10,000 live births and affects both genders equally and all races. Patients with FAP may be asymptomatic or may present with bleeding, diarrhea, abdominal pain, or mucous discharge. Other symptoms such as anemia, obstruction, or weight loss usually occur as polyps grow larger in size or number and may foreshadow the presence of cancer. The hallmark feature of FAP is colorectal adenomatous polyposis, but the phenotype varies per patient, even within the same family. Severe FAP is characterized by thousands of colorectal adenomas. Oftentimes there is little normal mucosa between the adenomatous polyps. Mild

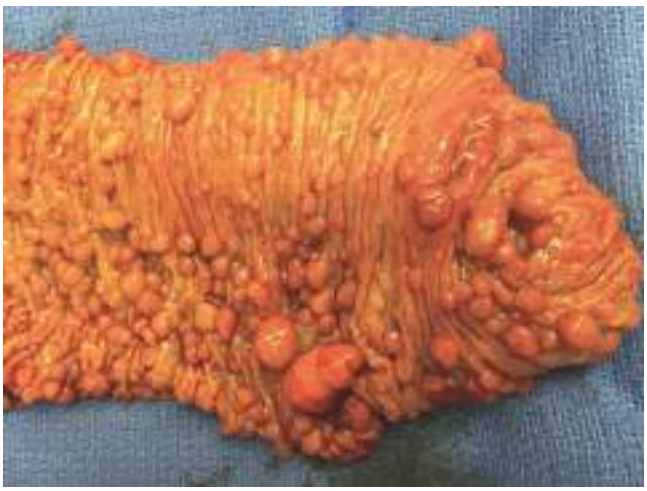

FIGURE 23-4. Moderate to severe polyposis in the resected specimen of a 22-year-old woman with familial adenomatous polyposis. Photo is courtesy of Matthew F. Kalady, MD.

polyposis is described as having between 100 and 1000 colorectal adenomas. Patients with fewer than 100 adenomas are considered to have attenuated FAP. Nearly 100 % of patients with FAP will develop CRC if left untreated. Figure 23-4 provides an example of moderate to severe polyposis.

FAP is a multisystem disease and may present with various extracolonic lesions. These include gastroduodenal adenomas and carcinoma, desmoid disease, osteomas, epidermoid cysts, papillary thyroid carcinoma, small bowel polyps and carcinoma, congenital hyperplasia of the retinal pigment epithelium (CHRPE), and dental anomalies. These extracolonic manifestations and their management recommendations are discussed later.

Two specific subtypes of FAP are based on a specific constellation of extracolonic manifestations. Gardner's syndrome is FAP with desmoid tumors, osteomas, epidermoid cysts, or extranumerary teeth [12]. Turcot syndrome is FAP associated with malignant tumors of the central nervous system [13]. Both syndromes are also caused by mutations in *APC*.

Underlying Genetics

FAP is caused by an inherited mutation in the *APC* gene on chromosome 5q21. As patients are born with only one functional copy of the "gatekeeper" gene, loss of the second allele via sporadic mechanisms leads to rapid development of hundreds to thousands of colorectal adenomas. More than 850 different mutations have been described, most of which produce a stop codon that ceases protein translation which yields a truncated APC protein. Depending on the location of the "stop," the truncated protein has variable functional abilities, likely accounting for some of phenotypic variation seen with different mutations. About 25 % of patients with FAP have a de novo mutation and thus have no family history.

Diagnosis

FAP may be diagnosed genetically or clinically. Genetic testing reveals an *APC* germline mutation in approximately 80 % of cases. Indications for genetic counseling referral and testing include a family history of FAP, personal history of more than ten adenomas, personal history of adenomas, and an extracolonic manifestation of FAP. For at-risk individuals in families with a known mutation, genetic testing is directed for that mutation. Approximately 20 % of patients will not have an identified germline mutation but still have the clinical phenotype. Additionally, some patients or families refuse genetic testing for various reasons. In this situation, a clinical diagnosis of adenomatous polyposis is made.

CRC Risk

FAP carries a near 100 % CRC risk. Cancers develop at a median age of 39. The goal of surveillance and intervention is to reduce the risk of death from colorectal cancer via colectomy or proctocolectomy before cancers develop. The risk of CRC in attenuated FAP is approximately 70 %, and cancers develop at a relatively later age (average 58 years) compared to classical FAP [14].

FAP Extracolonic Manifestations

Upper Gastrointestinal Tract

Approximately 90 % of patients with FAP develop duodenal adenomas. Despite the high incidence of adenomas, only about 5–10 % of patients will develop periampullary cancer [15]. Nonneoplastic gastric fundic gland polyps are a common finding, occurring in about 50 % of patients. These have a minimal risk of malignancy [16]. Rare gastric cancers in FAP are felt to develop from gastric adenomas that form in the gastric antrum in about 10 % of FAP patients.

Desmoids

Desmoid disease affects approximately 5 % patients with FAP. About half of FAP-associated desmoid tumors arise intra-abdominally in bowel mesentery and 40 % develop in the abdominal wall. The remainder present in the back, neck, or limbs. Desmoids can manifest as flat, fibrous, sheetlike lesions or as defined discrete masses (see Figure 23-5). Desmoids have been associated with female gender, a family history of desmoids, and *APC* mutations at the 3′ end of codon 1440. The majority of desmoids develop within 5 years after abdominal surgery, presumably as part of an inflammatory response [17, 18]. Church has proposed a desmoid risk factor score to delineate desmoid risk which incorporates gender, extracolonic FAP manifestations, and family history of desmoids, both with and without using genotype [19]. A recent study from the Cleveland Clinic reported that desmoid disease can occur with nearly any *APC* mutation,

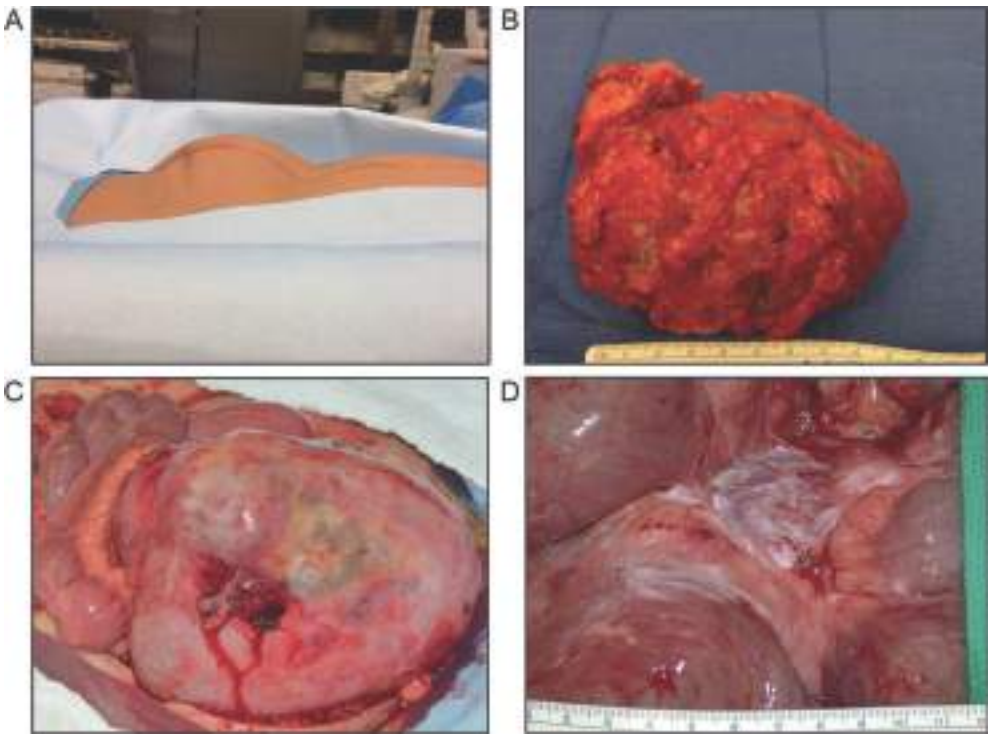

FIGURE 23-5. Different manifestations of desmoid disease. (**a**) Abdominal wall desmoid occurring 1 year after total proctocolectomy for familial adenomatous polyposis. (**b**) Resected abdominal wall desmoid. (**c**) Large intra-abdominal desmoid arising from the root of the small bowel mesentery. (**d**) Sheetlike desmoid tumor arising in the mesentery with associated desmoid reaction. Photos in (a) and (b) are courtesy of Matthew F. Kalady, MD. Photos in (**c**) and (**d**) are courtesy of Dr. James Church.

regardless of the location of the mutation in the gene. However, there is an increased propensity to develop desmoids, and clinically more severe desmoids, when the mutation is at the 3′ end of the gene [20].

Thyroid Cancer

Although the risk of thyroid cancer in FAP is only 2 %, it is double the risk of that for the general population. The incidence is 17 times higher in women than in men and it develops at a young mean age of 27 years. The primary histology is papillary carcinoma [21–24].

Other Malignant Tumors

There are several rare extracolonic malignant tumors associated with FAP that have a higher incidence than the general population. These include pancreatic adenocarcinomas (relative risk 4.5; lifetime risk 1.7 %) [25], hepatoblastoma in children (RR 750–7500; absolute risk 2 %) [26, 27], and medulloblastoma (RR 7; lifetime risk (0.025 %) [28].

Other Benign Lesions

Several benign lesions are associated with FAP that do not necessarily require intervention but can be used to help make a diagnosis. Congenital hypertrophy of the retinal pigment epithelium (CHRPE) is characterized as well-delineated grayish-black or brown oval spots seen in 60–85 % of FAP patients [29]. Boney lesions including dental abnormalities and mandibular and skull osteomas are found in approximately 20 % of patients. Multiple cutaneous and subcutaneous lesions are associated with FAP including epidermoid cysts, lipomas, and fibromas. These are benign and intervention is not necessary unless they cause symptoms. The presence of these on the face, scalp, and extremities rather than on the back in young patients should raise suspicion for possible FAP.

Management

Screening

Colorectal: The goal of colorectal screening and surveillance in FAP is to limit CRC risk by timely intervention and surgical referral. Screening should be done on all individuals with a genetic diagnosis or in first-degree relatives of persons with a clinical diagnosis of FAP. If no genetic mutation is found in a family but they have a clinical diagnosis, all first-degree relatives should be screened. Screening begins at age 12 and can be initiated with flexible proctosigmoidoscopy. If polyps are seen, a full colonoscopy is warranted. If no polyps are identified on the initial proctosigmoidoscopy, the exam should be repeated every

Table 23-2. Scores of duodenal adenoma characteristics and management recommendations according to Spigelman criteria

Duodenal disease grading scale (points assigned)			
Assigned points	1	2	3
Number of polyps	1–4	5–20	>20
Size of polyps (mm)	1–4	5–10	>10
Histology	Tubular	Tubulovillous	Villous
Dysplasia	Mild	Moderate	Severe
Recommendations based on Spigelman score			
Total points	Spigelman stage	Recommendation	
0	0	Repeat endoscopy in 5 years	
1–4	I	Repeat endoscopy in 5 years	
5–6	II	Repeat endoscopy in 2–3 years	
7–8	III	Repeat endoscopy in 6–12 months	
9–12	IV	Surgical evaluation	

1–2 years or earlier if symptoms develop. For those without a genetic diagnosis, first-degree relatives who are not found to have any polyps by age 40 can safely be transitioned to screening guidelines for the general population.

Duodenal and gastric: Upper gastrointestinal endoscopic screening is a key part of FAP disease management. Screening is done with a side-viewing endoscope and should begin at age 20–25 years. Screening intervals are based on the Spigelman staging system (Table 23-2).

Desmoids: There are not recommendations for routine screening for desmoid disease.

Thyroid: Annual thyroid screening by ultrasound should be recommended to FAP patients. In a prospective study utilizing annual thyroid ultrasound on 192 asymptomatic patients with FAP, five patients (2.6 %) were found to have a thyroid cancer. Four of the five cancers were papillary carcinoma. Importantly, an additional 72 patients (30 %) had other thyroid nodules discovered during the screening examination [24].

Other neoplasia: Due to the overall low incidence of other rare tumors in FAP, routine screening is not recommended. Specific examinations may be considered if there is high penetrance of a particular extraintestinal cancer type within a family.

Treatment

Colorectal

The goals of FAP treatment are to remove or limit the CRC risk while maximizing quality of life. As CRC is near certain, surgical removal is the mainstay of treatment. The timing of surgery and choice of operation require consideration of multiple aspects of the disease and the patient. These choices are discussed below.

Timing of Surgery

Decisions for colorectal surgery in FAP depend on the presence of symptoms, the age at diagnosis, and personal patient circumstances. Patients with symptoms should be offered surgery both to treat the symptoms and to prophylactically treat potential occult cancer. For asymptomatic teenagers with FAP, surgery can be reasonably delayed until the late teen years or early twenties when they have reached physical and emotional maturity. CRC before the age of 20 is extremely rare and is usually accompanied by symptoms. Since cancer risk increases with age, patients diagnosed in their third decade or beyond should be offered surgery at the time of diagnosis.

Delaying surgery in an asymptomatic patient may be considered in specific circumstances. Examples include women with a low polyp burden who wish to have children. Since pelvic surgery decreases fecundity [30], it is reasonable to delay proctectomy as long as the patient remains in a strict surveillance program. Morbidly obese patients who wish to undergo ileal pouch-anal anastomosis (IPAA) may delay surgery, if they are able to lose weight, so that a restorative proctectomy may be more feasible. Also, patients who have desmoids in their family or have risk factors may delay surgery, as most desmoids develop after surgery. Deferral of surgery should only be done in patients who are asymptomatic, motivated, and adherent to surveillance protocols.

Extent of Resection

For patients without evidence of rectal cancer, surgical options include colectomy with ileorectal anastomosis (IRA) or total proctocolectomy (TPC) with or without restoration of the gastrointestinal tract. There are oncologic and functional implications of both procedures. Decisions are made based on balancing future cancer risk with quality of life associated with bowel function, as valued by both the patient and surgeon. TPC removes all or nearly all at-risk mucosa and almost completely eliminates future CRC risk. Restoration of the gastrointestinal tract via an ileal pouch-anal anastomosis (IPAA) results in more frequent bowel movements, higher incidence of incontinence, and decreased quality of life compared to colectomy and IRA [31–33]. The improved function of an IRA is countered by cancer risk in the residual rectum.

Patient selection is key to minimizing risk. An IRA is the preferred approach for patients who have a relatively low colorectal polyp burden. Church et al. have used polyp burden as one guide in determining the extent of resection. At a median follow-up of 12 years, of 95 patients treated with colectomy and IRA who had fewer than 1000 adenomas in the colon and fewer than 20 adenomas in the rectum, none required proctectomy. Conversely, of 33 patients who underwent an IRA and had more than 1000 colon adenomas and more than 20 rectal adenomas, 56 % underwent subsequent proctectomy for symptoms, uncontrolled polyp burden, or advanced neoplasia [34]. The genotype-phenotype correlation potentially influences decisions regarding the extent of resection. *APC* mutations at codons 1309 and 1328 are associated with severe polyposis and are independent risk factors for proctectomy after TAC in FAP [35].

In the presence of colon cancer and metastatic disease, decisions regarding whether to proceed with proctocolectomy instead of just colectomy should be based on the likelihood of cure and risk of metachronous cancer in the rectum if left in situ. Patients with locally advanced primary tumors (or those with possible metastatic disease) with minimal rectal polyp burden may be better served by abdominal colectomy and IRA (or proctocolectomy and ileostomy) vs. restorative proctocolectomy—where complications of surgery are more common and may delay administration of adjuvant chemotherapy. For patients who develop rectal cancer, total proctocolectomy should be performed with restoration of the gastrointestinal tract via an IPAA when possible. In the presence of stage IV disease with limited life expectancy, a proctectomy may be considered if there is no cancer in the colon and the polyp burden is minimal or controlled. If the rectal cancer is locally advanced and radiotherapy is required, it should be utilized in the preoperative period or not at all if a restorative proctocolectomy is planned, as postoperative radiotherapy is associated with toxicity and risk of ileal pouch loss. If an IPAA is not planned and radiotherapy is not given preoperatively, an omental pedicle flap or pelvic inlet mesh should be considered to occlude the small bowel from the pelvis in case postoperative radiotherapy is unexpectedly required. Adjuvant chemotherapy is given for stage III cancer.

Morbidity and quality of life should be considered when deciding the extent of surgery. Compared to colectomy and IRA, proctectomy is associated with increased urinary and sexual and urinary dysfunction complications [32], decreased fecundity in females [30], and reduced quality of life scores [33]. Given the fact that many of these operations are performed in young patients, the potential complications can be even more devastating. Therefore, an abdominal colectomy alone is favored, if appropriate from an oncologic standpoint and the patient is felt to be reliable with regard to surveillance.

Despite the argument that TPC removes the risk of CRC, a small percentage of patients may develop cancer in the anal transition zone or in the ileal pouch [36]. Debate exists over the use of mucosectomy and hand-sewn anastomosis vs. double-stapled anastomosis during TPC and IPAA as a means of reducing the risk of subsequent cancer. Mucosectomy to the dentate line theoretically removes all colorectal mucosa at risk for neoplasia. However, this technique potentially fails if an incomplete mucosectomy results in residual cells of rectal mucosa. Residual nests of rectal mucosa have been found either outside the ileal pouch or adjacent to the pouch-anal anastomosis in up to 21 % of patients undergoing prior mucosectomy [37].

This risk must be balanced against the cancer risk from a small anal transition zone that remains following a stapled IPAA. It may be preferable to have any at-risk mucosa in the lumen of the gut, where it can be observed over time, rather than implanted outside the ileal pouch at the time of mucosectomy, where it cannot be observed. In cases of rectal dysplasia or rectal cancer, many clinicians advocate mucosectomy, although definitive data regarding reduction in cancer risk are lacking.

The stapled IPAA leaves the distal anal mucosa and requires less manipulation of the sphincter complex, with less risk of postoperative incontinence. The Cleveland Clinic reported outcomes of the two different approaches in 119 patients treated by IPAA. Patients who underwent mucosectomy and hand-sewn anastomosis had worse seepage, higher incontinence rates, and more frequently used undergarment pads to protect against drainage [38]. The worse functional outcomes were tempered against less neoplasia. Fourteen percent of patients in the mucosectomy group developed adenomas in the anal transition zone, which was half of the rate of neoplasia in the non-mucosectomy, stapled anastomosis group. A meta-analysis by Lovegrove et al. included over 4000 patients from 21 studies comparing the two approaches. Worse nocturnal incontinence in the mucosectomy group correlated with anorectal physiology studies that demonstrate reduced and resting and squeeze pressures [39].

Duodenal Adenomas

Duodenal adenomas can progress to cancer, but this rate is relatively low and, as such, the lesions can usually be managed endoscopically. Burke et al. reported progression from adenoma to carcinoma in duodenal adenomas in 11 % of cases at 7-year follow-up [40]. Adenomas greater than 1 cm or those that contain high-grade dysplasia should be removed endoscopically [41]. If smaller polyps are not completely removed, representative biopsies need to be taken for accurate Spigelman staging which guides surveillance and treatment algorithms [42]. The Spigelman staging system estimates duodenal cancer risk based on several factors as given in Table 23-2. Early-stage lesions may safely be surveyed with low risk of cancer. However, those with Spigelman stage IV disease have a 36 % risk of adenocarcinoma [43]. Adenocarcinoma, persistent or recurrent high-grade dysplasia, or Spigelman stage IV disease warrants the consideration of surgery. Surgical options include pancreaticoduodenectomy or pancreas-preserving duodenectomy.

Desmoid Disease

Desmoid disease can be clinically devastating and is the second cause of death in FAP. Clinically, presentation ranges from asymptomatic to severe pain, obstruction, or fistulization. Treatment depends on symptoms, desmoid location, size, and extent of disease. Church has proposed a staging system for abdominal desmoids (Table 23-3) [44]. The Cleveland Clinic uses this staging system to guide medical management. Stage I desmoids are either observed or treated with a nonsteroidal anti-inflammatory drug such as sulindac (150–200 mg twice daily) [45]. Stage II desmoid treatment includes sulindac and antiestrogen therapy, such as raloxi-

Table 23-3. Proposed intra-abdominal desmoid disease clinical staging system

Disease stage	Clinical characteristics
I	Asymptomatic disease and not growing and <10 cm in maximum diameter
II	Minimally symptomatic and not growing or >10 cm in maximum diameter
III	Symptomatic disease or slowly growing or obstructive complications
IV	Symptomatic disease and rapidly growing or severe complications (e.g., fistula)

fene (60 mg twice daily) [46]. Stage III desmoids are usually treated with chemotherapy agents such as methotrexate and vinorelbine or Doxil [47, 48]. Stage IV desmoids are difficult to control and are treated with more aggressive anti-sarcoma chemotherapy such as Doxil or Adriamycin [49]. Although desmoid tumors are radiosensitive, the close proximity to the small bowel limits its use due to toxicity.

Surgery for abdominal desmoids is usually reserved for the treatment of disease complications such as bowel obstruction, enterocutaneous fistula, and ureteric obstruction. If possible, resection to negative margins is the goal. Intra-abdominal tumors are frequently located at the root of the small bowel mesentery and are often not resectable due to the proximity to critical small bowel blood supply. Enteroenteric or enterocolic bypass may provide a palliative option in these situations. Small bowel and multivisceral transplant have been described as treatment for desmoid disease and its complications. Intestinal transplantation for desmoid disease is a growing field, and there have been reports of success [50, 51].

Surgery is usually the first-line treatment for symptomatic abdominal wall desmoids. Due to the location, these tumors are usually able to be safely resected with minimal complications. The defect in the abdominal wall may need to be closed with tissue flaps or mesh.

Thyroid Neoplasia

Thyroid disease may be detected in FAP by evaluation of symptoms or routine ultrasound screening. Nodules larger than 1 cm should undergo fine-needle aspiration. Since cancers tend to be multifocal, thyroid cancer should be treated by total thyroidectomy and radioiodine ablation [52, 53].

Evaluation of At-Risk Relatives

As FAP is autosomal dominantly inherited, all first-degree relatives of an FAP patient have a 50 % chance of also having the disease. Therefore, all first-degree relatives in an FAP family should be evaluated. Due to the implications of both positive and negative results, pretest counseling, preferably with a genetic counselor, should be done. Potentially affected family members should be evaluated at the time of diagnosis or, for children, when they reach the age of 12. Evaluating a potentially affected family member depends on the family situation. If there is a known *APC* mutation in the family, then germline DNA testing is appropriate. Importantly, if no mutation is detected, genetic testing for *APC* mutations in the family is not indicated. The clinical diagnosis of FAP guides surveillance and treatment recommendations. At-risk relatives in a family without a genetic diagnosis should undergo screening by flexible sigmoidoscopy at age 12 years or colonoscopy if the initial screening is done as an adult. Subsequent testing intervals for children depend on findings at the initial proctosigmoidoscopy. If polyps are seen, a full colonoscopy is warranted. If no polyps are identified, the exam should be repeated every 1–2 years or earlier if symptoms develop. For those without a genetic diagnosis, first-degree relatives who are not found to have any polyps by age 40 can safely be transitioned to screening guidelines for the general population.

***MUTYH*-Associated Polyposis**

Clinical Presentation

Approximately 0.3 % of CRC patients have MAP. The clinical presentation is not distinct from other patients with colorectal polyps or cancer. Bleeding or obstruction may occur, but the disease is suspected on findings from a screening colonoscopy. The syndrome is primarily characterized by multiple colorectal adenomas and an increased risk for CRC at a younger age (40–50s), but the colorectal polyp phenotype is highly variable. Moderate polyposis (less than 100 adenomas) is the most common phenotype and occurs in 11–42 % of reported cases [54–56]. Biallelic *MUTYH* mutations are rare among patients with profuse adenomatous polyposis [57].

Polyposis is not necessary for an MAP diagnosis, and as many as 20 % of patients present with colorectal cancer without a history of colorectal polyps or synchronous polyps [58]. Some authors have proposed calling the syndrome MYH-associated neoplasia (MAN) instead of MAP to avoid diagnostic confusion given the lack of polyposis in a significant amount of patients [59]. MAP is the only hereditary CRC syndrome with an autosomal recessive inheritance pattern, and thus family history may help guide counseling and testing in patients who are suspected of having MAP.

Despite the similar colorectal phenotype to FAP, patients with MAP are less likely to have the extracolonic manifestations that are commonly seen in FAP. Approximately 20 % of patients with MAP will have duodenal polyposis, and gastric fundic polyps are rare. Osteomas, desmoids, and CHRPE are not associated with MAP.

Underlying Genetics

MAP is caused by inherited biallelic mutations in the *MUTYH* gene, which codes for a base excision repair protein. Approximately 1–2 % of the general population carries a

MUTYH mutation. Mutations at Y179C (previously referred to as Y165C) and G396D (previously referred to as G382D) cause approximately 80 % of MAP in persons who are of Northern European descent [60]. *MUTYH* is located on the short arm of chromosome 1 and encodes MYH glycosylase, a DNA base excision repair protein. Specifically MYH glycosylase repairs DNA G:C to T:A transversions and thus corrects potential mutations [61, 62]. A *MUTYH* causes defective base excision repair function and subsequently the accumulation of unrepaired G:C to T:A transversions caused by oxidative damage. Importantly, the phenotype of MAP is related to the gene that is affected by the unrepaired transversions. For example, *APC* contains an abundance of guanine nucleotides, and in the absence of MYH function, these transversions go unrepaired and the phenotype appears as if APC is defective. This explains why the phenotype of MAP is similar to that of FAP. When G:C to T:A transversions occur and remain uncorrected in a DNA mismatch repair gene, the mutator phenotype and microsatellite-unstable neoplasia ensue [63]. If a gene involved in control of methylation is predominantly affected by the transversions and a mutated MYH protein does not repair the errors, a methylated tumor may develop [64, 65].

Diagnosis

MAP diagnosis is confirmed by genetic testing for mutations in the *MUTYH* gene. Germline *MUTYH* testing should be offered to patients who have a recessive pattern of family history of colorectal cancer or polyposis, who have a clinical phenotype of FAP or attenuated FAP but test negative for an *APC* mutation, or who have a personal history of >10 colorectal adenomas. Nearly 30 % patients with a clinical phenotype of FAP without an identified *APC* mutation have biallelic *MUTYH* mutations [66, 67].

CRC Risk

The cumulative lifetime risk of developing colorectal cancer for patients with biallelic *MUTYH* mutations is estimated at 75 % for males and 72 % for females by age 70 [68]. Onset of cancer is earlier than sporadic colorectal cancer, with the mean age of diagnosis reported between 45 and 56 years old [54, 67, 69, 70]. The risk of CRC for monoallelic *MUTYH* carriers continues to be defined. Data from the Colon Cancer Family Registry estimate the cumulative lifetime risk of developing CRC for people with monoallelic *MUTYH* mutations at 7.2 % for males and 5.6 % for females by age 70 [68].

Extracolonic Cancer Risk

The spectrum of extracolonic neoplasia in MAP continues to be defined. An increased risk of upper gastrointestinal polyps and cancers is consistently reported [67, 71]. About 17 % of cases have duodenal adenomas with a lifetime duodenal cancer risk of 4 %. The overall incidence of malignancy outside the gastrointestinal tract is 38 %, almost double that of the general population. The most common extraintestinal cancers found in a study of 276 international cases from Germany, the United Kingdom, and the Netherlands were bladder, ovarian, and skin cancers with standard incidence ratios of 7.2, 5.7, and 2.8, respectively [71]. Some studies report an increased risk of thyroid cancer to approximately double that of the general population, at an average age at diagnosis of 25–33 years [71, 72]. Benign and malignant sebaceous gland tumors have also been reported in MAP.

Management

Screening

Screening and surveillance are difficult as most cases of MAP are diagnosed at the time of CRC detection. In the rare cases when an individual is diagnosed with biallelic *MUTYH* mutations (as may be done with appropriate genetic counseling and testing) but does not have an indication for colectomy, colonoscopy screening should begin at age 25–30 years. If no neoplasia is identified on the exam, it should be repeated every 3–5 years with consideration for decreasing the interval with advancing age [73, 74]. Any polyps found on colonoscopy should be removed and examined histologically. When polyps are present, the interval is shortened to 1–2 years depending on the findings. Patients with a polyp burden that cannot be controlled endoscopically should be referred for consideration of colectomy.

Esophagogastroduodenoscopy with side-viewing gastroscope should be performed to evaluate for duodenal adenomatous neoplasia. This screening should start at age 30 years and repeated every 3–5 years if the exam is normal. For patients with duodenal adenomas, management is similar to the recommendations for FAP patients with duodenal adenomas [74]. The American College of Gastroenterology also recommends annual thyroid ultrasound screening in patients with MAP. Despite the increased risk, the incidence is not high enough to warrant routine screening for the cancers outside the intestine [71].

As stated above, the risk of colorectal cancer development in monoallelic carriers is uncertain but most likely elevated. There is no consensus if routine screening should be done for these patients. Some clinicians have suggested screening these people by colonoscopy every 5 years, beginning 10 years earlier than the youngest patient afflicted with CRC in the family [74].

Treatment

The phenotype dictates treatment in MAP. Polyps should be removed endoscopically as able with follow-up colonoscopy at least annually. Indications for surgery include CRC,

high-grade dysplasia in an adenoma that cannot be removed endoscopically, or a polyp burden that cannot be safely managed by colonoscopy. Surgical options include total abdominal colectomy, subtotal colectomy, or proctocolectomy. A segmental colectomy may be considered in certain circumstances such as metastatic cancer or medical comorbidities that preclude extended resection. Since the entire colon is at risk, a total colectomy and ileorectal anastomosis are recommended for otherwise healthy patients with curable disease. Patients with rectal cancer in MAP should be considered for proctocolectomy and ileal pouch-anal anastomosis. Any remaining colorectum should be surveyed annually, with the removal of subsequent polyps. Despite this rationale, there are no prospective data that show extended resection reduces the risk of subsequent colorectal cancers. One small study retrospectively reviewed 11 patients with biallelic *MUTYH* mutations and polyposis who underwent total abdominal colectomy and ileorectal anastomosis. Endoscopic findings of the remaining rectum using a yearly surveillance regimen were reported. At a median follow-up of 5 years using an annual surveillance regimen, no patient developed rectal cancer [75].

Evaluation of At-Risk Relatives

As this syndrome is autosomal recessive, patients must have two abnormal alleles to manifest the disease. Each sibling of an affected individual has a 25 % chance of also having the disease. Different from other inherited colorectal cancer syndromes, it is the siblings of patients with MAP that are at greatest risk, rather than the parents or children. Genetic counseling and testing for specific *MUTYH* mutation in the family should be offered at the age of 18 years to reduce morbidity and mortality through early diagnosis and treatment. Children of biallelic patients will be at least a monoallelic carrier. Approximately 1 % of the general population is a monoallelic carrier. If the spouse of the affected patient is a carrier, then each offspring has a 50 % chance of having MAP. Therefore, the partner of the affected patient should be tested to evaluate risk to the offspring.

Polymerase Proofreading-Associated Polyposis

A new syndrome has recently been reported as polymerase proofreading-associated polyposis (PPAP). This syndrome continues to be defined and has only been characterized in a few families [76, 77]. It is inherited in an autosomally dominant fashion and caused by a germline mutation in proofreading regions of one of two DNA polymerases, POLE and POLD1. The resulting cancers are microsatellite stable and have chromosomal instability. The clinical phenotype is one of oligo-adenomatous polyposis and early-age CRC and endometrial cancer. Guidelines are in evolution, but expert opinions support surveillance via colonoscopy every 1–2 years starting at age 20–25 and EGD every 3 years. For females with a POLD1 mutation, endometrial cancer screening by ultrasound is recommended starting at age 40 years.

Hamartomatous Polyposis Syndromes

Hamartomas are nonneoplastic growths of an abnormal mixture of tissue that is normally found at that anatomic site. Juvenile polyps and Peutz-Jeghers polyps are hamartomatous polyps in the small bowel and colorectum. Although these lesions are generally not considered neoplastic, they can be the hallmark of inherited hamartomatous polyposis syndromes such as juvenile polyposis syndrome (JPS), Peutz-Jeghers syndrome (PJS), and the PTEN hamartoma tumor syndrome (PHTS). These syndromes are rare but clinically important as they predispose to colorectal and other cancers. Less than 1 % of all CRC is associated with hamartomatous polyposis syndromes. Recognition of these syndromes is important so that appropriate genetic counseling and testing may be performed and cancer risk can be accurately assigned and appropriate surveillance done.

Juvenile Polyposis Syndrome

Clinical Presentation

Juvenile polyps are usually round, smooth, cherry-red lesions that are often pedunculated on a long stalk. An abundance and overgrowth of the lamina propria with mucin-filled spaces are the characteristic histologic features. Chronic inflammatory cells are often seen which can lead to an inaccurate diagnosis of inflammatory polyp. Juvenile polyps occur throughout the gastrointestinal tract including the stomach, small bowel, colon, and rectum, starting in the first or second decade of life. The number of polyps varies from a few to hundreds. Symptoms are related to the polyps and most commonly include acute or chronic gastrointestinal bleeding, iron-deficiency anemia, prolapsed rectal polyps, abdominal pain, or diarrhea [78, 79]. JPS is also associated with extracolonic congenital malformations such as cardiac and cranial abnormalities, duplication of the renal pelvis, cleft palate, gut malrotation, and polydactyly [78, 80]. JPS along with a *SMAD4* mutation may present as hereditary hemorrhagic telangiectasia (HHT) [81]. HHT may manifest with skin and mucosal telangiectasias; cerebral, pulmonary, and hepatic arteriovenous malformations; and an increased risk of associated hemorrhage [82, 83].

Underlying Genetics

JPS is an autosomal dominantly inherited disease caused by germline mutations in *BMPR1A* or S*MAD4*. Approximately 20 % of JPS cases have detectable SMAD4 mutations whose

normal function is as a tumor suppressor in the transforming growth factor beta (TGF-β) signal transduction pathway [84]. Another 25 % of JPS cases will have an alteration in *BMPR1A* [84–86]. This gene is also involved in the TGF-β superfamily by regulating BMP intracellular signaling through SMAD4. ENG1 mutations have also recently been described to cause JPS [87]. About 60 % of JPS cases of JPS are familial, while the remaining 40 % occur sporadically [88].

Diagnosis

JPS diagnosis is based on clinical criteria which include the following: (1) more than five juvenile polyps of the colon or rectum, (2) juvenile polyps in the extracolonic gastrointestinal tract, or (3) any number of juvenile polyps and a positive family history [80]. Patients that satisfy any of these criteria should be offered genetic counseling and genetic testing. A causative germline mutation is identified in approximately 50 % of cases.

CRC and Extracolonic Risk

JPS patients have an approximately 50 % lifetime CRC risk, with reports of varying incidence between 17 and 68 % [89–91]. The mean age of CRC diagnosis is 43 years [92], but CRC may develop at a young age and there is a case report of CRC in a 15-year-old patient [80]. The stomach, duodenum, pancreas, and jejunum are at increased risk for cancer in JPS. The risk of gastric or duodenal cancer is 15–21 % [90, 93]. *SMAD4* mutations are associated with a higher risk of extracolonic cancer compared to patients with *BMPR1A* mutations [94].

Management

Screening

Screening by colonoscopy should begin at age 12–15 or earlier if symptoms are present [74, 95]. The interval between colonoscopies depends on the exam findings. If there are no polyps, colonoscopy should be repeated in 2–3 years. Any polyps seen should be removed at colonoscopy and examined histologically. When polyps are present and removed, colonoscopy should be done annually until an exam is clear, after which the interval may be extended to every 2–3 years. Upper gastrointestinal screening should begin between ages 15 and 25 or earlier if symptoms develop. Endoscopic management principles follow those as given for adenomas of the upper GI tract.

Treatment

Surgical indications include the presence of high-grade dysplasia or cancer or if the polyp burden cannot be effectively managed endoscopically. Prophylactic colectomy may be considered for patients with poor surveillance compliance or those with a family history of CRC. For colorectal disease, surgical options include colectomy and ileorectal anastomosis, subtotal colectomy with ileosigmoid anastomosis, or total proctocolectomy. The authors favor abdominal colectomy with ileorectal anastomosis unless there is rectal cancer or symptoms referred to rectal disease. Risk of proctectomy after colectomy is approximately 50 % at 9 years, with a range of 6–34 years in one small retrospective study [96].

Surgery for the upper gastrointestinal tract is indicated for significant symptoms, malignancy, or development of protein-losing gastropathy or enteropathy. For gastric disease, subtotal gastrectomy is usually done. For small bowel disease, treatment is segmental resection.

Evaluation of At-Risk Relatives

If a specific mutation is identified in an individual, all at-risk family members should be counseled and tested for that mutation. Approximately 75 % of patients will have an affected parent. If a parent carries the mutation, then siblings of the parent as well as siblings of the proband should be tested as they have a 50 % chance of also having the mutation. Children of the proband should also be tested after counseling and testing in the early teenage years. If a mutation is not found in the family, at-risk individuals should be initially screened for gastrointestinal polyps and followed accordingly based on results.

Peutz-Jeghers Syndrome

Clinical Presentation

Nearly 90 % of PJS patients will develop hamartomatous polyps [97], most commonly in the small bowel, followed by the colon, stomach, and rectum in decreasing frequency. Polyps vary in size from a few millimeters to several centimeters and tend to become pedunculated as they grow larger. Peutz-Jeghers polyps differ histologically from juvenile polyps in that they arise due to an overgrowth of the muscularis mucosa, rather than the lamina propria. They have less inflammatory infiltrate and less mucin than juvenile polyps. Multiple branching of the muscularis mucosa gives the histologic appearance of a tree under the microscope. Although the polyp burden is usually low (<20), the larger size of the polyp often cause symptoms of obstruction, pain, gastrointestinal bleeding, polyp prolapse per anus, or small bowel intussusception. Symptoms usually develop by the teen years or early twenties.

The classical extraintestinal lesion seen in PJS is benign mucocutaneous pigmentation, which is present in approximately 95 % of cases. The pigmentation is usually a small, dark-brown or blue-brown macule that is obvious in infancy but may fade in adolescence. The most common locations are the vermillion border of the lips (94 %), buccal mucosa (66 %), hands (74 %), and feet (62 %) [98, 99].

Underlying Genetics

PJS is autosomal dominantly inherited and caused by germline mutations in *STK11* [100]. This gene encodes a member of the serine/threonine kinase family, which functions as a tumor suppressor.

Diagnosis

PJS is a clinical diagnosis based on meeting any one of the following World Health Organization criteria: (1) three or more histologically confirmed Peutz-Jeghers polyps; (2) any number of Peutz-Jeghers polyps with a family history of PJS; (3) characteristic, prominent, mucocutaneous pigmentation with a family history of PJS; or (4) any number of Peutz-Jeghers polyps and characteristic prominent, mucocutaneous pigmentation [98]. An individual meeting any of the above criteria should be offered genetic counseling and testing.

CRC and Extracolonic Risk

Patients with PJS have an increased risk of developing colorectal and extracolonic cancers. PJS patients have more than 90 % estimated lifetime risk of developing cancer of some type [101]. The risk for developing breast, colon, pancreatic, and gastric cancer is 54, 39, 36, and 29 %, respectively. In addition, males are at risk for Sertoli cell testicular tumors and women for sex cord tumors with annular tubules of the ovary and adenoma malignum of the cervix.

Management

Surveillance

Given the broad spectrum of disease in PJS, surveillance is complex and includes multiple organs. Randomized controlled trials have not been performed to evaluate the efficacy of cancer surveillance protocols, and published recommendations are based on expert opinion. Specific testing depends on the patient's age and gender. The NCCN recommends starting screening at age 8–10 years via evaluation of the small bowel, with the interval exam based on findings. If initial exam is normal, then the repeat evaluation is recommended at age 18 years and then at 2–3-year intervals [73]. Males should undergo annual testicular physical examination starting at age 10 years, and females should undergo annual pelvic examination and Papanicolaou stain starting at age 18–20 years. Women should have breast physical examinations every 6 months and yearly mammogram and breast MRI starting at age 25 years. Colonoscopy and upper endoscopy should in the late teens be repeated every 2–3 years for both genders. Pancreatic cancer screening involves endoscopic ultrasound or MRCP along with serum CA19-9 every 1–2 years starting at age 25–30 years. Other screening regimens have been proposed by other authors [95, 98, 99].

Polypectomy

Endoscopic intervention plays a key role in the management of PJS. Polypectomy treats polyp-related symptoms and prophylactically prevents development of symptoms. As with the surveillance guidelines, intervention recommendations are based on expert opinion. Asymptomatic gastric or colonic polyps larger than 1 cm should be removed endoscopically. Small bowel polyps larger than 1–1.5 cm or those that are have grown rapidly from prior exam should be removed to decrease future complications such as bleeding and intussusception. Some symptomatic polyps may be beyond the reach of conventional endoscopy, and intervention may require push enteroscopy or combined laparoscopy/laparotomy with endoscopy in the operating room, which allows guidance of the endoscope further distally into the small bowel.

Surgery

Surgery is most commonly reserved for symptoms, the most common being obstruction and bleeding in the small bowel. Obstruction is often caused by intussusception. Most cases resolve spontaneously, but if the obstruction persists more than a few hours, surgery is required. The goal of surgery is to remove the affected segment, preserving as much bowel as possible. If surgery is required, a "clean sweep" at surgery is recommended to reduce the need for future operations [102]. This technique involves evaluating the entire small bowel and removing all polyps. An endoscope may be placed through the open resection ends of the bowel or via an enterotomy.

As in the other syndromes, development of high-grade dysplasia, colorectal cancer, or an uncontrolled colorectal polyp burden is indication for colorectal surgery. Total abdominal colectomy and ileorectal anastomosis are the preferred operation unless the pathology is in the rectum.

Evaluation of At-Risk Relatives

For individuals with a specific known mutation, at-risk family members should be tested for that mutation. Approximately 50 % of individuals will have an affected parent, and parents should be evaluated for PJS traits. If one of the parents is affected, then testing should be offered to the siblings of the proband. Additionally, all children of the proband have a 50 % risk of inheriting the mutation and should be tested accordingly. Genetic testing for at-risk family members may be performed at age 8 after appropriate genetic counseling and informed consent [98]. If a specific mutation is not identified in the affected individual, at-risk family members are surveyed as if they potentially have the disease. This includes surveillance of the colon, stomach, small bowel, pancreas, breast, ovary, uterus, cervix, and testes as described above.

PTEN Hamartoma Tumor Syndrome (PHTS)

PHTS is a spectrum of extremely rare hereditary syndromes that are characterized by hamartomatous polyps in the gastrointestinal tract and abnormalities of the skull, skeleton, and skin. The two main syndromes are Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome (BRRS).

Clinical Presentation

About 95 % of Cowden syndrome patients have colorectal polyps, ranging from few to hundreds in number and are distributed throughout the colorectum [103, 104]. The most common polyps are hamartomas, accounting for about 30 % of all polyps [103, 223]. Other types of polyps include adenomas, juvenile polyps, inflammatory polyps, leiomyomas, lipomas, fibromas, neurofibromas, and ganglioneuromas. Any of these polyps may present with obstruction or bleeding. The majority of patients have multiple histologic types of polyps. About 30 % of Cowden syndrome patients have macrocephaly. Trichilemmomas are considered to be pathognomonic. Other benign and malignant lesions of the breast, thyroid, uterus, and skin are seen in Cowden syndrome.

Underlying Genetics

Cowden syndrome and BRRS are both autosomally dominant inherited disorders associated with a *PTEN* mutation. *PTEN* is a tumor suppressor gene that encodes a phosphatase that is involved in the PI3K/AKT signaling pathway. It plays a key role in apoptosis. Approximately 80 % of patients who meet the diagnostic criteria for Cowden syndrome, and 60 % of patients with BRRS, have PTEN mutations [105, 106].

Diagnosis

The International Cowden Consortium developed clinical diagnostic criteria for Cowden syndrome, including both major and minor criteria [99, 107]. Major criteria include breast cancer, thyroid cancer (especially follicular), macrocephaly, endometrial cancer, and Lhermitte-Duclos disease. Minor features include benign thyroid changes (such as a goiter), mental retardation, hamartomatous intestinal polyps, fibrocystic changes in the breast, lipomas, fibromas, genitourinary tumors (such as kidney cancer or uterine fibroids), or malformations. Cowden syndrome is diagnosed if a patient has either macrocephaly or Lhermitte-Duclos disease and one other major feature. A diagnosis of Cowden is also made when a person has one major feature and three minor features or at least four minor features. Definitive diagnosis is based on a *PTEN* mutation.

Specific diagnostic criteria for BRRS are not established, but patients with macrocephaly, hamartomatous colonic polyposis, lipomas, and pigmented macules of the glans penis should be considered for genetic testing [108].

CRC and Extracolonic Risk

A recent study reported CRC in 13 % of *PTEN* mutation carriers in Cowden syndrome with early age of onset, all before the age of 50 years. The adjusted standardized incidence ratio was 224 (95 % confidence interval, 109.3–411.3; $P<0.0001$) [103]. Other groups have supported a 9–16 % lifetime risk for CRC cancer [104, 109, 110]. It is uncertain if the cancers develop from the hamartomatous or adenomatous polyps in PHTS. Most of PHTS cancer risk is extracolonic. Women have a 50 % lifetime risk of developing breast cancer and a 5–10 % lifetime risk of developing endometrial cancer. Men and women with Cowden syndrome have a 10 % lifetime risk of developing epithelial thyroid cancer.

Approximately half of the patients with BRRS will have hamartomatous polyps in the digestive tract, particularly in the ileum and colon [108] These polyps can become symptomatic but are not believed to increase the risk of colon cancer. Patients with BRRS have similar extracolonic malignancy risks as those with Cowden syndrome.

CRC Risk Management

There is debate regarding the need for colonoscopy screening in PHTS. Given the recent findings of increased CRC risk, we recommend starting colonoscopy at age 35, with repeat examinations every 1–2 years. Colectomy should be considered if the polyp burden cannot be controlled endoscopically or if cancer develops.

Evaluation of At-Risk Relatives

At-risk relatives should be counseled and tested for the presence of PTEN mutation. For families with PHTS but no detected gene mutation, at-risk individuals should be initially surveyed as if they have the disease. Screening includes the evaluation of the colorectum, stomach, small bowel, thyroid, breast, uterine, kidney, and skin [74].

Serrated Polyposis Syndrome (SPS)

Clinical Presentation

SPS is usually asymptomatic and is often detected on screening colonoscopy. Bleeding and diarrhea may be present if polyps become large or numerous. More than 90 % of SPS patients are of white European descent. It affects both men and women nearly equally with a slight female inclination. The median age at diagnosis ranges from 44 to 62 years, with extremes of age including SPS in a 10-year-old and a man in his eighties [111–114].

SPS encompasses a variety of clinical phenotypes and is likely a heterogeneous disease that has not yet been characterized genetically. It can be characterized by the presence of

either multiple or large serrated colorectal polyps (see WHO diagnosis below). Serrated polyps are a family of polyps characterized by a classic serrated or sawtooth appearance of the arrangement of glands. The family consists of hyperplastic polyps, sessile serrated adenomas (SSAs) which are also called sessile serrated polyps (SSPs), SSAs or SSPs with dysplasia, and serrated adenomas. Different phenotypes have been described based on the size and number of serrated polyps. Some patients have multiple small polyps distributed throughout the colon, while others have a few large, right-sided polyps. The cancer risk is similar for both phenotypes [114]. In addition to serrated polyps, SPS patients often are prone to having adenomas [114, 115]. First-degree relatives do not have increased risk of extracolonic malignancy [116].

Underlying Genetics

A causative germline mutation has not been identified for SPS. There is no genetic testing for this syndrome.

Diagnosis

SPS is diagnosed by clinical criteria as defined by the World Health Organization as follows: (1) >20 serrated polyps of any size, distributed throughout the colon, (2) at least five serrated polyps proximal to the sigmoid colon with two or more of these being >10 mm, and (3) any number of serrated polyps proximal to the sigmoid colon in an individual who has a first-degree relative with SPS [117].

CRC Risk

Although the true incidence of CRC in SPS is yet to be defined by prospective studies, it is consistently reported as increased compared to the general population. Reports are variable from multiple relatively small series, ranging from 0 to 77 %, with an estimate of around 25 % [112–114, 118–125]. The initial SPS diagnosis is often made at the time of cancer diagnosis, and thus the natural history progression from SPS to cancer is uncertain [111, 114]. Bopari reported a 20 % CRC rate in a retrospective review of 77 SPS patients (without CRC at SPS diagnosis) who were followed for a mean of 5.6 years [111]. Cancer risk seems to be similar regardless of the polyp phenotype [114]. Identification of a genetic cause of SPS will allow for a more precise definition of cancer risk.

Management

Screening

For patients with an established SPS diagnosis, colonoscopy should be performed every 1–2 years. The goal is to diminish or eliminate the risk of CRC development by detection and timely removal of precancerous polyps (see treatment below). Management guidelines are based on clinical experience and expert opinion [126, 127]. Although some studies suggest an association with extracolonic malignancies, the data are not strong enough to justify surveillance recommendations for extracolonic neoplasia.

Treatment

Treatment is determined by the clinical phenotype and patient's wishes. The goal of treatment for SPS patients is to decrease or eliminate CRC risk by removing polyps before they become cancer. Expert panels recommend removing any single polyp larger than 5 mm for histologic evaluation. For clusters of small (3–4 mm) left-sided polyps, which are likely benign hyperplastic polyps, representative biopsies should be performed. Screening colonoscopies should be done yearly, with consideration of the number, size, and histology of the polyps to adjust the interval. If successive colonoscopies reveal no polyps, the interval to the next examination may be extended to 2–3 years, but this should be considered on a case-by-case basis [126].

Hazewinkel et al. demonstrated effective cancer risk reduction using annual colonoscopy with polypectomy of lesions greater than 3 mm in size for 50 patients with SPS. The cumulative risks of detecting CRC, advanced adenomas, and large (≥10 mm) serrated polyps were 0 %, 9 %, and 34 %, respectively. Of note, 12 patients (24 %) underwent preventative surgery [128].

Endoscopic management alone is often difficult as polyps are large, flat, and right sided. If the polyp burden cannot successfully be controlled via colonoscopy and polypectomies, surgery should be considered. The development of CRC or adenoma with high-grade dysplasia that cannot be adequately or safely removed endoscopically is an indication for surgery. The inability to adequately examine or remove polyps on a yearly basis and rapidly changing size or number of polyps at interval screening examinations are also reasonable indications for surgical consultation. As the risk of neoplasia is not limited to the specific location of the cancer but rather the entire colorectal mucosa, extended surgery should be entertained. This includes a subtotal or total colectomy and ileosigmoid or ileorectal anastomosis, respectively. Decision-making for the extent of surgery should be taken for each individual and evaluated within the context of medical comorbidities and anal sphincter function. A segmental colectomy may be considered for patients with focal disease (few large right-sided polyps) and who are not medically fit for extended resection. Any remaining colorectum should undergo annual endoscopy to prevent manage future neoplasia [126, 127].

Evaluation of At-Risk Relatives

Compared to the general population, first-degree relatives of patients with SPS have an approximately fivefold increased CRC incidence [111, 129]. As there is no genetic test to

screen for SPS, colonoscopy serves as the screening mechanism. Hazelwinkel evaluated 77 asymptomatic first-degree relatives of SPS patients who underwent annual colonoscopy. They identified significant polyps (adenomas, SSP, or proximal HP) in 43 % of cases of first-degree relatives, including 8 % with advanced adenomas and 9 % with multiple polyps. No cancers were identified, but the substantial neoplasia seen led the authors to conclude that screening is warranted [130]. Expert panels recommend colonoscopy screening for first-degree relatives, particularly those older than 40 years. Endoscopic findings and polyp histology should guide the interval to the next colonoscopy. Patients with a normal colonoscopy may reasonably be evaluated every 5 years. As more information is learned, more precise definitions and intervals may be determined. First-degree relatives do not have increased risk of extracolonic malignancy [116].

Lynch Syndrome

Lynch syndrome (LS), previously used as a synonym for hereditary nonpolyposis colorectal cancer (HNPCC), accounts for 3–5 % of all CRCs and 10–19 % of CRCs diagnosed before age 50 [131–134]. The underlying genetic cause is a germline mutation in a DNA mismatch repair (MMR) gene, which results in a nonfunctioning MMR protein. As the normal function of the MMR system is to detect and correct DNA replication errors, a defective system enables accumulation of genetic errors and confers increased susceptibility to colorectal, endometrial, and other cancers. The syndrome follows an autosomal dominant inheritance pattern. As discussed in detail below, when an individual is suspected to have LS based on clinical features, every effort should be made to identify the pathogenic or disease-causing germline mutation through genetic counseling and genetic testing. This information is critical for guiding the management of the proband and for establishing the risk of transmission but also enables efficient identification of other at-risk family members who would benefit from strategies to prevent or reduce their cancer risks.

Historical Perspective, Nomenclature, and Definitions

More than 100 years have elapsed since Sir Aldred Scott Warthin first reported the remarkable pedigree of intestinal and gynecologic cancers in the original family G of a local seamstress in 1913 [135]. Over this time period, a variety of nomenclature and definitions have been developed, reflective of our evolving understanding of this disease. In 1966, Dr. Henry Lynch comprehensively described two families with extensive history of endometrial and stomach cancers and used the terms “site-specific colon cancer syndrome” and “family cancer syndrome” [136]. In 1984, “Lynch syndrome” was coined to refer to this disorder, and Lynch I and II defined two main patterns of disease: Lynch I for families with CRC only and Lynch II for families with colorectal and other malignancies. Later, the term “hereditary nonpolyposis colorectal cancer (HNPCC)” arose to distinguish LS from the inherited polyposis syndromes that also confer CRC predisposition. In an effort to more accurately characterize the families that were being treated and studied, the International Collaborative Group on HNPCC convened in Amsterdam in 1991 and defined the Amsterdam criteria (Table 23.4). With increasing awareness that extracolonic malignancy was prevalent in the syndrome, Amsterdam II criteria (Table 23.4) were defined in 1999 to be more inclusive. While Amsterdam I criteria are highly specific for LS, they are not as sensitive as Amsterdam II criteria. Once the genetic defect underlying HNPCC was identified, a more precise characterization of the disease could be established [137]. By 2004, the revised Bethesda Guidelines (Table 23-4) were developed to identify individuals whose tumors should be evaluated for MSI and who should subsequently undergo genetic counseling and evaluation [138, 139]. At this time, it was felt that the term “HNPCC” was a misnomer because patients can develop many non-colorectal cancers, as well as one or more polyps or adenomas. The term “LS” was reintroduced, and it continues to be used today to define patients with hereditary pathogenic germline mutations in DNA MMR genes. Thus, LS is a genetic definition, independent of personal or family history.

There are several conditions that should be distinguished from LS as defined above. First, a subgroup of the HNPCC patients meeting Amsterdam criteria has microsatellite-stable, rather than microsatellite-unstable, tumors. These patients are called familial colorectal cancer type X. The CRC risk is between that of the general population, and patients with LS develop CRC at later ages compared to LS and do not have increased extracolonic malignancy risk. The exact genotype remains to be elucidated [140–142]. Second, in contrast to LS where an inherited mutation is present in one allelic copy of a MMR gene, a rare group of patients has inherited mutations of the MMR gene in both of their alleles. These patients have constitutional mismatch repair deficiency (CMMRD) syndrome. Patients exhibit a distinct phenotype with the development of CRC at very young ages (before age 20), multiple adenomatous polyps numbering between 10 and 100, café-au-lait skin lesions, hematologic malignancies, and brain tumors [143]. Finally, there are patients who present with MSI-H tumors, but subsequent germline mutation testing fails to detect a pathogenic mutation in any of the major MMR genes. The terms “Lynch-like syndrome” [144], “suspected LS” [145, 146], and “mutation-negative LS” [147] have been utilized, and the molecular characterization of these patients represents areas of active research. The remainder of this chapter will focus on LS.

TABLE 23-4. Clinical criteria defining hereditary nonpolyposis colorectal cancer (HNPCC) and the revised Bethesda Guidelines for testing colorectal tumors for microsatellite instability

Amsterdam I criteria (1991)
Three or more relatives with colorectal cancer, plus all of the following:
1. One affected patient is a first-degree relative of the other two
2. Colorectal cancer involves at least two generations
3. At least one case of colorectal cancer is diagnosed before the age of 50 years
Amsterdam II criteria (revised International Collaborative Group on Hereditary Non-Polyposis Colorectal Cancer (ICG-HNPCC) criteria 1998)
Three or more relatives with HNPCC-associated cancer (colorectal cancer or cancer of the endometrium, small bowel, ureter, or renal pelvis) plus all of the following:
1. One affected patient is a first-degree relative of the other two
2. Two or more successive generations are affected
3. Cancer in one or more affected relatives is diagnosed before the age of 50 years
4. Familial adenomatous polyposis is excluded
5. Pathologic diagnosis of cancer is verified
The revised Bethesda Guidelines for testing colorectal tumors for microsatellite instability (MSI)
Tumors from individuals in the following situations should be tested for MSI:
1. Colorectal cancer diagnosed in a patient before age 50
2. Presence of synchronous/metachronous colorectal or other HNPCC-related tumors (including: endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract, brain (usually glioblastoma), sebaceous gland adenomas and keratoacanthomas, and carcinoma of the small bowel), regardless of age
3. Colorectal cancer with the MSI-H histology (defined by: presence of tumor-infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern) diagnosed in a patient before age 60
4. Colorectal cancer diagnosed in at least one first-degree relative with an HNPCC-related tumor, where one cancer was diagnosed before age 50
5. Colorectal cancer diagnosed in at least two first- or second-degree relatives with HNPCC-related tumors, regardless of age

Modified from Genetic/Familial High-risk Assessment: Colorectal. Version 1.2015. www.ncc.org. and from Umar A, Boland CR, Terdiman JP, Syngal S, de la Chapelle A, Ruschoff J, et al. Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. Journal of the National Cancer Institute. 2004;96(4):261–8

Underlying Genetics and Molecular Profile

Patients with LS harbor an inherited dominant mutation in an MMR gene on one allele. This germline mutation, propagated through all somatic cells, confers susceptibility for cancer but requires a "second hit" within the specific somatic tissue for malignant transformation (Figure 23-6). The "second hit" alters the wild-type copy of the allele, leading to loss of DNA MMR activity in the somatic cell and further cancer development. Thus, malignant tumor cells in patients with LS harbor DNA MMR gene mutations in both alleles (one inherited and another acquired as a "second hit").

The four major DNA MMR genes responsible for LS are *MLH1*, *MSH2*, *MSH6*, and *PMS2*. Additionally, mutations in the gene *EPCAM* (or *TACSTD1*) upstream of *MSH2* can silence or disrupt MSH2 expression and lead to clinical features similar to LS [148, 149]. Based on data from 12,624 observations worldwide, it has been estimated that *MLH1* accounts for 39 %, *MSH2* for 34 %, *MSH6* for 20 %, and *PMS2* for 8 % of the entries in the International Society for Gastrointestinal Hereditary Tumours (InSiGHT) database (www.insight-group.org/mutations/), and up to 3 % of the cases are due to *EPCAM* mutations [150, 151].

The underlying genetic mutations and mismatch repair deficiency yield molecular changes within the tumor that can be examined as part of the screening process toward an LS diagnosis. As discussed earlier, MSI is the hallmark molecular feature of LS CRC. DNA microsatellites are tandem sequences of mono-, di-, or trinucleotide repeats that are particularly susceptible to replication errors when MMR function is impaired. These differences can be measured by the PCR-based MSI test, which assesses a standard panel of (typically five) microsatellite markers in paired tumor and normal tissue (Figure 23-6). By consensus, a tumor is considered MSI-H if 30 % or more of the markers tested show instability and microsatellite stable (MSS) if none of the markers are unstable. MSI-low connotation is reserved for tumors that have some markers that are unstable but fewer than 30 % [152, 153]. MSI low is infrequently encountered and its clinical significance has been regarded similar to that of MSS tumors.

Measuring expression of mismatch repair proteins using immunohistochemistry is the other means of determining mismatch repair proficiency or deficiency of a tumor. In vivo, the MMR protein products function as dimers, with MSH2 forming a complex with MSH6 and MLH1 with PMS2 protein (Figure 23-7). Thus, mutations in either *MSH2* or *EPCAM* genes typically result in loss of staining in both MSH2 and MSH6 protein products, while mutations that lead to loss of MLH1 protein result in the loss of staining for both MLH1 and PMS2 proteins. On the other hand, mutations in *MSH6* and *PMS2* genes typically result only in the loss of the respective single gene product [154]. While IHC is widely available, test accuracy depends on antibody fixation and other technical issues [155]. Also, lack of expression does not elucidate whether the protein loss expression is secondary to an under-

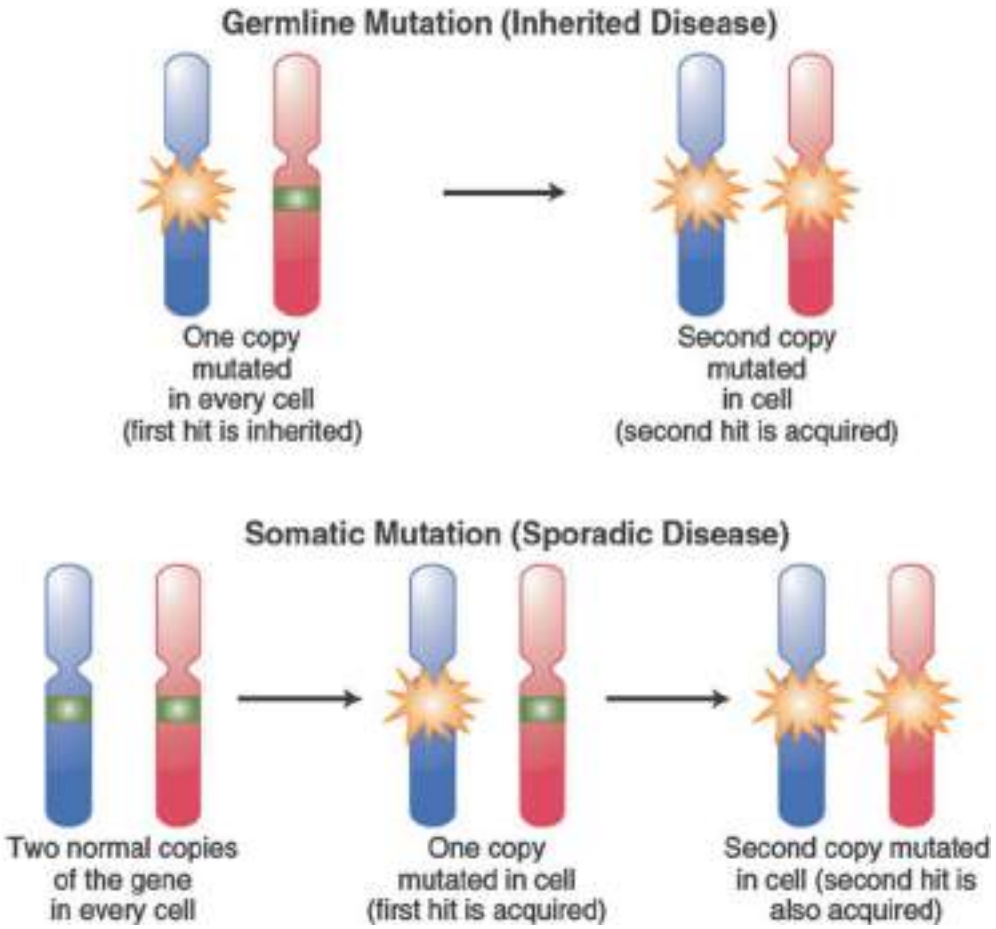

FIGURE 23-6. A germline MMR gene mutation confers susceptibility for cancer but requires a "second hit" within the specific somatic tissue for it to develop into a malignancy. The "second hit" causes the wild-type copy of the allele to also become mutated, leading to loss of DNA MMR activity in the somatic cell and further cancer development.

lying germline mutation or acquired somatic loss. Nonetheless, IHC has demonstrated 92 % sensitivity for identifying dMMR in tumors from known LS patients with a germline pathogenic mutation [155]. As discussed above, the vast majority of MSI-H in CRC is caused by methylation of the *MLH1* gene promoter as seen in the methylator pathway. Mutations in the *BRAF* oncogene are strongly associated with the methylator pathway and are rare in LS-related CRC. Thus, the presence of a somatic *BRAF* mutation within a CRC is often used to rule out further screening for an LS diagnosis [156, 157]. Rarely, dMMR tumors can arise from acquired double somatic mutations in the MMR genes. In these patients, germline DNA extracted from blood or other normal tissue shows no genetic defect in the MMR genes [158].

Distinguishing Lynch from Sporadic Epigenetic Changes: Methylation of MLH1 Gene Promoter

Approximately 85 % of mismatch repair deficiency in CRC is caused by methylation of the promoter region of *MLH1* gene. This epigenetic phenomenon silences MLH1 expression in the tumor tissue [159]. These tumors characteristically arise in elderly female patients and in the right colon [159]. Identifying *MLH1* promoter methylation from tumor tissue can help eliminate the diagnosis of LS. However, should *MLH1* promoter methylation be encountered in young patients with a family history suggestive of LS, the clinicians should be aware of two rare exceptions: (1) the patient may have LS with an inherited *MLH1* mutation and *MLH1* promoter methylation may have developed as the "second hit," leading to cancer development [154]; (2) germline *MLH1* hypermethylation has been reported in rare families which exhibit characteristic cancers associated with LS [160].

Clinical Presentation and Spectrum of Disease

Genotype-Phenotype Correlations

While the clinical hallmarks of LS are CRC and extracolonic malignancies, the cancer risks are highly variable within and among families with LS. Genotype-phenotype correlation studies have shown that the lifetime risks of

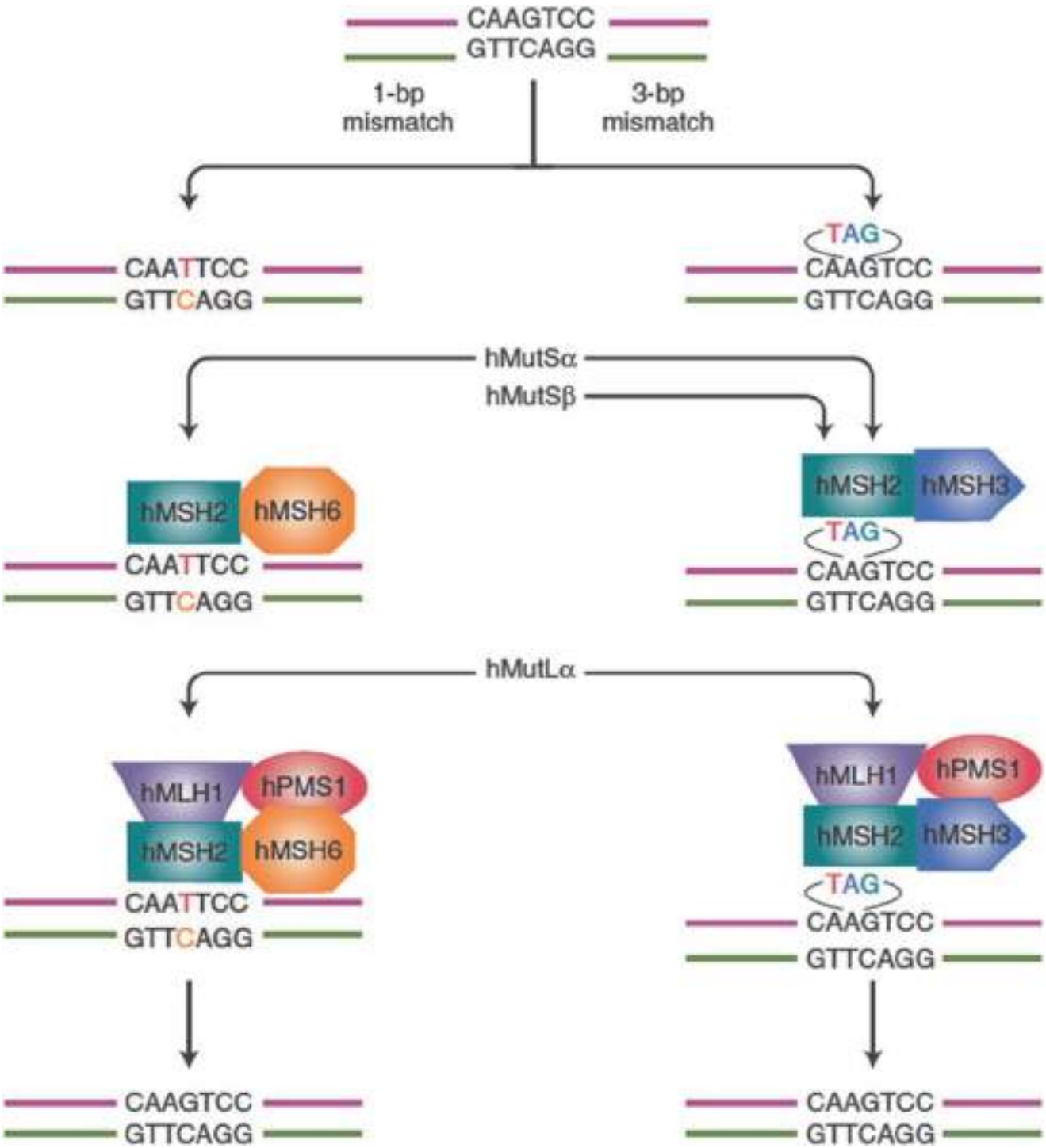

FIGURE 23-7. The DNA mismatch repair system functions to repair single base-pair mismatches or larger loops of inappropriately matched DNA. MSH2 forms a dimer complex with MSH6 which together recognizes the area of DNA mismatch. The second dimer complex of MLH1 and PMS2 is then recruited to excise and correct the mismatch area.

LS-related malignancies vary by gender and the mutated gene (Table 23-5). For example, *MSH2* mutations appear to be associated with later age of onset of malignancies and higher incidences of rectal and extracolonic cancers, when compared to *MLH1* mutations. On the other hand, the risk for endometrial cancer is highest among *MSH6* mutation carriers [161, 162]. The presence of risk-modifying genes that may modulate cancer risks conferred by the MMR genes has also been recognized. For example, two variants (rs16892766 and rs3802842) on chromosomes 8 and 11, previously shown to be associated with sporadic CRC, have been shown to elevate the risk of CRC among LS patients [163, 164]. The potential impact of risk modifiers on clinical practice needs to be further elucidated.

Table 23-5. Summary of reported cumulative risks of colorectal and extra-colorectal cancers by age 70 in patients with Lynch syndrome

Cancer	Mutated gene	Cumulative risk, %		Mean age at diagnosis (years)
Colorectal	*MLH1/MSH2*	Male: Female:	27–74 22–53	27–46
	MSH6	Male: Female:	18–22 10–18	54–63
	PMS2	Male: Female:	20 15	47–66
Endometrial	*MLH1/MSH2*		14–54	48–62
	MSH6		17–71	54–57
	PMS2		15	49
Ovary			4–20	43–45
Stomach			0.2–13	49–55
Genitourinary			0.2–25	52–60
Hepatobiliary			0.02–4	54–57
Small bowel			0.4–12	46–49
Brain/central nervous system			1–4	50
Sebaceous skin neoplasms			1–9	Unknown

These reported risks and mean ages of diagnosis should not be used to exclude the possibility of Lynch syndrome in a patient who have suggestive clinical features

Modified from Giardiello FM, Allen JI, Axilbund JE, Boland CR, Burke CA, Burt RW, et al. Guidelines on genetic evaluation and management of Lynch syndrome: a consensus statement by the US Multi-society Task Force on colorectal cancer. The American Journal of Gastroenterology. 2014;109(8):1159–79. [11]

Muir-Torre Syndrome (MTS)

Muir-Torre syndrome (MTS) is a clinical variant of LS, where patients are affected by skin sebaceous gland neoplasms (sebaceous adenomas and carcinomas) and/or hair follicle neoplasms (keratoacanthomas). MTS can be associated with mutations in any of the MMR genes, but *MSH2* mutation appears most common [165]. Sebaceous adenoma, especially when multiple or when arising from the trunk or extremities, is characteristic for MTS [166, 167]. Sebaceous tumors can occur before, with, or after the development of other cancers, and CRC and genitourinary tumors are the most common visceral malignancies associated with MTS. Referral for genetic counseling and for colonoscopic screening should be considered in patients with sebaceous neoplasm, especially when there is suggestive personal or family history. However, there is currently no uniform recommendation for systemic screening of sebaceous neoplasms for dMMR [166, 168].

Turcot Syndrome

Turcot syndrome describes patients with CRC and brain tumors. Turcot syndrome is not considered an independent entity, and it can be associated with two main types of germline genetic defects: mutation of the *APC* gene in association with anaplastic astrocytoma, ependymoma, or medulloblastoma or mutation of an MMR gene that is usually associated with glioblastoma [28]. Although excellent survival of more than 3 years has been reported in patients with Turcot syndrome, whether LS patients with these tumors have more favorable prognosis remains unestablished [169].

Colorectal Cancer Risk

The lifetime risk for CRC ranges from 30 to 74 % among *MLH1* and *MSH2* mutation carriers but only 15–20 % among *PMS2* carriers and 10–22 % among *MSH6* carriers [74, 161, 170]. The mean age of diagnosis for LS-related CRC is 44–61 years, significantly younger than the average age of CRC onset in the United States which is 72 years. The LS-associated CRCs show a predilection for the right colon when compared to sporadic CRC, but left-sided colon cancers, rectal cancers, and synchronous lesions at different sites of the colon and rectum are also common presentations. Among LS patients who have had an initial CRC treated by less than a total colectomy, the risk for metachronous CRC is 16% at 10 years, 41 % at 20 years, and 62 % at 30 years [171]. Furthermore, the adenoma-to-carcinoma sequence progresses more rapidly in LS patients secondary to more rapid accumulation of errors due to the deficiency in MMR genes. Adenoma may progress to carcinoma within 2–3 years, compared with from 4 to 10 years in the general population [161, 172]. Up to 70 % of the mutation carriers develop at least one adenoma by age 60 [173]. The adenomas tend to be larger and flat and are more likely to show high-grade dysplasia at the time of diagnosis. It has been estimated that endoscopic polypectomy can prevent one CRC for every 2.8 adenoma removed in an LS patient, compared to one CRC for every 41–119 adenomas in the general population [174]. Finally, unique histologic features have been described for MSI-H CRCs, including greater proportion of tumors showing poor differentiation, mucinous or signet-ring cell histology, tumor-infiltrating lymphocytes, and lymphoid (Crohn's-like pattern and/or peritumoral lymphocytes) host response [138]. In summary, common, but not exclusive, features of LS-associated CRC include early age of onset, right-side predominance, high rates of synchronous and metachronous lesions, rapid adenoma-to-carcinoma sequencing, and unique histologic features.

Endometrial and Ovarian Cancer Risk

Endometrial cancer is the most common extracolonic malignancy in patients with LS. It poses the highest risk in women with *MSH6* and *MSH2* mutations, in whom the lifetime risk can be up to 44 % (Table 23-5). The lowest risk (15 %) is

observed among *PMS2* mutation carriers [175, 176]. The mean age at diagnosis ranges between 48 and 62 years. LS-associated endometrial cancers are more commonly of endometrioid histology and arise from the lower uterine segment [177, 178]. Synchronous endometrial and ovarian cancers have been reported in 7–21 % of the women with LS [179].

Other LS-Associated Cancer Risks

The spectrum of other extracolonic cancers associated with LS is wide and continues to evolve. Classically, LS is associated with increased lifetime risk of genitourinary tumors including transitional cell carcinoma of the ureter, renal pelvis, and bladder, as well as cancers of the stomach, hepatobiliary tract, and small bowel, brain cancer (glioblastoma), and sebaceous skin neoplasms (Table 23-5) [180]. More recently, studies have demonstrated that compared to the general population, patients with LS may face two- to 2.5-fold higher risk for prostate cancer [181], 8.6-fold increased risk for pancreas cancer [182], and possibly also elevated risks for breast cancer [180, 183]. The true risk of breast and prostate cancer remains an area of research and debate.

Diagnosis

LS is diagnosed by the identification of a germline mutation in one of the MMR genes as described above. Current commercial germline testing detects both sequence changes and large rearrangements in these genes. It is most commonly performed on DNA isolated from peripheral blood or buccal mucosa samples. Independent of tumor tissue, germline testing can be performed in patients who are affected or unaffected by malignancy.

Genetic testing should be preceded by genetic counseling to ensure that the patients are fully informed of the significance, advantages, and disadvantages of genetic testing. Key components of genetic counseling include: (1) assessment of genetic risk based on personal history and family pedigree; (2) education about genetic syndrome and genetic testing; (3) promoting informed choices regarding testing, including information about insurance coverage and genetic discrimination; (4) disclosing test results and recommending surveillance plans; and (5) counseling for psychosocial and emotional concerns [162]. In 2008, the Genetic Information Nondiscrimination Act (GINA) removed the finding of a pathogenic germline mutation as a preexisting condition for health insurance or employment purposes [184].

Screening and Diagnostic Strategies

Appropriately determining which patients should undergo genetic counseling and testing remains a challenge. Both clinical and cost-based strategies have been proposed ranging from screening all CRCs for MSI to only screening patients who meet strict criteria. The diagnostic approach somewhat depends on the clinical situation as discussed below.

CRC in a Patient Without Known LS

This is the most frequently encountered indication for testing in clinical practice. Over the past several decades, the approach to diagnostic testing has moved from a selective approach, where patients deemed to be at elevated risk of harboring MMR mutations by clinicopathologic criteria undergo testing, to a universal approach, where CRCs are screened using MSI or immunohistochemistry.

The selective approaches utilize clinicopathologic criteria and prediction models to select patients to undergo germline mutation testing. Amsterdam I and II criteria (Table 23-4) require knowledge about CRC age of onset and other LS-associated cancers in both the proband and first- and second-degree relatives. The reported sensitivity for diagnosing LS using these criteria is only 22 % [133, 185]. Revised Bethesda criteria (Table 23-4) consider the above information but also tumor characteristics. These criteria were intended as triggers for testing CRC for MMR deficiency by IHC or MSI. Patients with deficient MMR CRC are then referred for genetic counseling and confirmatory germline testing. When patients who meet at least one of the five revised Bethesda criteria are tested, the reported sensitivity for diagnosing LS may be as high as 82 % [186, 187]. In addition, several prediction models have recently been introduced to calculate the probability of an affected individual harboring a pathogenic MMR gene mutation. The MMRPro (http://www4.utsouthwestern.edu/breasthealth/cagene/) [188] and PREMM1,2,6 (http://premm.dfci.harvard.edu/) [189] models are most commonly used in the United States. The specific inputs of the various models differ, but personal and family history of colorectal and endometrial cancers, ages of onset of cancers, CRC tumor histology, location, and synchronous/metachronous presentation, as well as tumor IHC test result if available, are collected. Each model outputs a probability of an identifiable germline mutation in *MLH1*, *MSH2*, and *MSH6* genes. It has been shown that when a probability cutoff of 5 % was used as a criterion for undergoing germline genetic testing, the sensitivity of the models can approach 90 % [162, 185, 187, 190]. Collectively, although these selective approaches do not depend on the availability of tumor tissue and of tumor molecular tests (i.e., IHC, MSI), they are subject to the accuracy, the availability, and the recall bias of the personal and family histories obtained.

As tumor molecular testing has become increasingly available, a universal screening approach for all CRCs for MMR deficiency has been advocated as the most sensitive strategy to identify patients at risk for LS. This two-step approach involves a screening step where all CRCs are tested for evidence of MMR deficiency independent of somatic mechanisms, followed by a confirmatory step where patients

undergo germline MMR mutation testing. Tumors may be testing for MSI and/or MMR protein expression. If the tumor is MSI-H and/or if one of the MMR proteins is not expressed, further exploration is warranted. Since the majority of CRC MSI is not caused by MLH1 loss secondary to hypermethylation of the *MLH1* promoter region, strategies to evaluate MSI with MLH1 IHC loss have been used before proceeding with genetic testing. CRC lacking expression of MLH1 may be further evaluated for DNA hypermethylation of the *MLH1* promoter or for *BRAF* mutations which are highly associated with sporadic MSI-H tumors. If the tumor is methylated and/or has a BRAF mutation, the likelihood of LS is less and testing does not need to be pursued unless there is a strong suspicion based on clinical or family history. If MSH2, MSH26, or PMS2 is lost, then it is highly likely to be caused by a germline mutation, and directed testing for that particular gene proceeds along those lines [191]. One algorithmic approach to screening for LS in CRC is demonstrated in Figure 23-8 [133, 150, 187, 192].

The success and effectiveness of a universal screening strategy depends on availability of tumor tissue, accuracy of tumor molecular testing, and on a significant infrastructure for navigating the patients between tumor-based and germline testing along with genetic counseling [151]. Indeed, a key determinant of the cost-effectiveness of universal testing is the participation rate of at-risk blood relatives who undergo subsequent testing for LS [193]. In other words, if more at-risk relatives are screened and diagnosed before cancers develop, more people will be effectively enrolled in appropriate preventative surveillance programs. The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) [194], the National Comprehensive Cancer Network (NCCN) [191], and the US Multi-Society Task Force on Colorectal Cancer [162] recommend universal screening of CRC. A cost-effective analysis identified that the cost per incremental life year gained was half if universal testing for CRC patients aged 70 and younger is compared to those without an age cutoff [193].

Whichever strategy is used, one must be able to interpret and take action on germline testing results. In general, germline testing yields one of three possible results: (1) a deleterious (pathogenic) mutation, (2) a variant of unknown significance, or (3) uninformative negative or no mutation found. Finding of a pathogenic mutation confirms the diagnosis of LS in the patient. The latter two findings should be considered inconclusive, in the setting of a dMMR tumor without evidence of *MLH1* promoter methylation and/or BRAF mutation. Patients with an MSI-H tumor and loss of MMR protein expression but without a confirmatory germline mutation are considered to have "Lynch-like syndrome" [146]. About 50 % of these patients can be explained by biallelic somatic alterations and do not have LS [195], although routine commercial tumor testing for biallelic somatic testing is not routinely available at this time. In the absence of

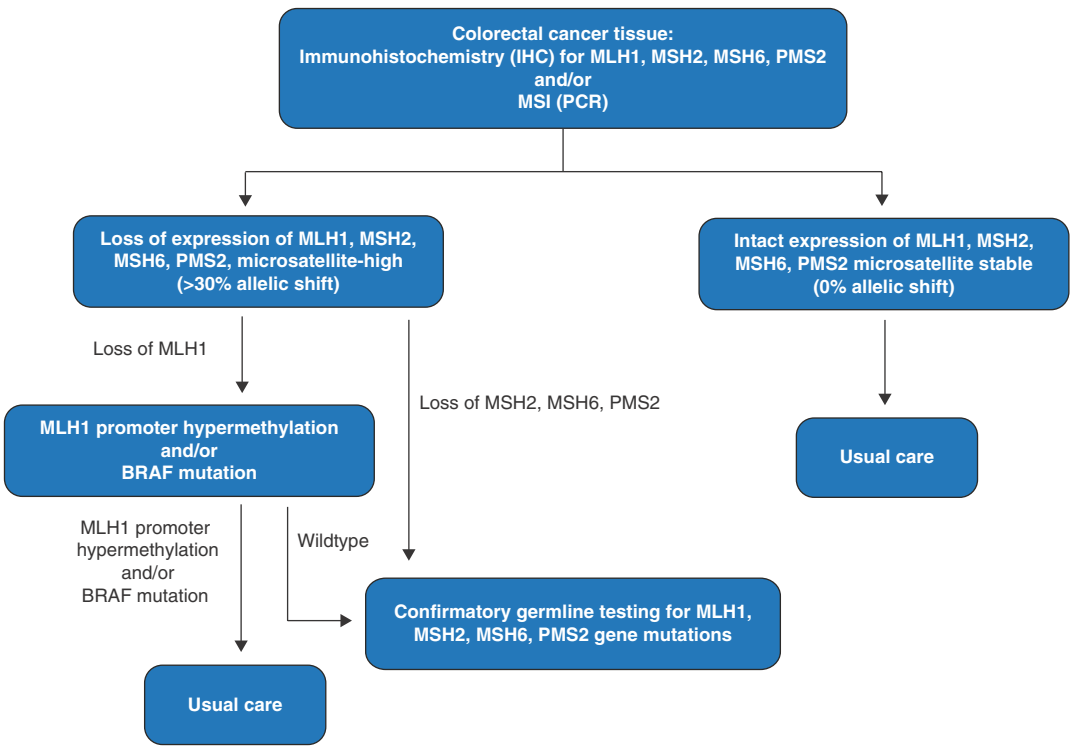

Fig. 23.8. One algorithm for testing of colorectal tumors for MMR deficiency as a first step to screen for patients with Lynch syndrome.

clearly defined cancer risks for patients with Lynch-like syndrome, it remains the most prudent today to clinically manage these patient and families in the same way as LS patients [145, 172]. One caveat is that strategies that involve only germline testing (i.e., based on Amsterdam criteria or predictive models) without accompanying tumor MMR status testing are thus at risk for missing patients who might have "Lynch-like syndrome."

The proportions of patients with pathogenic mutations vs. inconclusive results vary inversely with the sensitivity of the selective approach to testing [147]. A variant of unknown significance is a variation in genetic sequence whose clinical consequence and associated disease risk are unknown. Variant reclassification is an extensive process that involves accumulation of clinical and pedigree data, functional studies, and in silico predictions [147]. Therefore, patients who have an inconclusive result on initial germline testing should be encouraged to undergo periodic repeat assessments as new genetic data emerge. Patients with a VUS should be managed based on family history and clinical suspicion for LS.

Individual with a Family Diagnosis of LS

Once a pathogenic mutation is identified in a proband, all at-risk blood relatives should undergo site-specific germline testing for the known family mutation. In these cases of site-specific testing (for affected relatives) or predictive testing (for unaffected relatives), there are two possible results: (1) true positive, when the specific mutation is identified and the individual is confirmed to have LS, and (2) true negative, when it is a conclusive negative result and effectively rules out LS in the individual, who carries only general population risks for malignancies [151, 162].

Individual Whose Family Meets Amsterdam Criteria But Does Not Have Any Clinical Phenotype

It is not uncommon for a healthy individual from an Amsterdam criteria family to seek consult regarding his/her own screening recommendations. The initial evaluation should begin with a detailed personal and family cancer history. The most informative individual to evaluate would be a relative with an LS-associated cancer, particularly at a young age. If tumor is available, screening may be conducted as discussed above. If a pathogenic mutation is found, then directed germline testing can be performed for at-risk relatives. If tumor screening is not feasible, germline testing of an affected individual within the context of appropriate genetic counseling is an option. We do not recommend broad germline genetic testing for an unaffected individual as the yield is low and inconclusive results such as variant of unknown significance or uninformative negative would be clinically difficult to interpret in an unaffected individual [162]. More recently, panels that include multiple genes that confer a range of CRC risks have emerged and may be most efficient in differentiating patients with pedigrees that could be consistent with LS, attenuated polyposis syndromes, or other syndromes [196]. Involvement of a certified genetic counselor is recommended in these cases.

Clinical Management

Screening

For patients with LS, key elements of their lifelong care include screening for cancers in unaffected individuals and surveillance for recurrent, metachronous, or other syndromic cancers in affected individuals (Table 23-6). For CRC, young age of disease onset, accelerated progression from adenoma to carcinoma, and right-sided dominance have led to the recommendation that patients with LS undergo colonoscopy every 1–2 years starting at age 20–25 years [161, 162, 191]. Surveillance colonoscopy has been shown to reduce CRC incidence (62 % reduction), disease stage at diagnosis, and CRC-related mortality (72 % reduction) in LS patients who undergo colonoscopy compared to those who do not [197]. Recent guidelines have suggested varying the age to initiate colonoscopy depending on family history (at least 2–5 years younger than the earliest affected age in the family).

LS patients are also at increased risk for developing extracolonic malignancies that can potentially benefit from screening of asymptomatic individuals. A definitive survival benefit has not been proven by prospective studies, and management is based on expert opinion and published

Table 23-6. Summary of possible surveillance regimen for Lynch syndrome patients

Cancer	Test	Frequency (years)	Age to commence (years)
Colorectal	Colonoscopy	1–2	20–25 or 2–5 years prior to earliest colon cancer before age 25
Endometrial and ovarian	Transvaginal ultrasound with endometrial sampling; consideration for serum CA-125	1–2 years	30–35
Gastric/small bowel	Consideration for extended esophagogastroduodenoscopy	3–5	30–35
Urinary tract	Consideration for urinalysis	1	25–30
Sebaceous neoplasms	Physical examination	1	25–30
Brain/central nervous system	Physical/neurologic examination	1	25–30

Modified from the National Comprehensive Cancer Network Guideline on Genetic/Familial High-risk Assessment: Colorectal. Version 1.2015. www.ncc.org

guidelines. Women with LS should be educated regarding symptoms of endometrial cancer, including abnormal uterine bleeding and pain. There is no established evidence for annual screening, but pelvic examination, CA-125, transvaginal ultrasound, and endometrial biopsy (performed under sedation in coordination with colonoscopy) have been commonly performed [191]. Upper endoscopy and small bowel X-ray and/or upper endoscopy can be utilized to screen for gastric and small bowel cancers, while urinalysis and cytology have been considered for urothelial cancers [198]. Finally, annual or biannual dermatologic patients with LS can be considered too for the detection of sebaceous skin neoplasms [161, 162]. An example of screening strategies is listed in Table 23-6.

Modifiers of Risk for Colorectal and Other Cancers

Lifestyle and environmental factors may influence the risk for adenoma and CRC in patients with LS. The GeoLynch study prospectively analyzed 486 subjects with LS for their modifiable lifestyle factors. Dietary patterns particularly those with high meat and high snack contents are associated 1.7 and 2.2 times risks for developing colorectal adenomas [199]. Active smoking [200] and obesity (with body mass index $\geq$25 kg/m^2) [201] also increase the risk of developing colorectal neoplasia when compared to nonsmokers or normal weight men, respectively.

Resistant starch and aspirin are two chemoprevention agents studied in patients with LS. The Colorectal Adenoma/Carcinoma Prevention Programme 2 (CAPP2) randomized 727 participants to resistant starch (30 g per day) or placebo and 693 participants to aspirin (600 mg per day) and placebo in a 2×2 design. After a median follow-up of 52.7 months, resistant starch did not impact on CRC development [202]. However, after a mean follow-up of 55.7 months, 18 vs. 30 participants developed CRC (63 % fewer CRCs) after 4 years of aspirin use [203]. An intention-to-treat analysis of all LS cancers (i.e., colorectal, endometrial, ovarian, pancreatic, small bowel, gallbladder, ureter, stomach, kidney, and brain) also showed a benefit of aspirin vs. placebo (hazard ratio 0.65; $p=0.005$). Although the incidence of adverse events did not differ between the aspirin and placebo groups during treatment, whether the high dose is necessary for benefit remains to be elucidated in the proposed CAPP 3 study [204]. Currently the evidence is not sufficiently mature to recommend routine use of high-dose aspirin in LS patients [161, 162, 191].

Surgery for Colorectal Cancer

Surgical treatment of LS-associated colon cancer starts with the same oncologic principles as those for sporadic colon cancer. Colectomy should be performed with adequate proximal, distal, and radial resection margin, regional lymphadenectomy, and R0 and en bloc resection of all malignant tissue [205]. The extent of resection (segmental colectomy or total abdominal colectomy with ileorectal anastomosis) depends on balancing surgical morbidity, patient comorbidities and wishes, and risk of future malignancy in the remaining colorectum. Factors to consider include the presence of synchronous pathology, age of the patient, disease prognosis and life expectancy, risk of metachronous CRC, expected compliance with surveillance, morbidity of reoperation, bowel function, and patient preferences. The American Society of Colon and Rectal Surgeons recommends extended colectomy for patients with colon cancer and LS, based mainly on metachronous cancer risk. Multiple retrospective studies have demonstrated a higher rate of metachronous colorectal cancer following segmental colectomy compared to extended colectomy [195, 206–209]. In a large international study from the Colon Cancer Family Registry, 332 LS patients with colon cancer treated with segmental colectomy were compared to 50 LS patients treated with extended colectomy. The cumulative risk of metachronous CRC after segmental colectomy was 16, 41, and 62 % at 10, 20, and 30 years, respectively [171]. These risks may vary further depending on the compliance with endoscopic surveillance and feasibility of endoscopic removal of premalignant polyps. There have not been prospective studies to prove that extended colectomy improves survival in LS patients. In a Markov model, the calculated gain in life expectancy from extended compared to segmental colectomy was 2.3 years if surgery were performed at age 27 years, 1 year at age 47 years, and 0.3 years at age 67 years, and these numbers became 3.4 years at age 27 years, 1.5 years at age 47 years, and 0.4 year at age 67 years if the colon cancer were stage I [210]. Therefore, extended colectomy may have the most benefit in young patients with early-stage disease only. Advanced CRC stage, significant medical comorbidities, and other LS-associated malignancies that pose competing risks to the patient's life expectancy should also be considered.

Functional expectations of each operation should be discussed with patients. In a retrospective review of bowel function for 201 patients undergoing total colectomy and ileorectal anastomosis, 56 % reported dietary restrictions and 20 % used daily medications, and compared to preoperative levels, patients reported restricted social activity (32 %), housework (20 %), recreation (32 %), and travel (43 %) [211]. Another study of 52 LS patients treated with extended colectomy reported increased stool frequency, decreased social life, and more defecation difficulties compared to 51 patients who had segmental colectomy [212]. Despite the bowel function reports, no measurable differences in quality of life have been reported after either procedure, suggesting that most patients adapt to their choice of the operation over time. Current guidelines suggest that extended colectomy is

preferred treatment for LS-associated colon cancer, but segmental colectomy might be an option in older patients [161, 162, 191].

Management of rectal cancer in LS involves complex decision-making. The cancer should be managed like any other rectal cancer in terms of indications for multimodality therapy and oncologic principles. However, just as in colon cancer in LS, the extent of the resection is determined by many factors. The surgeon and patient must decide between a proctectomy and total proctocolectomy (TPC) with or without sphincter preservation as determined by the tumor location. Compared to TPC with an ileal pouch reconstruction, proctectomy alone results in less frequent bowel movements and less incontinence [213]. However, proctectomy without colectomy leaves the entire colon in situ and at risk for subsequent cancer. There are a few retrospective studies that have reported the risk of colon cancer after proctectomy in LS to be between 15 and 54 %, although the inclusion criteria of the study cohorts were heterogeneous [37, 214–217].

Data from the Colon Cancer Family Registry reported the cumulative risk of metachronous colon cancer after proctectomy in 79 LS patients to be 19 % at 10 years, 47 % at 20 years, and 69 % at 30 years [214].

The need for pelvic radiation should be considered when an ileal pouch is to be done. A recent analysis of 157 IPAA patients who received preoperative pelvic radiation showed no significant elevation of 30-day morbidity rate compared to patients who did not receive pelvic radiation [218]. However, little data exists regarding the long-term functional outcome of an IPAA performed after pelvic radiation, but there is general reluctance to perform this based on perceived risks for radiation enteritis, pelvic fibrosis, and pouch dysfunction.

Given the high risk of metachronous neoplasia after a segmental proctectomy, the risks and benefits of TPC with IPAA should be discussed with all Lynch syndrome patients presenting with non-stage IV rectal cancer. Total proctocolectomy for rectal cancer in LS remains debated, and several factors including the patient's age, medical comorbidities, rectal cancer stage, the need for pelvic radiation, sphincter function, and compliance with surveillance regimens should be evaluated with the patient in the larger clinical picture.

Prophylactic Surgery for Endometrial and Ovarian Cancer

In women undergoing surgical treatment of CRC, concomitant prophylactic gynecologic surgery may be considered and discussed with the patient. In a case-matched study of LS women who underwent prophylactic total abdominal hysterectomy and salpingo-oophorectomy, the procedure successfully eliminated the risks of endometrial and ovary cancers [219]. When several risk-reducing strategies were compared in a cost-effectiveness model, annual gynecologic screening (with CA-125, transvaginal ultrasound, and endometrial biopsy) and prophylactic surgery at 40 years were the most cost-effective strategies, with the former being favored where the cost of screening is low [220]. Thus, the age of the patient and the availability and expected compliance with screening are key factors to consider in decision-making regarding prophylactic gynecologic surgery for LS.

Evaluation of At-Risk Relatives

When an LS or an MMR pathogenic mutation has been identified in an individual, genetic counseling and site-specific testing for the pathogenic mutation should be offered to all first-degree relatives (parents, siblings, and children). Due to the considerable psychosocial issues associated with germline testing, it is usually not recommended for at-risk individuals younger than age 18 years. Surveillance of asymptomatic at-risk relatives for premalignant lesions or early manifestations of cancer is appropriate and has been recommended to commence 5–10 years younger than the youngest age of onset of cancer in the family or between age 20 and 25 [161, 191]. A major reason to identify individuals with LS is to optimize the care of their at-risk relatives, with the goal of ultimately minimizing the morbidity and mortality of LS.

Probands and their at-risk relatives with LS greatly benefit from enrollment in a hereditary CRC registry. Such a registry is typically associated with an established institutional infrastructure and with access to expert clinical care, innovative research, patient education, and support networks. Multidisciplinary care teams including gastroenterologists, surgeons, medical oncologists, and genetic counselors are coordinated to provide lifelong and multi-organ cancer screening or surveillance. Families often gain access to research protocols investigating novel diagnostic, screening, treatment, or chemoprevention strategies. Finally, registry provides a support network for families and a basis for knowledge and experience exchange [221]. Registration and screening reduce CRC incidence and mortality in LS patients [222]. Surgeons play an integral role in the care of the patients with LS, from clinical recognition and genetic diagnosis to cancer treatment and guidance of family and long-term care.

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24
Colorectal Neoplasms: Screening and Surveillance After Polypectomy

Evie H. Carchman and Charles P. Heise

Key Concepts

- Screening can reduce colorectal mortality.
- Screening recommendations are based upon risk for polyp/cancer development (family history of cancer or polyps, personal history cancer/polyps, genetic syndromes (FAP, MYH, and HNPCC), and inflammatory bowel disease).
- Surveillance after polypectomy depends on the histology of polyp and the completeness of its resection.
- The decision to perform colectomy for a polyp that contains cancer depends on the extent of invasion (Haggitt staging for pedunculated polyp and Kikuchi classification for sessile polyp).

Introduction

Colorectal cancer is the second leading cause of cancer-related deaths in the United States in men and women combined [1]. In 2014, the National Cancer Institute (NCI) estimated 96,000 new colon cancer and 40,000 new rectal cancer cases, and the estimated number of deaths for both colon and rectal cancer combined was 50,310. The fortunate news is that the death rate from colorectal cancer has been decreasing over the last 20 years. This reduction in the number of new cancer cases and cancer-related deaths is a consequence of current screening programs [2, 3]. The rationale for the above is that adenomatous polyps are considered precursors to cancer, and through their early endoscopic removal, carcinoma can be prevented. In addition to the therapeutic roles of colonoscopy, it also allows for the identification of individuals at higher risk for accelerated carcinogenesis (e.g., multiple polyps, unfavorable histology, dysplasia, and large polyps (≥1.0 cm)), who may benefit from more frequent screening.

Of further interest and consideration is that upon following current routine screening recommendations, the potential to identify large groups of patients with adenomatous polyps also exists. This creates a huge burden on the healthcare system (costs, risks, and resources) in terms of surveillance of these patients.

Recommended Screening Guidelines

Guidelines from the American Cancer Society (ACS), the American Society of Colon and Rectal Surgeons (ASCRS), and the American Gastroenterological Association (AGA) all recommend that colorectal cancer screening begin at the age of 50 for both men and women with average risk (i.e., no family history of colorectal cancer, no personal history of inflammatory bowel disease, and asymptomatic) [4–6]. These accepted guidelines are based on joint efforts set forth in 2008 by the ACS, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology (ACR) [7]. Screening regimens can be divided into two categories: fecal testing and structural examinations. While structural examinations are designed to detect both polyps and cancer, fecal testing primarily detects already established cancers or possibly advanced adenomas. It is the opinion of the above organizations that the goal of colorectal cancer screening should be that of prevention. There are various screening options for asymptomatic individuals. The recommended time intervals are listed below and will be further evaluated in this section [7].

Screening Options and Timing for Average-Risk Individuals

- Colonoscopy every 10 years
- CT colonography (virtual colonoscopy) every 5 years
- Flexible sigmoidoscopy every 5 years
- Double-contrast barium enema every 5 years
- Guaiac-based fecal occult blood test (gFOBT) every year
- Fecal immunochemical test (FIT) every year
- Stool DNA (sDNA) test every 3 years

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It is important to note that in order for the above to be effective, each of these screening regimens should be performed at regular intervals. In addition, if any of the non-colonoscopy screening tests listed are abnormal, a full colonoscopy is warranted, and the patient should be made aware of this possibility prior to initiation of screening.

Screening Guidelines for Individuals at an Increased Risk Based on Family History

1. If there is a history of colorectal cancer or adenomatous polyps in a first-degree relative before age 60, or in two or more first-degree relatives at any age (non-hereditary syndrome), then screening should begin at age 40 or 10 years prior to the youngest case, whichever is earlier. A colonoscopy is the recommended test in this instance, with screening every 5 years.
2. If there is a history of colorectal cancer or adenomatous polyps in a first-degree relative aged 60 or older, or in at least two or more second-degree relatives at any age, then screening should begin at age 40. Any of the screening options for average-risk individuals may be recommended along with the same screening intervals [8].

Screening Guidelines for Individuals Considered at High Risk Based on Genetics

1. If there is positive genetic testing for familial adenomatous polyposis (FAP) or suspected FAP without testing, then screening should begin at age 10–12 years. Screening should include yearly flexible sigmoidoscopy and consideration for genetic testing if not yet performed. Consideration for colectomy is recommended when testing is positive.
2. If there is a genetic or clinical diagnosis of Lynch syndrome or an individual at increased risk for Lynch, screening should begin at age 20–25 years or 10 years prior to the youngest case. This should include colonoscopy every 1–2 years and genetic testing if not yet performed. In addition, genetic testing should be offered to all first-degree relatives if a Lynch mutation is identified.
3. Individuals with inflammatory bowel disease (chronic ulcerative colitis or Crohn's disease) should begin screening 8 years after the onset of pan colitis or 12–15 years after the onset of left-sided colitis. Screening should be performed by colonoscopy every 1–2 years with biopsies assessing for dysplasia [8].

Screening Cessation

The US Preventive Services Task Force recommends screening up to the age of 75. Screening should be discontinued in individuals aged 76–85 years, if they have had routine screening. However, screening may be considered in this age group if never screened previously and according to each individual's health status and risk. Screening should not be performed in individuals after the age of 85 years [9].

Methods of Screening

Colonoscopy

The use of colonoscopy as a screening and therapeutic modality has become widespread since its initial undertaking by Wolf and Shinya in 1969 [10]. In 2009, there were 11.5 million colonoscopies performed in the United States [11]. In fact, colonoscopy has become one of the most commonly performed medical procedures performed today. The major advantages for colonoscopy as a screening regimen are that it allows visualization of the entire colon, along with the identification, biopsy, or removal of encountered polyps or cancer. Although colonoscopy is widely utilized in the United States for colorectal cancer screening, there are no prospective, randomized trials demonstrating a reduction in the incidence of, or the mortality from, colorectal cancer as a result of colonoscopy. However, as other screening modalities result in subsequent therapeutic colonoscopy after polyp detection, there is indirect evidence suggesting that colonoscopy is beneficial in reducing cancer incidence. This is evident from the Minnesota Colon Cancer Control Study, a randomized, controlled trial which demonstrated a 20 % reduction in colon cancer incidence after subsequent colonoscopy and follow-up based on FOBT screening [12]. Furthermore, studies evaluating cancer incidence after initial complete colonoscopy with polypectomy also demonstrate significant reductions in the incidence of colorectal cancer, ranging from 76 to 90 % depending on the reference population [2, 13]. More recently, subsequent follow-up of the National Polyp Study with a median surveillance period of 15.8 years after colonoscopic polypectomy also demonstrated a 53 % reduction in colorectal cancer-related mortality [14]. It is therefore evident that colonoscopy has the ability to effectively screen and remove adenomatous polyps, thereby reducing the risk of colorectal cancer development and mortality.

Although the use of colonoscopy as a screening modality has major benefits in risk reduction, there are also associated drawbacks with this procedure. Colonoscopy is usually done with sedation and thus requires a chaperone to accompany the patient for transportation. In addition, a complete bowel preparation is required and is often the most difficult part of the process for the patient. However, it is also one of the most important components to completing the procedure successfully and is critical in terms of quality. Rex et al. published an update of several quality indicators set forth by the American Society for Gastrointestinal Endoscopy (ASGE) and American College of Gastroenterology (ACG) Task Force on Quality in Endoscopy [15]. In this update, proposed quality indicators and performance targets are summarized for colonoscopy examinations in the pre-procedure, intra-procedure, and post-procedure periods (Table 24-1). It is imperative that each individual endoscopist be familiar with these targets and utilize them for guidance when screening.

Table 24-1. Proposed quality indicators in colonoscopy

Quality indicator	Grade of recommendation	Measure type	Performance target (%)
Pre-procedure			
1. Frequency with colonoscopy is performed for an indication that is included in a published standard list of appropriate indications, and the indication is documented	IC+	Process	>80
2. Frequency with which informed consent is obtained, including specific discussion of risks associated with colonoscopy, and fully documented	IC	Process	>98
3. Frequency with which colonoscopies follow recommended post-polypectomy and post-cancer resection surveillance intervals and 10-year intervals between screening colonoscopies in average-risk patients who have negative examination results and adequate bowel cleansing (priority indicator)	IA	Process	≥90
4. Frequency with which ulcerative colitis and Crohn's colitis surveillance is recommended with proper intervals	2C	Process	≥90
Intraprocedure			
5. Frequency with which the procedure note documents the quality of preparation	3	Process	>98
6. Frequency with which bowel preparation is adequate to allow the use of recommended surveillance or screening intervals	3	Process	≥85 of outpatient exams
7. Frequency with which visualization of the cecum by notation of landmarks and photodocumentation of landmarks is documented in every procedure (priority indicator)	1C	Process	
Cecal intubation rate with photography (all examinations)			≥90
Cecal intubation rate with photography (screening)			≥95
8. Frequency with which adenomas are detected in asymptomatic average-risk individuals (screening) (priority indicator)	1C	Outcome	
Adenoma detection rate for male/female population			≥25
Adenoma detection rate for male patients			≥30
Adenoma detection rate for female patients			≥20
9a. Frequency with which withdrawal time is measured	2C	Process	>98
9b. Average withdrawal time in negative-result screening colonoscopies	2C	Process	≥6 min
10. Frequency with which biopsy specimens are obtained when colonoscopy is performed for indication of chronic diarrhea	2C	Process	>98
11. Frequency of recommended tissue sampling when colonoscopy is performed for surveillance in ulcerative colitis and Crohn's colitis	1C	Process	>98
12. Frequency with which endoscopic removal of pedunculated polyps and sessile polyps <2 cm is attempted before surgical referral	3	Outcome	>98
13. Indication of perforation by procedure type (all indications vs. colorectal cancer screening/polyp surveillance) and post-polypectomy bleeding	1C	Outcome	
Incidence of perforation—all examinations			<1:500
Incidence of perforation—screening			<1:10,000
Incidence of post-polypectomy bleeding			<1 %
14. Frequency with which post-polypectomy bleeding is managed without surgery	1C	Outcome	≥90
15. Frequency with which appropriate recommendation for timing of repeat colonoscopy is documented and provided to the patient after histologic findings are reviewed	1A	Process	≥90

This list of potential quality indicators is meant to be a comprehensive listing of measurable end points. It is not the intention of the task force that all end points be measured in every practice setting. In most cases, validation may be required before a given end point may be adopted universally

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Selected important target areas include: (1) cecal intubation rates for screening with photodocumentation of ≥95 %, (2) an overall adenoma detection rate of ≥25 % (≥30 % for males, ≥20 % for females), (3) average scope withdrawal time of ≥6 min, (4) incidence of perforation during screening of <1:1000, (5) incidence of post-polypectomy bleeding of <1 %, and (6) the frequency with which appropriate recommendations for timing of repeat colonoscopy are documented and provided to the patient of ≥90 %. Furthermore, an adequate bowel preparation is also necessary in this context and is also listed as a pre-procedure quality indicator. The target recommendation for the frequency for which bowel preparation is adequate should be ≥85 %. Sherer et al. reported that in cases where poor bowel preparation was recorded, the detection rate of advanced histology was significantly affected as compared with adequate preparation [16].

Unfortunately, despite best efforts, there are reported miss rates for both polyps and cancers with the use of colonoscopy. A systematic review evaluating miss rates by same-day colonoscopy revealed a miss of 2.1 % for polyps ≥10 mm and 13 % for polyps 5–10 mm in size [17]. Higher miss rates were noted when concomitant CT colonography was utilized

rather than tandem colonoscopy. With this approach, a miss rate of 11.8 % was noted for polyps ≥10 mm in size [18]. Similarly, potential miss rates for cancer are reported to be 3.4 %, especially lesions within the proximal colon (5.9 %), based upon evaluation of patients who have received a screening colonoscopy within 3 years of diagnosis [19]. While there may be several reasons for failure of neoplasia detection, it only further stresses the importance of adequate bowel preparation and adherence to evaluation guidelines in order to minimize miss rates.

It also appears that miss rates may be somewhat dependent on location within the colon in that the proximal colon may not be as reliably or consistently evaluated. Again, Bressler et al. noted that most cancer misses occurred within the right colon compared to the left side (5.9 % vs. 2.3 % in the sigmoid or rectum) [19]. Similarly, Baxter et al. revealed that colonoscopy screening reduced the number of deaths due to left-sided colorectal cancer, but not right-sided, suggesting that screening colonoscopy for right-sided lesions may be less effective [20]. This finding was not evident with the use of CT colonography; however, Pickhardt et al. revealed that misses can occur throughout the colon, usually behind the proximal aspect of a fold and even within 10 cm of the anal verge [18]. In any event, it is apparent that even with our best screening modality, the ability to screen reliably is not without error.

Incomplete Colonoscopy

As noted in Table 24-1, recommended rates of incomplete colonoscopy (without cecal intubation) should be <5 % during screening and <10 % overall. Unfortunately, there are no apparent guidelines or consensus as to the best management strategies in cases of incomplete colonoscopy. Advanced neoplasia is noted in 4 % of these cases within the non-visualized portion of the colon [21]. When colonoscopy is incomplete, options include repeat colonoscopy, use of other endoscopic modalities (i.e., smaller endoscope, double balloon endoscopy), CT colonography, or barium enema. The decision of which modality is best suited is dependent on both the reasons for the incomplete exam and the institution-specific resources available [22].

Adjuncts to Colonoscopy

In an effort to improve colonoscopy screening, more recent technical developments in colonoscopic imaging have targeted advancements in polyp detection. These advances have included (1) techniques applied to current colonoscopy methods, including high-definition monitors, chromoendoscopy, or cap-assisted colonoscopy (CAC), and (2) colonoscope enhancements to current imaging, such as narrow band imaging (NBI), autofluorescence imaging (AFI), and Fujinon intelligent color enhancement (FICE).

The addition of high-definition white light (HDWL) and high-definition monitors to standard colonoscopy may optimize mucosal visualization. A meta-analysis evaluating five studies comparing high-definition to conventional colonoscopy revealed a slight improvement (3.5 %) in adenoma detection rates [23].

Pan-colonic chromoendoscopy (PCC) involves the topical spray application of a dye, usually 0.4 % indigo carmine via the colonoscope. The dye is not absorbed but rather highlights irregular, flat, or small lesions that may be less obvious. Possible advantages to this technology are noted in two prospective, randomized trials comparing chromoendoscopy to either standard or HDWL colonoscopy. While a marginal, though not significant, improvement in overall adenoma detection rate was noted when compared to HDWL, there were improvements in flat adenoma detection [24]. In contrast, compared to standard colonoscopy, Pohl et al. found improvements in both flat and overall adenoma detection rates. However, PCC required more time to complete the procedure as well [25].

CAC attaches a clear cap to the tip of the colonoscope. This allows for deflection of mucosal folds without obscuring visualization, potentially improving detection in these locations. However, the findings of randomized, controlled trials are mixed as to whether CAC offers improvements in adenoma detection rates over conventional colonoscopy [26, 27].

A virtual chromoendoscopy technique, NBI, involves the placement of narrow band filters behind the light source to remove red light and thus increase blue and green wavelengths. This enhances mucosal surface vascularity and therefore polyp visualization. A meta-analysis comparing NBI with standard colonoscopy demonstrated no improvements in adenoma detection with the addition of NBI [28]. Similarly, systematic comparisons between high-definition NBI and HDWL colonoscopy also failed to show improvements in adenoma detection [29]. However, there is a suggestion that high-definition NBI may have an advantage over standard colonoscopy with respect to minimizing polyp and adenoma miss rates [30].

Other virtual techniques include AFI which utilizes a blue filter to create an autofluorescent image from the tissue. Neoplastic tissue will take on a red-green fluorescence in contrast to surrounding normal mucosa [31]. Similarly, FICE utilizes a computed spectral estimation technology that narrows light bandwidth without the use of filters and allows for visualization at various wavelengths. In particular, this allows for enhancement of mucosal vascular and pit patterns [32]. In a randomized study of over 1600 subjects, neither NBI nor FICE increased the adenoma detection rate when compared with standard colonoscopy [33]. A meta-analysis of 42 studies assessed each of the previously discussed colonoscopy enhancement modalities, including each of the virtual capabilities in their ability to improve adenoma detection rates over standard high-definition/white light colonos-

copy. In doing so, only chromoendoscopy with indigo carmine demonstrated potential improvement [34].

Complications

Complications related to colonoscopy have included cardiopulmonary events, bleeding, perforation, diverticulitis, and post-polypectomy syndrome. The risk of unplanned cardiopulmonary events after colonoscopy is 1.1 % and is usually related to the effects of conscious sedation [35]. In a review by Rutter et al., the overall 30-day risk of serious adverse events after colonoscopy was 4.7 per 1000 screening colonoscopies and 6.8 per 1000 follow-up colonoscopies. The risk of perforation was 0.04 % for screening (0.07 % with polypectomy) and 0.12 % after follow-up. Most related bleeding occurs after polypectomy, with a rate of 0.27 % for screening and 0.50 % after polypectomy. Post-polypectomy bleeding can be immediate or delayed. Older age was associated with higher rates of perforation or bleeding [36]. Post-polypectomy syndrome is related to an electrocautery full-thickness burn resulting in localized peritonitis. In a review by Ko et al., the risk of post-polypectomy syndrome ranged from 0.003 to 0.1 %, while the risk of diverticulitis ranged from 0.04 to 0.08 % and the overall risk of death from 0 to 0.09 % [37]. Overall, there is a 1.17 % admission rate after colonoscopy for the above complications.

CT Colonography or Virtual Colonoscopy

CT colonography (CTC) or virtual colonoscopy is a minimally invasive, radiographic option for colorectal cancer screening. It utilizes computed tomography to generate two-dimensional (2D) images that allow for further three-dimensional (3D) reconstruction with the assistance of software technology. Together, evaluation of both 2D and 3D images allows for accurate neoplasia detection. Figure 24-1a–d demonstrates 2D and 3D imaging of a pedunculated sigmoid polyp and subsequent colonoscopic identification.

CTC still requires adequate bowel preparation and must have gaseous distension of the colon to allow for adequate examination. This entails insertion of a rectal catheter to allow for manual or automated inflation with carbon dioxide, infused continuously as images are acquired. Tagging of residual stool contents with an oral delivery of dilute barium (2 %) and residual fluid tagging with water-soluble iodinated contrast (diatrizoate) have further increased sensitivity [38]. As with optical colonoscopy, meeting appropriate quality parameters is also important in CTC. These parameters as recommended by the ACR should include (1) adequate colon cleansing and distension, (2) complete anatomic coverage of the colon and rectum, (3) visualization of each colonic segment in at least one position, (4) appropriate physician training for CTC performance and interpretation, and (5) proper documentation and communication of clinical findings [39].

CTC does not require sedation, and the exam can be performed rather quickly. However, in cases where polyps are detected, subsequent therapeutic colonoscopy is required. Ideally, this should be performed on the same day since bowel preparation is already complete. This requires program coordination between gastroenterology and radiology departments. In cases where polyps are detected, findings of one or more polyps ≥10 mm or three or more polyps ≥6 mm should be referred for subsequent colonoscopy and polypectomy. Though somewhat controversial, isolated polyps in the 6–9 mm range may also be referred for therapeutic intervention [38, 40]. Since very small polyps (≤5 mm) carry low clinical risk, reporting and referral for these isolated lesions are currently not recommended [39, 41]. A further advantage of CTC is that it allows for a limited evaluation for extracolonic findings as well [42]. Of these potential findings, it was noted that 7.4 % were clinically relevant with 2.1 % gaining clinical benefit from detection [43].

Complications related to CTC are very rare. A survey of a virtual colonoscopy working group reported no perforations in more than 11,000 CTC screening examinations, and two perforations in more than 10,000 exams for diagnostic indications (0.02 %), only one of which was symptomatic [44]. Although often discussed, the radiation exposure associated with CTC is also quite low, reportedly around 5 mSv for screening purposes [45]. This is well below the 100 mSv threshold often considered when attempting to address associated health risk [46].

In an early assessment of over 1200 asymptomatic subjects undergoing same-day CTC and optical colonoscopy, a 94 % sensitivity for the detection of adenomas greater than 1 cm was noted and 89 % for adenomas ≥6 mm [47]. More recently, the American College of Radiology Imaging Network (ACRIN) national, multicenter CTC trial assessed over 2500 patients. The per-patient sensitivity for the detection of polyps or cancer ≥10 mm was 90 % and 78 % for polyps ≥6 mm [48]. Furthermore, when considering detection rates for cancer only, meta-analysis conferred a 96 % sensitivity for the detection by CTC with a prevalence of 3.6 % [49]. These findings compare favorably to optical colonoscopy. In a parallel screening program utilizing both colonoscopy and CTC in over 3100 patients, similar detection rates for advanced neoplasia (polyps and cancer) were noted (3.4 % and 3.2 %, respectively). There were many more polypectomies performed in the optical colonoscopy group and also more procedure-related complications [50]. Upon assessing the outcomes in over 1000 cases where screening CTC exams were negative, one interval cancer and 11 large adenomas were noted after a mean follow-up of 4.7 years [51]. Together, these studies suggest that CTC is an

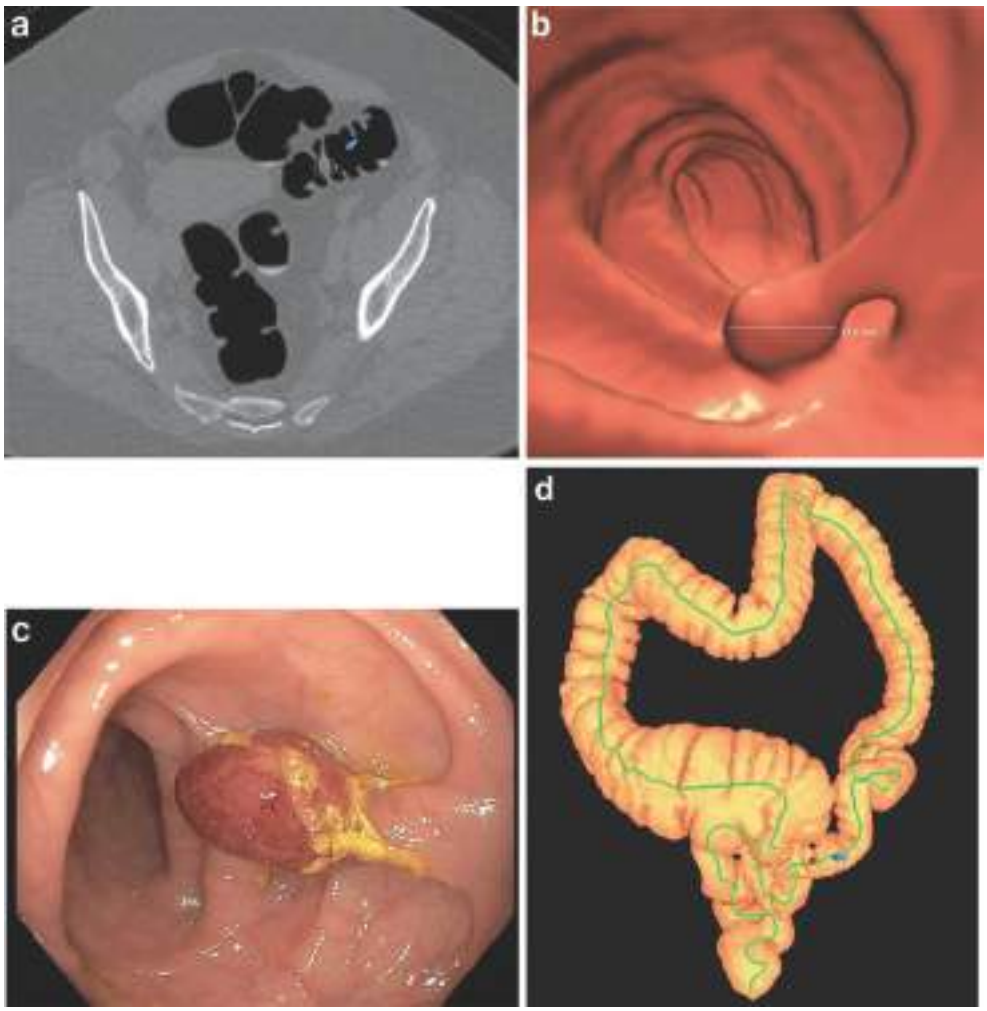

FIGURE 24-1. CT colonography images demonstrate both (**a**) 2D and (**b**) 3D imaging of a pedunculated sigmoid polyp, and subsequent (**c**) colonoscopic identification (**d**) demonstrates the virtual location of the polyp by CT imaging.

acceptable alternative to optical colonoscopy and that current 5-year screening intervals are appropriate.

Flexible Sigmoidoscopy

Flexible sigmoidoscopy may be useful as a component of the screening regimen for colorectal cancer. The standard sigmoidoscope is 60 cm in length. To be effective as a screening modality, the quality of the evaluation must be adequate. Therefore, it has been recommended that the scope be advanced to a minimum of 40 cm in order to minimize the risk of missing a distal colorectal cancer [52]. In addition, if distal pathology is identified, it must be properly biopsied in order to best determine the need for further evaluation. With adenoma detection, the risk of harboring concomitant disease more proximally is at least twofold and thus requires formal colonoscopy [53]. The advantages of flexible sigmoidoscopy lie in the ability to perform the procedure without sedation (although with some potential patient discomfort), by a variety of healthcare professionals and after only minimal bowel preparation.

The major problem with sigmoidoscopy lies in its inability to evaluate the more proximal colon. Despite this, meta-analyses have demonstrated a beneficial reduction in the incidence of colorectal cancer and long-term mortality when compared with no screening [54]. When considering only intention to treat analyses, a reduction in the incidence of distal colorectal cancer and mortality was reported as 31 % and 46 %, respectively [55]. Results of a large randomized, clinical trial demonstrated a 21 % reduction in colorectal cancer incidence and a 26 % reduction in mortality. However, mortality from proximal colorectal cancer was not affected, with a mortality reduction of 50 % when considering only distal colorectal cancer [56]. Finally, a more recently published randomized, controlled trial compared the use of flexible sigmoidoscopy alone or in combination with fecal occult blood testing (FOBT) as a one-time screening regimen in age groups beginning at both 50 and 55 years of age. Patients with positive findings with either test were then offered a colonoscopy. This study revealed a 63 % rate of adherence to screening and a 28 % reduction in the incidence of colorectal cancer and a 12 % reduction in mortality. Interestingly, there

was no difference noted between groups receiving flexible sigmoidoscopy alone or in combination with FOBT [57].

Complications

The risk of GI complications including perforation with flexible sigmoidoscopy is extremely low, reported to be 0.02 % [58]. Gatto et al. reported an incidence of perforation after flexible sigmoidoscopy of 0.88 per 1000 procedures for patients aged 65 or older [59].

Fecal Occult Blood Testing/Fecal Immunochemical Testing

FOBT is aimed at detecting subtle blood loss in the gastrointestinal tract. Based on randomized, controlled trials, annual screening for FOB is recommended for detecting cancer and precancerous polyps in average-risked patients starting at the age of 50. There are two general types of FOBT based on the analyte detected: guaiac versus immunochemical. With positive testing, the patient will then need to undergo appropriate diagnostic testing (colonoscopy or flexible sigmoidoscopy) within a year of the abnormal result. Previous reports demonstrated that only 25–59 % of patients with a positive FOBT receive diagnostic evaluation after a positive test [60].

A stool guaiac test (gFOBT) is done by smearing feces onto an absorbent paper that has been chemically treated. Hydrogen peroxide is then placed onto the paper, and if a trace amount of blood is present, the color will change. The color change is due to the fact that heme has peroxidase-like activities that breakdown hydrogen peroxide. Optimal use depends on following strict dietary adjustments prior to collecting the stool sample. This test requires at least 2 mL of blood loss a day to become positive. There have been several randomized, controlled trials that demonstrate a benefit of FOBT in reducing mortality from CRC (about 15 % reduction) [61, 62].

FIT utilizes specific antibodies to detect globin. FIT has replaced most gFOBT tests in that it is both cheap and quantitative. There is evidence that FIT has higher sensitivity and specificity over gFOBT (13–25 % vs. 81 %). FIT can pick up as little as 0.3 mL of blood in the stool, and patients are not required to follow any dietary restrictions prior to testing. A recent systematic review demonstrated an overall accuracy of 95 % for CRC detection with 79 % sensitivity and 94 % specificity [63]. However, it does have a lower sensitivity in terms of adenoma detection (only 28 %) [64].

Stool DNA Testing

Perhaps the most recent advancement in colorectal cancer screening involves the use of DNA testing of stool samples. Tumor cells and their associated DNA are continuously passed into the stool. Tumor DNA constitutes a very small amount of the fecal content; therefore, a large stool sample is needed for analysis. This assay tests for DNA mutations and methylations of common genes associated with colorectal cancer (i.e., KRAS mutations). These tests also assay for human hemoglobin similar to FIT. This test concomitantly tests for beta-actin to allow for an estimation of the total amount of human DNA present. The results of the assay allow for a composite score that is compared to a standardized value in order to determine a positive or negative test result. There are no dietary restrictions with this test. In a recent study in asymptomatic patients, stool DNA testing detected significantly more cancers than did FIT but also had more false positives [65]. In screening and surveillance, polyps greater than 1 cm can be detected with stool DNA testing, unlike FIT testing [66]. Its sensitivity for polyps greater than 1 cm is 57 %, for greater than 2 cm is 73 %, and for greater than 3 cm is 83 % (the same rate for detecting polyps with high-grade dysplasia) [67].

Double-Contrast Barium Enema

With the more widespread use of the previously described screening entities, the use of contrast enema has diminished as a screening modality. However, it may still be utilized in regions where other screening modalities are not available. Double-contrast barium enema (DCBE) involves coating the colonic mucosal surface with barium followed by distension with air through a rectally placed catheter. Fluoroscopic and standard radiographic imaging is utilized during various positional changes to assess the entire colon. Prior bowel preparation is also required to allow for removal of adherent fecal content.

A small number of studies utilized both colonoscopy and DCBE to assess neoplasia detection. Winawer et al. reported the sensitivity of DCBE to detect polyps ≤5 mm, 6–10 mm, and >10 mm as 32 %, 53 %, and 48 %, respectively [68]. Similarly, Rockey et al. noted sensitivities of 48 % for lesions ≥10 mm and 35 % for lesions 6–9 mm [69]. Furthermore, a meta-analysis comparing DCBE and CTC demonstrated lower sensitivities for detecting polyps ≥6 mm with DCBE [70]. When considering only colorectal cancer detection, the sensitivity of DCBE increases to 85 % [71]; however, the rate of new or missed cancers following DCBE has also been reported as high as 22 % [72]. These findings suggest that DCBE may be inferior to other methods of screening. In addition, the use of DCBE may be less attractive to both patient and radiologist, due to the nature and labor intensiveness of the exam [7].

Screening Reality

Although there are several modalities available for colorectal cancer screening, the ACS reports that in 2012 only 59 % of Americans over the age of 50 were screened according to current guidelines. Furthermore, there appears to be a wide variability in screening patterns by state of residence [73].

Surveillance

Guidelines for Surveillance After Polypectomy

History

In the 1970s, the follow-up recommendations for post-polypectomy included a repeat colonoscopy on an annual basis. In 1997, guidelines were published by the gastrointestinal consortium, based on the results of the 1993 National Polyp Study [2], which recommended that the first follow-up examination after polypectomy occur at 3 years. These guidelines were then updated in 2003 based on risk stratification into low-risk and higher-risk adenomas, the goal of which was to identify predictors of future advanced adenomas and cancers to create risk stratification for patients. Higher-risk patients are categorized as those with ≥3 adenomas, high-grade dysplasia, villous features, or an adenoma ≥1 cm. Lower-risk patients are those with 1–2 adenomas with no high-grade dysplasia. With this stratification system, the secondary goals were to decrease the surveillance burden on the system and to decrease the risks to the patients by tailoring follow-up based on risk. It is important to note that the current guidelines for surveillance are to be applied only after high-quality baseline colonoscopy with complete removal of all detected lesions. If either of these two criteria is not met, then repeat examination should be planned. Also, discontinuation of surveillance should be considered in patients with serious comorbidities with less than a 10-year life expectancy. Finally, these guidelines apply only to asymptomatic individuals; new symptoms need diagnostic workup.

Surveillance Based on Pathology of Polyp

Hyperplastic and Serrated Polyps

Serrated lesions of the colon and rectum are classified by the World Health Organization (WHO) into three general categories based on cytological features, architectural features, and location. The categories include hyperplastic polyps, sessile serrated adenoma/polyps, and traditional serrated adenomas (Figure 24-2a, b). These lesions are usually located proximally, sessile or flat in morphology, and pale in color, with indistinct borders, and usually have a mucus cap. Due to their indistinct appearance, there is a high rate of incomplete resection. NBI and chromoendoscopy techniques can be used to facilitate identification and delineation of borders. Given that incomplete resection rates are high in serrated adenomas greater than 1 cm, it seems reasonable to tattoo these lesions so that they can be identified on repeat endoscopy in 3–6 months [74].

Most international post-polypectomy surveillance guidelines do not recommend surveillance for serrated polyps. However, there is increasing awareness that these lesions may be major precursor lesions to cancer development in about 1/3 of colorectal cancer cases. The US Multi-Society Task Force guidelines for post-polypectomy surveillance are 1–5 years depending on the number, size, and presence of dysplasia. Recent reviews on the management of serrated lesions recommended complete removal of all lesions except for ≤5 mm in the sigmoid or rectum. Those small lesions should be randomly biopsied for histology.

Those patients with small rectal hyperplastic polyps are considered to have normal colonoscopies and therefore should be screened every 10 years. The exceptions to this are those patients who have hyperplastic polyposis syndromes (HPS). HPS is a rare syndrome characterized by multiple hyperplastic and/or serrated adenomas. Patients with this syndrome have a lifetime risk of colorectal cancer of up to 50 % [75]. The WHO criteria for HPS are defined as meeting one of the following criteria: having five or greater serrated lesions proximal to the sigmoid colon (with two being greater than 1.0 cm) or more than 30 serrated lesions throughout the colon. There are no evidence-based guidelines for surveillance for these patients, but most physicians are screening them annually or biennially [76]. First-degree relatives of patients with HPS should undergo colonoscopy at the age of 40 or 10 years before the age of diagnosis of HPS. With regard to patients with serrated adenomas that do not have HPS, there are limited observational studies to make strong recommendations for surveillance. However, there are consensus recommenda-

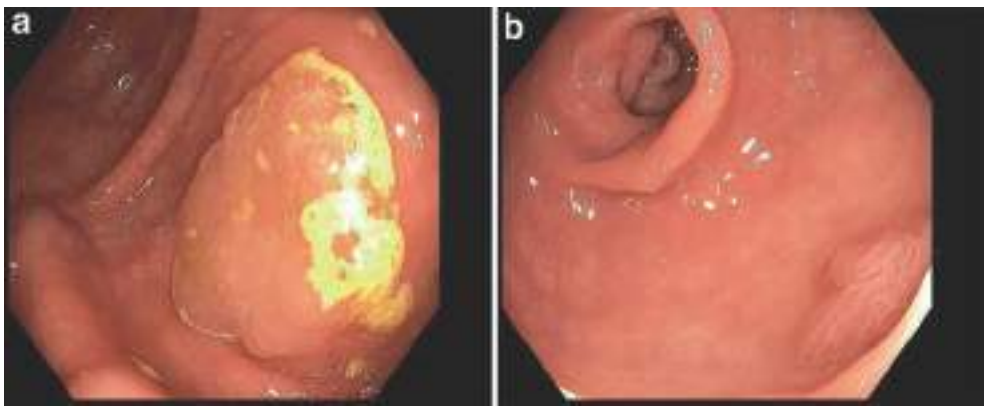

FIGURE 24-2. Endoscopic views of two different types of serrated polyps. (**a**) Sessile serrated adenoma/polyp in the cecum and (**b**) a traditional serrated adenoma of the rectum.

TABLE 24-2. Recommendations for screening intervals based on consensus guidelines for patients with serrated polyps based on histology, number, location, and size[a]

Histology	Size (mm)	Number	Location	Interval in years
HP	<10	Any number[b,c]	Rectosigmoid	10
HP	≤5	≤3	Proximal to sigmoid	10
HP	Any	≥4	Proximal to sigmoid	5
HP	>5	≥1	Proximal to sigmoid	5
SSA/P or TSA	<10	<3	Any	5
SSA/P or TSA	≥10	1	Any	3
SSA/P or TSA	<10	≥3	Any	3
SSA/P	≥10	≤2	Any	1–3[d]
SSA/P w/dysplasia	Any	Any		1–3[e]

[a]The interval recommendations presented here represent consensus opinion based on low-quality or very low-quality evidence. They are likely to change as higher quality evidence becomes available, and alternatives may be equally reasonable

[b]Patients with >20 HPs in the rectosigmoid meet the World Health Organization definition of serrated polyposis if there are additional serrated lesions proximal to the sigmoid

[c]Some panel members follow a policy of 5 years if there are multiple HPs 6–9 mm in size in the rectosigmoid

[d]Patients with two or more serrated polyps ≥10 mm in the proximal colon meet the World Health Organization criteria for serrated polyps if three additional serrated lesions of any size are proximal to the sigmoid are identified

[e]SSA/P with cytological dysplasia is a more advanced lesion than SSA/P. Depending on the size of the lesion, the confidence in complete endoscopic resection and other associated lesions, intervals shorter than 3 years may be appropriate

Note 1: Patients with both significant serrated findings and concurrent adenomas may be at a more advanced stage in the progression toward cancer. Closer follow-up may be indicated in some cases based on clinical judgment

Note 2: In general, these recommendations for surveillance are for the first follow-up. For findings with short follow-up recommendations, a longer subsequent follow-up interval may be appropriately applied when a follow-up exam shows improvement in findings, i.e., reduction in the number, size, and/or histologic severity of lesions

Note 3: Because of interobserver variation in the pathologic differentiation of HP from SSA/P, proximal colon serrated lesions >10 mm in size that are designated HP may be considered to be SSA/P by clinicians

tions that were made in 2012 where surveillance intervals were made based on histology (HP, SSA/P, or TSA), size, number, and location (Table 24-2) [77].

Adenoma

Adenomas can be classified histologically as tubular, villous, or tubulovillous. According to the World Health Organization criteria, tubular adenomas have less than 25 % villous component, tubulovillous 25–75 %, and villous greater than 75 % [78]. Tubular adenomas are the most common type of adenoma found followed by tubulovillous and then villous. Tubular adenomas have <5 % of harboring cancer, while the risk of tubulovillous is 20–25 % and villous adenomas is 35–40 % [79]. Screening series have reported an adenoma prevalence rate of 15–30 %. With the addition of high-definition colonoscopy, this number has been quoted as high as 50 % [80].

The recommendations for post-polypectomy surveillance in patients with one or two small polyps that are less than 1 cm in size range from 3 to 10 years post-polypectomy, depending on which recommendation is followed. The ASGE and the Polyp Guidelines from the ACG recommend follow-up in 5 years. The ACS recommends follow-up in 3–6 years. The Multi-Society Task Force and the Joint ACS and Multi-Society Task Force recommend follow-up in 5–10 years [81]. If low-grade dysplasia is identified on pathology for these patients, the surveillance guidelines do not change.

Patients with 3–10 adenomas, any adenoma ≥1 cm, any adenoma with villous features, or high-grade dysplasia should have their next colonoscopy in 3 years provided the entire polyp was removed in a non-piecemeal fashion (Figure 24-3).

Those patients with sessile adenomas that were removed in piecemeal should be reexamined in 2–6 months to confirm complete removal. If on follow-up colonoscopy there are only 1–2 tubular adenomas, the interval to screening is increased to 5 years. A meta-analysis evaluated the safety and efficacy of endoscopic resection specifically for large polyps (greater than 2 cm). They found a recurrence rate of 14 % with the majority of recurrences being amenable to further endoscopic therapy. It was noted that endoscopic submucosal dissection appeared to reduce the risk of recurrence, while invasive cancer on histology was the main reason for endoscopic failure [82].

Those patients with >10 adenomas at one examination should have follow-up in less than 3 years and should be referred for consultation with a genetic counselor.

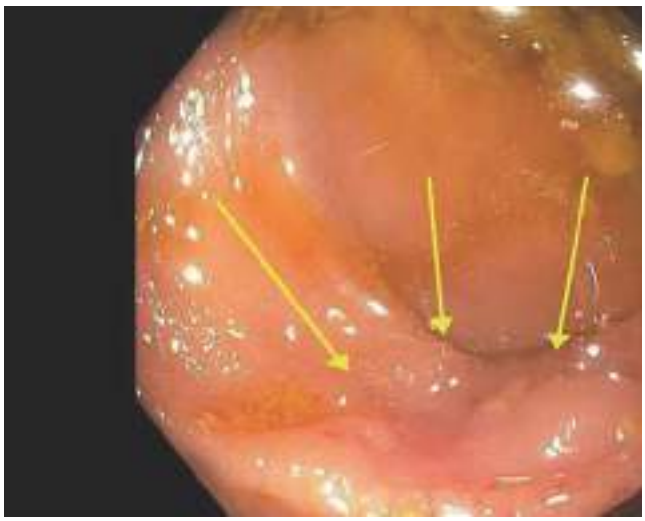

FIGURE 24-3. Endoscopic view of a cecal ulceration which pathology after biopsy demonstrated colonic mucosa with adenomatous change and focal high-grade dysplasia.

Inflammatory Polyps

Inflammatory polyps include benign lymphoid polyps and pseudopolyps (such as those seen in ulcerative colitis). Benign lymphoid polyps are composed of the normal lymphoid tissue and therefore do not require any surveillance if this is seen on pathology. Pseudopolyps are discussed below in the inflammatory disease section.

Hamartomatous Polyps

Hamartomatous of the colon and rectum include juvenile polyps and polyps seen in Peutz-Jeghers disease. Juvenile polyps, as the name suggests, occur in children. These are not frequently seen after 15 years of age. In 70 % of cases, there is only one polyp identified. Juvenile polyposis syndrome (JPS) is a disorder of multiple juvenile polyps. These polyps may cause bleeding, abdominal pain, or obstruction. The diagnosis is made when there is any one of the following: (1) more than five juvenile polyps of the colon or rectum, (2) juvenile polyps in other parts of the gastrointestinal tract, and (3) any number of juvenile polyps and one or more affected family members. Three different types of JPS have been described based on the signs and symptoms of the disease. Most juvenile polyps are benign. It is estimated that people with JPS have a 10–50 % risk of developing cancer of the gastrointestinal tract (most commonly colon and rectal cancer). This disorder is associated with mutations in the BMPR1A and SMAD4 genes. It is inherited in an autosomal dominant fashion. Treatment depends on size and number of polyps found. When there are only a few polyps identified and the polyps are small enough, they can be removed endoscopically. Polyps that are too large or too numerous to be removed this way may require an operative resection. If a polyp is seen on endoscopy, it should be removed, and screening should be done yearly until no polyps are found. Thereafter, patients with juvenile polyps should be screened every 3 years if endoscopies are negative [83].

Peutz-Jeghers syndrome (PJS) is an autosomal dominant disorder characterized by intestinal hamartomatous polyps along with a distinct pattern of skin and mucosal melanin deposition. These patients have a 15-fold increased risk of developing intestinal cancers compared to the general population. The genetic mutation identified with this syndrome is in the STK11 gene (also known as LKB1). A clinical diagnosis of PJS requires the presence of one of the following: (1) two or more histologically confirmed PJ polyps, (2) any number of PJ polyps detected in a patient with a family history, (3) characteristic mucocutaneous pigmentation in an individual who has family history of PJS, and (4) any number of PJ polyps in an individual who has the characteristic mucocutaneous pigmentation. Those patients that met clinical criteria should undergo genetic testing for a germline mutation. In terms of surveillance, these patients should undergo a colonoscopy every 2–3 years starting in late adolescence. They should also have upper endoscopies every 2–3 years. Small bowel interrogation (CT enterography) should also occur every 2–3 years [84].

Inflammatory Bowel Disease

In patients with inflammatory bowel disease (IBD), the presence of chronic inflammation puts them at an increased risk for dysplasia and cancer. Polyps detected in patients with IBD are referred to as a dysplasia-associated lesion or mass (DALM). DALM lesions are then divided into three categories based on endoscopic appearance and location: (1) It is a sporadic adenoma if the polyp resembles an adenoma both endoscopically and histologically and is located outside an area of histologically proven colitis. Complete polypectomy with routine surveillance is adequate with these lesions. (2) It is an IBD-associated adenoma-like polypoid dysplasia if

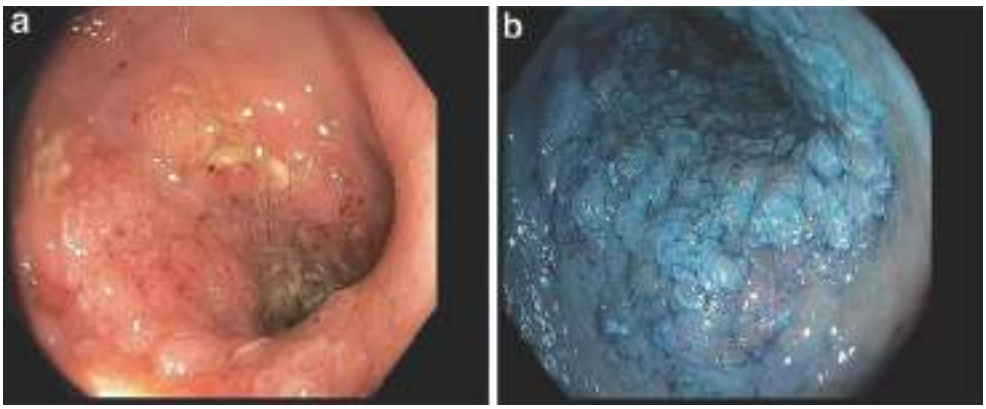

FIGURE 24-4. (**a**) Endoscopic view of a polyp in the sigmoid colon of a patient with ulcerative colitis. (**b**) The use of chromoendoscopy in 4 Ballows for better visualization of the borders of the polyp compared to the images without indigo carmine in 4A.

the lesion resembles an adenoma endoscopically and histologically and is located in an area of colitis. For these lesions, if they are not associated with flat dysplasia or carcinoma, polypectomy with surveillance at a shortened interval is recommended. (3) Finally, IBD-associated non-adenoma-like dysplasia, which is considered a true DALM, is a lesion that is irregular and broadly based and is located in an area of colitis. These lesions are at high risk for associated carcinoma and should be treated with colectomy after the diagnosis of dysplasia is confirmed by an experienced pathologist (Figure 24-4a, b) [85].

Surveillance with Cancer Resection

Patients who are undergoing curative resection for colon cancer are recommended to obtain a colonoscopy 1 year after resection. If the examination at 1 year is normal, then the interval should be extended to 3 years. If that subsequent one is normal, then the interval is again increased to 5 years.

For those patients who are undergoing resection for rectal cancer then there should be periodic examinations to identify early recurrence. This usually entails proctoscopic examination every 3–6 months for the first 2–3 years.

Early Cancer (T1) Within Polyp

There are two classification systems that are established for the identification of cancer within a polyp. The first is Haggitt classification which is utilized for quantifying the extent of invasion in pedunculated polyps. The second is the Kikuchi classification for sessile polyps.

Haggitt Classification

- Haggitt level 0: Noninvasive.
- Haggitt level 1: Cancer invades into the submucosa but limited to the head of the polyp.
- Haggitt level 2: Cancer invades into the neck of the polyp.
- Haggitt level 3: Cancer invades the stalk of the polyp.
- Haggitt level 4: Cancer invades the submucosa of the bowel wall below the stalk.

The risk of spread to the lymph nodes is less than 1 % for levels 1–3. For Haggitt level 4, the risk of lymph node disease ranges from 12 to 25 % [86, 87].

Kikuchi classification of the submucosa is divided into three levels:

- SM1 is invasion of the upper one-third.
- SM2 is invasion of the middle third.
- SM3 is invasion into the lower one-third.

Haggitt levels 1–3 are equivalent to SM1 and Haggitt level 4 can be SM1, SM2, or SM3. There have been several factors identified that increase the risk of lymph node metastases. These factors include lymphovascular invasion, poor differentiation, gender, extensive budding, and SM3 invasion [88].

For low-risk cancers, Haggitt levels 1–3, Kikuchi SM1, or no evidence of poor differentiation or angioinvasion, where the lesion has been completely resected in one piece with negative margins, endoscopic or local excision is regarded as adequate treatment. However, patients should be made aware that although the risk of nodal metastases is very low, it is not zero and that there is no effective surveillance that will reliably detect nodal metastases prior to distant metastatic spread. Although surveillance colonoscopy is recommended at frequent intervals (e.g., yearly), the risk of tumor growth is in the nodes, not in the lumen, calling into question the value of frequent colonoscopy. Surveillance is usually continued for 5 years. There has been some debate on this matter, however, in that there are studies that demonstrate that the risk for recurrence extends past 5 years post-polypectomy [89]. Formal surgical resection is indicated for high-risk cancers (Haggitt level 4, Kikuchi SM3, lymphovascular invasion, poor differentiation, or positive resection margin, cancer in sessile lesions removed in piecemeal fashion).

When to Tattoo an Area After Polypectomy

Current guidelines strongly recommend tattooing of suspicious lesions during colonoscopy. Given that the risk of cancer arising from a polyp in the National Bowel Cancer Screening Program increased significantly when the polyp was greater than 1 cm in size, most would recommend tattoo of all polyps greater than 1 cm (Figure 24-5a, b). In addition, when sessile lesions are removed in piecemeal fashion, the risk of recurrence is high. Tattoo at the site of polypectomy should be considered to help identify the area at subsequent colonoscopy.

Benefits of Surveillance

There have been several studies that have examined the benefits of post-polypectomy surveillance in terms of cancer prevention [90, 91]. These studies identified the risk of colorectal cancer after adenoma resection that depended not only upon the characteristics of the adenoma (advanced or non-advanced) but also colonoscopy surveillance practices. None of these studies are randomized, controlled trials, so there is no direct evidence on the exact benefit that is obtained through surveillance. Most of these studies emphasize the importance of surveillance especially in high-risk adenomas, but there is evidence of the importance of surveillance in low-risk lesions. A recent meta-analysis found that patients with low-risk adenomas had a relative risk of 1.8 (95 % CI: 1.3–2.6) for a metachronous advanced neoplasm compared to those without adenomas, though the absolute risk noted in both groups was low [92].

Reality of Surveillance

Surveys demonstrated that 50 % of endoscopists are not following the guidelines for post-polypectomy surveillance [93]. Levin indicated that failure to follow these guidelines was due to uncertainty, fear of malpractice, and financial incentives [94].

Chemoprevention

A variety of oral agents have been evaluated as possible chemopreventive strategies for both adenoma and carcinoma formation. These agents have included nonsteroidal anti-inflammatory agents, folic acid, calcium, and various antioxidants. A systematic review identified several randomized, controlled trials evaluating for the potential benefits of these agents [95]. They concluded that the use of aspirin (81–325 mg/day) in individuals with a history of adenomas or colorectal cancer (CRC) resulted in a 21 % reduction in adenoma recurrence. Though not evident until after a prolonged follow-up period (23 years), a 26 % reduction in CRC incidence was noted in the general population in studies evaluating a larger aspirin dose (300–1500 mg/day). Furthermore, nonaspirin anti-inflammatory medications such as celecoxib (400 mg/day) have also demonstrated benefit in patients with a history of adenomas, revealing a 34 % reduction in adenoma recurrence.

Though the use of folic acid failed to show benefit with respect to adenoma recurrence, calcium intake (1200–2000 mg/day) was found beneficial with an 18 % risk reduction after a history of prior adenomas. Finally, there was no significant benefit toward adenoma recurrence noted with antioxidant ingestion (vitamins A, C, and E, beta-carotene, or selenium) after a history of adenoma removal.

Conclusion

Proper screening recommendations are based on age and risk, which can be based on personal or family history. Screening for colorectal cancer now has several options, though colonoscopy currently remains most common. CT colonography, although not therapeutic, is an ideal alternative to colonoscopy. It also has the potential to reveal extracolonic lesions. Surveillance after colonoscopic polypectomy is dependent on polyp type, size, and number. When an occult cancer is encountered within a polyp after colonoscopic excision, management considerations should be based

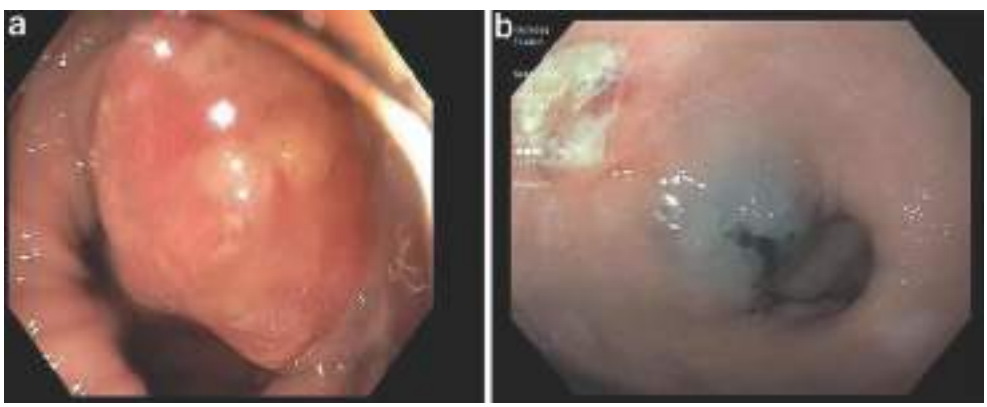

FIGURE 24-5. (**a**) A 2 cm rectal polyp noted endoscopically. (**b**) Polyp was resected and tattooed based on size criteria. Final pathology demonstrated moderately differentiated invasive colonic adenocarcinoma with mucinous features arising from tubulovillous adenoma. Carcinoma was present at cauterized margins.

on histology and polyp morphology (sessile vs. pedunculated). Adherence to recommended guidelines and monitoring of published quality indicators may improve outcomes and minimize polyp miss rates during colonoscopy.

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Colon Cancer: Preoperative Evaluation and Staging

Cary B. Aarons and Najjia N. Mahmoud

Key Concepts

- Total colonic evaluation is recommended prior to surgical intervention to exclude synchronous tumors that may alter surgical plan.
- Evaluation for metastatic disease by cross-sectional imaging is recommended prior to surgical intervention, as it may alter treatment decisions.
- Preoperative carcinoembryonic antigen (CEA) level should be obtained, as changes in CEA may herald tumor recurrence.
- Tumor location should be identified preoperatively.
- Tumor grade, lymphovascular invasion, margin status, and immunohistochemical assessment of mismatch repair proteins may have prognostic significance and should be routinely reported.

Background

Colorectal cancer remains a challenging clinical entity worldwide—affecting more than one million individuals annually [1–3]. Marked geographic variations exist, with industrialized countries bearing significantly higher incidences that are believed to be attributed to a mix of diet and environment [2, 3]. In the United States, it is the third leading cause of cancer-related deaths and is the third most common cancer following lung cancer and prostate and breast cancers in men and women, respectively [2–4]. In recent years, it has been estimated that annually there are roughly 100,000 new cases of colon cancer and more than 40,000 cases of rectal cancer [5–7]. Fortunately, both the incidence and mortality of colorectal cancer have declined steadily in the past three decades—largely due to more effective screening programs and improvements in treatment modalities [5–7]. However, despite these measurable gains, there remain significant disparities in incidence and mortality, particularly among African Americans [8–10]. Overall, the lifetime risk of developing colorectal cancer in the United States is approximately 5 % with a likelihood rising notably after 50 years of age. It is estimated that up to 90 % of cases occur in individuals over the age of 50 [11].

Once the diagnosis of colon cancer is made, the goal of preoperative evaluation is to establish the location of the tumor, assess for metastatic disease and adjacent organ invasion, and identify other patient and tumor factors that may affect outcome or alter the medical or surgical approach to treatment. The primary importance of staging in colon cancer is to rule out additional pathology and distant metastatic disease (stage IV), which can affect treatment approach. This differs from rectal cancer where estimates of locoregional tumor stage have a greater effect on treatment planning.

Clinical Presentation

Colon cancer presents in three common ways: an asymptomatic lesion detected during routine screening examination; manifestation of vague but suspicious symptoms such as change in bowel habits, weight loss, and fatigue that lead to further investigation; and emergently, with perforation or obstruction.

Early colon cancers are often asymptomatic, which underscores the importance of routine screening. Even so, it is estimated that about 30 % of all cancers are diagnosed by endoscopy in the absence of symptoms [12]. Routine screening detects the majority of early cancers, but the definition of "effective screening" is in flux and overall compliance with colonoscopic screening in the United States is still quite low—below 50 % for most average risk adults. Rates of screening can vary widely between states and regions. The Centers for Disease Control and Prevention estimates that when surveyed for appropriate screening which could include fecal occult blood testing alone within 1 year, flexible sigmoidoscopy within 3 years, or colonoscopy within 10 years, the highest rates recorded are in the northeast topping out at 75 % and the lowest in the west with maximal screening

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compliance rates of 54 % [13]. When symptoms do occur, patients commonly present with abdominal pain, gastrointestinal bleeding, iron-deficiency anemia, change in bowel habits, or vague nonspecific symptoms such as lethargy, weight loss, and loss of appetite [4, 14, 15]. Symptoms will often manifest differently depending on tumor location and size. Late findings can include palpable abdominal mass, severe weight loss, intestinal obstruction, and, in rare cases, perforation leading to peritonitis or fistulization to adjacent organs.

Abdominal pain in the setting of colon cancer is often poorly localized and, therefore, a nonspecific finding. Patients may describe a vague visceral discomfort, which changes to crampy, colicky pain as luminal narrowing occurs—resulting in partial or complete colonic obstruction. While rectal bleeding is a common finding, its clinical manifestation can be varied; therefore, taking a careful history is imperative. Patients with distal, left-sided lesions will often present with bright red bloody stools, while more proximal lesions will cause melena or occult bleeding that results in iron-deficiency anemia [3, 14]. This anemia can ultimately result in dizziness, weakness, or generalized fatigue. Similarly, changes in bowel habits will be affected by tumor location within the colon. Typically, patients will report changes in the caliber, frequency, and consistency of their stools. This is more notable with left-sided lesions, which are more likely to cause narrowing of the colon lumen and impede passage of solid stool. Since the luminal diameter tends to be wider in the proximal colon and stool more liquid, alterations in stools generally coincide with large, exophytic lesions or cancers that obstruct the ileocecal valve.

Approximately 20–25 % of colon cancer will present with metastatic disease at the time of diagnosis; therefore, it is also critical to evaluate patients for signs and symptoms associated with metastatic disease. On the whole, widely advanced cancers can result in constitutional symptoms such as unintentional weight loss, cachexia, weakness, and anorexia [3].

Colon cancer typically spreads via lymphatic, hematogenous, or intraperitoneal extension, and the most common sites include the liver, lungs, and peritoneal surfaces. Spread to the brain or CNS and bones is less likely but possible. While symptoms of liver metastasis are uncommon, some patients may develop right upper quadrant pain, abdominal distention, anorexia, weakness, or jaundice when the burden of liver metastases is high. Direct local invasion of colon cancers into adjacent structures such as the small intestine, bladder, or abdominal wall can result to bowel obstruction, abscesses, pneumaturia, fecaluria, or enterocutaneous fistula. A Virchow node (left supraclavicular node) or Sister Mary Joseph node (umbilical nodule) is another uncommon finding that has been associated with the distant spread of colon cancer [3]. Patients who present with symptoms seem to be at much higher risk of having advanced disease at diagnosis than those for whom the primary is detected by routine screening. For example, in one study of over 1000 patients with colorectal cancer, only 217 were found during screening. Those that came to attention via symptoms were twice as likely to have a transmural tumor, twice as likely to present with stage III disease, and over three times as likely to have distant spread at diagnosis and have double the risk of recurrence [16].

Preoperative Evaluation

The evaluation of a patient with a new diagnosis of colon cancer should begin with a complete history and physical examination [11]. The history should focus on the duration and severity of symptoms associated with the primary tumor such as intestinal obstructive symptoms, anemia, and abdominal pain, as well as those associated with metastatic disease such as weight loss and fatigue. Information should also be obtained about any family history of colorectal cancer or other cancers known to be associated with inherited colon cancer syndromes. Finally, details regarding the patient's overall health will provide initial insight into their readiness for any surgical intervention. A focused physical examination can elucidate important signs such as a palpable mass, distant adenopathy, tenderness, or distention [11].

Assessment of Inherited Risk

The vast majority of colorectal cancers are sporadic in nature. However, there are factors associated with the development of colorectal cancer. Modifiable risk factors include low-fiber, high-fat diet, obesity, smoking, and heavy alcohol consumption. The primary inherent risk factor for colorectal cancer is increasing age; however, having a personal history of colorectal cancer, polyps, or inflammatory bowel disease will substantially increase risk. Approximately 5–10 % of colorectal cancers can be linked to discrete inherited syndromes, among which familial adenomatous polyposis (FAP) and Lynch syndrome are the most common. It is important to identify these risk factors, particularly inflammatory bowel disease, personal history of colorectal neoplasia, and presence of inherited colorectal cancer syndromes, as they will guide choice of therapy, surveillance strategies, and screening of at-risk relatives. For example, a patient with long-standing ulcerative colitis who is found to have a colon cancer should be considered for total proctocolectomy. A patient with colon cancer who is suspected of having Lynch syndrome should be considered for subtotal colectomy, as well as total abdominal hysterectomy and bilateral salpingo-oophorectomy in women.

Colonoscopy

If not completed at the time of diagnosis, a thorough endoscopic examination of the entire colon is critical as it provides added information about any synchronous cancers or polyps, which may need to be removed or marked preoperatively. The rate of synchronous cancers is understood to be about 5 %, and the overall rate of synchronous neoplasia that

would change operative approach is somewhat higher [17]. If a synchronous polypoid neoplasm is detected outside of the normal field of planned resection for the primary tumor, it is optimal to attempt complete endoscopic resection preoperatively. This will allow for histologic analysis—if cancer is found, then a more extensive colectomy than was originally planned may be indicated [4]. Colonoscopy allows for the localization and biopsy of the primary tumor; however, it is important to keep in mind that the flexible scope may not provide an exact measurement of distance. Therefore, it is important to assess known landmarks and whenever possible to mark the location of the cancer with an endoscopic tattoo, particularly if the cancer was contained within a polyp and therefore entirely resected. This is increasingly important for smaller lesions that may not be easily palpated at the time of surgery or if a laparoscopic approach is planned. It is not unusual for the endoscopist to resect a large polyp only to find an occult cancer within it requiring formal resection on pathology. Rapid reevaluation of the colon via colonoscopy with marking is essential. Typically, if the colon can be reevaluated within 2 weeks, a healing ulcer can be identified and tattooed.

Over time, a number of agents for endoscopic marking have been evaluated. Only India ink and SPOT (GI Supply, Camp Hill, PA) have been widely accepted. Both agents are colloid suspensions of fine carbon particles. India ink is suspended in a 0.9 % solution of saline at a 1:100 dilution and sterilized by autoclaving or being passed through a Millipore filter. SPOT is a marker composed of highly purified, fine carbon particles and is the only FDA-approved marking solution for endoscopic tattooing. Both have been tested extensively and are safe as well as durable. Identification of the endoscopic tattoo can be made well after the 1-year mark and commonly after 2 or more years. Other agents that have been used include methylene blue, hematoxylin, and toluene blue. Brevity of duration of marking and mucosal ulceration has limited use of these other agents. Technique of injection has been studied fairly extensively. Four-quadrant injection of 2–4 cm^3 of agent at or near the level of the lesion allows for accurate identification even if the lesion is on the mesenteric aspect of the colon lumen. Submucosal injection limits intraperitoneal spread that can make intraoperative identification confusing or difficult. Some advocate for placing a tattoo both proximally and distally to the tumor or polyp to help identify the extent or length of the lesion; however, this may confuse the surgeon if only one of the tattoo marks is visible. Other surgeons advocate marking only distal to the lesion. While there are no current recommendations regarding this aspect of marking, it seems clear that good documentation of technique in the report is mandatory and will limit misunderstandings or confusion [18]. Additional benefits of tattoo placement may include increased nodal harvest by virtue, most likely, of the ability to see and enumerate lymph nodes that take up the colloid carbon particles. A number of studies, both prospective as well as retrospective, have noted a significant increase in the number of specimens with >12 lymph nodes harvested when tattooing had taken place [19, 20].

An alternative to marking with tattoo is deployment of endoscopic metal clips followed by immediate plain radiograph. The colon outline is frequently visible due to retained air from colonoscopy. CT can also be obtained within a few days; the clips are usually retained and the tumor site can be clearly localized. Another strategy is to perform intraoperative colonoscopy to localize a small tumor. This can be performed immediately prior to operation or after exploration of the abdomen. The use of carbon dioxide as an insufflation gas is preferred, in order to limit bowel dilatation.

If colonoscopy cannot be completed preoperatively, then a suitable radiographic study, such as CT colonography or contrast enema, should be considered or intraoperative colonoscopy performed via the colon proximal to the tumor. For cases of obstructing cancers that preclude adequate endoscopic or radiographic assessment preoperatively, intraoperative colonic lavage and colonoscopy should be considered. If this is not possible, the proximal colon should be palpated intraoperatively, and if no obvious lesions are detected, a full colonoscopy should be performed when safe to do so after surgery [4].

Carcinoembryonic Antigen

Preoperative evaluation should also include routine laboratory studies, including a complete blood count (CBC) with focus on anemia that may need to be corrected before surgery. Another important test is the serum CEA level, which has been shown to provide some prognostic information [21]. CEA is a glycoprotein primarily involved in intercellular adhesion [22]. It is produced by columnar and goblet cells and can be found in normal colonic mucosa. Additionally, it can be found in low levels in the circulation of healthy individuals, but it is overexpressed in a variety of cancers, including colorectal cancer. Elevated serum levels may be identified in heavy smokers and in benign conditions such as pancreatitis and inflammatory bowel disease as well as malignancies outside of the gastrointestinal tract [22]; therefore, CEA is not a sensitive or specific screening tool for colorectal cancer [3, 23]. However, it is an important tool in CRC surveillance after surgical resection since its elevation may be the first indication of locally recurrent or metastatic disease [24].

Patients with preoperative serum CEA >5 ng/mL have a worse prognosis, stage for stage, than those with lower levels. Elevated preoperative CEA levels have been shown to be associated with poorer survival and increased recurrence in several studies; however, contradictory studies do exist [23, 25–29]. Therefore, there is currently insufficient evidence to support the use of elevated preoperative serum CEA levels as an absolute indication for adjuvant chemotherapy [4, 28].

Current American Society of Clinical Oncology (ASCO) guidelines recommend that serum CEA levels be obtained preoperatively in patients with demonstrated colorectal cancer for posttreatment follow-up and assessment of prognosis. Elevated preoperative CEA levels that do not normalize following surgical resection imply the presence of persistent disease. Furthermore, serial testing of CEA levels should be performed for 5 years for patients with stage II and III disease in those eligible for surgery or chemotherapy if metastatic disease is discovered. Rising CEA levels after surgical resection imply recurrent disease and should prompt consideration of radiologic and endoscopic evaluation to look for treatable disease [28].

Radiographic Evaluation

Preoperative radiographic imaging is fundamental for initial staging of newly diagnosed or recurrent colon cancers [4]. Computed tomography (CT) scans are the most widely used studies in this setting as they provide valuable preoperative information about liver or lung metastasis and are cost effective. This test should be done with both oral and intravenous contrast if there is no contraindication (anaphylaxis to contrast or renal insufficiency) to maximize accuracy of visualization of the abdominal viscera as well as highlight vascular structures and better determine the relationships between lymphatics, ureters, and vessels [30]. Additionally, cross-sectional imaging also facilitates more precise tumor location and delineates the extent of any extracolonic invasion of adjacent organs or the abdominal wall, all of which are important for operative planning [31]. In these cases, the appropriate consulting services can be mobilized if necessary for en bloc resections. CT scan has a sensitivity ranging from 75–90 % for detecting distant metastasis; however, the ability to accurately detect nodal involvement or small peritoneal metastasis is poor. The routine use of CT for imaging of the chest remains controversial for initial staging of colon cancer, as compared to rectal cancers. In asymptomatic patients in whom the suspicion of lung metastasis is low, a plain chest X-ray will suffice. Any suspicious findings on chest X-ray can be investigated with a noncontrast chest CT scan.

As imaging technology has improved, so has the sensitivity of CT scans for identifying liver metastases. However, there are studies that suggest that contrast-enhanced magnetic resonance imaging (MRI) is particularly valuable in evaluating smaller suspicious liver lesions (especially in the presence of fatty liver changes) with sensitivities up to 97 % [3, 32]. In routine clinical practice, MRI should be reserved for the evaluation of suspicious liver lesions not clearly characterized on CT scan and for operative planning prior to liver metastasectomy.

Positron emission tomography–computed tomography (PET/CT) scan has emerged as a useful imaging modality in the evaluation of many cancers. However, for initial staging of colorectal cancer, the routine use of PET/CT remains controversial. While it has been shown to be more sensitive in the detection of liver metastases as well as extrahepatic disease as compared with routine CT scan, other studies suggest that it does not add significant information [14, 33–35]. The strongest evidence for use of PET/CT in the management of colorectal cancer is in the evaluation of patients with recurrent disease [34–36]. It is often more helpful as an adjunct to conventional imaging studies in patients suspected of having metastasis, especially those with a rising CEA level [31, 37]. Additionally, in patients with potentially resectable metastatic disease, PET/CT has been shown in a randomized trial to reduce the number of unnecessary laparotomies [38].

Preoperative Evaluation of Coexisting Medical Conditions

Regardless of the operative approach, colorectal procedures carry inherent risks, which can be divided into procedure-specific risks and cardiopulmonary risks. Therefore, a thorough history and physical examination encompassing the patient's comorbidities is also vital. This is immensely important because surgical morbidity and mortality can be greatly improved by a careful assessment of organ-specific risks and, if feasible, preoperative optimization. Additionally, a detailed knowledge of the patient's prior abdominal surgery will aid in the appropriate operative planning.

Routine preoperative testing should be obtained and should include a CBC, a metabolic panel, type and screen, and a 12-lead electrocardiogram in older patients with cardiac risk factors. Liver function tests are not sensitive for liver metastasis and, therefore, are not required in the initial preoperative testing. Similarly, nutritional panels are not generally required unless there are significant concerns for underlying malnutrition. Complete optimization of nutritional parameters, either parenterally or enterally, typically takes weeks, which would delay surgery unnecessarily.

There are several classification systems that have been reported, which aim to gauge the overall risk of the surgical patient. The American Society of Anesthesiologists (ASA) classification is the simplest and most commonly used system, which highlights the patient's underlying illnesses that may impact outcomes from surgery [39, 40]:

- ASA I—a normal healthy patient
- ASA II—a patient with mild systemic disease
- ASA III—a patient with severe systemic disease
- ASA IV—a patient with severe systemic disease that is a constant threat to life
- ASA V—a moribund patient who is not expected to survive without the operation
- ASA E—emergency

The preoperative cardiac assessment should include a history of recent or remote myocardial infarction, angina, valvular disease, arrhythmias, or heart failure. Baseline functional status should also be quantified using metabolic equivalents (METs) [41]. Perioperative risk of an adverse cardiac event can then be estimated using the Goldman cardiac risk index or the revised cardiac risk index (Table 25-1), which are among the most widely used tools for cardiac risk assessment [39].

Chronic obstructive pulmonary disease (COPD), obesity, obstructive sleep apnea, pulmonary hypertension, recent respiratory infection, and smoking are some of the most important pulmonary risk factors that should be considered prior to surgery. These comorbidities can be gleaned from a thorough history and should prompt further investigation; however, this testing should be selective. The routine use of chest X-ray varies by institution and is often of limited value for the evaluation of significant pulmonary disease; therefore, this study should be reserved for patients with known cardiopulmonary disease or those older than 50 years of age as recommended by the American College of Physicians [42]. Because CXR is a part of staging of colon cancer, it is necessarily included in the preoperative evaluation. Pulmonary function testing and baseline arterial blood gases are not indicated routinely prior to abdominal surgery [43]. Complex patients with high-risk underlying pulmonary illnesses should be referred for pulmonary consultation prior to surgery for medical optimization and to outline appropriate perioperative strategies.

Smoking cessation should be emphasized but should not delay surgery, as any substantial benefits would not be realized for several weeks. However, there may be measurable gains in improving postoperative wound healing [44]. A recent meta-analysis of randomized trials demonstrated that smoking cessation was associated with a 41 % relative risk reduction in postoperative pulmonary complications [44].

In patients with renal insufficiency, care must be taken with choosing preoperative bowel preparation, and special attention must be paid to perioperative fluid balances. Additionally, diuretics, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers should be held the day prior to surgery to minimize the risk of profound hypotension during surgery.

Staging of Colon Cancer

The preferred staging system for colon and rectal cancers is the TNM staging system put forth by the American Joint Committee on Cancer and the International Union Against Cancer (UICC) [4, 36]. This system, which is summarized in Table 25-2, consists of three categories: tumor depth of invasion, nodal involvement, and distant metastasis. Based on the clinical and pathologic data, the combination of these categories forms the final stage, which correlates with the overall prognosis. Recent analysis of survival outcomes in a large group of patients with invasive colon cancer from the Surveillance, Epidemiology, and End Results (SEER) population-based database has led to the revision of the CRC TNM staging system in the 7th edition of the *AJCC Cancer Staging Manual* [45]. These changes include [6]:

- Stage II is further subdivided into IIA (T3N0), IIB (T4aN0), and IIC (T4bN0).
- Satellite tumor deposits in the pericolonic adipose tissue are classified as N1c.
- Several stage III groups have been revised based on survival outcomes.
- N1 and N2 subcategories are further subdivided according to the number of involved nodes to reflect prognosis.
- T4 lesions are subdivided as T4a (tumor penetrates the surface of the visceral peritoneum) and as T4b (tumor directly invades adjacent organs or structures).

Table 25-1. Revised cardiac risk index (RCRI)

Risk factors	
1. High-risk type of surgery (intraperitoneal, intrathoracic, or suprainguinal vascular procedures)	
2. Ischemic heart disease	
3. Congestive heart failure	
4. History of cerebrovascular disease	
5. Insulin therapy for diabetes	
6. Preoperative serum creatinine > 2.0 mg/dL	
Risk classification (*one point is assigned to each risk factor present*)	*Rates of major cardiac complications*[a] (%)
Class I (0 points)	0.50
Class II (1 point)	1.30
Class III (2 points)	3.60
Class IV (≥3 points)	9.10

[a]Major cardiac complications include myocardial infarction, pulmonary edema, ventricular fibrillation or primary cardiac arrest, and complete heart block
Adapted from Lee, TH et al., Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery Circulation 1999;100(10):1043–9 [63]

TABLE 25-2E. TNM classification and AJCC 7th edition staging of colon cancer

Primary tumor staging (*T*)			
T0		No evidence of primary tumor	
Tis		Carcinoma in situ	
T1		Tumor invades submucosa	
T2		Tumor invades the muscularis propria	
T3		Tumor invades through the muscularis propria into the pericolonic tissue	
T4a		Tumor penetrates to the surface of the visceral peritoneum (serosa)	
T4b		Tumor invades and/or is adherent to other organs or structures	
Regional lymph node staging (*N*)			
N0		No regional lymph node metastasis	
N1a		Metastasis in one regional lymph node	
N1b		Metastasis in 2–3 regional lymph nodes	
N1c		Tumor deposits in subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastases	
N2a		Metastasis in 4–6 regional lymph nodes	
N2b		Metastasis in seven or more regional lymph nodes	
Distant metastasis staging (*M*)			
M0		No distant metastasis	
M1a		Metastasis confined to one organ or site	
M1b		Metastasis in more than one organ/site or the peritoneum	
Stage	*T*	*N*	*M*
0	Tis	N0	M0
I	1–2	N0	M0
IIA	T3	N0	M0
IIB	T4a	N0	M0
IIC	T4b	N0	M0
IIIA	T1–T2	N1–N1c	M0
	T1	N2a	M0
IIIB	T3–T4a	N1–N1c	M0
	T2–T3	N2a	M0
	T1–2	N2b	M0
IIIC	T4a	N2a	M0
	T3–T4a	N2b	M0
	T4b	N1–N2	M0
IVA	Any T	Any N	M1a
IVB	Any T	Any N	M1b

With permission from Chang GJ et al., Practice parameters for the management of colon cancer. Dis Colon Rectum 2012;55(8):834. © Wolters Kluwer [4]

- M1 is subdivided into M1a (single metastatic site) and M1b (metastasis to more than one organ or the peritoneum).

The completeness of resection should also be noted by the surgeon [4, 6, 46]:

- R0—complete tumor resection with negative margins
- R1—incomplete tumor resection with microscopic involvement of the margin
- R2—incomplete tumor resection with gross residual disease that was not resected

In addition to the aforementioned components of the TNM staging system, there are several other histologic criteria that should be reported routinely. These include histologic grade, tumor ("satellite") deposits, lymphovascular invasion, perineural invasion, and margin status (distal, proximal, and radial). Each of these features provides important prognostic information.

Histologic Grade

Histologic grade has consistently been shown to be a stage-independent prognostic factor and is determined by the degree of differentiation in the colon tumor. While most systems stratify cancers into four grades, ranging from well differentiated (grade 1) to undifferentiated (grade 4) [46], histologic assessment is often plagued by interobserver variability. Consequently, the AJCC has recommended a two-tiered system for reporting: low grade (well and moderately

differentiated) and high grade (poorly differentiated and undifferentiated) [21, 46, 47].

There are histologic variants such as mucinous adenocarcinomas and signet ring cell adenocarcinomas that are also important in assessing overall prognosis. Mucinous adenocarcinomas are characterized by extracellular mucin in greater than 50 % of the tumor volume. When compared with conventional invasive adenocarcinomas, mucinous adenocarcinomas typically behave more aggressively, especially in patients without microsatellite instability (MSI). Signet ring cell adenocarcinomas are rare but when they occur in the colon, they carry a worse prognosis as compared with conventional adenocarcinomas [14]. These tumors are characterized histologically by greater than 50 % tumor cells with signet ring features—prominent intracytoplasmic mucin vacuole that pushes the nucleus to the periphery [47].

Lymph Node Evaluation

Other than radial margin status, lymph node status is the most important prognostic factor following resection of colon cancer [14]. The identification of at least 12 lymph nodes has been suggested as a key quality indicator in the resection of colon cancers [6]. While there are patient-related factors that influence lymph node yield, the completeness of mesenteric resection and the interest of the pathologist in obtaining the maximal number for nodes for examination are also paramount. Numerous studies have shown that increasing the number of lymph nodes examined is associated with improved survival in stage II and stage III patients [48]. Tumor deposits that are found in the pericolonic fat that do not show any evidence of residual lymph node are not counted as lymph nodes replaced by tumor and are designated as N1c. The number of these nodules should be reported as they confer a poor prognosis [6, 49].

During the past 20 years, there has been interest in improving harvest of at-risk lymph nodes and in better identification of tumor in lymph nodes. Some investigators have proposed injection of vital dye around the tumor at the time of operation as a method of identifying lymph nodes at greatest risk for metastases (sentinel node mapping).

Studies of sentinel lymph node mapping have focused on the detection of metastatic lesions in nodes that would ordinarily be missed by routine nodal retrieval and pathologic processing. However, with few exceptions, the "sentinel" nodes retrieved in these studies have been subjected to ultra-processing (microsectioning, immunohistochemical analysis, or RT-PCR), while other "nonsentinel" nodes have been examined by bivalving and hematoxylin and eosin staining only, biasing the results heavily in favor of sentinel lymph node mapping. Even with this bias, results have varied widely in the literature, with false-negative rates (patients with negative "sentinel" nodes and positive "nonsentinel" nodes/total patients with positive nodes) of 9–60 % [50–52]. Variation in reported success rates may also result from different methods of data analysis and presentation.

The ultimate goal of any protocol examining lymph nodes in nonstandard fashion is to identify patients with occult nodal metastases, to treat them with chemotherapeutic agents, and to improve survival. At present, there is no definitive evidence that treatment of patients with occult nodal metastases with chemotherapy improves survival.

Margin Status

Surgical resection with curative intent requires removal of the entire tumor as well as the associated lymphatics and nodal basin at risk, which will vary based on the location of the primary tumor. It would seem obvious that it is of critical importance to resect the entire tumor when operating for colon cancer. However, the concept that the radial margin of resection is important was largely ignored by the surgical and pathology communities until recently. Just as with rectal cancer, it is important to ink the radial margin of resection and assess it histologically, as it has profound prognostic significance and will drive some decisions regarding adjuvant treatment and can be used as an assessment of surgical quality. It should be noted that the visceral peritoneum is not considered a surgical margin. However, pathologists often have difficulty in assessing this layer in relation to margin status, making inking of the nonperitonealized radial margin all the more critical.

The proximal and distal margin of resection should also be measured and reported. Traditionally, some authors have advocated obtaining a 5 cm segment of normal bowel on the proximal and distal sides of the tumor to avoid local failure [4, 46, 53]. However, this recommendation has little to do with the primary tumor, as colon cancers do not often spread longitudinally in the wall of the bowel in occult fashion. Rather, the recommendation arises from the need to resect mesentery surrounding the tumor to ensure adequate removal of at-risk lymph nodes. Adequate resection of the mesentery, including named feeding vessels, will result in devascularization of the colon surrounding the tumor, thus mandating resection of the colon rendered ischemic.

Other Prognostic Features

The presence of lymphovascular and perineural invasion has been shown to be significantly associated with poorer prognosis [21, 46, 54–57]. Tumor budding refers to small clusters of undifferentiated cancer cells ahead of the invasive front of the lesion. While this is not a routinely examined pathologic parameter, there is increasing evidence that the quantitative

assessment of tumor budding reflects clinical aggressiveness of colon cancers. This has also been shown by some to be a poor prognostic feature [46, 54].

DNA Mismatch Repair/Microsatellite Instability

A germ line mutation in one of the DNA mismatch repair (MMR) genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*) is typically found in Lynch syndrome. In sporadic colon cancers, mismatch repair defects occur in approximately 20 % of cases and results from the hypermethylation of *MLH1* [3, 58]. Patients with dropout of *MLH1* on immunohistochemistry (IHC) can be accurately identified as either a sporadic or germ line mutation by staining for *BRAF*. If *BRAF* is mutated as well, then a sporadic mutation is 96 % likely in MLH1 [59]. Typically, tumors found to be lacking in MMR expression are subject to *BRAF* analysis. If *BRAF* mutation is detected, then Lynch syndrome is unlikely, and in most cases, the patient can be considered to have a sporadic cancer and genetic testing will cease. However, if *BRAF* is normal, then Lynch syndrome is likely and genetic counseling and testing should be considered.

The presence of MMR proteins in tumor tissue can be assessed by IHC and should be done routinely in patients suspected of having Lynch syndrome, based on the clinical criteria [36]. In many hospitals, IHC testing for MMR is done routinely for patients under the age of 50. Increasingly, because of the prognostic implications, many urge IHC for MMR proteins to be assessed on all patients with colorectal cancer in an effort to align pathology with prognosis and therapy.

MSI is another indicator of DNA repair defects caused by defective mismatch repair proteins. It is typically assessed by PCR amplification of repeated single nucleotide units of DNA, or microsatellites, in tumor tissue. Tumors are characterized as MSI high (MSI-H) or MSI low (MSI-L) based on the number of microsatellite sequences that appear. If the tumor has two or more mutated sequences, it is termed MSI-H, while if only one sequence is mutated, it is classified as MSI-L. Finally, if no mutation is present, then the tumor is microsatellite stable (MSS) [47, 60]. Recent studies demonstrate that stage II patients with MSI-H tumors did not have the same survival benefit from 5-FU-based adjuvant chemotherapy as compared with those that had MSI-L and MSS tumors although differences were slight [36, 50–52, 61–63].

Summary

Assessment of the patient and the tumor preoperatively is increasingly important. Today, treatment decisions are made by careful preoperative evaluation of the health of the patient, the genetics of the tumor, and the extent of disease. A sophisticated, organized, and educated approach to preoperative evaluation yields the best long-term results.

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26
The Surgical Management of Colon Cancer

Matthew G. Mutch

Key Concepts

- Complete clinical staging for colon cancer includes a total colon exam; computed tomography of the chest, abdomen, and pelvis; and a serum CEA level.
- The principles of an oncologic resection include a total mesocolic resection, a ligation of the primary vessel at its origin, a wide mesenteric resection with >12 lymph nodes examined, and at least a 5 cm resection margin.
- There is no difference in cancer-related outcomes for open and laparoscopic resections.
- Anastomotic assessment for left-sided anastomosis is associated with a decreased leak rate.
- Surgical resection is the most effective therapy for patients who present with obstruction colon cancers.
- Endoscopic stenting of an obstructing colon cancer is an effective bridge to surgery within 72 h.
- Perforated cancers should be treated with an oncologic resection.
- First-line therapy for patients with metastatic colon cancer and an asymptomatic primary tumor is chemotherapy.

Introduction

Our understanding of the pathogenesis, staging, and management of adenocarcinoma of the colon has evolved greatly over the last decade. Today, it is accepted that colorectal cancers develop via one of three distinct genetic pathways: (1) chromosomal instability, (2) mismatch repair, and (3) CpG island hypermethylation. This increased understanding of the genetics of colorectal cancer development has led to the identification of several putative molecular markers to predict their biologic and clinic behavior. However, pathologic staging using the TNM system remains the most valuable prognostic tool available, with depth of invasion (T stage) and lymph node involvement (N stage) being the best markers to risk stratifying regional and distant metastatic spread, respectively. Preoperative imaging has allowed for more accurate clinical staging and earlier detection of metastatic disease that may impact the treatment of the patient. Advances in chemotherapy have allowed for improved outcomes for patients with selected stage II and stage III and IV cancers. Despite all of these advances, surgical resection remains the cornerstone and most important facet in the management of colon cancer. An intimate understanding of the anatomy of the colon, its vasculature, and the retroperitoneum are critical to performing an appropriate oncologic resection for colon cancer. This chapter will focus on the technical aspects of the principles of an oncologic resection such as the importance of total mesocolic resection, ligation of primary vasculature at its origin, obtaining an adequate lymph node harvest to ensure an examination of >12 lymph nodes, and obtaining appropriate distal and proximal margins for open and laparoscopic resections. Special topics such as laparoscopic colectomy for cancer, management of obstructing and perforated colon cancers, treatment of the primary tumor in the setting of metastatic disease, and the short-term and long-term outcomes for colectomy for cancer will be addressed.

Preoperative Preparation

When preparing to take a patient to the operating room for resection of his/her colon cancer, it is imperative to have a complete understanding of the patient's physiologic status, tumor location, and clinical staging. Being able to provide patients with individualized risk stratification for complications after colorectal surgery is becoming more and more important because of the increasing scrutiny of patient safety and outcomes. The general population in the USA is getting older and has an increasing number of comorbidities, so surgeons will be making more and more challenging decisions regarding the management of patients with colorectal cancer.

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Physiologic Assessment

A variety of scoring systems are available for stratifying a patient's risk of perioperative morbidity and mortality after undergoing major digestive system surgery. Each scoring system differs in the included parameters and the outcomes that they measure. The most widely utilized scoring system is the American Society of Anesthesia (ASA) score, but it only provides assessment of an anesthesia complication for a given patient's physiologic status. In contrast, the Physical and Operative Severity Score for the Enumeration of Mortality and Morbidity (POSSUM) and modified Portsmouth-POSSUM scoring systems provide an assessment of the risk of postoperative mortality and morbidity [1]. The scoring system includes 12 preoperative physiologic factors such as age, blood pressure, heart rate, electrocardiogram status, hemoglobin, and electrolytes. It can also be reevaluated in the postoperative period using six additional intraoperative parameters including operative procedure, estimated blood loss, peritoneal contamination, presence of malignancy, and urgency of the operative procedure. However, it has been repeatedly shown that POSSUM and P-POSSUM scores underestimate the risk of morbidity and mortality for patients undergoing major colorectal surgery. In an effort to improve the performance prediction of patients undergoing colorectal resections, a colorectal-specific POSSUM (CR-POSSUM) score was developed [2]. Multiple retrospective and prospective studies have demonstrated improved accuracy with the CR-POSSUM compared to POSSUM and P-POSSUM for predicting mortality after colorectal surgery for a variety of diseases such as cancer and diverticulitis [3, 4]. The CR-POSSUM scoring system has also been validated in multiple health-care systems around the globe such as the USA, the UK, India, Middle East, Caribbean, and Asia [5, 6]. Furthermore, the CR-POSSUM scoring system has improved accuracy in elderly patients defined as >80 years of age when compared to P-POSSUM [7]. There are also suggestions that physiologic health status of an elderly patient is more important than the type of surgery when attempting to predict mortality in this age group. The American College of Surgeons developed a surgical risk calculator using data from National Surgical Quality Improvement Program (NSQIP) to provide patient-specific postoperative risks of various complications. The scoring system is based on over 1.4 million patients with over 1500 unique Current Procedural Terminology (CPT) codes and has performed very well for predicting mortality, overall morbidity, and risk of six specific complications (pneumonia, cardiac, surgical site infection, urinary tract infection, venous thromboembolism, renal failure, and return to the operating room) [8–10]. The NSQIP risk calculator has been shown to underestimate the risk of complications for colorectal resections, and more surgeon- and patient-specific data are needed. However, it remains a useful tool to preoperatively assess morbidity and mortality risk. The risk calculator is available at http://riskcalculator.facs.org.

Tumor Localization

Accurate tumor localization is a critical component of the preoperative assessment of the patient and operative planning. Intraoperative tumor localization can be challenging from several standpoints such a small or early tumor, obese patient, adhesions, laparoscopy, or inadequate tattooing. The utilization of intraluminal anatomic markings for tumor localization is inaccurate, 12–14 % of the time, and may be higher if cecal and rectal tumors are excluded [11]. In other words, the colonoscopy will not accurately locate the tumor 1 out of 7 times. Localization with endoscopic tattooing provides the most accurate method for localization. The tattoo should be placed distal to the lesion and in three separate areas around the circumference of the lumen (Fig. 26.1). A single injection into the mesenteric border or sprayed into the peritoneal cavity may be difficult to identify. Chou et al. reported that endoscopic tattooing provided accurate localization in 94 of 97 (98 %) tumors [12]. This study also examined radiographic methods for tumor localization and found barium enema and CT colonography to be 93 % and 95 % accurate, respectively. Alternatively, endoscopic placement of metal clips at the site of the tumor with immediate plain radiograph (or CT) will localize the tumor with a high degree of accuracy. The ultimate fallback to identify a lesion is intraoperative colonoscopy, ideally using carbon dioxide as the insufflation gas to limit bowel dilatation.

Patients who present with endoscopically obstructing lesions can be effectively evaluated with CT colonography to complete their total colon exam prior to surgery. CT colonography has replaced contrast enema studies in many situations because of improved accuracy in detecting synchronous lesions and often provides better tumor localization. A study of 411 consecutive patients evaluated with CT colonography for incomplete colonoscopy due to a stenosing colorectal cancer and the preoperative CT colonography was compared to the intraoperative and pathologic findings [13]. The study demonstrated a sensitivity of 100 % for detecting

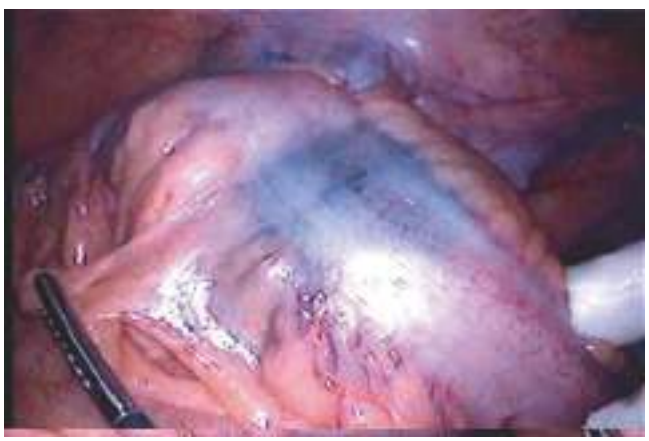

FIGURE 26-1. Tattoo localization of a sigmoid colon cancer.

proximal synchronous cancers and negative predictive value of 97 % for identifying advanced neoplastic lesions (advanced adenomas or cancers). Other studies have demonstrated similar results [14–16]. CT colonography can safely be used in the acute and subacute settings as demonstrated by Maras-Simunic et al. [17]. They examined 44 patients who presented with signs and symptoms of a large bowel obstruction, and CT colonography was able to accurately identify the cause of obstruction as a cancer in 41 and due to a benign process in nine patients. It was also able to accurately detect two synchronous cancers in this small study population. Therefore, if it is safe and feasible, patients presenting with a distally obstructing lesion (clinically or endoscopically) who have a negative CT colonography can be safely treated with a segmental resection without significant risk of missing of synchronous, proximal lesions.

Surgical Technique

Extent of Resection

The National Comprehensive Cancer Network provides the recommended principles of surgical resection for colon cancer, which include obtaining an adequate proximal margin, distal margin, and lymphadenectomy [18]. Colon cancers tend to grow circumferentially around the lumen of the colon, extend out radially and, to a lesser degree, longitudinally along the bowel. Therefore, a 5 cm proximal or distal margin has always been recommended. This is important to remove all tumors bearing mucosa but also to resect all lymph nodes with potential to drain tumor cells. A retrospective study by Rorvig et al. compared final pathologic stage in resected colon cancer specimens with a tumor margin <5 cm to those with a >5 cm margin. The node positivity rate for tumors with a margin <5 cm was 37 % versus 51 % for a margin >5 cm [19]. This highlights that even though the primary tumor does not grow in a longitudinal fashion, lymphatic drainage can extend in a longitudinal or somewhat aberrant fashion. In order to obtain an adequate lymphadenectomy, the feeding vessel to the resected segment of the colon should be taken at its origin. For example, the ileocolic pedicle should be ligated at its origin on the superior mesenteric artery, and the inferior mesenteric artery should be ligated at the level of the aorta. The goal is to clear all regional lymph nodes and provide a minimum of 12 lymph nodes for pathologic evaluation. The impact of an adequate lymph node harvest and evaluation on the accuracy of pathologic staging is well documented and is addressed in Chap. 34. The concept of high versus low ligation of the primary feeding vessel had been debated throughout the literature. Historical data and recent prospective randomized trials have demonstrated no difference in morbidity associated with high ligation [20–23]. However, the rate of positive lymph nodes along the IMA above the level of aortic bifurcation has been reported to be as high as 8 % and when resected is associated with better disease-free survival [22]. Therefore, to maximize the lymph node harvest and to ensure complete resection of potentially metastatic lymph nodes, the mesentery should be resected with the primary vessel ligated at its origin and at least a 5 cm margin distal or proximal to the tumor.

Mesocolic Resection

The concept of total mesorectal excision (TME), which was popularized by R.J. Heald, also pertains to the resection of the colon and associated mesentery along the appropriate fascial planes. Just as the mesorectum is enveloped in a fascia, the mesocolon also has a visceral fascial plane that separates it from the retroperitoneum (parietal fascia). A serosal surface on the bowel and mesentery excludes the anterior aspect of the mesentery from the perineal cavity. Therefore, a complete mesocolic excision (CME) is the sharp dissection of the visceral fascia from the parietal fascia of the retroperitoneum and central ligation of the primary vasculature. Hohenberger et al. adopted this concept in the mid-1990s and published their results on 1329 consecutive patients [24]. They reported an improvement in 5-year local recurrence and 5-year survival from 6.5 to 3.6 % and 82.1 to 89.1 %, respectively, after adoption of CME plus central ligation of the mesenteric vessels. Subsequent studies have demonstrated several other benefits of CME such as increased lymph node harvest, longer vascular ligation, increased resection of extranodal tumor deposits, and increased upstaging, which led to no differences in morbidity but improved locoregional control and survival [25, 26]. The technical concept of sharp dissection of the colon and mesocolon off the retroperitoneum, excision of the mesentery along the lines of resection, and central ligation of the vasculature is as important to colon cancer as TME is to rectal cancer.

Right Colectomy

Tumors located anywhere from the cecum to the proximal transverse colon can safely be treated with a right colectomy. The basic tenets of resection of a right-sided tumor include full abdominal exploration, full mobilization of the right colon, and hepatic flexure with a mesenteric resection including ligation of the ileocolic and right branch of the middle colic vessels at their origin. The resection can be performed safely and effectively via either an open or laparoscopic approach. Data regarding laparoscopy and colorectal cancer is presented in detail below.

Open Approach

The peritoneal cavity can be accessed with a midline incision or as some surgeons prefer a right-sided transverse incision. Once the abdomen is open, explored, and the tumor is located, the wound should be protected with a wound protector. The first step in mobilizing the right colon is to access the retroperitoneum, which can be accomplished laterally along the

white line of Toldt, inferiorly near the cecum, posteriorly under the small bowel mesentery, or superiorly through the lesser sac. Once the retroperitoneum is entered, the mesentery and hepatic flexure are mobilized. The duodenum should be identified and reflected into the retroperitoneum. The omentum associated with the resected colon should be resected as well. With the colon completely mobilized, the vascular pedicles can be ligated. Regardless of the approach used, the step is the same and only their order is different.

Lateral Approach

The surgeon stands on the patient's left side and the first assistant on the patient's right side. The right colon is grasped, and the peritoneum is incised just anterior to the white line of Toldt from the cecum to the hepatic flexure. This allows access to the retroperitoneum or the avascular plane between the visceral and parietal planes of the colon and retroperitoneum. It is important not to violate the mesenteric side of this plane in order to ensure a total mesocolic resection. Under tension, the right colon is separated sharply from the retroperitoneum. The duodenum should be identified and reflected into the retroperitoneum. The cecum is then mobilized off the retroperitoneum, and the posterior attachments of the small bowel mesentery are divided all the way up to the duodenum. This provides the mobility of the small bowel for the anastomosis. With the duodenum safely reflected posteriorly, the hepatic flexure can be mobilized. The surgeon's left hand is placed under the colon and its mesentery and brought out laterally to expose the superior attachments along the inferior edge of the liver. Eventually, the lesser sac is entered, and the lesser omentum is divided. Care must be taken so the plane between the omentum and the transverse colon mesentery is separated, and dissection into the transverse colon is avoided. These two planes are typically fused up to the midline, and beyond this point, the proper lesser sac is entered. After the right colon and hepatic flexure are completely mobilized, the cecum is put on stretch, and the ileocolic pedicle can easily be identified. Since the right colon and its mesentery have been mobilized, there should be bare areas on the cephalad and caudad aspects of the ileocolic pedicle. The peritoneum is incised along the lines of resection for both bare areas allowing isolation of the pedicle so it can be ligated at its origin on the superior mesenteric vessels. The terminal ileal mesentery is divided so that a 5 cm margin on the terminal ileum is obtained. The right branch of the middle colic vessels is identified by elevating the transverse colon mesentery. The pedicle should become evident either by it bowstringing under tension or there should be another bare area where the omentum has been dissected free during the exposure of the lesser sac. The peritoneum should be incised from the distal site of transection of the colon to the base of the pedicle and across the pedicle to the cut edge of the right colon mesentery. The pedicle can then be ligated at its origin. Ileocolic anastomotic techniques will be discussed later.

Posterior Approach

The small bowel is eviscerated and reflected toward the right upper quadrant to expose the posterior aspect of the small bowel mesentery from the ligament of Treitz to the cecum (Fig. 26.2). The peritoneum is incised along this entire length, and the retroperitoneum is entered (Fig. 26.3). The duodenum is readily identified and reflected into the retroperitoneum.

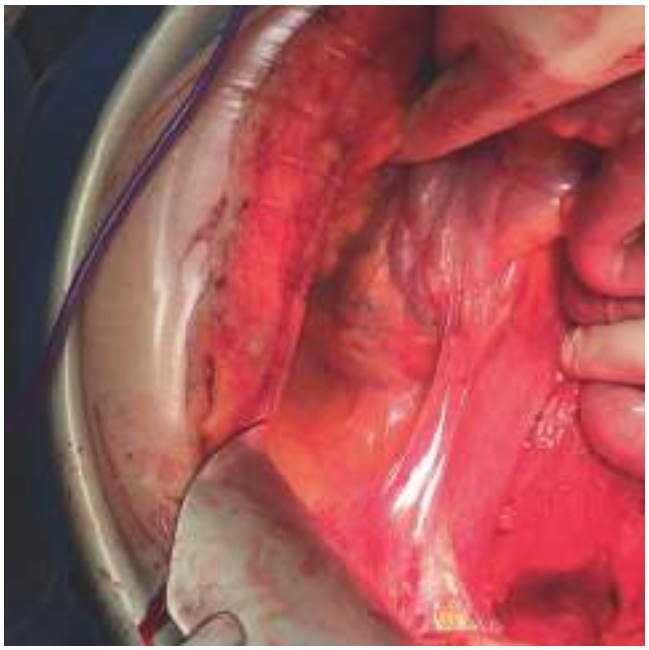

FIGURE 26-2. Exposure of the posterior aspect of the small bowel mesentery for the posterior approach to a right colon.

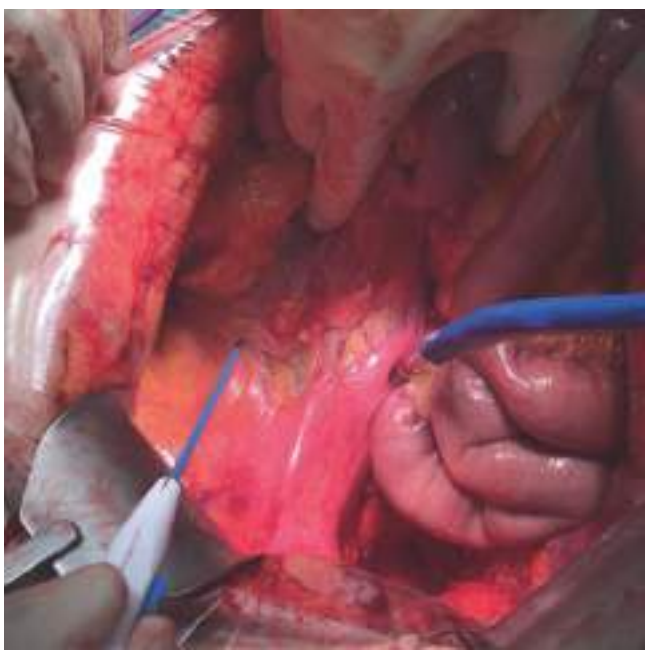

FIGURE 26-3. Entry into the retroperitoneum from the posterior approach to a right colectomy.

The right colon mesentery is elevated off the retroperitoneum out beyond the ascending colon laterally and the transverse colon superiorly. The further this dissection can be performed from a medial-to-lateral direction beyond the transverse colon, hepatic flexure, and ascending colon, the easier the lateral dissection becomes as all that remains are the lateral peritoneal and lesser omental attachments. At this point, starting at the level of the cecum, the surgeon while standing on the patient's left side places his/her left hand under the right colon mesentery and lateral to the colon to expose the lateral peritoneal attachments. These are then divided heading up toward the hepatic flexure. If the dissection is continuing easily, the lesser omentum is separated from the transverse colon mesentery in order to enter the lesser sac. If this plane is difficult to develop, the distal site of transection is identified, and the lesser sac can be entered at this point. This begins by dividing the greater omentum to the level of the colon, and the lesser omentum is bluntly separated from the colon and its mesentery to enter the lesser sac. Once the lesser sac is entered, this plane is developed toward the hepatic flexure. Eventually, the posterior retroperitoneal dissection plane is entered. With the duodenum free, the remaining attachments along the inferior liver can be safely divided. The right colon and hepatic flexure are completely mobilized so the vascular pedicles can be ligated and the mesentery can be resected as described above.

Superior Approach

This dissection begins at the distal site of transection of the transverse colon. This is accomplished by elevating the transverse colon to expose its inferior aspect of the mesentery so the right branch of the middle colon vessels can be identified. It is the first pedicle medial to the bare area of the duodenum and should bowstring under the tension of elevating the transverse colon. The greater omentum is divided up to the transverse colon, and the lesser omentum is separated from the colon and mesentery to enter the lesser sac. As this plane is developed toward the hepatic flexure, the lesser omentum is divided. The stomach superiorly and duodenum posteriorly should be identified and separated from the colon mesentery. Once the lesser omentum or hepatic attachments to the colon are divided beyond the hepatic flexure, the hepatic flexure can be elevated under tension to develop the retroperitoneal plane, identify and free the duodenum, and divide the lateral peritoneal attachments of the right colon. With the peritoneal attachments divided, the remaining colon is mobilized in the same manner as described in the lateral approach. The superior approach is very useful for big bulky or locally advanced tumors of the cecum and proximal ascending colon because it allows for complete mobilization of the colon and mesentery before addressing the site of the tumor.

Anastomosis

The anastomosis can be accomplished via handsewn or stapled techniques. For the handsewn technique, the anastomotic orientation can either be end to end or side to side, and it can be created in a single or double layer of sutures. However, an end-to-end anastomosis is often difficult given the significant size discrepancies between the lumens of the small bowel and colon, so only the side-to-side technique will be presented. For the handsewn technique, the bowel is divided with a stapler or sharply, and the cut edges are closed with an absorbable monofilament 3-0 suture. To close the enterotomy, a Connell stitch is used in a running fashion, and this suture line can be dunked with interrupted Lembert stitches using an absorbable 3-0 suture. The bowel is then oriented in a side-to-side, antiperistaltic fashion. A single-layer anastomosis can be created using an absorbable monofilament 3-0 suture in either a running or interrupted fashion. For a single-layer, interrupted anastomosis, a 6–7 cm enterotomy is created. The first two stitches are placed 180° from each other in the proximal and distal corners, which allows for the "back walls" of the anastomosis to be aligned. With the "back wall" edges of the anastomosis inverted, the next stitch is placed in a bisecting position, and the subsequent stitches are placed in the same bisecting fashion until the "back wall" is complete. For the "front wall" of the anastomosis, sutures are alternately placed at proximal and distal corners until they meet in the middle. The suture is place from an inside out of the first lumen to the outside in of the second lumen. This technique places the knot of the suture intraluminally and inverts the two edges of the bowel. The last stitch will need to be placed in an out-to-in and in-to-out fashion, so the knot is on the outside of the bowel. For a running handsewn anastomosis, two sutures are placed in the middle of the "back wall" of the anastomosis, so one suture will run the anastomosis in the proximal direction and the other suture will run in the distal direction, and after completing the "front wall," the two sutures will be tied together. For the "back wall" of the anastomosis, the suture can be run in an overlapping, baseball-type fashion as the two bowel edges are already inverted. At each corner as the "front wall" of the anastomosis is created, the stitch should be transitioned to a Connell stitch, so the front edges will be inverted as well. For a double-layered anastomosis, the first step is to place the back row of Lembert stitches along the length of the anastomosis. The enterotomies are then made parallel to the Lembert stitches, and the inner layer is created in the same fashion of the running anastomosis described above. The front outer layer of Lembert stitches are then placed once the inner layer is completed.

Stapled anastomoses are most commonly performed in a side-to-side fashion but can also be performed in a side-to-end configuration as well. The traditional side-to-side, stapled anastomosis is created by individually dividing the proximal (Fig. 26.4) and distal limbs (Fig. 26.5) of the bowel with a stapler. The antimesenteric corner of each staple line is then excised, and forks of the stapler are placed into the lumen of each limb of the intestine. The stapler is reassembled and fired with the bowel in an antiperistaltic and antimesenteric fashion (Fig. 26.6). The resulting common enterotomy is reapproximated, so the longitudinal staple lines are offset, which prevents the intersection of more than two staple lines (Fig. 26.7). This common enterotomy can be

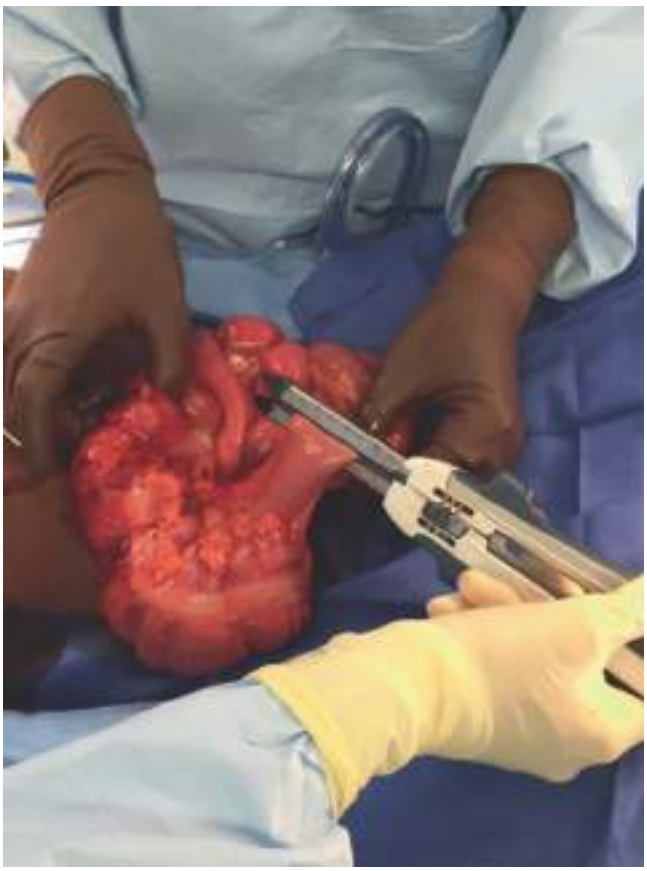

FIGURE 26-4. Division of the terminal ileum. Courtesy of Howard Ross, M.D.

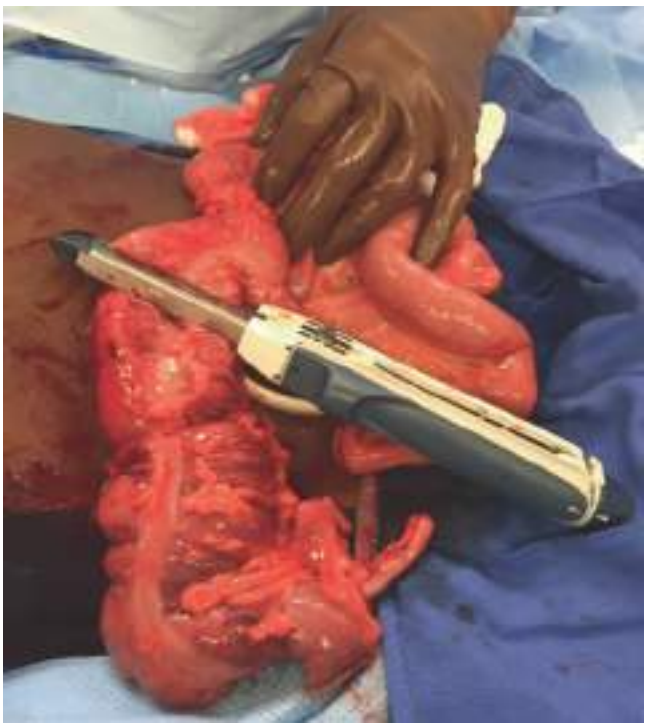

FIGURE 26-5. Division of the transverse colon. Courtesy of Howard Ross, M.D.

FIGURE 26-6. Firing of the linear stapler for a side-to-side stapled anastomosis. Courtesy of Howard Ross, M.D.

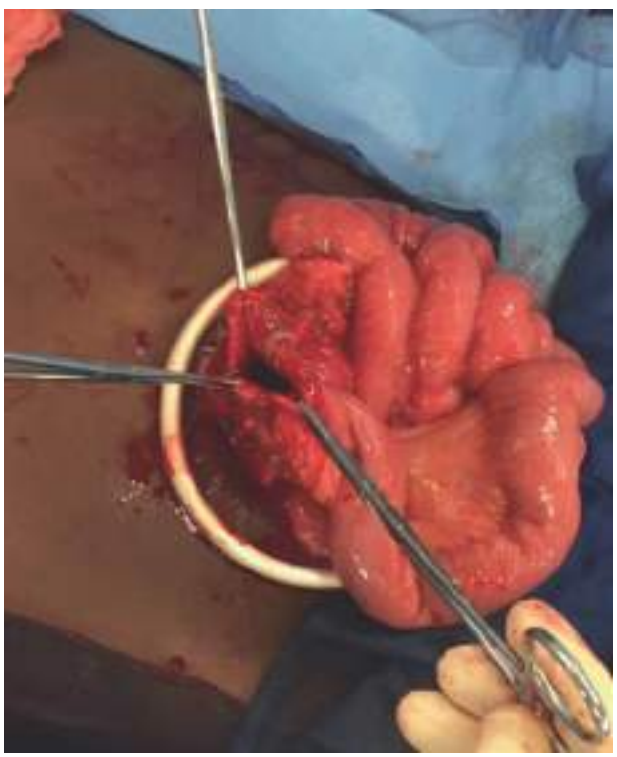

FIGURE 26-7. Closing the common enterotomy by offsetting the longitudinal staple line. Courtesy of Howard Ross, M.D.

closed with suture or staples (Figs. 26.8 and 26.9). An alternative method for creating the side-to-side anastomosis is not to divide the proximal and distal bowel. Enterotomies are then made on the antimesenteric side at the site of transection. The forks of the staple are then passed through each enterotomy where they are reassembled and fired in an antiperistaltic and antimesenteric fashion. The common enterotomy is once again reapproximated with the longitudinal staple lines offset, and then it is closed with a firing of the stapler that incorporates the proximal and distal limbs of the bowel. This technique saves the use of two stapler loads.

A stapled anastomosis can also be created in a side-to-end fashion. This anastomosis is created with an end-to-end anastomotic (EEA) stapler. The distal limb is divided sharply; a purse string is placed; and the stapler anvil, typically 28 or 29 mm, is placed inside. The proximal limb is also divided sharply, and the stapling cartridge is passed into the lumen of the proximal bowel. It is aligned for the spike to come out through the antimesenteric border. The spike should be positioned proximal enough, so the distal aspect of the circular staple line is at least 4 cm proximal to the cut edge of the bowel. This is important to ensure that the distal strip of the bowel remains viable once the enterotomy is closed. The end enterotomy of the proximal limb is then closed with a linear stapler or can be handsewn.

Laparoscopic Approach

Proper room setup and instrumentation are critical for success. A mechanical bed is essential, so the patient can be placed in extremes of positions to maximize the use of gravity for retraction and exposure. The patient needs to be safely secured to the bed, and there are a myriad of techniques to accomplish this such as bean bags, nonskid pads, or shoulder braces. Placing the patient in stirrups has the advantage of allowing the assistant or surgeon to stand between the legs, which allows for visualization in the direction of the dissection and minimizes working against the camera angle. Instrumentation is up to the surgeon's preference, but the use of atraumatic graspers is recommended. There are several energy devices available such as monopolar cautery, bipolar vessel sealers, and ultrasonic sealers that can be used for dissection and ligation of appropriate vessels. With regard to port placement, there are no hard-set rules, and they should be based on the surgical approach and surgeon's preference (Fig. 26.10a, b). Laparoscopic colectomy is a multi-quadrant procedure, so placement of the camera port as to maximize visualization is important. The most optimal place for the

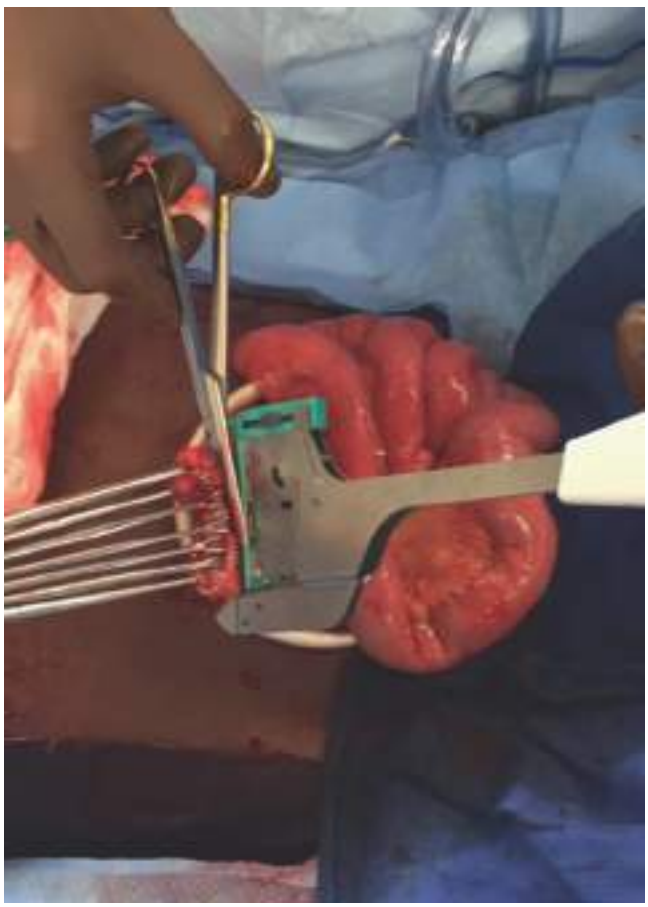

FIGURE 26-8. Closing the common enterotomy for a side-to-side anastomosis. Courtesy of Howard Ross, M.D.

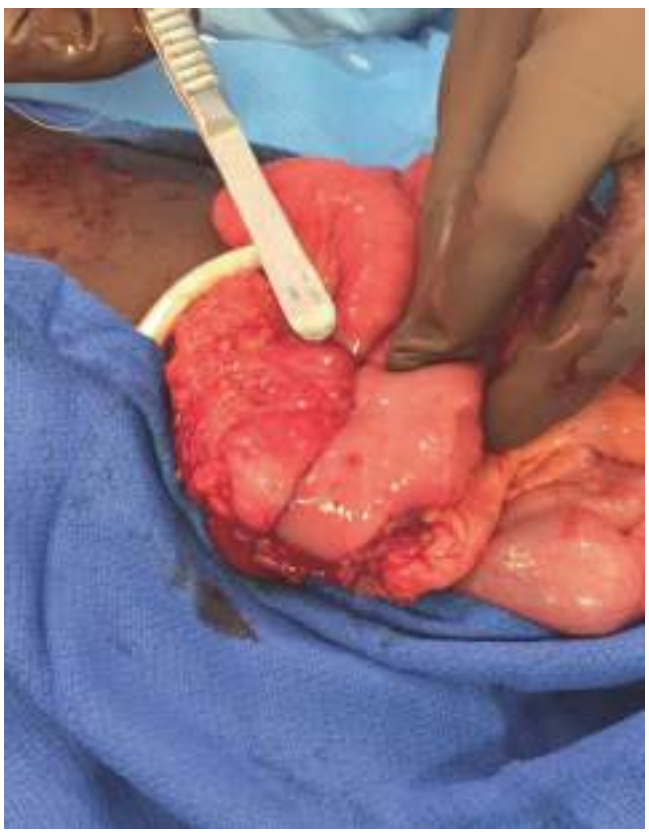

FIGURE 26-9. Complete side-to-side ileocolic anastomosis. Courtesy of Howard Ross, M.D.

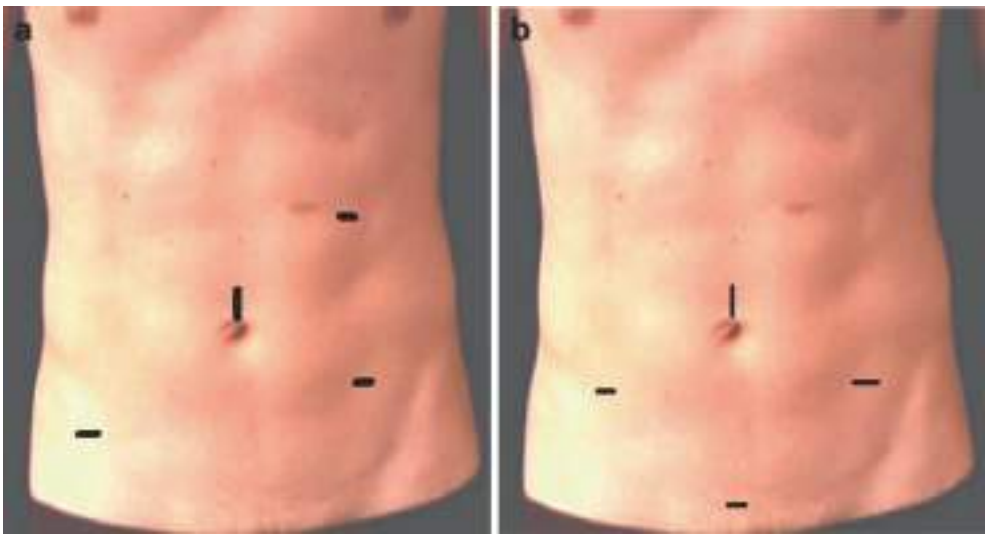

FIGURE 26-10. (**a**) Port placement for a laparoscopic right colectomy, (**b**) port placement for a laparoscopic right colectomy.

camera port is at the apex of the pneumoperitoneum. This is typically in the midline and at the midpoint between the xiphoid process and the pubic symphysis, which can either be above or below the umbilicus. Once pneumoperitoneum is established and the abdomen is adequately explored, the dissection can be carried out in a medial-to-lateral, lateral-to-medial, or posterior approach. For this chapter, the medial-to-lateral and posterior approaches will be presented.

Medial-to-Lateral Approach

Once the peritoneum is accessed, pneumoperitoneum is established and the ports are placed, the abdomen is completely examined, and the tumor is localized. The patient is then placed in steep Trendelenburg and airplaned right-side up. The omentum is placed in the upper abdomen to expose the transverse colon and the hepatic flexure. The small bowel is moved to the left side of the abdomen to fully expose the right colon mesentery. The first step of the dissection is to grab the mesentery at the junction of the terminal ileum and cecum and pull it to the right lower quadrant. This puts the ileocolic pedicle on tension and can be identified as it creates a bowstring in the mesentery. The pedicle is then grasped more proximally, and the peritoneum on the caudad aspect is incised in a direction parallel to the vessels. A wider incision in the peritoneum provides better exposure. Blunt dissection is used to get through the mesentery into the retroperitoneum. Once in the retroperitoneum, the duodenum is readily identified and reflected into the retroperitoneum. This dissection is aided by providing sufficient traction allowing tension, and 15 mmHg of CO_2 pressure aids the development of the avascular planes between the visceral and parietal fascia of the retroperitoneum. The dissection is done bluntly and carried cephalad and lateral as far as possible to safely separate the duodenum from the right colon mesentery, which allows the ileocolic pedicle to be isolated and ligated at its origin from the superior mesenteric vessels. The pedicle can be ligated with clips, staples, or vessel-sealing devices. In order to identify and isolate the right branch of the middle colic vessels, the transverse colon mesentery is elevated under tension. The pedicle is then identified as the vessel that bowstrings just medial to the cut edge of the right colon mesentery. This will help identify the distal site of transection of the colon. The peritoneum from the colon medial to the pedicle is scored down to the base of the pedicle and across it to the mesenteric cut edge. The pedicle is isolated with gentle blunt dissection along this plane. Once through the transverse colon mesentery, the omentum may be adherent to the mesentery in the lesser sac, so it may need to be dissected free to isolate the pedicle. With the pedicle ligated, the window through the mesentery into the retroperitoneum is wider, and the right colon mesentery should be mobilized off the retroperitoneum from the mid-transverse colon, out to the hepatic flexure, and lateral to the ascending colon. Ideally, all that remains at this point is the lateral peritoneal and omental attachments. The cecum is grasped and reflected medially and cephalad, the peritoneum is incised, and the dissected retroperitoneal space is entered. The posterior peritoneal attachments of the small bowel mesentery need to be divided up to the level of duodenum, so the small bowel has enough mobilization for extraction, resection, and anastomosis. Now the lateral attachments of the right colon are divided under tension all the way up the hepatic flexure. If the dissection is proceeding well, the hepatic flexure can be mobilized in this same direction by separating the hepatocolic/lesser omentum from the transverse colon mesentery to enter the lesser sac. If it is difficult to get adequate exposure, the approach can be altered by returning the colon to its anatomic position and identifying the distal site where the colon will be divided. The greater omentum is then divided at this point, and the

lesser sac is entered by separating the lesser omentum from the transverse colon and its mesentery. This is an avascular plane, so it can be separated bluntly under tension. Once this plane has been developed, the dissection progresses toward the hepatic flexure by dividing the lesser omentum. As the dissection progresses beyond the pylorus, the retroperitoneal dissection plane should be entered, and the remaining attachments along the liver can be safely divided because the duodenum has been dissected free of this tissue. The colon is now completely mobilized and can be extracted via the surgeon's site of choice. For cancer cases, the use of a wound protector for extraction is highly recommended to minimize the risk of a wound recurrence. Once the colon is extracted, it is resected, and the anastomosis can be created using one of the techniques described earlier.

Posterior Approach

The peritoneal cavity is entered, ports are placed, and the abdomen is thoroughly explored. The patient is placed in steep Trendelenburg, and the omentum is reflected over the transverse colon to expose the hepatic flexure. The small bowel is placed in the right upper quadrant to expose the posterior aspect of the small bowel mesentery. The patient should not be tilted right-side up, so the small bowel will stay in the right upper quadrant. To obtain the exposure, the terminal ileum is identified and reflected toward the right colon. This will expose the fold of where the small bowel mesentery joins the retroperitoneum. Moving the small bowel to the right upper quadrant and following this fold in a cephalad direction will expose the fourth portion of the duodenum (Fig. 26.11). An instrument in the surgeon's right hand elevates the proximal aspect of the small bowel mesentery under tension, and the first assistant via a right lower quadrant port elevates the distal aspect of the small bowel mesentery, which provides exposure of the duodenum and posterior peritoneum of the small bowel mesentery. With the use of an energy source, the peritoneum is incised from the duodenum to the cecum allowing access to the retroperitoneum, and the right colon mesentery can be elevated off the retroperitoneum. The duodenum is reflected posteriorly, and the mesentery is elevated from the mid-transverse colon, out to the hepatic flexure, and down the ascending colon to the cecum (Fig. 26.12). The further this dissection is carried beyond the colon laterally and superiorly, the easier the lateral and hepatic flexure mobilization will be. Now the patient is airplaned right-side up, and the small bowel and omentum are pulled to the left side of the abdomen to expose the lateral aspect of the right colon. The lateral attachments are divided by grabbing the cecum and retracting it medial and cephalad toward the spleen (Fig. 26.13). The attachments are divided toward the hepatic flexure as far as possible. Just like that described in the medial-to-lateral approach, if the lesser sac can be easily developed and entered, the dissection can proceed in this direction. If this approach is too difficult, place the colon back in its anatomic position, and identify the distal site where the colon will be

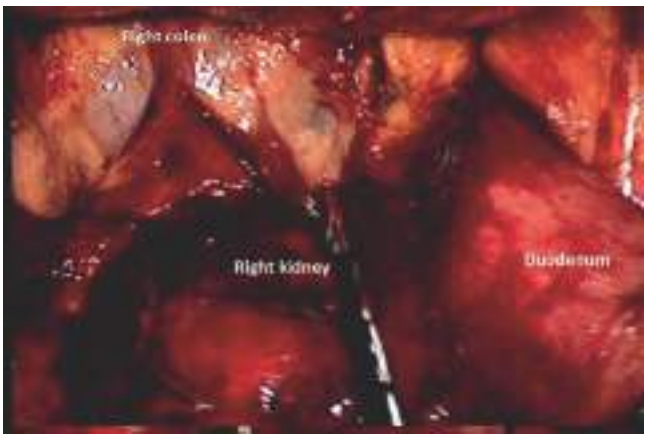

FIGURE 26-12. Posterior mobilization of the right colon mesentery off the retroperitoneum.

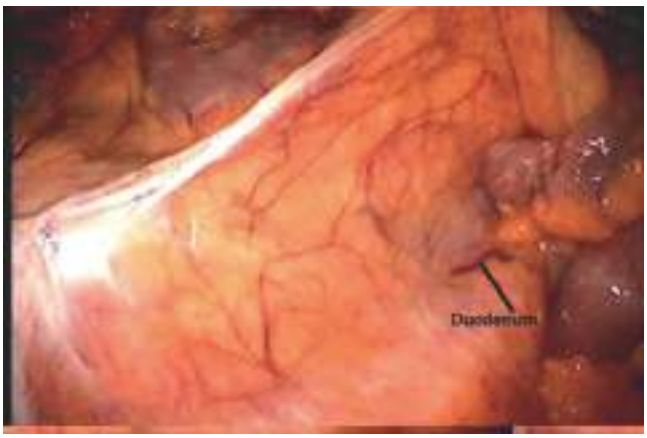

FIGURE 26-11. Exposure of posterior aspect of the small bowel mesentery for a laparoscopic posterior approach.

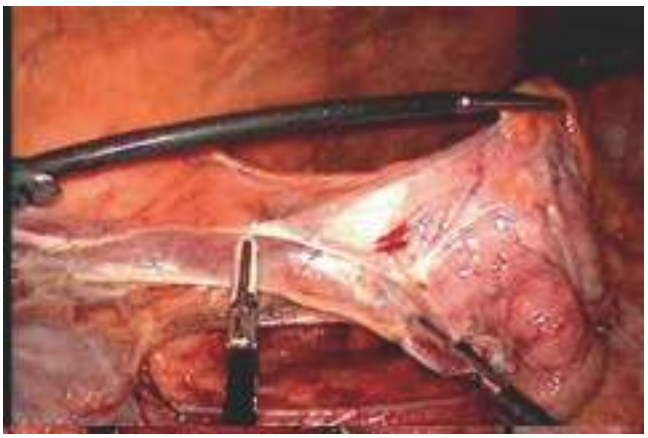

FIGURE 26-13. Exposure of the lateral attachments after the posterior dissection.

divided. This is accomplished by elevating the transverse colon mesentery and putting the right branch of the middle colic vessels on stretch (Fig. 26.14). The vessel is medial to the bare area of the right colon mesentery. The greater omentum is then divided at this point, and the lesser sac is entered by separating the lesser omentum from the transverse colon and its mesentery (Fig. 26.15). This is an avascular plane, so it can be separated bluntly under tension. Once this plane has been developed, the dissection progresses toward the hepatic flexure by dividing the lesser omentum. As the dissection progresses beyond the pylorus, the retroperitoneal dissection plane can be identified by the purplish tissue planes indicative of the previous posterior dissection. This plane can be safely entered, and the remaining attachments along the liver can be safely divided because the duodenum has been dissected free of the right colon mesentery (Fig. 26.16). At this point, the right colon and hepatic flexure have been completely mobilized. The next step is to isolate and ligate the vasculature. The ileocolic pedicles are identified by grasping the mesentery on the inside of the ileocecal valve and pulling to the right lower quadrant. The pedicle will bowstring, and because it has been mobilized off the retroperitoneum, bare areas can be seen on the caudad and cephalad (bare area over the duodenum) aspects (Fig. 26.17). The peritoneum on the caudad aspect is scored parallel to the pedicle, and blunt dissection through the mesentery will allow entry into the retroperitoneum. The duodenum can be visualized to ensure it is completely free of the pedicle. The peritoneum is then scored over the base of the pedicle toward the cephalad bare area, and the pedicle is safely isolated and ligated. The medial cut edge of the mesentery near the right branch of the middle colic vessels is grasped and reflected to the video right, allowing any remaining attachments to the duodenum, stomach, or omentum which can be seen and gently sweep free. The transverse colon mesentery is then elevated under tension, which allows for the right branch to bowstring, and, ideally, a bare area is seen medial to the vessel (Fig. 26.18). The peritoneum is then scored from the colon down to the base of the vessel and then across it to connect with the cut edge of the mesentery. Blunt dissection of the bare area will allow access into the lesser sac and for safe ligation of the pedicle. Because the omentum has been previously dissected free from entering the lesser sac, the vessel can be safely ligated without the risk of injury to

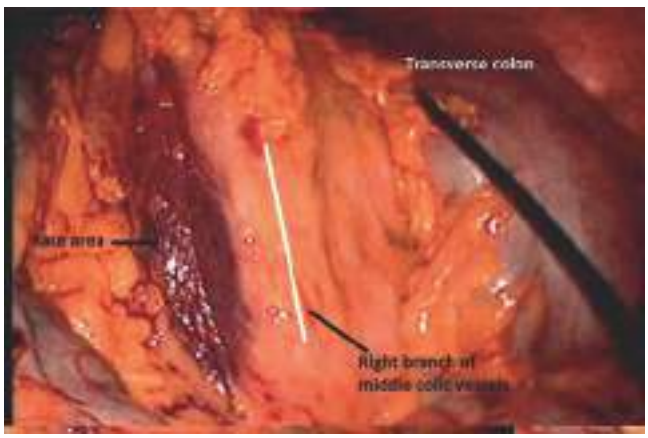

FIGURE 26-14. Exposure of the right branch of the middle colic vessels.

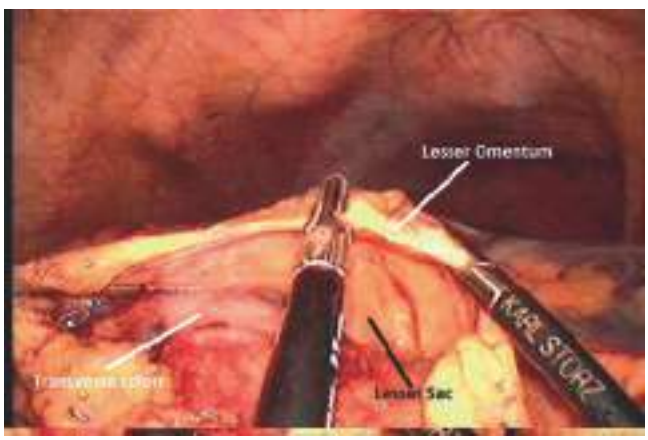

FIGURE 26-15. Entering the lesser sac by separating the lesser omentum from the transverse colon at the distal site of transection.

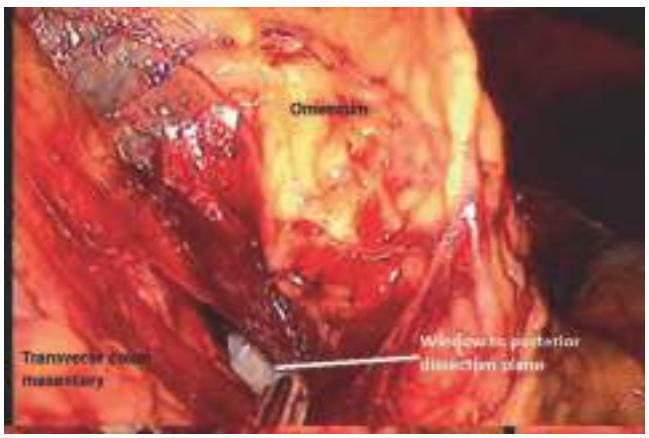

FIGURE 26-16. Exposure of posterior dissection plane from the superior approach.

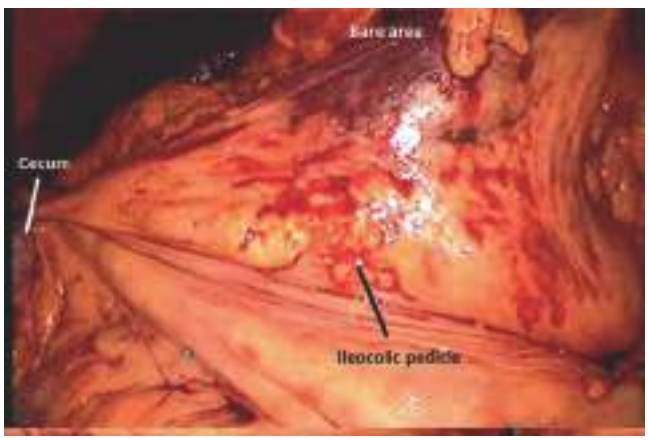

FIGURE 26-17. Identification of the ileocolic pedicle.

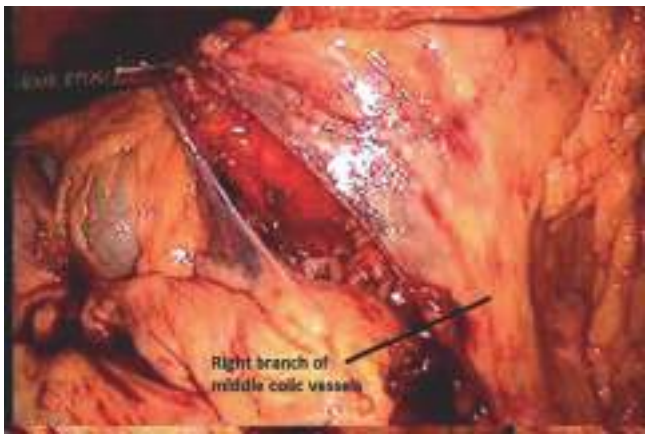

FIGURE 26-18. Identification of the right branch of the middle colic vessels.

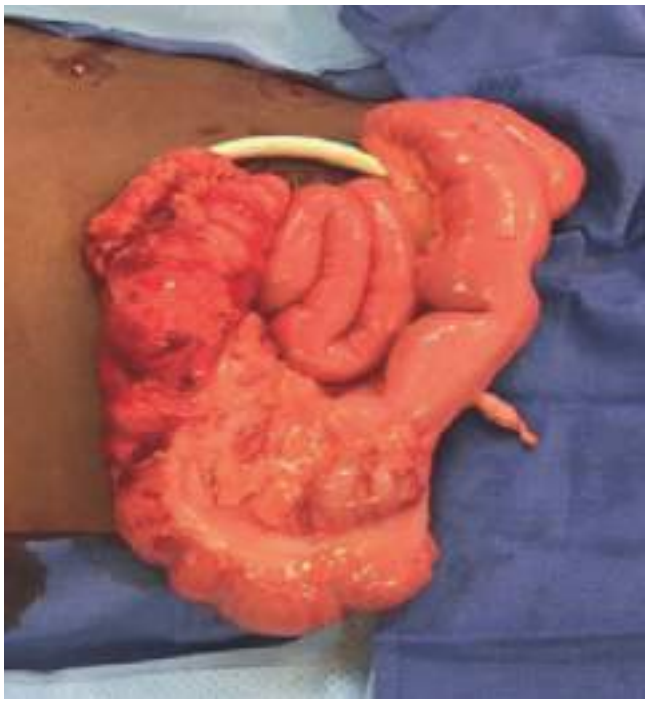

FIGURE 26-19. Extraction of the right colon.

surrounding structures. The colon can now be extracted and resected and the anastomosis created as described in the medial-to-lateral section (Fig. 26.19).

Left Colectomy

Open

The patient is placed in the lithotomy position to have access to the perineum for the anastomosis and anastomotic assessment. One of the patient's arms can be tucked to his/her side, and the Mayo stand for the scrub nurse can be placed over the patient's head, or the scrub nurse can stand off one of the patient's hips. The peritoneum is entered via a midline incision that allows for complete exploration and mobilization of the splenic flexure. With the abdomen open, a wound protector can be inserted, and a self-retaining retractor can be utilized. Initial exposure of the left colon anatomy is accomplished by packing the small bowel in the right upper quadrant, so the base of the left colon mesentery includes exposing the inferior mesenteric artery (IMA) at its origin (Fig. 26.20) and the inferior mesenteric vein (IMV) as it courses near the ligament of Treitz and inferior border of the pancreas (Fig. 26.21). The cecum and terminal ileum are also

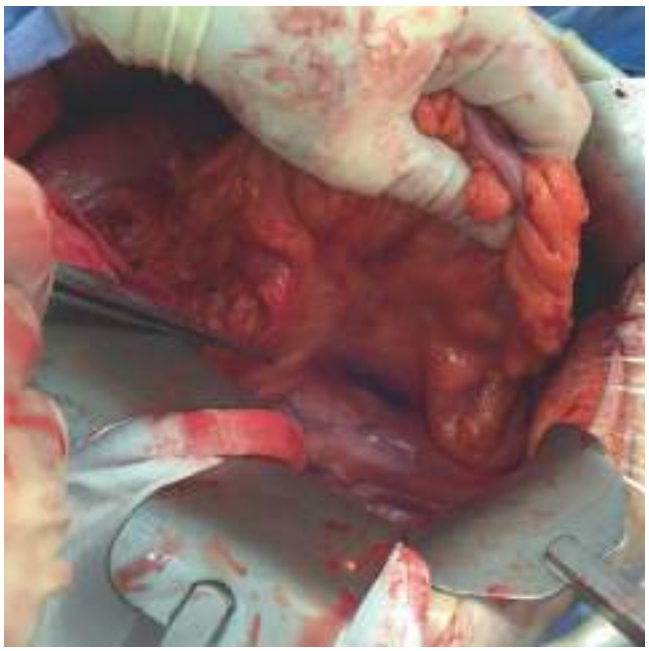

FIGURE 26-20. Medial exposure of the IMA.

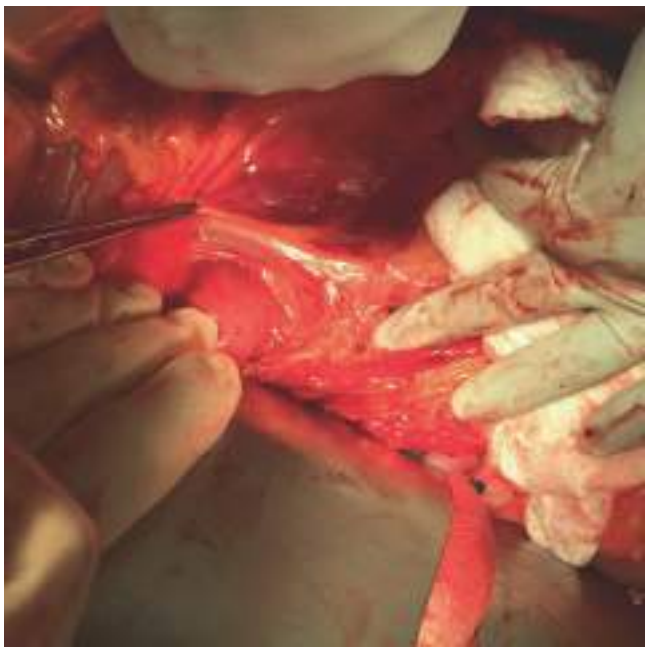

FIGURE 26-21. Medial exposure of the IMV.

packed away to provide complete exposure into the pelvis and the sacral promontory. The dissection begins with division of the lateral attachments of the sigmoid colon to allow for visualization of the white line of Toldt from the upper rectum to the proximal descending colon. The sigmoid colon and descending colon are elevated and retracted medially, and a long incision is made in the peritoneum to enter the retroperitoneal plane. With adequate tension on the colon and its mesentery, the areolar plane of dissection along the retroperitoneal plane is easily identified. The dissection is facilitated by exposing and dividing the retroperitoneal attachments along a plane of dissection as long as possible. The sigmoid colon and its mesentery should be completely medialized to the midline to expose and identify the left ureter. The dissection is then carried toward the splenic flexure. Mobilization of the splenic flexure can be facilitated by dissecting the posterior aspect of the mesentery up to the inferior border of the pancreas. The anatomy of the splenic flexure can be obscured by attachments of the omentum to the descending colon or medial aspect of the transverse colon. Separating these attachments restores normal anatomy, which can make the splenic flexure mobilization much easier. The next goal is to enter the lesser sac, and this is accomplished by separating the omentum from the transverse colon. By incising the peritoneal layer along the length of the transverse colon, the lesser sac is eventually entered, and the posterior attachments of the omentum to the colon mesentery can be exposed and divided. This will allow the lesser sac to be completely exposed from the flexure to beyond midline. This will also expose the remaining lateral attachments of the flexure which can be divided by either retracting the colon medially or placing a hand into the retroperitoneum and rolling the colon medially over the hand. With the lesser sac completely open and the flexure mobilized, the posterior attachments along the inferior border of the pancreas can be divided. With the posterior mesenteric dissection carried all the way up to the inferior border of the pancreas, the surgeon's right hand is passed into the retroperitoneum in the lateral-to-medial direction. The fold of the splenic flexure mesentery can be palpated and separated from the inferior aspect of the pancreas, and the overlying peritoneum is divided to the midline. Care should be taken not to injure the IMV as the dissection is carried medially. With the left colon and splenic flexure completely mobilized, the vascular pedicles can be isolated and ligated. The sigmoid colon is elevated and retracted laterally to expose the base of the mesentery at the level of the sacral promontory. The peritoneum is incised from just below the promontory toward the attachments of the proximal jejunum and ligament of Treitz. This will allow for the superior rectal artery to be elevated off the retroperitoneum and expose the lateral plane of dissection. The surgeon can then pass his/her right hand under the superior rectal artery and divide the cephalad attachments, so the IMA can be isolated at its origin from the aorta (Fig. 26.22). The artery is isolated by creating a window on its cephalad side and medial to the IMV. It can then be ligated once the left ureter is clearly out of harm's way. The IMV is now elevated off the retroperitoneum and isolated at the inferior border of the pancreas, and its ligation will ensure adequate mobilization for a tension-free anastomosis (Fig. 26.23). This allows for complete exposure of the retroperitoneum (Fig. 26.24). The proximal site of transection is dependent upon the location of the tumor and should ensure a minimum of a 5 cm margin. The distal site of transection should be at the proximal rectum to ensure an adequate distal margin and avoid having distal sigmoid colon

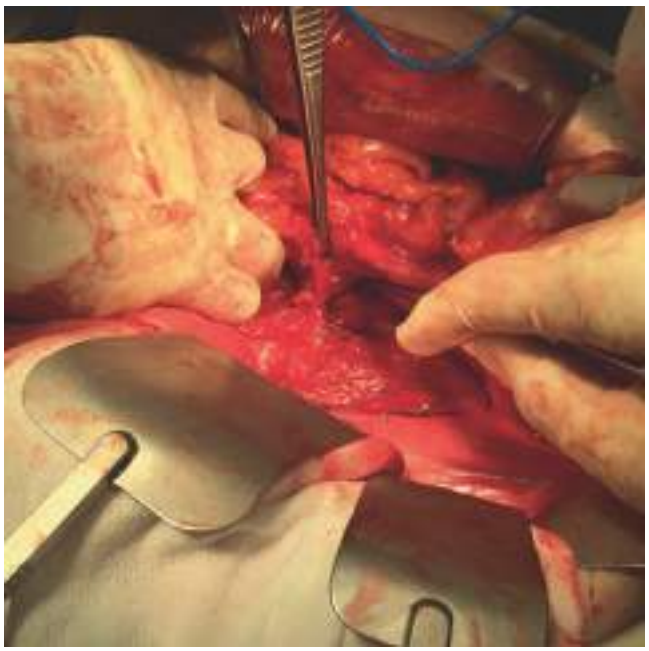

FIGURE 26-22. Isolation of the IMA.

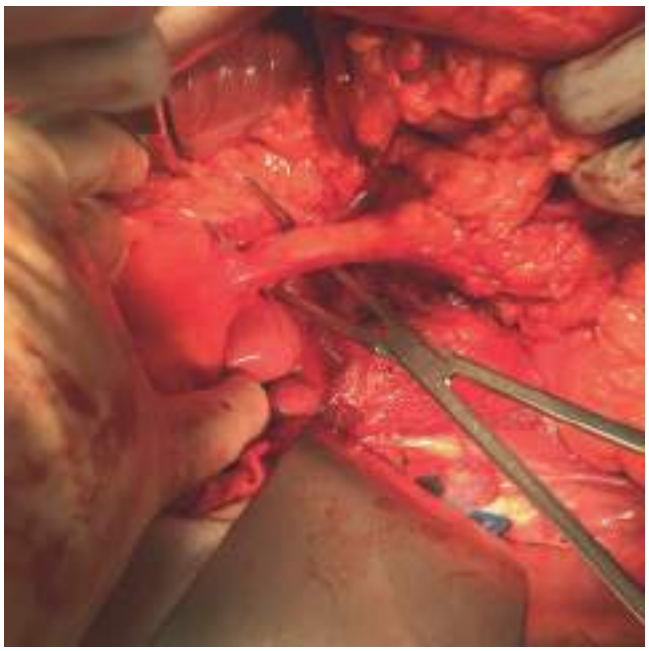

FIGURE 26-23. Isolation of the IMV.

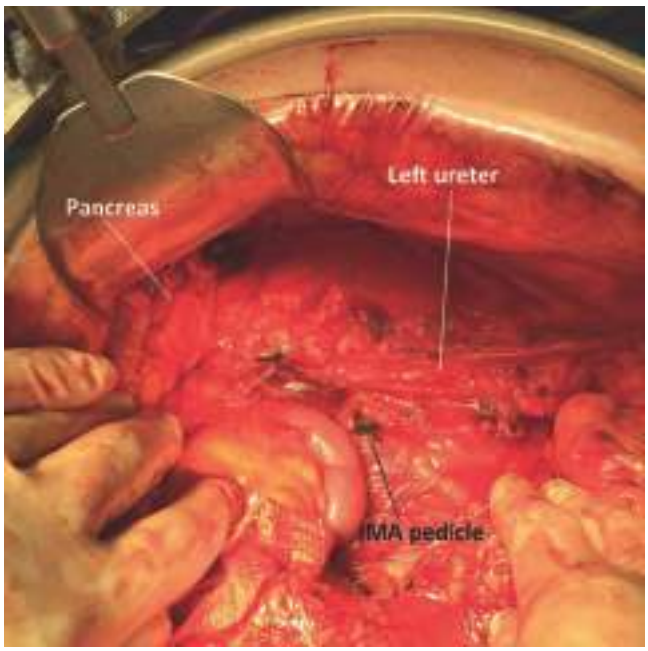

FIGURE 26-24. Left retroperitoneum.

included in the anastomosis. The rectum is stapled and divided with a linear stapler. The anastomosis is most easily accomplished with an end-to-end double-stapled technique (see Chap. 9). The anvil is placed in the proximal colotomy after the creation of a purse string. The purse string is tightened while ensuring that the edges of the colotomy are everted, so all edges of the colotomy are incorporated into the purse string. The stapling cartridge is passed transanally to the top of the rectal stump. The stapler head should be flushed with the transverse staple line. A rectal fold or pelvic adhesion will sometimes prevent the stapler head from sitting flush. If a rectal fold is preventing this, the rectum can be further mobilized and divided a few centimeters lower, and if it is a pelvic adhesion preventing passing of the stapling cartridge, further mobilization of the rectum will often be adequate to get the stapler up to the staple line. The spike of the stapler is deployed just anterior or posterior to the transverse staple line. The anvil is reassembled to make sure there is no twist in the left colon and its mesentery.

Anastomotic Assessment

Anastomotic assessment with either an air leak test alone or combined with endoscopic visualization is critical to ensuring a safe anastomosis. Anastomotic assessment has been shown to be associated with a decreased incidence of anastomotic leak from left-sided anastomosis. Kwon et al. audited the data from the Washington state's Surgical Care and Outcomes Assessment Program regarding the utilization and outcomes associated with routine testing of colorectal anastomosis [27]. For this study, anastomotic testing consisted of insufflation of Betadine, methylene blue, or air under pressure, and an adverse event included a return to the operating room for an ostomy creation, anastomotic revision, or drainage of abscess associated with a documented leak. For hospitals where the surgeons routinely performed anastomotic leak tests (defined as occurring in >90 % of cases), there was a 75 % lower risk of anastomotic leak (adjusted OR, 0.50; 95 % CI, 0.05–0.99) compared to those hospitals that employed selective leak testing (adjusted OR, 2.68; 95 % CI, 1.14–6.26). A retrospective review by Ricciardi et al. demonstrated an overall leak rate of 4.8 % for 998 patients that underwent a left-sided colorectal anastomosis without proximal diversion [28]. Ninety percent of patients underwent air leak testing, and the associated leak rates were 7.7 % with a positive air leak test, 3.8 % with a negative air leak test, and 8.1 % when no air leak test was performed ($p<0.03$). Additionally, they examined the measures taken to address the positive air leak test and the associated outcomes. Suture repair alone resulted in a leak rate of 12.2 % versus 0 % ($p=0.19$) for either anastomotic revision or proximal diversion. The lack of statistical significance is most likely related to the small number of leaks. Despite this, it is clear that anastomotic testing is critical, and an anastomosis with a positive leak test can be safely managed with a low incidence of a clinical leak. An acceptable alternative to the above-described leak testing is an endoscopic assessment. Li et al. compared the outcomes of patients with left-sided colorectal anastomosis who underwent routine intraoperative endoscopy (107 patients) versus those who had selective intraoperative endoscopy (137 patients) [29]. The routine endoscopy group had a 0 % anastomotic leak rate, and 0.9 % of the patients had bleeding from the staple line that required intervention. Twenty-two percent of the patients in the selective group underwent endoscopic assessment with a 5 % incidence of an anastomotic complication. This was not statistically significant, but it does highlight the safety and utility to assess for and address anastomotic complications intraoperatively. A second study examining the utility of intraoperative endoscopy included 415 consecutive patients with 17 patients having an anastomotic abnormality identified [30]. Fifteen patients had an air leak from the staple line, and all were managed safely without an anastomotic leak. The data above clearly supports the routine use of anastomotic assessment for left-sided anastomosis, which can be performed with either an air leak test alone or in conjunction with endoscopic visualization. However, successful anastomotic healing is also dependent upon both ends of the bowel having adequate blood supply and the creation of a tension-free anastomosis using soft, pliable, normal bowel.

Straight Laparoscopic Medial-to-Lateral Approach

The patient is positioned and secured to the operating table in the same manner as described above for the laparoscopic right colectomy. Typically, both arms are tucked to the patient's sides, and the legs are in the lithotomy position. The

abdomen is accessed via an open or closed technique in the supraumbilical position. There are various options for port placement, and the choice is dependent upon surgeon preference (Fig. 26.25). Typically, there are three working ports—two for the surgeon and one for the assistant. Once the abdomen has been thoroughly explored and the lesion located, the patient is placed in steep Trendelenburg and airplaned so the left side is up. This allows gravity to retract the small bowel to the right upper quadrant and expose the left colon mesentery. The omentum is reflected cephalad to the transverse colon to expose it and the splenic flexure. The IMV and the superior rectal artery are the vascular landmarks to be identified. At the level of the sacral promontory, the superior rectal artery is grasped and elevated with the surgeon's right hand. This will allow for the course of the artery to be seen and traced to its origin. With the energy source of choice in the left hand, the peritoneum is incised from below the sacral promontory to the IMA origin on the aorta. The wider the incision, the wider the window to the retroperitoneum will be, and this will maximize visualization of the retroperitoneum. Once the incision is made, the facial covering of the artery can be identified. Early in this dissection, the proper retroperitoneal plane is often difficult to see because it is heading up and away from the view as it follows the curve of the pelvic brim anteriorly. With a wide window to the retroperitoneum, the superior rectal artery can be elevated and pulled slightly toward the camera to visualize the proper plane. The retroperitoneum is swept posteriorly until the left ureter is identified. If the left ureter is difficult to identify, an alternative approach should be taken, and it will be described below. Once the left ureter is safely swept into the retroperitoneum, the superior rectal artery is dissected free to the origin of the IMA at the aorta. The peritoneum is then scored across the base of the IMA and medial to the IMV. The vein is then grasped and elevated off the retroperitoneum by scoring the peritoneum up to the ligament of Treitz. This will allow access into the retroperitoneum once again, and the plane is developed in a caudad direction to join with the original retroperitoneal dissection plane. The IMA is safely isolated, and the left ureter can be traced from the pelvic brim up to near the kidney. The IMA can be ligated with any energy source of choice. Next, the IMV can be isolated by separating the mesentery from the retroperitoneum to the inferior border of the pancreas. Once isolated, it can be safely ligated. Now there is a giant window into the retroperitoneum, and the left colon mesentery is mobilized out beyond the colon laterally. This dissection should extend from the sigmoid colon up to the splenic flexure, so all that remains are the lateral attachments. Beginning near the pelvic brim, the lateral peritoneum is incised by retracting the sigmoid colon medially and cephalad. This will allow for entry into the medial plane of dissection, and the lateral dissection continues toward the splenic flexure. As the splenic flexure is neared, there needs to be a transition from dividing the lateral peritoneal attachments to separating the omentum from the colon, and this is dependent upon the adhesions between the two structures. Mobilization of the splenic flexure usually requires a third working instrument. The omentum just above its attachment to the colon is retracted anteriorly, and the colon is retracted posteriorly, which puts the plane to be incised in a vertical position. This superficial peritoneal plane is incised toward the midline, and the lesser sac is eventually entered. Once the lesser sac is entered, the deeper attachments of the omentum and transverse colon can be divided. These deeper attachments are identified by pulling the colon down to the lower abdomen and watching for where the omentum moves or is attached. The omentum and colon are grabbed at this point, and by making the plane vertical, they are divided. The lesser sac is completely opened in this fashion so that all that remains are the peritoneal attachments to the inferior border of the pancreas. These attachments are divided by retracting the splenic flexure medially and caudad while elevating it off the retroperitoneum. This will allow for visualization along the retroperitoneal and lesser sac sides of this attachment. Division of this attachment to the midline will allow for adequate mobilization for extraction, resection, and tension-free anastomosis. The rectum can be divided either intracorporeally or in an open fashion through a suprapubic extraction site. If the rectum is divided intracorporeally, the colon can be extracted through either a left lower quadrant or suprapubic site. With either method of rectal division, the colon is extracted and resected, and the anvil is placed in the same method as described above for an end-to-end anastomosis. The proximal colon is then returned to the abdomen, and the extraction port can be closed temporarily or definitively. Under laparoscopic visualization, the stapler is passed transanally up to the top of the rectal stump, and the anvil is reassembled making sure there is no twist in the left colon and its mesentery. An air leak test or endoscopic assessment is performed under laparoscopic

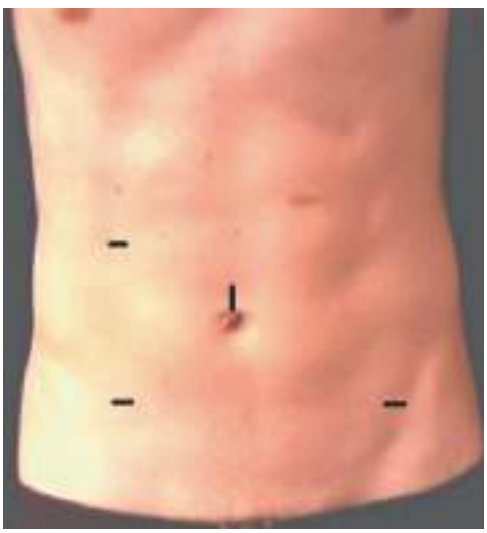

FIGURE 26-25. Port placement for laparoscopic left colectomy.

visualization. Typically, only 10–12 mm port sites need to have the fascial defect closed, and this can be accomplished open via the skin incision or laparoscopically using a transfascial suture passer.

Hand-Assisted Medial-to-Lateral Approach

Patient preparation and position are the same as for the straight laparoscopic approach. The hand port can be placed in the suprapubic, periumbilical, or left lower quadrant based on surgeon preference (Fig. 26.26). A suprapubic hand port has the advantage of having direct access to the pelvis to aid the pelvic dissection, divide the rectum, perform the anastomosis, and manage anastomotic complications. The port can be placed through a vertical midline or Pfannenstiel incision. For a suprapubic hand port, the camera port is placed in the supraumbilical position to avoid interfering with the hand port. A working port is placed on the right side, half the distance between the hand and camera ports and lateral to the rectum muscle. A second working port is placed in the left lower quadrant to help with the lateral and splenic flexure mobilization. This port is placed lateral to the rectus muscle and as low as possible to minimize the time working against the camera. With the patient placed in steep Trendelenburg and left-side up, the small bowel is put in the right upper quadrant, and the omentum is reflected to the upper abdomen. This exposes the left colon mesentery and splenic flexure as previously described. The surgeon stands on the patient's right side and places his/her right hand in the abdomen. The superior rectal artery at the level of the sacral promontory is grasped and elevated (Fig. 26.27), and the peritoneum is incised as described above (Fig. 26.28). The hand acting as a retractor elevates the vessel to expose the retroperitoneum. The identification of the left ureter and its reflection into the retroperitoneum is the same as described above (Fig. 26.29). Once the left ureter is identified and separated from the mesentery, the index finger is used to elevate

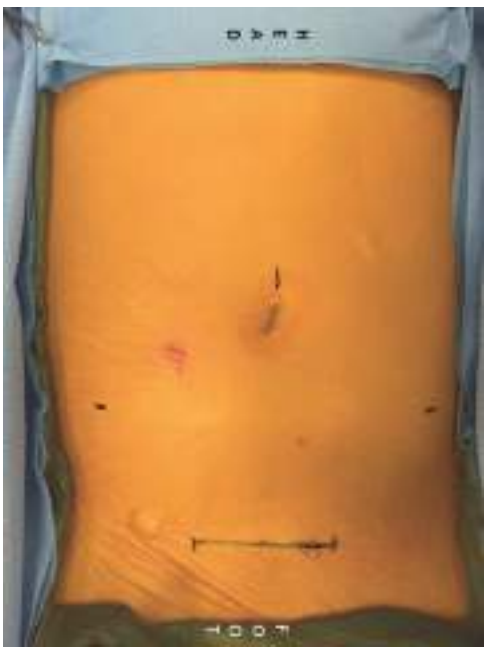

FIGURE 26-26. Port placement for HALS left colectomy.

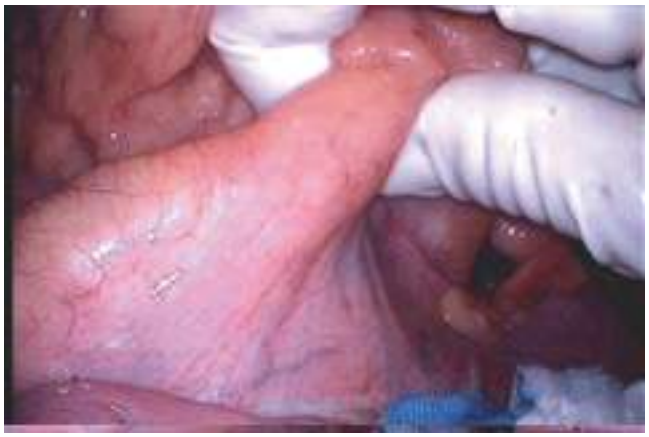

FIGURE 26-27. Isolation of the superior rectal artery at the level of the sacral promontory.

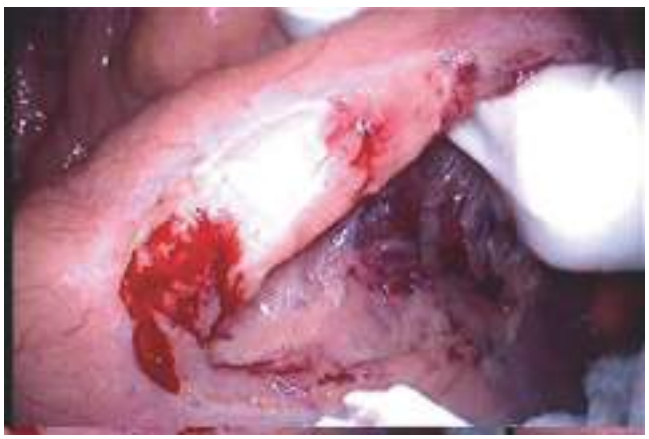

FIGURE 26-28. Accessing the retroperitoneum at the level of the sacral promontory.

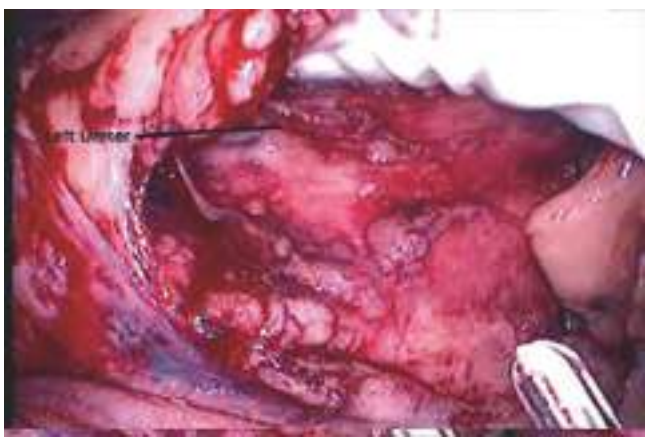

FIGURE 26–29. Identification of the left ureter from a medial-to-lateral approach.

the superior rectal artery under tension. The middle finger can then bluntly sweep down the retroperitoneum working toward the origin of the IMA (Fig. 26.30). Care should be used to sweep the retroperitoneal tissue and associated sympathetic nerves posteriorly to avoid their injury during the ligation of the vessel. This dissection is carried cephalad to the vessel to expose and elevate the window medial to the IMV. The peritoneum is incised across the IMA origin, and the retroperitoneum can be entered medial to the IMV. The hand now elevates the IMV, and the peritoneum is incised up to the ligament of Treitz (Fig. 26.31). The retroperitoneum is swept down, and the thumb elevates the IMV and mesentery to keep it on tension. Once the retroperitoneal plane is adequately developed, the index finger elevates the IMV, and the middle finger sweeps the retroperitoneum down as the IVM is elevated to isolate it at the inferior border of the pancreas (Fig. 26.32). Now that both vascular structures are safely isolated and the left ureter is safely in the retroperitoneum, both vessels can be ligated (Fig. 26.33). For ligating both the artery and vein, the index and middle fingers are placed in the retroperitoneum behind the vessel to create space, the fourth and fifth fingers lay in front of the vessel to protect the small bowel, and the thumb can help elevate any mesentery or fat obscuring the view (Fig. 26.34). With both pedicles ligated, the hand is placed palm down under the mesentery. It elevates the mesentery under tension, so the retroperitoneal dissection can be carried out laterally beyond the colon (Fig. 26.35). The extent of the dissection should be from the

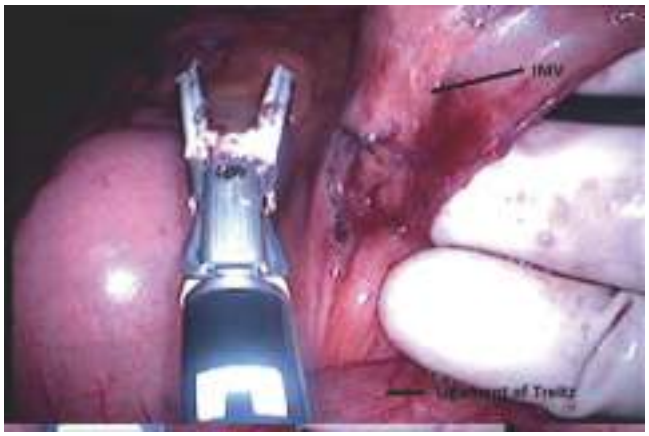

FIGURE 26-32. Isolating the IMV near the ligament of Treitz and the inferior border of the pancreas.

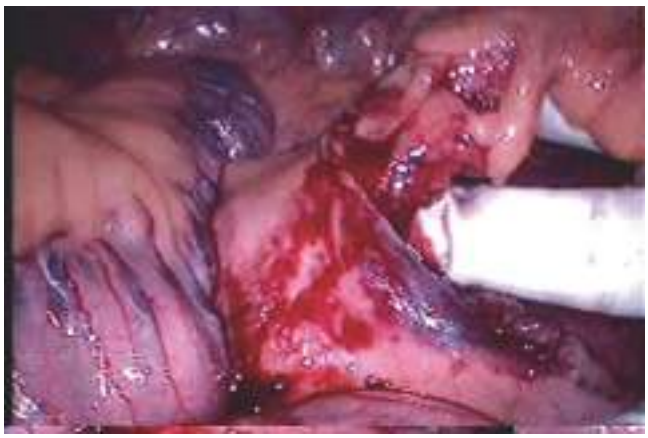

FIGURE 26-30. Isolating the IMA at its origin.

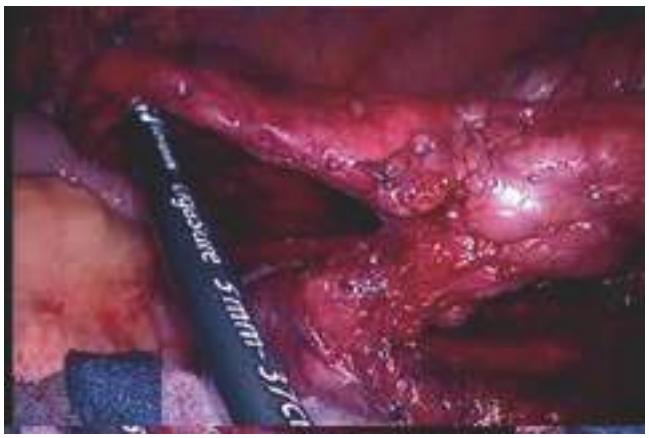

FIGURE 26-33. Safe isolation of the IMA.

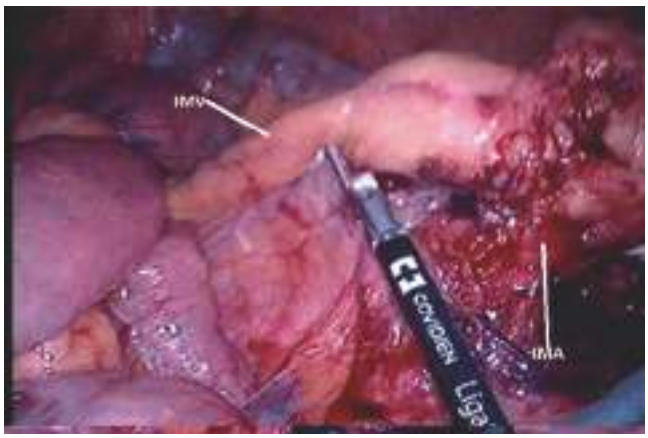

FIGURE 26-31. Accessing the retroperitoneum medial to the IMV.

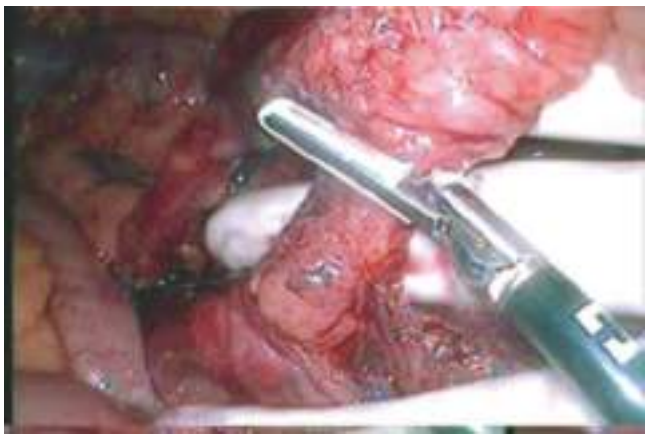

FIGURE 26-34. Hand position for ligating the IMA and IMV.

sigmoid colon caudad up to the splenic flexure cephalad and along the inferior border of the pancreas medially. The lateral dissection begins by mobilizing the sigmoid colon. Often, the hand gets in the way for this dissection, so solutions include depressing the sigmoid colon with the fingers and passing the energy device between the fingers to get the proper angle or removing the hand and placing an instrument through the hand port to begin the dissection straight laparoscopically. Once the retroperitoneal dissection plane is entered (Fig. 26.36), the hand can be passed into the retroperitoneum, and the lateral attachments can be exposed on the hand just like an open case (Fig. 26.37). The assistant stands between the legs and uses the left lower quadrant port to divide the tissue. The dissection continues toward the splenic flexure until the need to transition to the omentum. At the omental attachments, the omentum is elevated and pulled to the video right with the grasper, and the colon is retracted down with the hand (Fig. 26.38). Pulling with the grasper to the right helps to keep it out of the way of the energy device during this dissection. The peritoneum is incised along the transverse colon, and the lesser sac is eventually entered. With the hand and instrument, the colon is pulled to the lower abdomen, and the next level of omental attachments is identified. At this point, the omentum is elevated, and the colon is depressed allowing for the attachments to be divided. This is continued until the lesser sac is wide open from the splenic flexure to the midline (Fig. 26.39). The only remain-

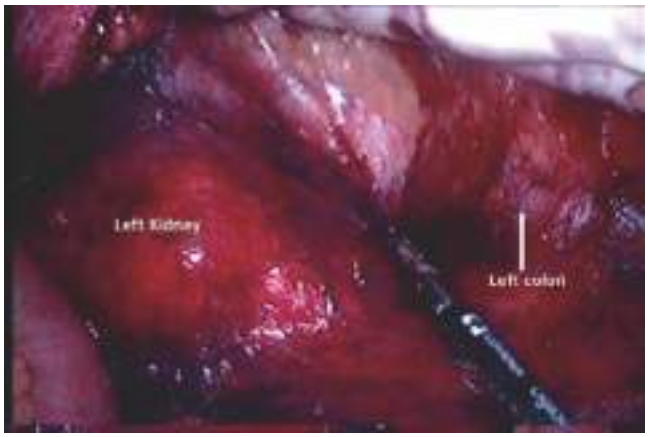

FIGURE 26-35. Medial-to-lateral mobilization of the left colon mesentery off the retroperitoneum.

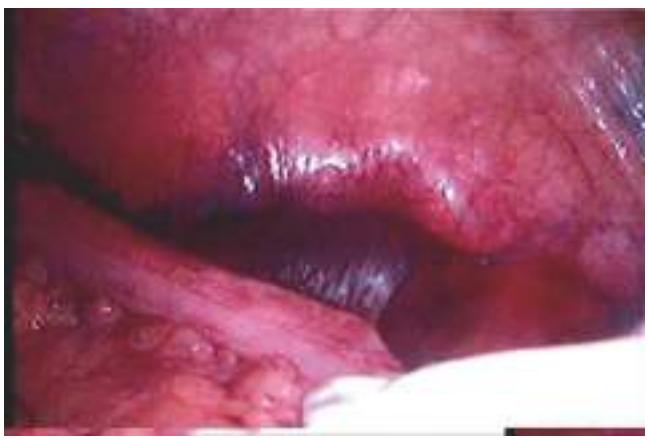

FIGURE 26-36. Incision of the lateral attachments and entry into the retroperitoneal plane.

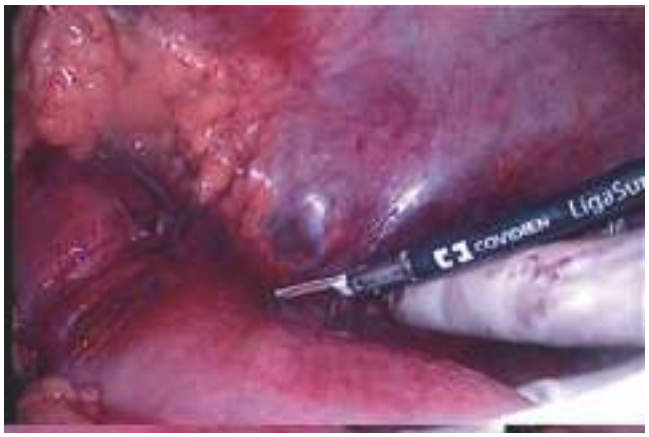

FIGURE 26-37. Lateral mobilization of the left colon.

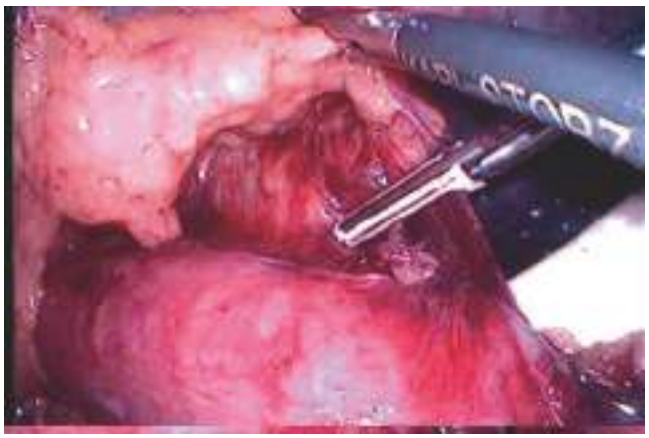

FIGURE 26-38. Entering the lesser sac by separating the omentum from the transverse colon.

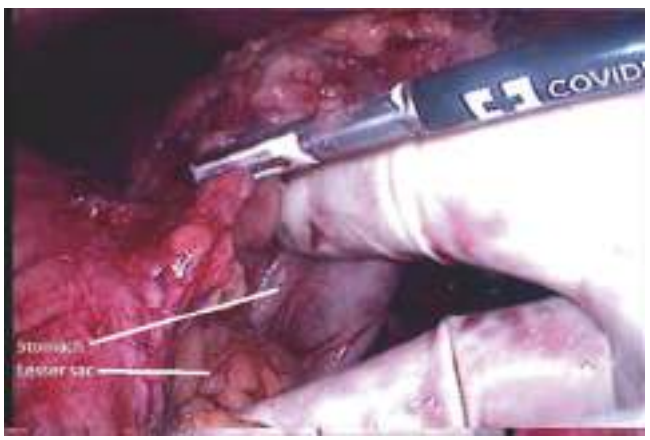

FIGURE 26-39. Completing the opening of the lesser sac.

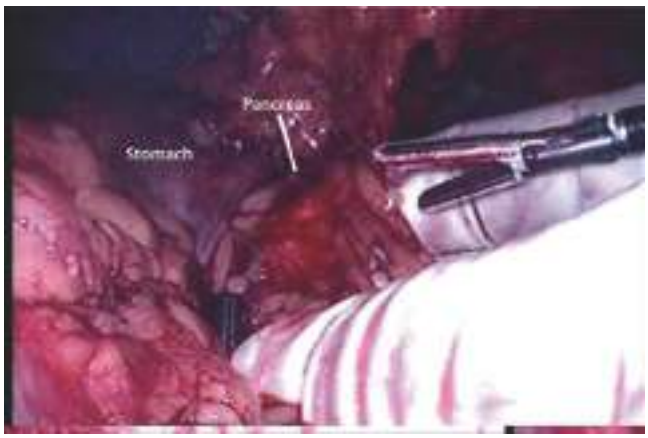

Figure 26-40. Division of the peritoneal attachments between the transverse colon mesentery and the inferior border of the pancreas.

ing attachments are along the inferior border of the pancreas. With the colon pulled to the lower abdomen, the lateral cut edge of the mobilization is seen. The hand is passed into the retroperitoneum along the inferior border of the pancreas. Much like the open approach, the fold of the mesentery can be palpated and separated from the pancreas allowing for safe division to the midline (Fig. 26.40). The colon is completely mobilized at this point and can be extracted for resection and anastomosis. Typically, the proximal colon is divided, the stapling anvil is placed, and the rectum is divided. This procedure has been previously described. However, this can be difficult in patients with a fat or bulky mesentery. This can be managed by dividing the rectum and the mesorectum first allowing for easier extraction of the proximal colon. The anastomosis and anastomotic assessment can be performed under direct vision via the hand port or laparoscopically.

Laparoscopic Identification of the Left Ureter

The IMA or IMV should not be ligated until the left ureter is clearly identified and safely dissected free of the left colon mesentery. There is a simple three-step algorithm that can help facilitate safe identification of the left ureter. The first approach is at the level of the superior rectal artery as the retroperitoneum is accessed at the level of the sacral promontory as described above. If the ureter is not easily identified, the approach should change to the IMV. The IMV is grasped and elevated, and the medial aspect of the peritoneum is incised. The retroperitoneum is accessed and the plane developed. This part of the retroperitoneum is flat, so identification of the proper plane is much easier. Once in the proper plane, the dissection can be directed in a caudad direction to see if the original plane started at the level of the sacral promontory can be entered to identify the ureter. If the left ureter can still not be identified, the colon can be mobilized in a lateral-to-medial direction. If unable to identify the ureter at this point, consider conversion to an open procedure, or, if using a hand port, remove the top of the port and identify it in an open fashion through the hand port. A ureteral stent should be employed at the discretion of the surgeon.

Subtotal Colectomy

Tumors of the transverse colon often increase the complexity of the required resection because of the need to divide most or all of the branches of the middle colic vessels. An extended right colectomy can adequately treat a tumor from the hepatic flexure to the mid-transverse colon. With complete mobilization of the small bowel mesentery and widely opening the lesser sac toward the splenic flexure, there should be adequate mobilization to create an ileocolic anastomosis with proper bowel orientation and without tension from either an open or laparoscopic approach. However, distal transverse colon tumors tend be more difficult to manage. Some surgeons advocate a transverse colectomy, but challenges associated with this type of resection include obtaining an adequate mesenteric resection and mobilization of the right and left colon to create a safe, tension-free anastomosis. For patients with a redundant and mobile transverse colon, it may be feasible to perform an extended left colectomy. If the transverse colon cannot be mobilized enough to reach the top of the rectum, it may be more appropriate to perform a subtotal colectomy. This entails resection of the right and transverse colon and creation of an ileo-descending colon anastomosis.

Open Approach

The right colon mobilization begins as described above, and as the hepatic flexure is mobilized, the lesser sac is entered by separating the omentum from the transverse colon mesentery. The plane to the right of the midline tends to be fused, but it is an avascular plane so it can be developed bluntly. With careful dissection under tension, the plane can be developed, and the proper lesser sac is entered. The lesser omentum is divided toward the splenic flexure as far as possible. With the right colon and hepatic flexure mobilized and the lesser sac completely open, the mesentery can be ligated. This begins with isolation and ligation of the ileocolic pedicle and division of the terminal ileum and its mesentery as described in the open right colectomy section. The middle colic vessels are isolated by pulling the transverse colon caudad and having the surgeon, who is standing on the patient's left side, pass his/her left hand through the ileocolic mesenteric defect from the retroperitoneal to peritoneal side. The index finger is elevated against the junction of the SMA and the origins of the middle colic vessels, which allows for a safe high ligation of these vessels. Now the left colon needs to be mobilized, and the surgeon switches to the patient's

right side packing the small bowel into the right upper quadrant. The sigmoid colon, left colon, and splenic flexure are mobilized as described in the open left colectomy section. The IMV is isolated by grasping and elevating it, so the peritoneum medial to it can be incised. This allows access into the retroperitoneal dissection plane, and the IMV can be isolated and ligated at the inferior border of the pancreas. The IMA is not isolated or ligated to preserve the blood supply to the distal colon. The distal bowel and mesentery are divided to provide an adequate distal margin. For the creation of a side-to-side ileocolic anastomosis, the orientation of the small bowel is very important. If the stapled end of the terminal ileum is brought over the top of the small bowel to perform a side-to-side anastomosis on the left side, this will create the potential for the small bowel to volvulize through the mesenteric defect. To avoid this complication, the small bowel needs to be rotated 180° counterclockwise, so the cut edge of the mesentery is brought underneath the remaining small bowel. This allows for the cut edge of the small bowel mesentery to pass under the small bowel and face the patient's left side in a straight line. Also, the entire small bowel from the ligament of Treitz to the anastomosis is on top of the mesenteric defect, so there is no risk of a small bowel volvulus. This will allow for a side-to-side stapled anastomosis to be performed.

Laparoscopic Approach

This extended resection can occur either straight laparoscopically or hand assisted. For the straight laparoscopic approach, the right colon is mobilized in the same fashion as described for right colectomy. Once the lesser sac is entered, the lesser omentum is divided as far as possible toward the splenic flexure. This exposes the lesser sac as much as possible and facilitates ligation of the middle colic vessels by clearing any posterior mesenteric attachments. With the ileocolic vessel ligated, the middle colic vessels are exposed. This is accomplished with the first assistant via one or two right-sided ports elevating the transverse colon in an ole-type fashion. The peritoneum from near the ligament of Treitz is scored across the base of the vessels to the cut edge of the mesentery on the right. This allows the individual branches of the middle colic vessels to be isolated and safely ligated. With the right colon and transverse colon mobilized and the mesentery ligated, attention is turned to the left colon. The patient is positioned as described for a laparoscopic left colon. The IMV is identified and elevated so the peritoneum can be incised allowing access to the retroperitoneum. The IMV is mobilized, isolated, and ligated at the inferior border of the pancreas. The mesenteric side of the IMV and the cut edge of the transverse colon mesentery are elevated, and the intervening mesentery is divided. Ideally, there should not be any remaining vessels in this remaining bit of mesentery. With the mesentery of the colon to be resected completely divided, the left colon mesentery is mobilized out laterally beyond the colon. To ensure adequate mobilization for extraction and the anastomosis, the sigmoid colon should be mobilized. The lateral attachments starting at the sigmoid colon are incised and divided toward the splenic flexure. The splenic flexure is mobilized as described in the left colectomy section. Once the colon is completely mobilized and before it can be extracted, the IMV needs to be divided again along the line of the distal resection margin. If it is not divided before extraction, the specimen will be tethered by this vessel preventing adequate exposure. Some surgeons will divide the entire specimen intracorporeally. Prior to performing the anastomosis, the small bowel and its mesentery must be oriented as described above. The specimen can then be extracted via a midline incision.

For a hand-assisted approach, the port placement is the same as described for the left colectomy. The dissection begins with mobilization of the right colon. The posterior approach will be described here. The small bowel is placed in the right upper quadrant exposing the posterior attachments of the small bowel mesentery to the retroperitoneum. The mesentery is grasped and elevated with the middle finger and thumb of the left hand. The index finger pointing toward the head swings over the pedicle to further expose the duodenum (Fig. 26.41). The peritoneum is incised from the duodenum to the cecum. With the hand palm down, the fingers elevate this peritoneal incision, and the retroperitoneum is entered. The hand continues to elevate the right colon mesentery, and the duodenum is exposed and reflected posteriorly (Fig. 26.42). This dissection is continued superiorly and laterally beyond the transverse colon, hepatic flexure, and ascending colon. The patient is then tilted right-side up to move the small bowel to the left side of the abdomen and expose the lateral planes. The lateral dissection begins at the level of the cecum by placing the hand in the retroperitoneal plane and lateral to the cecum and right colon to expose the lateral attachments (Fig. 26.43). They are divided heading toward the hepatic flexure, which is mobilized by entering

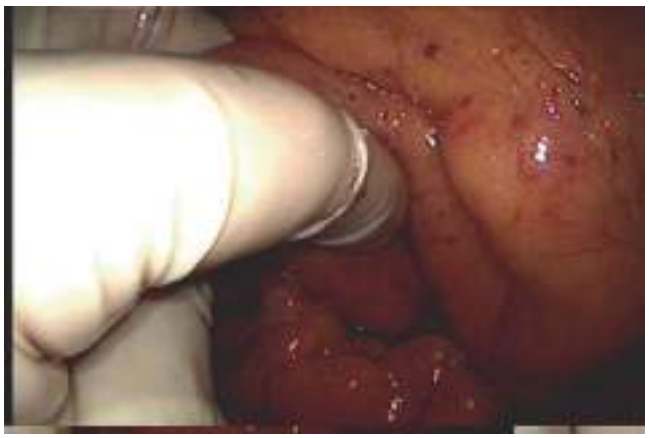

FIGURE 26-41. HALS exposure of the posterior aspect of the small bowel mesentery for the right colon dissection.

the lesser sac. The lesser sac is entered by separating the lesser omentum from the transverse colon mesentery (Fig. 26.44). Once the plane is developed, the cut edge of the lesser omentum is grasped with a grasper and elevated, so the hand can control the colon and develop the plane into the lesser sac. The lesser omentum is divided out toward the splenic flexure as far as possible. Now the right colon and transverse colon mesentery can be ligated. The ileocolic pedicle is isolated by pulling to the right lower quadrant. The peritoneum on the caudad aspect is incised, and the mesentery is dissected to expose the retroperitoneum. The index and middle fingers are passed through the mesenteric defect to expose the vessels and the bare area on their cephalad aspect (Fig. 26.45). The bare area is incised along the lines of resection to isolate and ligate the ileocolic pedicles. To isolate the middle colic vessels, the left hand is passed through the mesenteric defect into the retroperitoneum and lesser sac. The transverse colon mesentery is exposed by elevating the hand, and the first assistant via right lower quadrant port elevated the distal transverse colon (Fig. 26.46). The peritoneum is incised from the ligament of Treitz to the cut edge of the right colon mesentery. The hand is able to palpate each middle colic vessel to facilitate its isolation and ligation. With the right and transverse colon mesentery

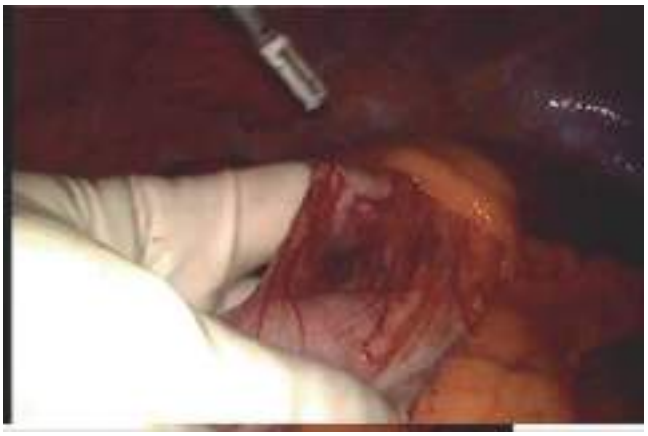

FIGURE 26-44. Mobilization of the hepatic flexure by entering the lesser sac.

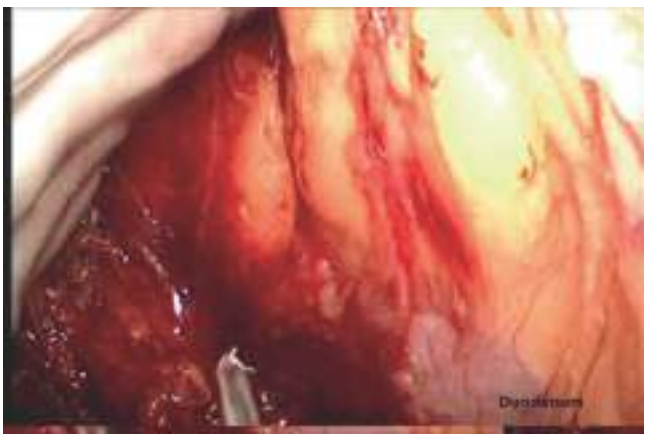

FIGURE 26-42. Accessing the retroperitoneal plane: elevating the right colon mesentery and dissecting the duodenum posteriorly.

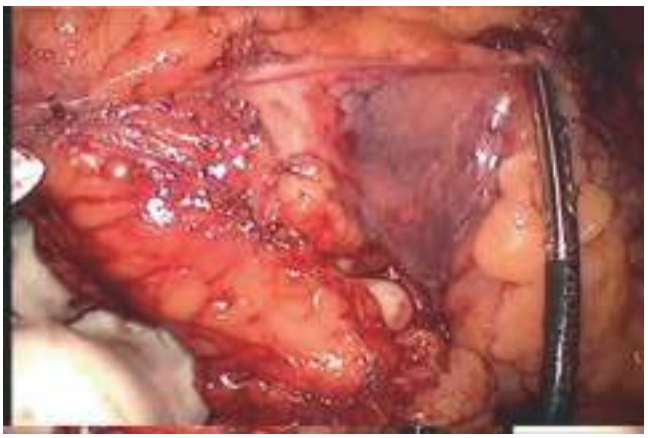

FIGURE 26-45. Isolation of the ileocolic pedicle by passing the hand through the mesenteric defect on the ileal side of the pedicle.

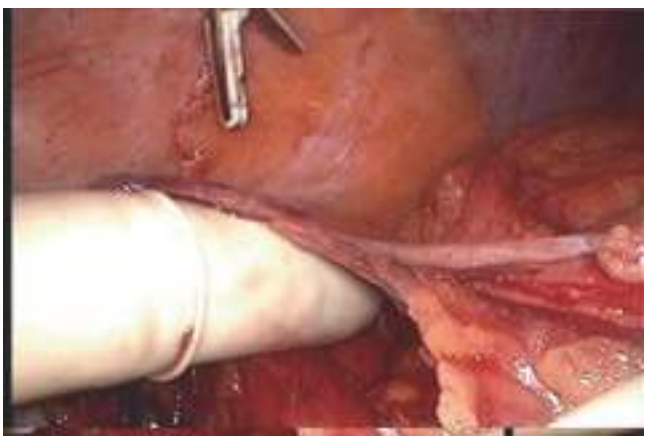

FIGURE 26-43. Division of the lateral attachments of the right colon.

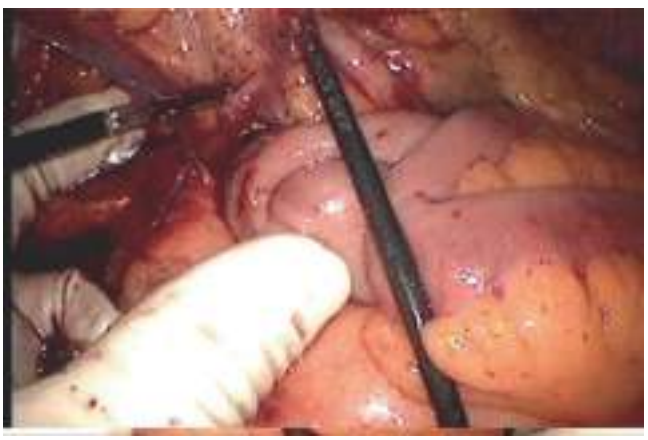

FIGURE 26-46. Exposure of the middle colic vessels.

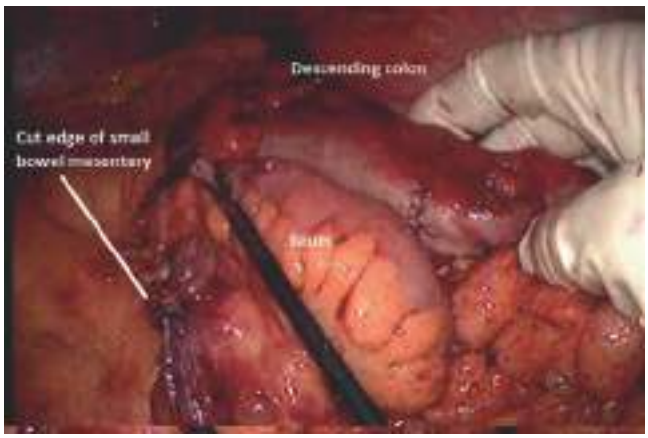

FIGURE 26-47. Orientation of the small bowel mesentery for an ileo-descending colon anastomosis.

divided, attention is turned to the left colon, and the left colon is mobilized as described in the paragraph above but using the hand-assisted technique for the left colon. The IMA is preserved to maintain blood supply to the sigmoid and descending colon. The IMV is then again divided at the distal resection margin, and the colon is then extracted through the hand port for resection. Just as described for the open approach, the small bowel and its mesentery are rotated 180° counterclockwise to allow the cut edge of the mesentery to face the patient's left side (Fig. 26.47). After the small bowel is properly oriented, a side-to-side anastomosis can be performed via the hand port.

Total Abdominal Colectomy with Ileorectal Anastomosis

Total abdominal colectomy may be indicated for patients with synchronous tumors or hereditary cancer syndromes such as hereditary nonpolyposis colorectal cancer or familial adenomatous polyposis. The entire abdominal colon is resected, and an ileorectal anastomosis can be performed in either an end-to-end, end-to-side, or isoperistaltic side-to-side fashion. Postoperative cancer surveillance can often be performed in the office, without sedation using either a rigid or flexible endoscopy.

Open Approach

The procedure begins with accessing the abdomen via a midline incision and performing a thorough exploration. The right colon and transverse colon are mobilized, and the associated mesentery is divided as described above in the open right colectomy and subtotal colectomy sections. The terminal ileal mesentery is divided up to the level of the bowel. For an end-to-end anastomosis, the bowel is divided sharply, the purse string is placed, and a 28 or 29 mm stapler anvil is placed inside the lumen. The purse string is cinched down making sure that all of the edges of the enterotomy are everted. It is rare that 28 or 29 mm anvil will not fit into the small bowel, so the need to use a smaller circular stapler is rare. The small bowel is then packed to the right upper quadrant and the left colon, and the splenic flexure is mobilized as described in the open left colectomy section. After the IMA is ligated at its origin and the IMV divided near the inferior border of the pancreas, the entire mesentery of the colon has been divided. The top of the rectum is identified, and the upper rectum is mobilized. At the site of distal transection, the peritoneum of the mesorectum is scored, and a window is created between the posterior rectal wall and the mesorectum. The rectum is then stapled and divided. The remaining mesorectum is then ligated. With the specimen removed, the anastomosis is completed by passing the stapling cartridge that is passed transanally to the top of the rectal stump. The spike is deployed, and the anvil is reassembled making sure the small bowel mesentery is not twisted. The small bowel should be oriented, so it is on the left side of the abdomen and the cut edge of the mesentery is facing to the patient's right side. The anastomosis must be tested with either an air leak test or endoscopically.

Laparoscopic Approach

The procedure can be performed by a straight laparoscopic approach or a hand-assisted approach based on the surgeon's preference. Port placement is typically symmetrical around the camera port. In other words, the surgeon's working ports are placed in same place for a right and left colectomy, so they are mirror images of each other. For a hand-assisted approach, the hand port is typically placed in the suprapubic position. Once again, the procedure begins with mobilization of the right and transverse colon with ligation of its mesentery as described in the laparoscopic right colectomy and subtotal colectomy sections. The left colon and its mesentery are resected as described in the laparoscopic left colectomy section. For the straight laparoscopic approach, the rectum and mesorectum are divided intracorporeally, and the specimen is extracted. The extraction site for a straight laparoscopic approach can be in the midline around the umbilicus or suprapubic or a muscle-splitting incision in the right or left lower quadrant. The terminal ileal mesentery is divided, and the terminal ileum is prepared for anastomosis. For the hand-assisted approach, the colon is extracted via the hand port. During the extraction, the small bowel must be passed underneath the colon, so when exteriorized, the small bowel mesentery will be properly oriented. The terminal ileum is resected and prepared for anastomosis, and the rectum and mesorectum are divided through the hand port. For the straight laparoscopic approach, the terminal ileum is returned to the abdomen, the extraction site is closed, and the anastomosis is created and tested laparoscopically. For the hand-assisted approach, this can be performed open through the hand port.

Special Circumstances

Laparoscopy

In 2004, the laparoscopic approach began its adoption into the surgeon's armamentarium for treating colon cancer with the publishing of the results of the US multicenter prospective randomized COST trial. The results of UK's CLASICC and European COLOR trials soon followed. Collectively, these studies demonstrated that the laparoscopic approach is not inferior to the open approach for the surgical management of colon cancer. Each study had unique findings that are worth discussing.

The COST Trial

The COST trial was designed as a non-inferiority study, which means it was designed to test the hypothesis that the laparoscopic approach was as effective as and not worse than the open approach for the treatment of colon cancer [31]. It included right and left colon cancers but excluded transverse colon cancers. Forty-eight centers and 66 credentialed surgeons participated and enrolled and randomized 435 patients to the laparoscopic group and 428 patients to the open group. The initial results were published with 4.4 years of follow-up and demonstrated that short-term outcomes favored the laparoscopic group with a shorter length of stay [5.6 days vs. 6.4 days ($p<0.001$)] and fewer days of intravenous and oral analgesics [3.2 days vs. 4.0 days ($p<0.001$) and 1.9 days vs. 2.2 days ($p=0.03$), respectively] [31, 32]. However, this did not translate into any significant difference in pain or quality of life scores, except that laparoscopy had a better global quality of life at 2 weeks after surgery only. There was a 21 % conversion rate and no difference in intraoperative complications, 30-day morbidity, or hospital readmission rates. Finally, there was no difference in the 3-year recurrence or overall survival rates [16 % vs. 18 % ($p=0.32$) and 86 % vs. 85 % ($p=0.51$) in the laparoscopic versus open groups, respectively], and these outcomes were similar stage for stage [32]. The initial results of this trial demonstrated that the laparoscopic approach was not inferior to the open surgical approach for the resection of colon cancer. The 5-year results confirmed the initial results as there was no difference in the primary endpoint of time to recurrence and secondary endpoints of disease-free (laparoscopic 69.2 % vs. open 68.4 %, $p=0.94$) and overall survival (laparoscopic 76.4 % vs. open 74.6 %, $p=0.93$) [33]. The site of first recurrence was also equivalent for each group [liver (5.8 % vs. 5.5 %)>lung (4.6 % vs. 4.6 %)>wound (0.5 % vs. 0.9 %), respectively]. Patients that underwent conversion had a worse 5-year overall survival compared to those completed laparoscopically and open. However, there was no difference in 5-year disease-free survival or recurrence associated with conversion. Long-term follow-up of quality of life data demonstrated that the laparoscopic group had a small but significant improvement in total quality of life index at 18 months after surgery, and those patients with poor preoperative quality of life were at higher risk of a "difficult" postoperative course [34].

The MRC CLASICC Trial

The CLASICC trial took place in the UK and included 27 medical centers. The surgeons were credentialed similarly to the COST trial. The study design was to assess short-term endpoints such as pathologic findings, hospital course, and quality of life and long-term endpoints of survival and recurrence at 3 and 5 years [35]. Patients were randomized 2:1 to the laparoscopic and open arms. Additionally, the study included both colon and rectal cancer patients. Two hundred seventy-three patients were randomized to the laparoscopic group and 140 patients to the open arm for colon cancer. Short-term outcomes showed no statistical difference in length of stay, return of bowel function, rate of curative resection, complications, and quality of life measures. There was a 29 % conversion rate, which steadily decreased over the course of enrollment into the study. Patients who underwent conversion were more likely to have a complication and less likely to have a curative resection, which highlights the importance of patient selection. Analysis of the cost of care and resource utilization for colectomy revealed that there was no difference in overall cost as well as cost of the operating room, equipment, recovery room, intensive care, and hospitalization [36]. An interesting sidenote was that the cost of laparoscopic surgery for rectal cancer was found to be higher than for open surgery. In 2007, the 3-year survival and recurrence data was published [37]. The 3-year overall survival ($p=0.51$) and 3-year disease-free survival ($p=0.75$) rates were similar for the laparoscopic and open arms of the colon cancer group. Additionally, these outcomes were equivalent for all stages. The results held up for the 5-year outcomes as well [38, 39]. They reported a median overall survival of 105.7 months in the open arm versus 81.9 months in the laparoscopic arm (log rank=0.87, $p=0.352$). There was no difference between overall survival and disease-free survival. However, conversion from laparoscopy to open for patients with colon cancer was associated with a worse overall survival (HR, 2.28; 95 % CI, 1.47–3.53; $p<0.001$) and disease-free survival (HR, 2.20; 95 % CI, 1.31–3.67; $p<0.007$). Therefore, based on the long-term data of the CLASICC trial, the utilization of the laparoscopic approach for colon cancer is equivalent to the open approach, but patient selection is critical to ensure an optimal outcome.

The COLOR Trial

The COLOR trial was a European-based prospective, randomized trial of laparoscopic versus open resection of colon cancer designed as non-inferiority study to identify a 7 % difference in outcome between each arm [40]. A total of 29 hospitals throughout Europe participated. The trial's primary

endpoint was a 3-year cancer-free survival. There were 534 patients in the laparoscopic arm and 542 patients in the open arm in the final analysis. The laparoscopic approach was found to have the short-term benefits of faster return of bowel function and shorter length of stay and was associated with a conversion rate of 19 % [41]. There was no difference in lymph node harvest or overall morbidity. Analysis of short-term outcomes with regard to hospital volume (high, medium, and low volume) demonstrated that operative times, conversions, and complications were lowest in the high-volume centers and were highest in the low-volume centers [42]. There was no difference in the 3-year disease-free survival at 74.2 % in the laparoscopic group and 76.2 % in the open group ($p=0.70$), which equated to a 2 % difference between the two treatment arms [43]. The final analysis was unable to rule out a difference in 3-year disease-free survival that favored the open approach because the upper limit of the 95 % confidence interval exceeds the predetermined non-inferiority boundary of 7 %. However, the authors felt the difference was small and clinically acceptable to justify that the laparoscopic approach for colon cancer is safe.

Other Trials

The Japan Clinical Oncology Group Study JCOG 0404 was a prospective randomized trial of laparoscopic versus open resection of T3 or T4 (without involvement of other organs) colon cancers [44]. It was a non-inferiority study design with 524 patients in the laparoscopic arm and 533 patients in the open arm. Short-term outcomes demonstrated shorter length of stay, faster return of bowel function, less narcotic use, and fewer complications in the laparoscopic arm. The 3-year oncologic results are pending at this point in time.

A prospective, randomized trial of laparoscopic versus open resection of colon cancer in Australia and New Zealand included a total of 587 patients [45]. The primary endpoints were 5-year overall survival, recurrence-free survival, and freedom from recurrence, and the long-term results demonstrated no difference in these outcomes between the two treatment groups.

These five prospective, randomized clinical trials all demonstrated short-term benefits for the laparoscopic approach with no associated differences in long-term overall survival, disease-free survival, and recurrence rates. Therefore, it is safe and effective to employ the laparoscopic approach for the surgical management of colon cancer.

Obstructing Colon Cancers

The management of obstructing colon cancers presents unique challenges in that the treatment of the acute or subacute obstructive process is dictating the oncologic management of the cancer. As a result, the overall outcome in terms of survival and recurrence is worse for patients whose initial presentation is with obstruction or obstructive symptoms. This is because by the time a tumor grows to the point of luminal obstruction, it is frequently a T3 or T4 lesion, and these tumors have a higher incidence of lymph node, peritoneal, or distant metastasis. Cortet et al. presented recurrence and survival data on 3375 colon cancers of which 8.5 % ($N=287$) presented with obstruction [46]. The 5-year risk of local recurrence [HR, 1.53; 95 % CI, 1.01–2.34 ($p=0.047$)] and distant recurrence [HR, 1.25; 95 % CI, 0.99–1.59 ($p=0.057$)] were higher for obstructing versus nonobstructing colon cancers.

The management options for obstructing colon cancers are many, and there are no well-established guidelines. For example, proximal diversion alleviates the obstruction but does not address the cancer, and resection of the primary tumor addresses both issues but carries significant morbidity and a high stoma rate. The introduction of self-expanding stents as a means for a bridge to therapy (surgery vs. chemotherapy) or as palliation in the setting of unresectable tumors is an additional option. The morbidity associated with urgent resection with ostomy creation or primary anastomosis can be as high as 60 % with wound complications, deep organ-space infections, respiratory complications, and intensive care unit admissions being some of the most common [47]. Therefore, the concept of endoscopically alleviating the obstruction, which would allow for complete colonic evaluation and elective, one-step resection, has significant appeal.

Initial single-institution reports demonstrated significant benefit of endoscopic stenting as a bridge to surgery compared to emergent surgery. These studies have reported a high incidence of technical and clinical success of greater than 90 % of cases and are associated with a stoma-free rate of 60–90 % [47–51]. The major complications associated with endoscopic stents are perforation, migration, and bleeding, which have been reported as being relatively low. It must be kept in mind that retrospective, single-institution studies suffer from many potential sources of bias such as patient selection, small numbers, and missing data. A multicenter, prospective, randomized trial of colonic stenting versus emergent surgery for acute left-sided malignant colon obstruction was undertaken in the Netherlands [49]. The study was scheduled to enroll 60 patients in each arm with the primary outcome being the mean global quality of life, and secondary outcomes were morbidity and mortality. The study was stopped after the enrollment of 47 patients in the stenting arm and 51 in the surgery arm due to six procedure-related perforations in the stent arm. The technical success rate of 70 % was felt to be too low compared to the previous published literature, and the study was stopped. Interestingly, there was no statistical difference between the two arms with regard to global quality of life, morbidity/mortality profiles, and stoma rates. There have been two subsequent meta-analysis that have examined the safety and efficacy of endoscopic stenting as a bridge to surgery. The review by Cirocchi et al. analyzed three clinical trials with a total of 97 patients

in the stent arm and 100 patients in the surgery arm [52]. The clinical success rate (which was defined differently in each study) was significantly higher in the surgery group (99 % vs. 52 %, $p<0.00001$), respectively. The stent group had a higher primary anastomosis rate (64.9 % vs. 55 %, $p=0.003$), and the overall stoma rate (45.3 % vs. 62 %, $p=0.02$) was lower. However, there was no difference in the overall or 30-day postoperative complication rates. A more recent meta-analysis, which included seven studies, confirmed the findings that endoscopic stenting is associated with increased rate of primary anastomosis, decreased stoma rate, and a trend toward improved complication rates [48]. Endoscopic stenting clearly has a role in the management of obstructing colon cancers, but proper patient selection is of paramount importance to its success [53]. Completely obstructing cancers, particularly when confirmed by contrast enema, have a low rate of technical success and increased likelihood of a stent-related complication. Stenting should also be avoided in patients with peritonitis, hemodynamic instability, or concern for impending perforation. Patients with obstructive symptoms but who are not completely obstructed have a normal white blood cell count and no peritonitis, and normal or correctable laboratory values are candidates for endoscopic stenting as a bridge to surgical resection 72 or more days later. Concern has been raised that endoscopic stenting can have a negative impact on the oncologic outcomes of these patients. There is limited data examining this issue, and what is available are small single-institution retrospective reviews. However, these studies have not demonstrated a deleterious effect of stenting on cancer-related outcomes [54].

Surgical intervention remains the mainstay of managing obstructed colon cancers as it provides alleviation of the obstruction and resection of the tumor in one setting. The extent of the operative procedure is highly dependent upon the condition of the patient and the extent of the obstruction. Proximal diversion alone should be performed only in selected situations such as complete obstruction with dilated small bowel that makes resection too difficult or in a setting where neoadjuvant therapy would be beneficial. The extent of resection and restoration of intestinal continuity remain to be debated and are dependent upon the physiology of the patient and the intraoperative findings. If there is evidence of impending perforation or ischemia of the proximal colon, resection of the entire colon proximal to the obstruction is recommended, and performing a primary anastomosis should be avoided. However, if the proximal colon is dilated, a healthy segmental versus extended colectomy can be performed based on the clinical situation. A recent literature review found no difference in morbidity or mortality between segmental resection and total abdominal colectomy for obstructing colon cancers. However, patients who underwent total abdominal colectomy have a significantly higher rate of bowel dysfunction. The creation of an end stoma is the technically easier procedure and eliminates the risk of anastomotic leak, but 40–60 % of the stomas created will remain permanent [55, 56]. The decision to perform a primary anastomosis is dependent upon the condition of the patient and quality of the proximal bowel. There is limited data comparing a Hartmann's resection with end colostomy or resection and primary anastomosis, but a recent review of the literature reported the anastomotic leak rate for primary anastomosis to range from 2 to 12 % [55, 56]. This appears to be comparable to the literature for elective left-sided resection and anastomosis, which ranges from 2 to 8 %. There does appear to be benefit of decreased anastomotic leaks and infectious complications when either manual disimpaction or on-table lavage of the proximal colon is performed prior to a primary anastomosis.

Perforated Colon Cancers

Perforated colon cancers present the challenge of adequately addressing the sepsis associated with a perforated colon while attempting to maintain the oncologic principles of resection for the malignant disease. The acute septic injury has the greatest impact on short-term outcomes, which in turn impacts the long-term outcome of the cancer. These patients typically present with a contained perforation much like diverticulitis or with a free perforation requiring an emergent operation. Either scenario results in a poorer outcome compared to non-perforated cancers. Cheynel et al. presented a comparison of the short- and long-term outcomes for 89 perforated colon cancers and 5462 uncomplicated colon cancers [57]. They reported that perforated cancers had higher operative mortality [20.2 % vs. 6.6 % ($p=<0.001$)] and 5-year local recurrence and peritoneal carcinomatosis rates [15.7 % vs. 7.8 % ($p=0.021$) and 13.8 % vs. 7.8 % ($p=0.036$), respectively] than uncomplicated colon cancers. Zielinski et al. compared 41 patients with free perforation and 45 patients with contained perforation to 85 non-perforated patients that were matched for age, stage, and resection status [58]. They found that patients with free perforation were more likely to get a stoma [79 % vs. 39 % vs. 29 % ($p=0.008$)] and had a higher rate of metastatic disease at the time of presentation. Interestingly, in the small study size, they found no difference in the rates of R0, R1, and R2 resections between the three groups. Sixty-seven percent of patients with free perforations were able to have all gross disease resected (R0 62 % and R1 5 %). The 5-year overall survival was significantly poorer in the free perforation versus the contained perforation group (24 % vs. 62 % ($p=0.003$)). Additionally, patients with a free perforation had a significantly higher operative morality, and their 5-year disease-free survival was significantly poorer. Interestingly, on the multivariate analysis, perforation (free or contained) was not a risk factor for adjusted survival, but residual gross disease after resection was a risk factor (HR, 1.94; 95 % CI, 1.09–3.46; $p=0.02$). Therefore, patients that present with perforated tumors should undergo an oncologically based resection if their physiologic state will allow as this will provide them with the best cancer-related outcome.

Management of Primary Colon Cancer in the Setting of Distant Metastasis

Advances in chemotherapy have greatly impacted our management strategies of patients who present with metastatic colon cancer. Current recommendations are for patients with symptomatic (bleeding or obstructing) primary tumors to undergo resection of their primary tumor before initiating systemic therapy for their metastatic disease. However, if the tumor is asymptomatic and the patient has a good performance status, the first-line treatment should be systemic chemotherapy, the rationale being that most patients will succumb to their metastatic disease before the primary tumor causes complications. This concept has gained traction with the significant improvement in tumor response to FOLFOX-based chemotherapies and a low rate of complications associated with leaving the primary tumor in situ. In 2007, Muratore et al. reported that patients with stage IV colon cancer with asymptomatic primary tumors who received FOLFOX chemotherapy had a 43 % rate of downstaging of metastatic disease to resectability, and none of the 35 patients developed symptoms related to their primary tumor while receiving chemotherapy [59]. A subsequent review of the literature examined seven studies comparing chemotherapy as initial therapy ($N=314$ patients) versus resection of the primary followed by chemotherapy ($N=536$ patients) [60]. For the patients who received chemotherapy first, the rate of symptoms associated with the primary tumor was obstruction 13 %, bleeding 3 %, and perforation/fistula 6 %. Ultimately, greater than 40 % of patients went on to have their liver lesions resected with curative intent. For the patients that had resection of their primary tumor as first-line therapy, the pooled major complication rate was 12 %, and the pooled minor complication rate was 21 %. The survival rate for the chemotherapy-first group ranged from 8.2 to 22 months, and the surgery first group was 14–23 months. Multivariate analysis identified the extent of hepatic disease and presence of peritoneal disease, performance statuses were independent predictors of the outcome, and resection status of the primary tumor did not impact survival. The benefit of FOLFOX-based chemotherapy has on the ability to downstage a patient to the point of resectability was reported in a recent literature review by Lam et al. [61]. They examined ten studies with 1886 patients who received neoadjuvant chemotherapy for liver metastasis. Sixty-four percent of patients had regression of their tumor with 22 % of these patients undergoing resection of the liver metastasis with curative intent. This translated to a 45-month overall median survival with 15 % of the patients remaining disease-free at that time point. Therefore, the literature supports a chemotherapy-first approach to stage IV colon cancer with an asymptomatic primary as a chemotherapy that has the ability to downstage metastatic disease, minimize the progression of symptoms associated with the primary tumor, and improve overall survival.

Outcomes for Colon Cancer

Short Term

Short-term outcomes for colectomy for cancer include morbidity, mortality, length of hospital stay, and intraoperative parameters such as conversion from laparoscopy. The most recent clinical trials that have examined operative techniques and the perioperative outcomes are the major multicenter, prospective, randomized trials comparing laparoscopic versus open colectomy for cancer, and they provide some of the best data for short-term outcomes. The COST trial reported an overall complication rate of 21 % for laparoscopy and 20 % for the open approach ($p=0.64$), with only 4 and 2 % ($p=0.11$) occurring intraoperatively, respectively [32]. The 30-day morbidity was similar between the groups, but the rate of specific complications was not reported. Overall mortality was 2 and 4 % ($p=0.40$). The conversion rate was 21 % and was associated with an increased length of stay and 30-day complication rate. The CLASICC trial reported an overall complication rate of 26 % in the laparoscopic group, 27 % in the open group, and 45 % in the converted group [35]. The mortality rate of laparoscopy was 2 and 4 % for open patients. They did include specific complications for the laparoscopic, open, and converted groups, which included wound complications of 5 %, 5 %, and 8 %; pneumonia rate of 7 %, 4 %, and 10 %; anastomotic leak rate of 3 %, 3 %, and 3 %; and deep venous thrombosis rate of 2 %, 0 %, and 0 %, respectively. The COLOR trial reported a similar morbidity and mortality profile [41]. The overall complication rate was 21 % for laparoscopy and 20 % for the open approach, with a 4 % and 3 % wound infection rate, 2 % and 2 % pulmonary complication rate, 1 % and 2 % cardiac complication rate, 2 % and 2 % rate of significant bleeding, 2 % and 2 % rate of urinary tract infection, 3 % and 2 % anastomotic leak rate, and 1 % and 2 % associated mortality, respectively. The complication profiles are very similar between the three clinical trials, so it would appear that this data sets a reasonable benchmark. It must be kept in mind that there were ASA and BMI exclusions for these studies, and those factors are associated with increased rates of morbidity and mortality. As mentioned in the beginning of the chapter, the ACS-NSQIP risk calculator can provide a reasonable assessment of operative and perioperative complication risk. Results regarding length of stay, return of bowel function, narcotic use, and quality of life were discussed previously.

Long-Term Outcomes

The 5-year survival and recurrence rates for colon cancer are dependent upon the stage of disease at the time of surgery. Based on data published from 2012 by the Surveillance, Epidemiology, and End Results Program (SEERS), the

5-year overall relative survival for stage I is 90 %, stage IIA is 87 %, stage IIB is 63 %, stage IIIA is 89 %, stage IIIB is 69 %, stage IIIC is 53 %, and stage IV is 13 % [62]. The survival has improved every 5 years since 1975, which reflects improvements in detection, surgical technique, and adjuvant therapy. The aspects of these statistics that need to be noted are that patients with stage IIB (T4, N0, M0) colon cancer behave similarly to patients with stage IIIB (T3–T4a, N1, M0; T2–T3, N2a, M0; or T1–T2, N2b, M0). Therefore, it is imperative for the surgeon to understand and recognize patients with stage IIB cancers, so they can be appropriately referred for adjuvant therapy in a timely fashion. Surgeons play a critical role in the referral of cancer patients to medical oncologist, so a comprehensive knowledge of the indications for adjuvant chemotherapy is essential. The other notable observation is that patients with stage IIIA (T1–T2, N1, M0 or T1, N2a, M0) do as well as those with stage IIA (T3, N0, M0). This highlights the importance of surgical technique and the importance of resecting all potentially metastatic lymph nodes. Additionally, the addition of adjuvant chemotherapy to node-positive colon cancer with FOLFOX-based therapies improved 5-year disease-free survival from 65 to 78 % [63, 64]. This improvement is significant, but it also demonstrates that surgical quality is the most important component of care because surgical clearance of potentially metastatic lymph nodes offers the greatest chance for cure.

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27
Rectal Cancer: Preoperative Evaluation and Staging

Jorge Marcet

Key Concepts

- Accurate preoperative staging of patients with rectal cancer helps identify patients at risk for local or distant metastasis and guides treatment decisions.
- Endorectal ultrasound (ERUS) is effective for staging the depth of invasion (T stage), especially for early-stage rectal tumors (uT0, uT1) that may be considered for local excision.
- Magnetic resonance (MR) has the ability to delineate the extent of locally advanced tumors and estimate the involvement of the mesorectal fascia.
- ERUS and MR use surrogate markers to estimate nodal involvement—size and node morphology—and are not particularly accurate in predicting nodal metastatic spread unless there are multiple large nodes in the mesorectum.
- The potential for understaging and overstaging of patients should be realized and taken into account when making treatment decisions.
- High-resolution computed tomography (CT) can detect distant metastatic lesions greater than 1 cm in diameter.
- Positron emission tomography (PET) scan is the most accurate assessment of total body tumor burden, especially when combined with CT (PET-CT).
- PET-CT is indicated when there are equivocal findings on CT and finding distant metastatic disease would alter therapeutic decisions.

Introduction

Careful pretreatment evaluation of the patient with rectal cancer is paramount for the successful management of their disease. By identifying the location of the tumor and its stage at the time of presentation, the surgeon is best prepared to discuss treatment options and prognosis with the patient and his or her family. As such, all healthcare providers caring for patients with rectal cancer should have a thorough understanding of the evaluation and staging of this disease.

Preoperative staging is performed according to the TNM classification of malignant tumors, estimating the depth of invasion into the rectal wall (cT), the presence or absence of lymph node metastasis (cN), and the presence of distant metastasis (cM). Also of importance is the determination of invasion of the anal sphincter and pelvic floor musculature, adjacent pelvic organs, or pelvic sidewall, all with significant consequences of planning and treatment to the patient.

The prefix "c" is used to indicate clinical staging, which is the estimate of stage based on physical examination and radiographic studies. Unfortunately, there is often confusion regarding this distinction, with some authors describing treatment recommendations for "T3N0" tumors as determined by pretreatment staging, when instead they should describe the tumor as "cT3N0." The difference at first glance appears trivial but can have significant consequences if the clinician fails to understand that estimates of tumor stage are just that, estimates, and that treatment planning must take into account the potential inaccuracy of these estimates. For example, understaging of the cancer preoperatively may result in the omission of preoperative radiotherapy/chemoradiotherapy and lead to an increased risk of local recurrence. Conversely, overstaging may lead to overtreatment, increasing the overall morbidity and cost of treatment.

Pretreatment evaluation begins with physical examination and colonoscopic evaluation. Radiographic studies may include computed tomography (CT), endorectal ultrasound (ERUS), magnetic resonance imaging (MRI), and PET. These tests are complementary, each with their own advantages and disadvantages, and may be used in combination. Laboratory evaluation includes determination of the carcinoembryonic antigen (CEA) level.

Physical Examination

When evaluating a patient diagnosed with rectal cancer, the patient's history is recorded, and an inquiry is made as to the duration of symptoms, changes in weight, bowel habits, bowel control, and presence of pain. If restorative proctectomy

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or local excision is to be contemplated, a detailed assessment of anal sphincter function and prior trauma (e.g., obstetrical history, prior anal operations) should be obtained. A general physical examination is performed with special attention for signs of muscle wasting, abdominal distension, hepatomegaly, and lymphadenopathy. A careful digital rectal examination is performed, noting the distance of the tumor from the anal verge and its proximity to the anal sphincter and pelvic floor. Tumors located in the anterior portion of the rectum have the risk of invasion into the genital structures, and special attention should be made to the potential for fixation to adjacent structures (i.e., prostate, vagina, sacrum, puborectalis). In a woman with an anterior rectal cancer, a pelvic examination should be done to ensure there is no invasion of the vaginal wall that may affect treatment. When the tumor is located in the posterior or lateral rectal wall, pelvic sidewall invasion should be considered. In addition, assessment of anal sphincter bulk and tone should be performed.

The texture of the tumor also gives a clue as to the stage. Benign adenomas are soft and the tumor may occasionally be difficult to detect on digital rectal examination. When a tumor invades the rectal wall, a desmoplastic reaction occurs and the resulting fibrosis will be felt as firm tissue. Evaluating the mobility of the tumor can also give information on how deep the tumor invades. A tumor tethered to the rectal wall, but that is otherwise mobile, is likely to invade into but not through the wall. Tumors that are fixed within the pelvis and are not mobile are locally advanced, deeply invading the full thickness of the rectal wall and possibly invading surrounding pelvic structures. Using these qualities of adherence of the tumor to the rectal wall and pelvis based on the digital rectal examination, Mason proposed a clinical staging system (CS-I to CS-IV) and recommended treatment options for patients with rectal cancer [1]. The digital rectal examination may occasionally also detect peritumoral lymphadenopathy, though this is often difficult. It should be noted that digital rectal examination has limitations in that only tumors of the distal rectal rectum can be adequately assessed. Furthermore, accuracy in staging depth of invasion is better for advanced tumors than for early tumors and improves with the surgeon's experience [2].

Clearance of the proximal large bowel, preferably by complete colonoscopy, should be performed in all patients with rectal cancer to exclude synchronous lesions and to confirm the histopathology of the tumor via biopsy. Other radiological testing may occasionally be used (i.e., CT colonography, air-contrast enema), though each has inherent limitations that providers should be aware of such as the need for an adequate preparation or failure to identify small lesions. Patients that are unable to be cleared prior to surgery due to an obstructing lesion should undergo proximal evaluation within 6 months after their operation. The endoscopic appearance of a tumor also gives a clue as to the relative degree of invasion, with benign tumors being soft to manipulation with the colonoscope or endoscopic forceps and malignant tumors being firm. Ulceration of the tumor implies invasion into the rectal wall, while deep ulceration may be a sign of transmural invasion.

Limiting pretreatment evaluation to digital rectal examination and colonoscopy prior to surgery for a rectal tumor is only appropriate for lesions that are considered benign. For patients with known or suspected rectal cancer, additional pretreatment locoregional imaging to stage depth of invasion and body scanning to detect distant metastasis should be performed prior to starting any treatment—whether with surgery, chemotherapy, or radiation.

Locoregional Imaging

Computed Tomography

Computed tomography (CT) is widely available and is one of the primary modalities used in preoperative staging of rectal cancer. CT accuracy is improved by administering oral, intravenous, and rectal contrast. CT can localize the tumor in the rectum but is not able to accurately delineate the layers of the rectal wall. For locally advanced tumors, CT may show extension beyond the rectal wall and invasion into surrounding structures. The addition of multidetector-row CT (MDCT) has improved accuracy for local staging of rectal cancer but still lacks the detail required. By including multiplanar (coronal, sagittal) images to standard axial images, this provides improved accuracy rates for higher T staging and N staging of rectal cancer than axial images alone [3].

Limitations to CT scanning for local staging of rectal cancer include the limited ability to define the mesorectal fascial layers and layers of the rectal wall. Although the mesorectal fat (MRF) surrounding a tumor can be clearly visualized on CT, perirectal fat stranding or induration secondary to rectal inflammation or peritumoral fibrosis cannot be definitively differentiated from tumor extension. In addition, the diagnosis of T4 tumors can be difficult due to lack of soft tissue resolution in the pelvis. Tumor involvement of an adjacent organ or the pelvic sidewall is also not accurate and is inferred by the loss of the fat plane between the tumor and the adjacent organ or structure.

Endorectal Ultrasound

On endorectal ultrasound (ERUS), the bowel wall is defined by five distinct sonographic layers of alternating hyper- and hypoechoic qualities [4]. Extending from the lumen outward, these layers correspond to (1) the interface between the ultrasound probe and the mucosa, (2) the interface between the mucosa and muscularis mucosa, (3) the submucosa, (4) the muscularis propria, and (5) the serosa or pericolic fat. The prefix "u" is used to describe ERUS T and N staging of rectal cancer (Figure 27-1, 27-2, 27-3, 27-4, and 27-5) [5].

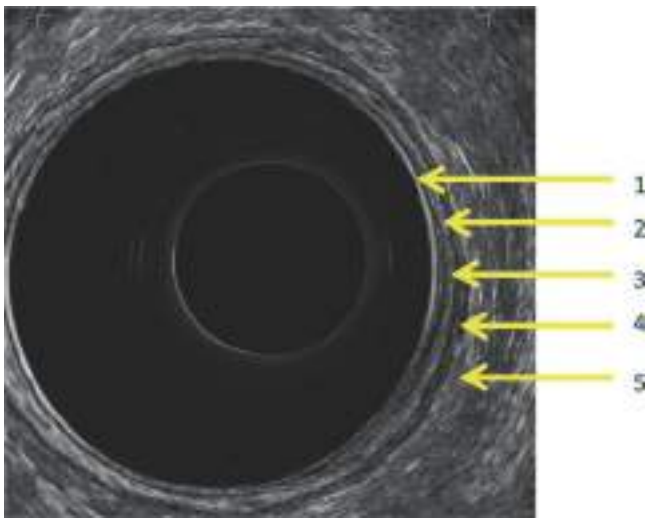

FIGURE 27-1. Endosonographic layers of the rectal wall. (1) Interphase of endoscopic balloon with mucosa. (2) Interphase of mucosa/submucosa. (3) Submucosa. (4) Muscularis propria. (5) Serosa and pericolic fat.

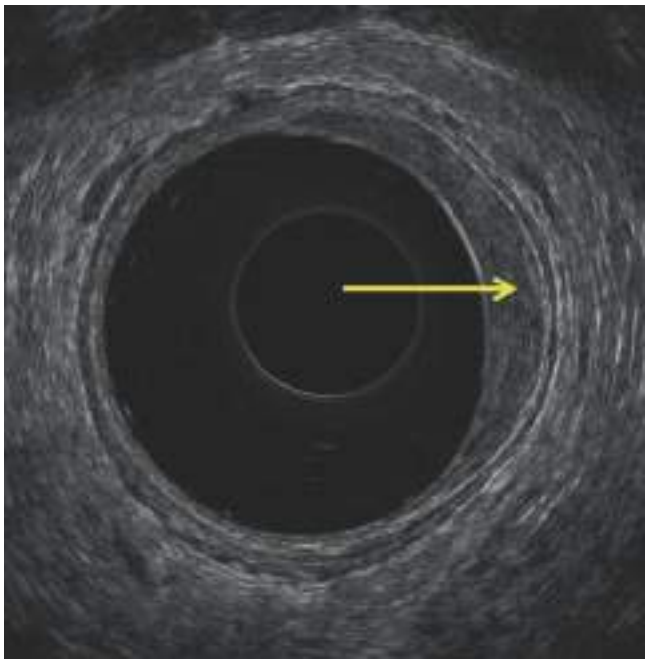

FIGURE 27-2. ERUS of uT0 tumor. Hypoechoic tumor (*arrow*) does not invade into the first hyperechoic layer. Notice that the submucosa (*white layer*) remains intact.

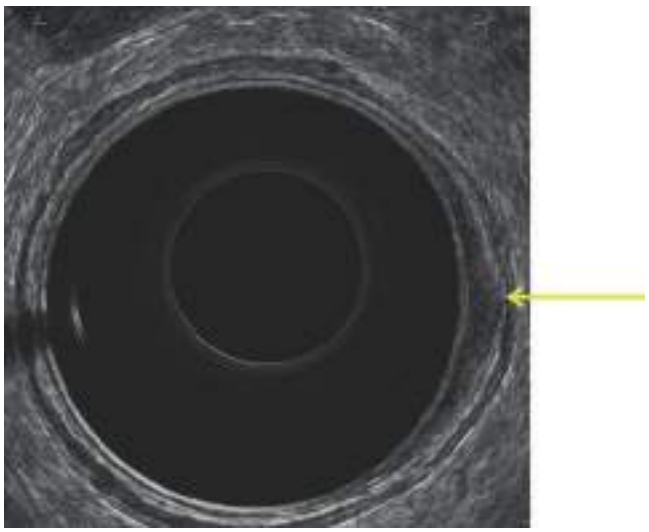

FIGURE 27-3. ERUS of uT1 tumor. Hypoechoic tumor invades into the middle hyperechoic layer (*arrow*) but does not invade the outer hypoechoic layer.

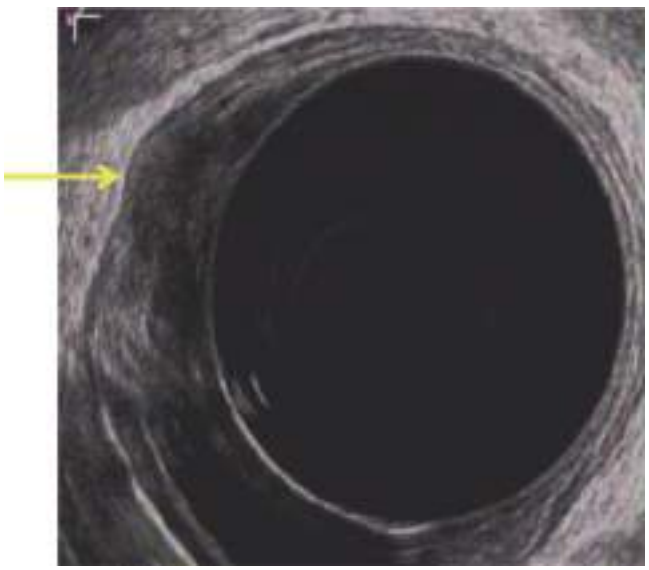

FIGURE 27-4. ERUS of uT2 tumor. Hypoechoic tumor invades through the middle hyperechoic layer and into the outer hypoechoic layer.

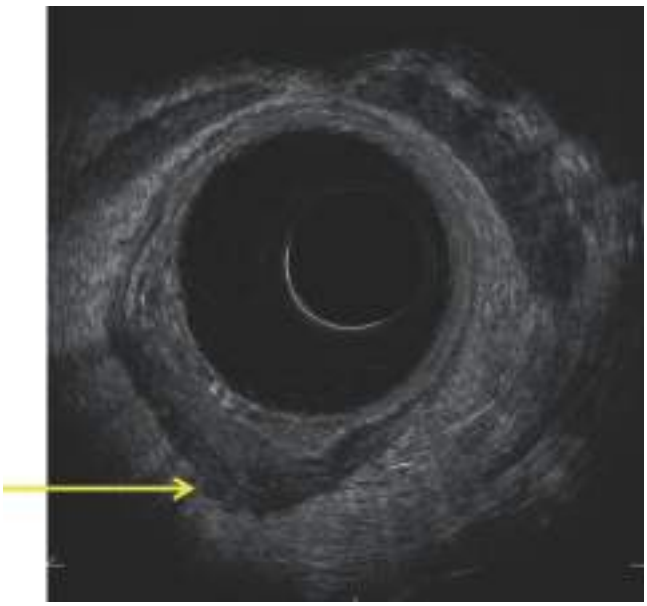

FIGURE 27-5. ERUS of uT3 tumor. Tumor extends through the second hypoechoic layer and into the outer hyperechoic layer (*arrow*).

ERUS has advantages in that it is simple to perform and inexpensive compared to CT or MR. The patient is given an enema to evacuate the rectum prior to the procedure. The procedure is often combined with a flexible or rigid proctosigmoidoscopy. Some patients require sedation to allay discomfort or anxiety. The ultrasound probe needs to pass proximal to the tumor in order to evaluate the entire extent of the tumor, thus making it difficult or impossible with obstructing lesions. 3-D ultrasonography records the image in real time and allows for subsequent manipulation of the image for axial, coronal, and sagittal evaluation. Malignant lymph nodes appear as hypoechoic and rounded peritumoral structures, whereas benign lymph nodes are less likely to be detected as they are isoechoic with the perirectal fat.

T Staging

There is variation in the reported accuracy of ERUS in accessing the T stage of rectal cancer, with an overall accuracy of about 84 % (ranging from 63 to 96 %), while the reported accuracy of CT and MRI is lower, 65–75 % and 75–85 %, respectively [6]. The accuracy of ERUS T staging in rectal cancer was analyzed in a meta-analysis of 42 studies ($N=5039$) where ERUS T stage was compared to pathological stage (Table 27-1) [7]. The authors reported that ERUS has a sensitivity of 81–96 % and a specificity of 91–98 %, showing a higher sensitivity for locally advanced rectal cancer or LARC (95 %), compared with early cancer (88 %). The authors concluded that ERUS should be the preferred test for preoperative tumor staging rectal cancer.

As with many interpretive studies, operator experience plays a significant role in staging accuracy. In a prospective, multicenter study conducted in 384 hospitals in Germany, investigators analyzed the diagnostic accuracy of preoperative ERUS (uT) with pathological (pT) findings in 7096 patients with rectal cancer who had not received neoadjuvant therapy [8]. The overall accuracy of uT to pT was found to be 65 %, with understaging occurring in 18 % and overstaging in 17 % of patients. The hospital volume of yearly ERUS procedures performed was found to affect the accuracy for staging, with uT-pT correlation of 63 % for hospitals undertaking ≤10 ERUS/year, 65 % for those performing 11–30 ERUS/year, and 73 % for hospitals where more than 30 ERUS/year were performed. The poorest correlation was found for T2 and T4 rectal cancers. The authors cautioned that ERUS is a useful tool for guiding the therapeutic strategy of rectal cancer only when performed by expert diagnosticians.

Several investigators have demonstrated a lower accuracy of ERUS in detecting T2 tumors compared to T1, T3, or T4 [9–11]. Reasons for this include difficulty in differentiating those tumors that have deep invasion into the muscularis propria from those with microscopic invasion into the perirectal fat and in differentiating peritumoral inflammation and edema from neoplastic infiltration. One group retrospectively subdivided patients with preoperative T2 tumors into uT2a, for tumors with focal invasion into the muscularis propria, and uT2b, for tumors with extensive invasion into the muscularis propria, and found improved weighted kappa accuracy (from 0.89 to 0.94) when the uT2b tumors were included in the enlarged uT3 group [12].

ERUS has been studied for the selection of patients with early-stage rectal cancer (T0, T1) who may benefit from transanal excision instead of traditional transabdominal rectal resection. In a study of 552 patients undergoing transanal excision of rectal tumors, investigators evaluated the accuracy of ERUS to clinical staging and found that ERUS had a sensitivity of 95 % vs. 78 % and a positive predictive value of 93 % vs. 85 % in detecting adenoma or T1 rectal carcinoma as compared to clinical staging, whereas specificity was similar in both (62 % vs. 58 %) [13]. A meta-analysis designed to evaluate the accuracy of ERUS in T0 staging of rectal cancers found 11 studies ($N=1791$) which met the inclusion criteria. The pooled sensitivity of ERUS in diagnosing T0 was 97.3 % (95 % CI: 93.7–99.1) and a pooled specificity of 96.3 % (95 % CI: 95.3–97.2) [9].

N Staging

Accuracy for detecting metastatic lymph nodes by endorectal ultrasound is less precise than for T staging, with a variable accuracy in reported studies of 63–85 % [6]. Differences in accuracy among studies may be due in part to differences in criteria used in defining nodal metastases. Hildebrandt et al. reported that hypoechoic, sharply demarcated nodes and those with heterogeneous pattern are more indicative of metastasis [14]. Katsura and associates found that nodes

Table 27-1. ERUS accuracy compared to histological stage.

Meta-analysis of 42 studies, $N = 5039$ patients		
T stage	Pooled sensitivity	Pooled specificity
T1	87.8 % (95 % CI 85.3–90.0 %)	98.3 % (95 % CI 97.8–98.7 %)
T2	80.5 % (95 % CI 77.9–82.9 %)	95.6 % (95 % CI 94.9–96.3 %)
T3	96.4 % (95 % CI 95.4–97.2 %)	90.6 % (95 % CI 89.5–91.7 %)
T4	95.4 % (95 % CI 92.4–97.5 %)	98 % (95% CI 97.8–98.7 %)

Adapted from Puli S, Bechtold M, Reddy J, Choudhary A, Antillon M, Brugge W. How good is endoscopic ultrasound in differentiating various T stages of rectal cancer? Meta-analysis and systematic review. Ann Surg Oncol 2009; 16:254–265 [7]

>5 mm, with well-defined boundaries and uneven and greatly hypoechoic patterns, were more likely to represent metastasis [15]. Akasu related the size of the short axis diameter of the largest lymph node to the rate of metastasis and found that for nodes <2 mm, the incidence of nodal metastases was 9.5 %, increasing to 47 % for nodes 3–5 mm in diameter and 87 % for nodes larger than 6 mm [16]. A meta-analysis of 35 studies evaluating the accuracy of EUS in diagnosing N stage in patients with rectal cancer showed a sensitivity of 73 % and specificity of 76 %. The data analyzed supported the hypothesis that ERUS is more accurate in excluding nodal involvement, rather than diagnosing it [17].

Staging accuracy for lymph node metastasis improves when the findings are associated with the T stage, with a higher risk of metastasis correlating with higher T stage. In a retrospective review of 134 patients with rectal cancer who underwent ERUS followed by radical surgery without neoadjuvant therapy, the accuracy of ERUS for N staging was 48 % for pT1 cancers, increasing to 84 % for pT3 cancers [18]. Notably, early rectal lesions are more likely to have lymph node micrometastases not detected by endorectal ultrasound. This may explain the somewhat high recurrence rates seen after local excision of early-uT-stage rectal cancer. On the other hand, CT has an accuracy of 55–65 % and MRI has an accuracy of 60–65 %. ERUS is more reliable than CT in being able to detect lymph nodes smaller than 1 cm and has comparable sensitivity and specificity to MRI [19].

Limitations to ERUS for staging rectal cancer include incomplete exams due to tumors that are bulky or stenotic. In women, these limitations may be overcome by vaginal insertion of the ultrasound probe [20]. Other causes of inadequate contact of the ultrasound probe with the tumor may be air or stool in the rectum or angulation of the tumor. Operator experience has also been shown to play a role in the accuracy of ERUS staging [21, 22].

Magnetic Resonance

High-resolution magnetic resonance (MR) with phased array pelvic coils is being increasingly used in the preoperative assessment of rectal cancer given its improved ability to evaluate the at-risk surgical circumferential resection margin. The pelvic coil is a wraparound surface coil placed around the pelvis. Patients are prepared with an enema on the morning of the examination. Thin-section (3 mm) T2-weighted fast spin-echo sequences are obtained in a plane orthogonal to the tumor [23]. Higher-resolution MRI allows improved definition of bowel and tumor infiltration [24]. MRI with endorectal coil is no longer recommended. Although endorectal MRI can show five layers of the rectal wall, the field of view is limited and the mesorectal fascia is not always visible. Additionally, the endorectal coil is more uncomfortable to the patient than the external coil and cannot be inserted in stenosing tumors [25]. Endorectal coil also has the potential to distort the tissues.

Three layers of the rectal wall are visible on a phased array external MRI. The innermost mucosa is thin and hypointense, the middle submucosa is hyperintense, and the outer muscularis propria is darkly hypointense. Below the peritoneal reflection, the rectum is surrounded by the MRF which is limited by the thin mesorectal fascia, which fuses with the rectoprostatic or rectovaginal fascia anteriorly and the presacral fascia posteriorly. The MRF surrounds the rectum completely only in the lower third and is best seen laterally as a thin hypointense line on T2W sequences. Inferiorly, the MRF thins out as it reaches the levator ani, which forms the roof of the ischiorectal fossa. MR is the best imaging modality to identify this avascular plane surrounding the mesorectum, which includes the mesorectum in its fascial envelope—the circumferential radial margin (CRM) (Figure 27-6).

In a meta-analysis of 21 studies designed to determine the accuracy of MR for T category (T1–2 vs. T3–4), lymph node metastases, and circumferential resection margin (CRM) involvement in primary rectal cancer that did not undergo preoperative chemoradiotherapy, MRI specificity was significantly higher for CRM involvement (94 %) than for T stage (75 %) or nodal metastases (71 %) [26]. Diagnostic odds ratio was significantly higher for CRM (56.1) than for nodal metastases (8.3) but did not differ significantly from T category (20.4) (Table 27-2). The authors concluded that MRI has good accuracy for both CRM and T category and should be considered for preoperative rectal cancer staging (Figure 27-7).

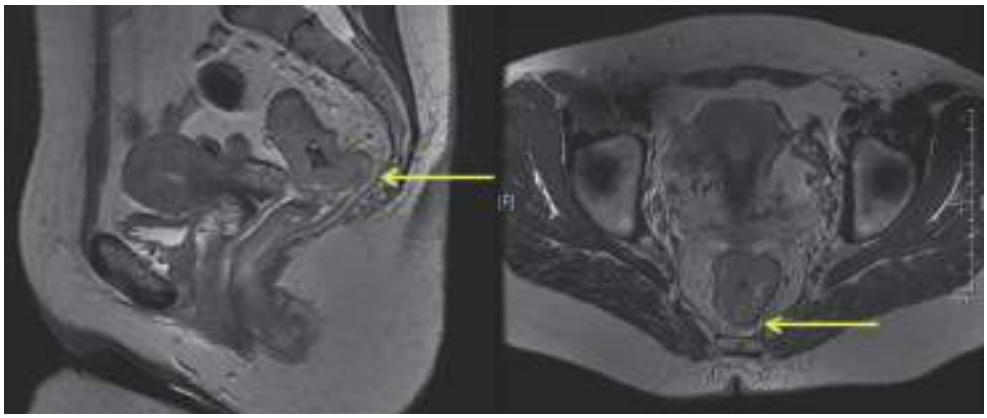

FIGURE 27-6. MR of cT3 tumor. Circumferential resection margin is preserved (*arrows*).

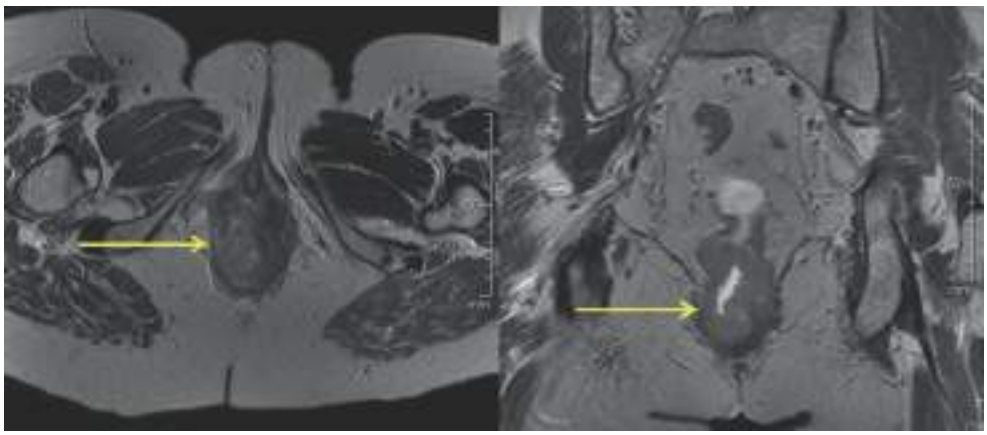

FIGURE 27-7. MR of cT4 tumor. Tumor invades the anal sphincter and levator ani (*arrows*).

TABLE 27-2. Meta-analysis of magnetic resonance accuracy in T stage, N stage, and circumferential resection margin (CRM)

	Specificity
T stage 19 studies ($N=1986$)	75 % (95 % CI 68–80)
N stage 12 studies ($N=1249$)	71 % (95 % CI 59–81)
CRM 10 studies ($N=986$)	94 % (95 % CI 88–97)

Adapted from Al-Sukhni E, Milot L, Fruitman M, Beyene J, Victor J, Schmocker S, Brown G, McLeod R, Kennedy E. Diagnostic accuracy of MRI for assessment of T category, lymph node metastases, and circumferential resection margin involvement in patients with rectal cancer: a systematic review and meta-analysis. Ann Surge Oncol 2012; 19:2212-2223 [26]

Park et al. [27] evaluated the accuracy of preoperative MRI in predicting pN stage by doing a node-for-node matched histopathology evaluation. The overall success rate of matching between the two techniques was 91 %. Preoperative MRI revealed a node-by-node sensitivity and positive predictive value of 58.0 and 61.7 %. Of the 341 nodes harvested, 120 were too small (<3 mm) to be depicted on magnetic resonance images, and 18 of these contained metastasis (15 %).

MR limitations include foreign bodies in patients that are MR incompatible. Foreign bodies that are compatible, such as surgical clips, may also obscure images. Movement-related artifacts may preclude accurate visualization of the rectal wall. MR is not portable to the operating room and is more expensive than ERUS [28].

Many referral centers with an expertise in rectal cancer treatment are now utilizing MR as the preferred locoregional staging evaluation, especially for locally advanced tumors.

ERUS is utilized for evaluation of early-stage lesions or used in combination with MR for select patients.

Whole Body Imaging

Computed Tomography

CT of the chest, abdomen, and pelvis is indicated in patients with rectal cancer to evaluate for distant metastasis, primarily of the liver and lung (Figure 27-8) [29]. The overall sensitivity of MDCT for liver metastases ranges from 77 to 94 % [30–32]. Most lesions measuring over 1 cm in size can be reliably differentiated from benign liver lesions (such as cysts or hemangiomas). However, for lesions under 1 cm in size, sensitivities drop to as low as 41.9 % [33]. The finding of small nonspecific hypodensities measuring <1 cm (also known as "too-small-to-characterize" hypodensities) is very common, perhaps present in as many as 17 % of all patients [34]. In the majority of cases, even in those patients with a known underlying malignancy, these small hypodensities in the liver are likely to be benign (~90 %) and can be followed over time.

Evaluation of lung metastases is also an important component of MDCT distant staging. In one study of 56 patients with rectal cancer, 18 % had evidence of at least one pulmonary metastasis on MDCT, with an increasing risk of pulmonary metastasis with rising tumor grade [35].

Positron Emission Tomography

PET is a whole body nuclear medicine imaging examination utilizing 2-(^{18}F) fluoro-2-deoxy-D-glucose (FDG) that exploits the increased rate of glycolysis in tumor cells to detect tumor. FDG is a glucose analog that is taken up by cellular glucose transport mechanisms and is phosphorylated by hexokinase. Most malignant cells have an increased metabolism of glucose and thus take up the FDG at a greater rate than surrounding tissues. FDG-6-phosphate then becomes metabolically "trapped" intracellularly, because of the relative lack of glucose-6-phosphatase activity in tumor cells. PET detects the increased FDG uptake. This uptake can be assessed both qualitatively (via visual examination of the degree of uptake of a tumor relative to other tissues) and quantitatively (via an SUV value). While PET was traditionally performed as a stand-alone examination, these studies are now typically performed in conjunction with CT to allow for more precise correlation of FDG activity with anatomy [30].

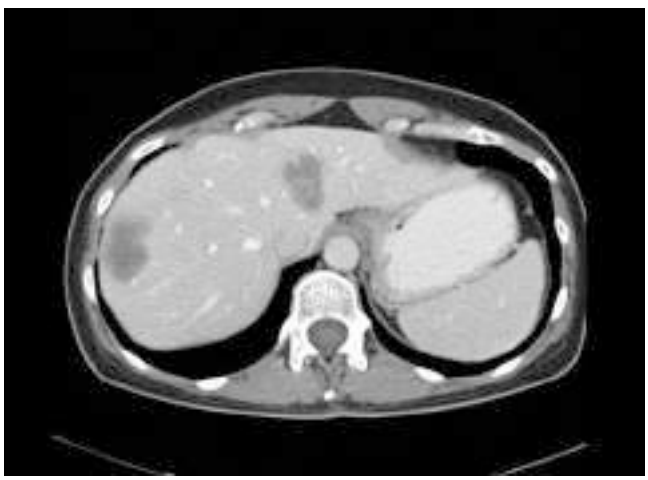

FIGURE 27-8. CT of the abdomen demonstrating two liver metastases.

Although PET has been demonstrated to be more accurate in the assessment of whole body tumor burden than a combination of conventional imaging [31], it does have limitations. There is a limit to the resolution of the scan, and lesions less than 1–2 cm may be missed. This makes accurate assessment of nodal metastases difficult. In addition, the activity of the primary tumor may interfere with detection of mesorectal lymph nodes due to the proximity of the primary rectal tumor. Lastly, mucinous adenocarcinomas may not be detected, given that the FDG uptake per unit volume of tissue is reduced as compared to non-mucinous tumor [31].

The role of PET in the management of patients with primary rectal adenocarcinoma is to investigate equivocal findings on CT, when the detection of metastatic disease would change treatment strategy. In addition, PET should also be performed prior to consideration of resection of distant metastatic disease or local pelvic recurrence, to exclude incurable occult disease that would make the operation palliative rather than curative. PET is extremely useful in the differentiation of pelvic scar from recurrent tumor in those patients who have undergone proctectomy for rectal adenocarcinoma.

In one study, PET-CT showed a diagnostic accuracy of 92 % (as opposed to 87 % for MDCT), changed the patient's stage in 13.5 % of cases, identified previously unknown disease in 19.2 % of cases, changed the patient's planned surgery in 11.5 % of cases, and changed the patient's therapy in 17.8 % of cases [32]. Another study found that PET-CT upstaged 50 % of patients, downstaged 21 % of patients, and changed the patient's treatment plan in 27 % of patients [36]. This study noted that PET-CT was particularly likely to identify "discordant" findings (i.e., findings not identified on MDCT) in patients with low rectal cancers due to the propensity of this group of lesions to metastasize to local lymph nodes in the pelvis (particularly nodes in the inguinal, femoral, or iliac chains), as PET-CT identified metastatic lymphadenopathy in 13.5 % of patients in this study which were not diagnosed on MDCT.

PET has been evaluated as a potential technique to determine histologic response to neoadjuvant chemoradiotherapy and better identify patients for local excision or nonoperative therapy, but like CT, MR and ERUS have not been found to be accurate in the assessment of residual tumor in the pelvis [37]. At present, PET is not recommended in the routine evaluation of patients presenting with primary rectal adenocarcinoma

[38] but is utilized to evaluate equivocal findings on CT when finding distant metastatic disease would alter management.

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28
Rectal Cancer: Neoadjuvant Therapy

Andrea Cercek and Julio Garcia-Aguilar

Key Concepts

- Neoadjuvant radiotherapy is associated with an improvement in local pelvic control following proctectomy for rectal cancer as compared to surgery alone.
- Neoadjuvant chemoradiotherapy is associated with an improvement in local pelvic control and has lower toxicity as compared to postoperative chemoradiotherapy.
- Short-course neoadjuvant radiotherapy has been demonstrated to have similar outcomes in terms of overall survival, disease-free survival, and local pelvic control when compared to long-course neoadjuvant chemoradiotherapy and is associated with lower cost and shorter time to multidrug systemic cytotoxic chemotherapy.
- Current research is focused on limiting the morbidity of therapy, by omitting either proctectomy or radiotherapy in select patients.

Introduction

Neoadjuvant therapy is a critical component of the multidisciplinary treatment of patients with rectal cancer. The objective of neoadjuvant therapy, either radiotherapy, combined chemoradiotherapy, or chemotherapy alone, is to reduce the risk of local recurrence in patients with locally advanced rectal cancer (LARC) undergoing surgical resection. But neoadjuvant therapy provides other potential advantages to rectal cancer patients. It allows early assessment of tumor responsiveness to therapy, which is closely correlated with long-term oncologic outcomes [1–3]. In addition, neoadjuvant therapy could potentially enable the consideration of organ preservation by allowing for more effective local excision and nonoperative management (NOM) strategies. Finally, delivering systemic chemotherapy before surgery in patients at risk for distant metastasis has the potential to improve survival by addressing micrometastatic disease earlier and improving treatment compliance. Maximizing neoadjuvant treatment response can therefore have a profound effect on both oncologic and quality-of-life outcomes.

In this chapter, we will focus primarily on neoadjuvant therapy for LARC, widely accepted to be clinical stage II (cT3–4, cN0) or stage III (any cT, cN1–2) invasive adenocarcinomas of the rectum. We will review various treatment paradigms and the data supporting each.

Historical Context

The story of neoadjuvant radiotherapy and chemoradiotherapy for patients suffering from rectal cancer is long and convoluted, and although much has been published on the topic, there is no universally agreed-upon treatment strategy. It is important for the reader to understand how we arrived at our current state of affairs so that the data from published trials can be put in the proper context.

The concept of neoadjuvant therapy for rectal cancer was first introduced by Janeway and Quick in c. 1917, who noted significant tumor response when gold filtered radon emanation seeds were implanted directly into rectal cancers [4]. In the era when the surgical mortality and morbidity for a rectal cancer operation was prohibitive, contact radiation with emanation seeds containing radium salts or radon was explored as a curative treatment. Surgery was considered a salvage procedure for patients with tumors resistant to radiation [5]. As surgery became safer and the limitations of contact radiation as the only treatment modality became apparent, radiation lost its role as a primary treatment and

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became an adjuvant to surgical resection. In fact, for many years, proctectomy alone became standard treatment for rectal cancer. It was eventually realized that the outcomes of surgery alone were often suboptimal, with 5-year local recurrence rates in published trials of 25–30 % [6–8]. It was demonstrated that adjuvant chemoradiotherapy improved oncologic outcomes, and in 1990 the National Institutes of Health advocated adjuvant external beam radiotherapy and chemotherapy for patients with stage II and stage III tumors [9]. In the United States, except for a few select referral centers, upfront proctectomy followed by selective postoperative chemoradiotherapy was the regimen utilized for most patients. However, postoperative radiotherapy is associated with relatively high toxicity and is poorly tolerated by many patients. Investigators in Europe and select US centers explored utilizing neoadjuvant radiotherapy and chemoradiotherapy, and eventually the benefits of administering radiotherapy in the preoperative period were demonstrated. In response to these data, many US clinicians simply moved the chemoradiotherapy package from the postoperative to the preoperative period. It is puzzling that, although much of the data demonstrating the benefits of neoadjuvant radiotherapy came from trials of short-course radiotherapy, and neoadjuvant short-course radiotherapy has been demonstrated to have similar oncologic outcomes as neoadjuvant long-course chemoradiotherapy in two prospective randomized trials [10, 11], the use of short-course radiotherapy has been limited in the United States.

At the same time that neoadjuvant radiotherapy was demonstrated to be more effective and less toxic than postoperative radiotherapy, there was a realization that oncologic outcomes following proctectomy for rectal cancer were highly technique dependent [12]. Wide variability in outcomes was seen, depending on who did the operation and how it was performed. So once again the wheel of opinion turned full circle, with some surgeons arguing that radiotherapy primarily compensated for“sloppy” surgery and that there was no need for the patient with non-fixed tumors to undergo radiotherapy if proctectomy was performed properly. Data from the Dutch Rectal Cancer trial and others, however, suggested that the oncologic benefits of neoadjuvant radiotherapy and good surgical technique were additive, not compensatory, with regard to pelvic control [13].

Clinicians are aware that therapies for rectal cancer are morbid and unfortunately the most effective treatment, proctectomy is associated witht he greatest chance of lasting morbidity. We continue to search for treatment regimens in which morbidity can be lessened while preserving the chance for cure, especially in patients with non-fixed tumors. Definitive chemoradiotherapy, or local excision +/− adjuvant chemoradiotherapy, would avoid proctectomy. Chemotherapy regimens are now more effective, and there is interest in upfront proctectomy in patients with mesorectal margins that are not threatened based on preoperative imaging followed by selective use of postoperative chemotherapy. In addition, there is interest in the use of neoadjuvant chemotherapy alone. Both of these strategies would avoid the toxicity of radiotherapy. Another approach that has been utilized extensively in Europe and in select US centers is to administer neoadjuvant short-course radiotherapy, followed by proctectomy and selective use of postoperative chemotherapy. The three aforementioned strategies allow the patient to receive effective systemic chemotherapy faster than the regimen commonly employed in the United States—long-course chemoradiotherapy (in which the patient receives only a radiosensitizing chemotherapeutic agent) followed by delayed proctectomy. This concept has intrinsic appeal, given that most patients with rectal cancer who ultimately fail treatment succumb to distant metastatic disease, not local pelvic recurrence, and that the benefit of neoadjuvant radiotherapy has primarily been to improve pelvic control without improvement in overall survival.

One of the difficulties in constructing guidelines for treatment of patients with rectal cancer is that treatment decisions must take into account multiple variables: tumor fixation, circumferential position in the rectum, relation to the pelvic floor musculature, pelvic morphology, clinical T and N stage, presence of symptoms, presence of metastases, continence status, planned operation, etc. It is virtually impossible to publish straightforward guidelines that account for all of these variables. At present, the clinician caring for the patient with rectal cancer must have a firm grasp of the rationale for, and the data supporting, any proposed treatment algorithm and be facile enough to tailor recommendations for therapy based on the characteristics of the patient and the tumor.

Postoperative Radiotherapy

Although currently out of favor, one of the advantages of the strategy of upfront proctectomy followed by selective chemoradiotherapy is that the exact stage of the tumor is known prior to initiation of radiotherapy, and radiation can be avoided in patients with early-stage tumors who may not derive benefit. A number of studies demonstrated that surgery followed by radiation, delivered in 180–200 cGy a day for a total dose of 45–50 Gy, was more effective than surgery alone in achieving local control in patients with stage II or III rectal cancer [14]. The Gastrointestinal Tumor Study Group (GITSG) trial was aimed to accrue 520 patients with rectal cancer located within 12 cm from the anal verge, extending to the perirectal fat or metastasizing to the regional lymph nodes, with no evidence of distant metastasis. After recovery from surgery, patients who had a complete resection were randomized to one of four arms: observation, postoperative radiation (40–48 Gy of total radiation in 1.8 or 2 Gy fractions), chemotherapy (bolus infusion 5-FU and semustine for 18 months), or radiation plus chemotherapy [6]. The study was terminated after 227 patients had been accrued because interim analysis showed statistical differences between

treatment arms. The combined modality therapy was superior to resection alone in preventing recurrence (33 % vs. 55 %; $p = 0.42$). Radiation and chemotherapy and chemotherapy were also associated with lower risk of recurrence compared to surgery alone, but the differences did not reach statistical significance [6]. A larger study from Denmark found that the probability of survival without local recurrence was higher when patients with Dukes' B or C rectal cancer received postoperative radiation, compared to surgery alone. The risk of distant metastasis was not influenced by radiation [15]. The Medical Research Council Rectal Cancer Group trial also demonstrated that postoperative radiotherapy reduced the risk of local recurrence with patients with mobile Dukes' stage B or C rectal cancer, without increasing the risk of serious late bowel complications. In this study, radiation did not affect the risk of distant metastasis or overall survival [16]. Finally, the NSABP-R02 protocol found that radiotherapy added to chemotherapy, either 5-FU/LV or 5-FU, semustine, and vincristine, reduced the risk of locoregional recurrence compared to chemotherapy alone in patients with Dukes' B or C rectal cancer [17].

Preoperative Radiotherapy

A number of prospective trials randomizing patients to preoperative radiation and surgery versus surgery alone provided mixed results [14–18]. These studies used variable total radiation doses, fractionation schemas, number of beams, portals, target volumes, radiation, and surgery. In general, only studies that use higher biologically equivalent radiation doses and a higher number of beams proved to reduce local recurrence in patients treated with preoperative radiation compared to surgery alone. The Swedish Rectal Cancer trial demonstrated that short-course preoperative radiation (25 Gy of radiation delivered in 5 equal doses in 5 consecutive days) improved not only local recurrence but also overall survival [7]. However, this study was later criticized because surgery was not standardized and the rate of local recurrence in the control arm was considered high for those years' standards. The Dutch Rectal Cancer trial (CKVO 95-04) was the first to prove that preoperative radiation also reduced the risk of local recurrence rate in patients having optimal surgery according to the principles of total mesorectal excision [13]. The study compared preoperative radiotherapy (5 Gy × 5) followed by quality-controlled TME with TME alone. In this study, the rate of local recurrence in the TME-only arm was substantially lower compared with patient treated with surgery alone in previous trials. Despite the improved surgical technique in both arms, the rate of local recurrence at 5 years was reduced from 10.9 % in the surgery-only group to 5.6 % in the radiotherapy plus surgery group ($p < 0.001$). While no benefit in overall survival was observed for the entire group, the 12-year updated results demonstrated that preoperative short-term radiotherapy significantly improved 10-year survival in patients with stage III disease and negative circumferential margins, and the benefit in terms of local control persisted [19].

Radiosensitizing Agents

Further improvements in local tumor control have been achieved by adding systemic chemotherapy to radiotherapy. Numerous chemotherapeutic agents including fluoropyrimidines (5FU) and capecitabine; irinotecan, oxaliplatin, and antiepidermal growth factor agents; and cetuximab and panitumumab have been tested in the neoadjuvant setting with radiotherapy. With the exception of fluoropyrimidines, however, none have been effectively validated in prospective trials.

Fluoropyrimidines

5-Fluorouracil (5-FU) is the primary agent for radiosensitization in rectal cancer. While its potential to create a state of radiosensitivity was recognized early on, numerous studies eventually led to the understanding that 5-FU's benefit was linked to the schedule of its administration. 5-FU must be present after radiation exposure to establish the radiosensitive state, and for this reason, bolus 5-FU quickly fell out of favor and continuous venous infusion (CVI) 5-FU 225 mg/m^2 daily became the standard [18, 20].

The GITSG proved the overall benefit of combining chemotherapy with postoperative radiation in patients with Dukes' B and C rectal cancer [6]. The North Central Cancer Treatment Group (NCCTG) study compared postoperative radiotherapy with 5-FU administered either as a bolus or as CVI. Patients in the NCCTG trial also received two months of systemic chemotherapy before and after the combined chemotherapy and radiation [21]. This study showed that CVI was associated with a significant decrease in the overall rate of local tumor relapse and distant metastasis, compared to bolus infusion of 5-FU during radiation [21]. Other trials from the Intergroup consortia have shown that CVI 5-FU was associated with lower hematologic toxicity compared to bolus 5-FU [22].

The European Organization for Research and Treatment of Cancer (EORTC) protocol 22921 was developed to assess the effect of adding chemotherapy (CT) to preoperative RT and the value of postoperative chemotherapy in LARC [23]. One thousand and eleven patients were randomized across four arms: (a) preoperative radiotherapy, (b) preoperative radiotherapy plus bolus 5-FU and leucovorin, (c) preoperative radiotherapy followed by postoperative CT, and (d) preoperative radiotherapy and bolus 5-FU and leucovorin followed by postoperative chemotherapy. Five-year local recurrence was significantly lower in all three arms receiving any form of chemotherapy (pre- or postoperative) compared to radiotherapy alone, though

there was no significant improvement in survival. Additional work by the Federation Francophone de la Cancerologie Digestive demonstrated that the addition of 5-FU to RT improves local control but not survival, consistent with the EORTC 22921 trial data [24]. More recently, in a randomized phase III trial, Hofheinz and colleagues were able to show non-inferiority of capecitabine, the oral prodrug of fluorouracil, when compared to 5-FU, providing us a convenient treatment alternative for reliable and motivated patients [25]. The equivalence of capecitabine and 5-FU has also been corroborated with the NSABP-R04 cohort [26].

Oxaliplatin

A number of large phase III trials have evaluated the potential role of oxaliplatin to increase radiosensitivity. The STAR-01 [27], the ACCORD 12/0405-PRODIGE2 [28], and the NSABP-R04 [26] trial each investigated the addition of oxaliplatin to a fluoropyrimidine as radiosensitizing agents. This combination, however, resulted in greater toxicity with no improvement in therapy. Conversely, the CAO/ARO/AIO-04 trial [28] found that the inclusion of oxaliplatin to a 5-FU-based CRT regimen led to a higher pCR rate, with no increase in toxicity [29]. While encouraging, their 5-FU dosing and schedule differed between the control arm and the arm with oxaliplatin, which could have affected the outcomes. At this point, oxaliplatin is not routinely included in the neoadjuvant regimens currently used for rectal cancer.

Irinotecan

This topoisomerase inhibitor has shown significant antitumor activity in metastatic colorectal cancer. While there have been small phase II trials to show that irinotecan may be effective and safe as an adjunct to traditional 5-FU and radiotherapy [30, 31], there has not yet been any trial to show its efficacy over 5-FU and radiotherapy alone.

EGFR Inhibitors

The success and efficacy of anti-EGFR agents like cetuximab and panitumumab in KRAS wild-type metastatic colorectal cancer have brought about a number of studies evaluating its use in the preoperative treatment of LARC. Response rates when EGFR inhibitors are used in the neoadjuvant setting with other agents and radiotherapy have been inconsistent, sometimes positive [32], but mostly equivocal or negative [33, 34]. Some studies have found worse response with their use, which suggests there may be mechanisms of response in tumors to these combined modality treatments that are not yet understood. EGFR inhibitors are not used in the setting of neoadjuvant chemoradiation.

Preoperative Versus Postoperative Radiation

Although there was once great debate on this subject, the preponderance of the evidence supports the use of neoadjuvant radiotherapy versus postoperative adjuvant radiotherapy. The rationale for this approach is logical: neoadjuvant radiotherapy requires less of a dose to achieve the same biologic effect, most likely due to the absence of postoperative scarring and tissue hypoxia in the pelvis. In addition the toxicity, both short term and long term, of neoadjuvant therapy is markedly reduced compared to postoperative radiotherapy, especially when the patient undergoes neorectal reconstruction. Lastly, the proportion of patients who can complete that therapy is markedly improved when radiotherapy is administered in the preoperative period. A small Scandinavian trial comparing preoperative short-course radiation (25.5 Gy in 1 week) for all rectal cancer patients with prolonged postoperative radiation (60 Gy in sever or 8 weeks) for patients with tumors that penetrated into the perirectal fat and/or involved the regional lymph nodes demonstrated that local recurrence was lower after preoperative radiation (13 % vs. 22 %), but survival was similar in both groups. Morbidity was also similar in both groups [35]. The RTOG 94-01 trial aimed to compare preoperative and postoperative CRT but closed after having accrued only 53 of the intended 770 patients. Similarly the National Surgical Adjuvant Breast and Bowel Project (NSABP R-03) also validated the role of neoadjuvant 5-FU-based chemoradiotherapy for LARC. While this study also failed to meet the accrual goal of 900 patients, the analysis of the 267 patients randomized before closure suggested that the preoperative CRT arm had better disease-free survival and probably better overall survival, but similar local recurrence compared to the postoperative arm [36].

The landmark German Rectal Cancer Study (CAO/ARO/AIO-94) compared pre- and postoperative chemoradiotherapy in 823 patients with LARC [37]. The local recurrence rate after 5 years was lower in the preoperative treatment group, 6 % vs. 13 % ($p = 0.006$), while overall survival and the frequency of distant metastases were not significantly different. Importantly, preoperative chemoradiotherapy was associated with a lower risk of grade 3 or 4 toxicities (27 %) compared to postoperative chemoradiation (40 %) [37]. Based on these studies, a commonly employed treatment paradigm for LARC is preoperative 5-FU-based chemoradiotherapy, followed by proctectomy and additional 5-FU-based adjuvant chemotherapy. Specifically, patients receive combined radiation (180 cGy/day/5 days a week for 5 weeks followed by a 540 cGy boost) and chemotherapy (either continuous infusion 5-FU or capecitabine), followed by proctectomy 6–8 weeks later, and postoperative systemic adjuvant chemotherapy, usually mFOLFOX6. In this treatment paradigm, now considered

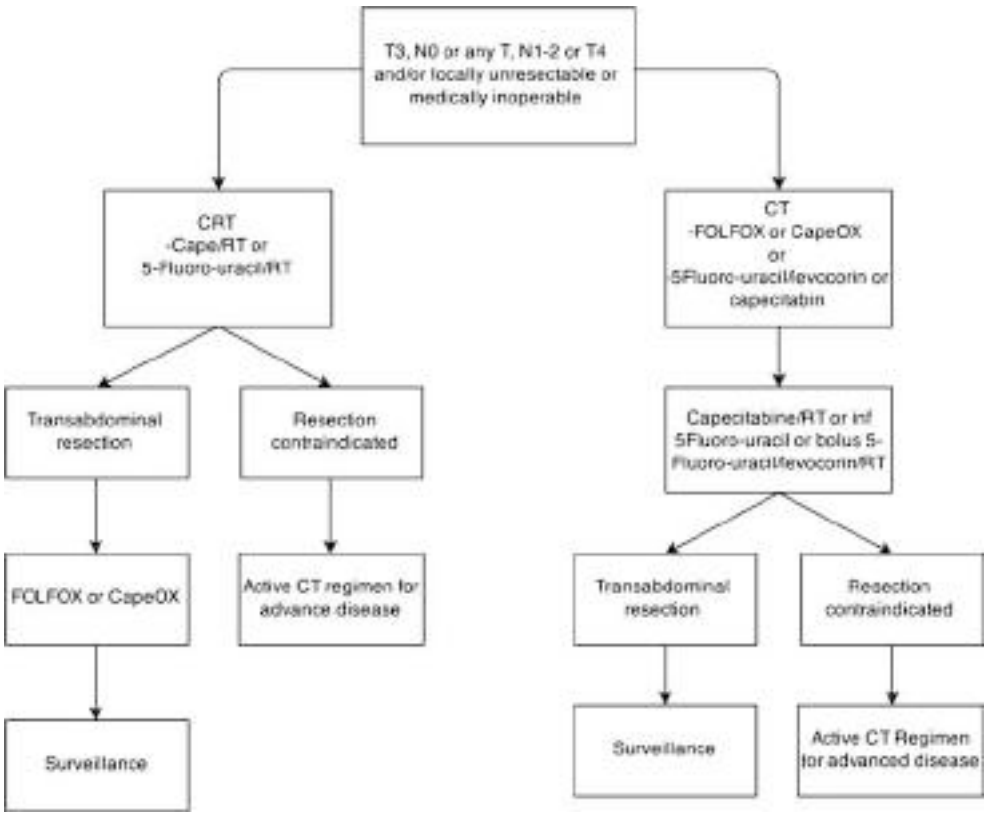

FIGURE 28-1. National Comprehensive Cancer Network guidelines for locally advanced rectal cancer. Permission from JCO/NCCN (*Cape* capecitabine, *CapeOx* capecitabine plus oxaliplatin, *CRT* chemoradiation, *CT* chemotherapy, *FLOX* fluorouracil, leucovorin, and oxaliplatin, *FOLFOX* infusional fluorouracil, leucovorin, and oxaliplatin; FU, fluorouracil, *inf.* infusional, *LR* local recurrence, *LV* leucovorin, *MRF* mesorectal fascia, *RT* radiotherapy, *TME* total mesorectal excision). With permission from Neoadjuvant chemoradiation therapy and pathological complete response in rectal cancer. Gastroenterology Report. Gastroenterol Rep 2015 doi: 10.1093/gastro/gov039. http://gastro.oxfordjournals.org/content/early/2015/08/19/gastro.gov039.full. Copyright © 2015 Oxford University Press and Digestive Science Publishing Co. Limited.

standard practice in the United States (Figure 28-1), imaging has become increasingly important for preoperative tumor staging and patient selection.

Short- Versus Long-Course Preoperative Radiotherapy

The effectiveness of radiation depends on the balance between the cytotoxicity against cancer and the preservation of adjacent normal tissues. There is now evidence of a dose-response relationship with radiotherapy, with an improved cytotoxic effect with higher total doses of radiation. However, the total dose of radiation depends on the dose per fraction and the number of fractions, the dose-fractionation schedule. But the dose per fraction and the number of fractions used in clinical practice vary widely. To compare different dose fractionation schedules, radiation therapists have introduced the concept of biologically equivalent doses. The most common dose-fractionation schedules used in rectal cancer, 1.8–2 Gy per day, 5 days per week for 5 weeks (usually in combination with a fluoropyrimidine) and 5 Gy as day for 5 consecutive days, are considered biologically equivalent. The advantages and disadvantages of each one of these regimens have been the subject of a heated debate. Proponents of long-course chemoradiotherapy point to a greater tumor response, although this may be an artifact of the greater time delay prior to proctectomy typically utilized after long-course chemoradiotherapy (typically 6–8 weeks) as compared to after short-course radiotherapy (typically 1 week). Those in favor of short-course radiation argue that improved patient convenience, lower cost, reduced toxicity in the neoadjuvant treatment period, and faster time to effective systemic chemotherapy are important advantages. Two trials have compared these two approaches directly.

Bujko and colleagues prospectively compared the two regimens, randomizing 316 patients with clinical T3 or T4 disease to either neoadjuvant long-course chemoradiotherapy or neoadjuvant short-course radiotherapy, and found that long-course chemoradiotherapy was associated with a significantly decreased incidence of positive radial margins (4.4 % vs. 12.9 %, $p=0.017$) and a higher rate of pCR (0.7 % vs. 16.1 %), but this did not carry over into a significant difference in pelvic control, disease-free survival, or overall survival [10]. Moreover, they reported greater radiation toxicity in the long-course chemoradiotherapy group and poorer compliance to treatment schedule. Their conclusion was that short-course radiotherapy was a viable alternative to long-course chemoradiotherapy with neither holding a long-term oncologic advantage, but with short-course radiotherapy potentially benefiting from lower cost and lower morbidity associated with its use. More recently, theTrans Tasman Radiation Oncology Group 01.04 randomized 326

patients with ERUS- or MRI-staged T3, N0–2, M0 tumors to short-course radiotherapy and surgery followed by 6 months of adjuvant chemotherapy or chemoradiotherapy and surgery followed by 4 months of adjuvant chemotherapy [11]. Their study was powered to detect a 10 % difference in local recurrence at 3 years, with a 5 % level of significance. Similar to the work of Bujko et al., the Trans Tasman trial found no difference in pelvic control, disease-free survival, and overall survival between the groups. Patient imbalances between groups have been called to attention, with fewer patients with low rectal cancers in chemoradiotherapy than the short-course radiotherapy arms (which would bias the results in favor of the chemoradiotherapy group) and varying rates of APR. The quality of surgery and accuracy of MRI staging have also been criticized [38, 39]. Nevertheless, two prospective randomized trials have demonstrated no obvious oncologic differences between neoadjuvant long-course chemoradiotherapy and neoadjuvant short-course radiotherapy.

The short-course and long-course divide has remained somewhat static across national boundaries, with a Western preference for long-course chemoradiotherapy and a majority of European countries favoring short-course radiotherapy. It is puzzling that, except for a few expert centers, short-course radiotherapy has not been embraced by US physicians. One could argue that it is the best-studied neoadjuvant radiotherapy regimen, with demonstrated efficacy in prospective randomized trials of neoadjuvant radiotherapy versus surgery alone, and shortens the time to administration of full-dose adjuvant cytotoxic chemotherapy.

Because of a current trend exploring the incorporation of therapies traditionally reserved for the adjuvant period into the neoadjuvant regimen, combinations of either short-course radiotherapy or long-course chemoradiotherapy with systemic therapies are being explored and gaining greater traction. Therefore, it may never be clearly determined whether short-course or long-course RT is more effective as independent modalities.

Impact of Pelvic Radiotherapy on Quality of Life

Another advantage of preoperative radiotherapy is the potential ability to downstage tumors and to increase the potential for sphincter-sparing surgery, which can improve long-term quality of life for patients with low-lying rectal cancers [37]. The issue of sphincter salvage, however, is complicated. As one might imagine, the assessment of whether a restorative proctectomy could possibly be performed based on initial evaluation of a patient is somewhat subjective. In addition, given that radiotherapy does not kill tumor in a wave front, and that multiple studies have demonstrated residual tumor scattered throughout the bed of the initial volume of tissue involved with the tumor, many surgeons would argue that changing the operation based on the clinically observed effect of radiotherapy is potentially dangerous. However, by improving the chances of an R0 resection and decreasing the rates of local recurrence, which can be associated with significant morbidity, radiotherapy can improve long-term quality of life. Nevertheless, pelvic radiotherapy remains associated with significant short- and long-term side effects. Overall short-term toxicity has been reported in as many as 50 % of patients [40]. Long-term side effects of pelvic radiotherapy include fibrosis and autonomic nerve injury, which can lead to bowel and bladder dysfunction, sexual dysfunction, and infertility due to hormonal effects and uterine incompetence. Moreover, because the pelvis is an active site of bone marrow function, patients who undergo pelvic irradiation can suffer from diminished hematopoiesis.

Adjuvant Systemic Chemotherapy in Patients Treated with Chemoradiotherapy and Proctectomy

Although prevention of local recurrences is important for patients' quality of life, most patients with rectal cancer succumb to metastatic disease. Consequently, similar to patients with stage III colon cancer, patients with LARC patients treated with neoadjuvant chemoradiotherapy and proctectomy are considered for postoperative adjuvant chemotherapy independent of the histologic tumor stage in the proctectomy specimen [41]. Patients with clinical stage II and III rectal cancer treated with preoperative chemoradiotherapy and proctectomy usually receive 5-FU or capecitabine plus oxaliplatin-based adjuvant chemotherapy [41]. While the use of postoperative adjuvant chemotherapy in rectal cancer is not supported unequivocally by a prospective randomized trial, a recent meta-analysis of 21 randomized controlled trials concluded that postoperative 5-FU-based chemotherapy is effective in patients with LARC [42].

In spite of these recommendations, up to 27 % of eligible LARC patients never start adjuvant chemotherapy and less than 50 % [43] receive the full prescribed treatment without interruptions or delay [23, 29] due to postoperative complications, slow recovery, interference with closure of their temporary ileostomy [44], or simply treatment refusal [45]. A systematic review of ten studies including more than 15,000 patients evaluated the effect of timing on the efficacy of postoperative adjuvant chemotherapy and demonstrated that each 4-week delay in treatment correlated with a 14 % decrease in OS [46].

It is interesting to note that, despite the common practice of administering chemotherapy, a recent meta-analysis of adjuvant chemotherapy in LARC did not demonstrate a survival benefit. In total 1196 patients with stage II or III disease and R0 resection were evaluated; 598 were observed while 598

received adjuvant chemotherapy [47]. However, of the four studies included in the analysis, only one used oxaliplatin in combination with fluorouracil, the CHRONICLE trial which contributed only 75 patients to this analysis [48]. Moreover, completion of planned chemotherapy was low in all of the studies (43–76 %). This low adherence could certainly have affected the results [47].

Due to the low rate of completion of planned adjuvant therapy, splitting adjuvant chemotherapy and delivering a limited number of cycles pre-chemoradiotherapy, then delivering the remaining cycles postsurgery, has been proposed to increase tumor response in LARC patients. A number of randomized phase II trials have reported mixed results, without clear survival advantage for the split neoadjuvant or the postoperative regimen [48–52].

Another potential approach is to deliver all chemotherapy upfront. This neoadjuvant chemotherapy has several potential advantages compared to the standard adjuvant chemotherapy; it theoretically treats occult micrometastasis several months earlier and increases treatment compliance, potentially enhancing the efficacy of chemotherapy and ultimately improving survival [53, 54]. Other benefits of neoadjuvant chemotherapy include increased response of the primary tumor, early identification of nonresponders, and earlier removal of the loop ileostomy. A recent study at Memorial Sloan Kettering Cancer Center (MSKCC) investigated the safety and efficacy of FOLFOX before CRT, demonstrating excellent treatment compliance and no evidence of serious adverse effects requiring treatment delay. All patients undergoing proctectomy had an R0 resection, and nearly half had a tumor response greater than 90 % including 30 % who had either a pCR or a clinical complete response (cCR) [55]. Induction chemotherapy before chemoradiation and proctectomy is now considered as a valid alternative to the more widely accepted neoadjuvant chemoradiation, proctectomy, and postoperative systemic chemotherapy (Figure 28-1).

Chemotherapy can also be delivered as consolidation (after chemoradiotherapy completion and before surgery). The Timing of Rectal Cancer Response to Chemoradiation Trial, which completed accrual in 2012, showed that delivering 2, 4, or 6 cycles of FOLFOX after chemoradiotherapy in LARC patients increased the pCR rates up to 25 %, 30 %, and 38 %, respectively, compared to CRT alone (18 %), without any associated increase in adverse events or surgical complications [56]. Eighty percent of patients received consolidation chemotherapy without interruption. These studies suggest that delivering systemic chemotherapy in the neoadjuvant setting, both before or after chemoradiotherapy, is well tolerated and has potential advantages for the patient. Although solid data from large prospective studies are still lacking, in the most recent edition of the NCCN guidelines, neoadjuvant chemotherapy is contemplated as an option for the treatment of LARC patients. However, none of these studies have reported long-term oncologic outcomes.

Setting the Right Limits

Chemoradiotherapy has clearly proved itself useful at improving local tumor control in patients with LARC. We find that the weight of evidence is also demonstrating that systemic chemotherapy—when applied in the neoadjuvant setting—is able to similarly control tumor progression, possibly acting on micrometastatic disease to improve distant control. But while the benefits of these intensive neoadjuvant regimens are alluring, they have also sparked a heated debate about whether all patients require such intensive treatment. The oncologic success in treating LARC has been achieved at the cost of significant morbidity and compromised quality of life [40]. The task before us is to develop treatment approaches that maximize oncological outcome while preserving quality of life by minimizing morbidity associated with this intense multimodality approach [57]. Do all patients with LARC really require chemoradiotherapy, chemotherapy, and proctectomy? The necessity of this intense multimodality approach is called into question.

The European Approach

In a number of European countries, the “right limits” have been framed around MRI-based measures of tumor aggressiveness. A risk stratification system that covers all rectal cancers and that incorporates the proximity of the primary rectal cancer to the mesorectal fascia, the depth of tumor invasion, the presence of metastatic lymph nodes, and the presence of venous invasion are used to classify LARC into “the good,” “the bad,” and “the ugly” [58, 59]. For the low-risk, “good” tumors, proctectomy alone is recommended; for intermediate-risk “bad” tumors, the recommendation is short-course radiotherapy followed by proctectomy; and for high-risk “ugly” tumors, chemoradiotherapy followed by proctectomy is recommended (Table 28-1). These MRI-based risk stratification schemas have been incorporated into clinical practice guidelines and clinical trial design (e.g., Expert-C and RAPIDO). However, the treatment approach guided by MRI risk categorization is based on prospective observational studies conducted in institutions with significant expertise in rectal cancer and has not been tested in prospective randomized trials.

Selected Adjuvant Systemic Chemotherapy

Many LARC patients experience variable degrees of response to chemoradiotherapy, and tumor response is now one of the most important prognosticators in LARC patients [2, 57]. The need for adjuvant chemotherapy in patients with a complete or near-complete response after chemoradiotherapy has been questioned [60–62]. Recent work from a multi-institutional, retrospective analysis of 3133 patients shows that the benefit of adjuvant therapy differs between LARC subgroups. For example, patients with ypT1-2 or ypT3-4 tumors benefitted

Table 28-1. European/Scandinavian model of stratification for patients with locally advanced rectal cancer based on magnetic resonance imaging and subsequent treatment decisions

Risk	Treatment
Low risk	
• T1–T3 (<5 mm) mid-/upper rectum • T1–T3 (superficial) lower rectum • N0 • Extramural vascular invasion: no mesorectal fascia clear • Risk of local recurrence <10%	Total mesorectal incision (TME)
Intermediate risk	
T3 (<5 mm)	• Preoperative short course radiation
T4 (posterior vaginal wall only), or N1/2, or Extramural vascular invasion: yes Mesorectal fascia clear (<1 mm) Risk of local recurrence: 10–20 %	• Total mesorectal excision • Adjuvant chemotherapy
High risk	
T4 (other than posterior vaginal wall)	• Preoperative chemoradiation
N01/2 Mesorectal fascia involved Risk of local recurrence >20 %	• Total mesorectal excision • Adjuvant chemotherapy

Modified from Smith JJ, Garcia-Aguilar J. Advances and challenges in treatment of locally advanced rectal cancer. J Clin Oncol 2005

the most from adjuvant therapy compared with ypT0N0 patients [63]. Some centers now use postoperative chemotherapy selectively based on tumor response to chemoradiotherapy. In the recently published ADORE phase II trial, which examined use of selective adjuvant chemotherapy, LARC patients with ypT3-4N0 or ypTanyN1-2 tumors after fluoropyrimidine-based chemoradiotherapy were randomized to adjuvant chemotherapy with either 4 cycles of 5-FU and LV or 8 cycles of FOLFOX. The administration of FOLFOX after surgery was associated with prolonged progression-free survival in stage III patients but not in stage II patients. Additionally, FOLFOX was associated with a prolonged overall survival for both stage II/III rectal cancer patients [64]. Identification of those patients who will most likely to derive benefit from adjuvant treatment will be better informed by carefully conducted correlative studies that more accurately delineate molecular, pathologic, and clinical markers of resistance.

Chemotherapy Only to Improve Local Tumor Control

The risk of local pelvic failure in LARC depends on tumor stage, but also on the distance of the tumor from the anal verge and the proximity of the tumor from the mesorectal fascia [13, 65]. Upper rectal tumors away from the mesorectal fascia have a low risk of local recurrence when treated with proctectomy. The added benefit of radiotherapy in these patients has been questioned [40, 66, 67]. A growing body of evidence suggests that radiotherapy could be safely avoided in patients with intermediate-risk rectal cancer (e.g., rectal cancers located between 5 and 12 cm from the anal verge that do not threaten the mesorectal fascia) on MRI [68, 69]. In a pilot phase II trial conducted at MSKCC, 32 patients with resectable, clinically staged II–III rectal cancer were treated with preoperative FOLFOX/anti-VEGF and selective chemoradiotherapy, based on tumor response. The 30 patients who completed preoperative chemotherapy had tumor regression and underwent proctectomy without preoperative chemoradiotherapy. Eight (27 %) had pathologic complete responses. No local recurrences were noted at 4 years, and an 84 % disease-free survival was achieved [70]. Given these data, a large multicenter phase II/III study is currently accruing patients. In the CALGB PROSPECT Study (Preoperative Radiation Or Selective Preoperative Evaluation of Chemotherapy and TME) [71], patients are randomized to either the standard arm (chemoradiotherapy, surgery, and adjuvant FOLFOX chemotherapy) or the selective arm with FOLFOX×6 cycles, evaluation of response followed by surgery or standard therapy with chemoradiotherapy if the reduction in the primary tumor is <20 % (Figure 28-2). Eligible patients must have biopsy-proven adenocarcinoma with the primary tumor located 5–12 cm from the anal verge. They must be candidates for sphincter-sparing surgery. The primary outcomes of the phase II component are R0 resection rate and time to local recurrence. The primary endpoints of the phase III components are time to local recurrence and disease-free survival. The selective chemoradiation arm will be favored if either the disease-free survival is superior compared to the standard arm or if it is non-inferior to the standard arm for both disease-free survival and local recurrence. In addition to this study, there is currently an ongoing study, the GEMCAD study, on induction chemotherapy with or without chemoradiation in intermediate-risk rectal cancer defined by MRI. This study was presented in abstract form in the 2010 annual ASCO meeting; the final data have not yet been presented [72]. In this study which is no longer accruing patients, patients with T3 or T1–2N1 tumors based on MRI were treated with bevacizumab and CapeOX (capecitabine and oxaliplatin) for three cycles followed by repeat MRI evaluation. Those patients with response went on to proctectomy, while nonresponders received standard chemoradiotherapy. A third study is a phase II randomized study of neoadjuvant FOLFOX/bevacizumab versus FOLFOXIRI/bevacizumab in patients with high-risk rectal cancer as defined by MRI. This study is not yet open to accrual but will also add insight into the response of the primary rectal tumor to chemotherapy alone [73]. These studies will provide important insight into the potential for a more individualized treatment approach through selective use of radiation in LARC.

Selective Nonoperative Management

Proctectomy is the cornerstone of the treatment algorithm for LARC patients. However, up to 33 % of LARC patients treated with neoadjuvant chemoradiotherapy exhibit

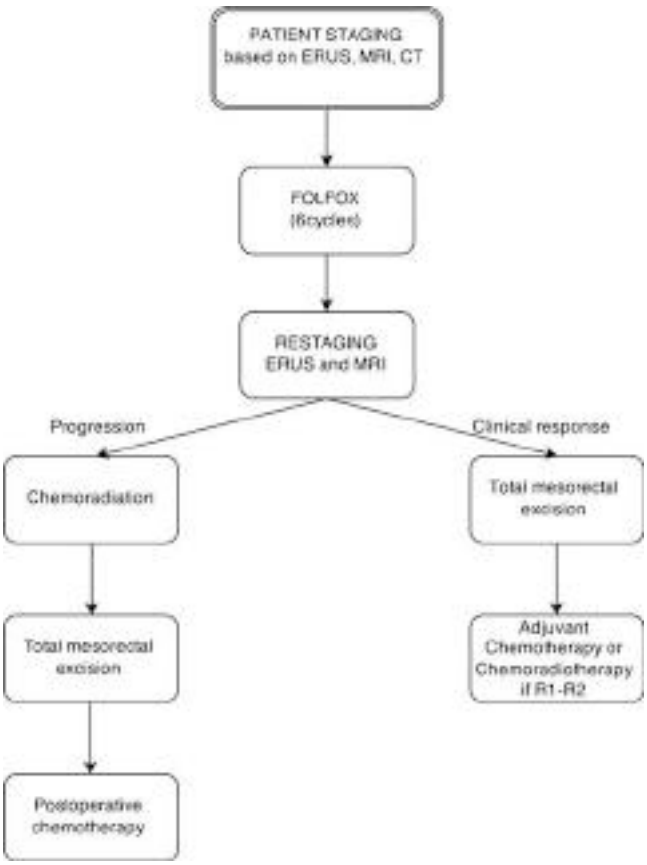

FIGURE 28-2. PROSPECT (Chemotherapy Alone or Chemotherapy Plus Radiation Therapy in Treating Patients with Locally Advanced Cancer Undergoing Surgery) trial schema. A phase II/III randomized study designed to evaluate the impact of selective use of radiotherapy compared with nonselective use of chemoradiation for patients with locally advanced rectal cancer. (*FOLFOX* infusional fluorouracil, leucovorin, and oxaliplatin, *LAR* low anterior resection, *FUCMT* fluorouracil or capecitabine plus radiotherapy, *TME* total mesorectal excision.) With permission from Neoadjuvant chemoradiation therapy and pathological complete response in rectal cancer. Gastroenterology Report. Gastroenterol Rep 2015 doi: 10.1093/gastro/gov039. http://gastro.oxfordjournals.org/content/early/2015/08/19/gastro.gov039.full. Copyright © 2015 Oxford University Press and Digestive Science Publishing Co. Limited.

a pathologic complete response (pCR) at the time of surgical resection [74, 75]. Patients with a pCR have improved oncologic outcomes with local recurrence rates of less than 1 % and a 5-year survival rate of over 90 % [3, 76], leading us to question the added benefit of proctectomy for these patients. The potential gains of avoiding proctectomy—reduced morbidity, improvement in quality of life, and potential reduction of health care expenses—could be significant. The current challenge lies in accurately identifying which patients have achieved a pCR and could safely avoid proctectomy [77]. Although cCR does not always correlate with pCR, and current imaging modalities cannot distinguish with certainty tumor remnants from tissue fibrosis [78, 79], a number of institutions have reported their experience with the selective use of an organ-preserving or NOM approach in patients with a complete clinical response after chemoradiotherapy (Table 28-2) [80–84]. The largest experience with the NOM approach to rectal cancer comes from Habr-Gama's group in Sao Paulo, Brazil [80–82]. Patients with persistent tumor underwent proctectomy; those with a complete clinical response were enrolled in a strict follow-up protocol. Patients with evidence of tumor relapse were directed to surgery, while patients with a sustained complete clinical response after 1 year continued surveillance every 3 months for an additional year and every 6 months thereafter. Twenty-seven percent of rectal cancer patients treated according to this protocol had a sustained complete clinical response and were spared from proctectomy. Of the patients who survived 1 year following treatment and did not show any evidence of tumor progression, local recurrence during follow-up developed in 10 %, but all had proctectomy with curative intent. The oncologic results in this NOM group were equivalent to those of patients who had a pathologic complete response after proctectomy. However, the authors did not evaluate patients on an intention-to-treat basis. By excluding those patients who failed treatment during the first year, results were heavily biased in favor of the NOM group. A group from Maastricht University in the Netherlands reported their NOM experience in 21 patients with complete clinical response as determined by clinical exam, MRI, and endoscopic biopsy among 192 patients treated with chemoradiotherapy between 2004 and 2010 [83]. After a mean follow-up of 25 ± 19 months, 1 patient developed LR, but was able to undergo curative salvage surgery. The other 20 patients are alive without disease. Outcomes in patients with complete clinical response treated according to the NOM protocol were similar to outcomes of patients with a pathologic complete response after proctectomy. At MSKCC, rectal cancer patients with a complete clinical response have been managed under an NOM strategy since 2006. Of the 32 patients starting treatment before 2010 who were followed for a median of 23 months, 6 patients developed relapse, and all underwent salvage surgery with curative intent; additionally, 3 of these patients also developed distant metastases [84]. The combined experience of these series suggests that NOM may be an alternative approach to proctectomy in highly select patients with distal rectal cancer who achieve a complete clinical response to neoadjuvant therapy (Table 28-2). However, the safety and efficacy of the NOM approach outside of centers specializing in the treatment of rectal cancer is controversial. It is now clear that even with strict complete clinical response definitions, some patients will later develop local recurrence, emphasizing the importance of close surveillance, because the success of this approach relies on the early diagnosis of recurrences and timely salvage therapy. In addition, the risk of distant metastases in patients with an apparent complete clinical response that develop local tumor regrowth and subsequent outcomes is unknown. Therefore, at the present time, the NOM of rectal cancer should be considered experimental.

The design of large, prospective randomized trials investigating the efficacy of the NOM approach is challenging,

TABLE 28-2. Summary of the most representative series, nonoperative vs. operative management of LARC after CRT

Series	# cCRs	%	Mean interval to LR	# Patients	OS				DFS			
					NOM		Operative arm		NOM		Operative arm	
					Survival	%	Survival	%	Survival	%	Survival	%
Habr-Gama et al. [80]	71	27	60	2	5 years	100	5 years	88	5 years	92	5 years	83
Habr-Gama et al. [81]	90	49	17	28	5 years	91	NA		5 years	68	NA	
Maas et al. [83]	21	11	22	1	2 years	100	2 years	91	2 years	89	2 years	93
Smith et al. [84]	32	NA	11	6	2 years	97	2 years	88	2 years	100	2 years	88
Dalton [90]	12	24	24[a]	6	26 months	100	26 months	100	26 months	100	26 months	100[b]

cCR clinical complete response, *CRT* chemoradiotherapy, *DFS* disease-free survival, *LARC* locally advanced rectal cancer, *LR* local recurrence, *NA* not available, *NOM* nonoperative management, *OS* overall survival, *RT* radiotherapy, *pCR* pathological complete response

[a]Mean time to surgery

[b]All six with pCR

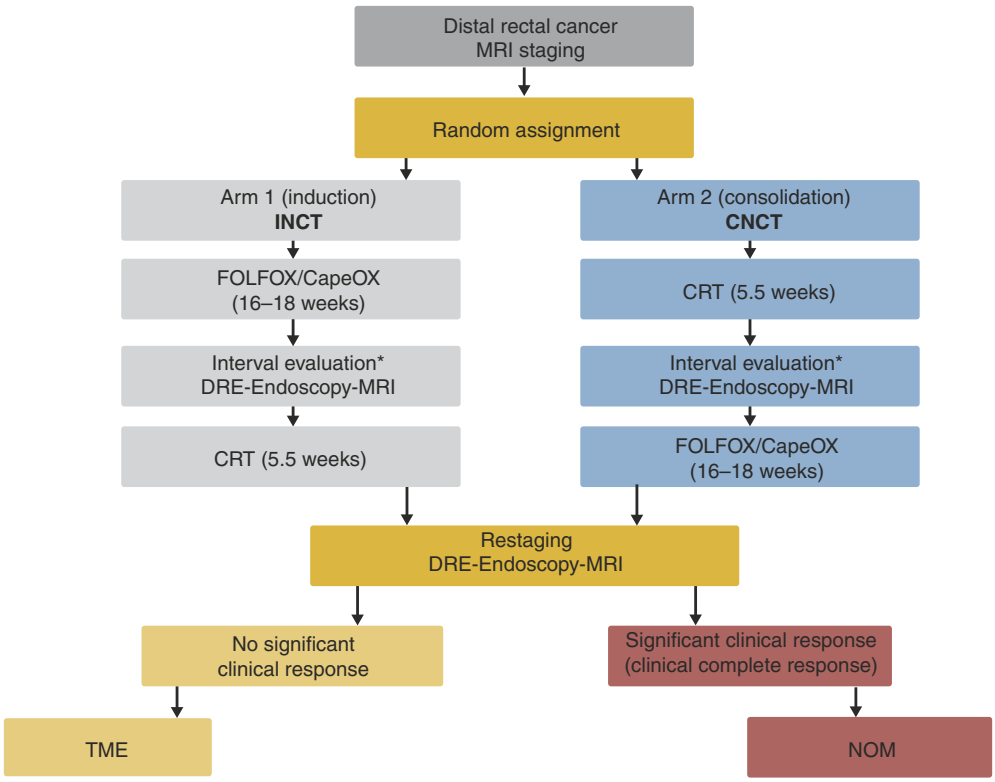

FIGURE 28-3. Memorial Sloan Kettering Cancer Center phase II trial schema that is underway to test the feasibility of incorporating a nonoperative management (NOM) to the multimodality treatment of rectal cancer in a multi-institutional setting. (*Cape* capecitabine, *CapeOx* capecitabine plus oxaliplatin, *CNCT* chemotherapy plus consolidation CRT, *CRT* chemoradiation, *DRE* digital rectal examination, *FOLFOX* infusional fluorouracil, leucovorin, and oxaliplatin, *FU* fluorouracil, *FUCMT* fluorouracil or capecitabine plus radiotherapy, *INCT* induction chemotherapy, *MRI* magnetic resonance imaging, *RT* radiotherapy, *TME* total mesorectal excision.) Courtesy of Julio Garcia-Aguilar.

given the relatively small proportion of patients with a complete clinical response to standard neoadjuvant chemoradiotherapy and the disparity of the treatment arms—observation versus proctectomy. However, a number of prospective observational studies [85–87] and phase II trials, including our own (Figure 28-3), are underway to test the feasibility of incorporating an NOM approach to the multimodality treatment of rectal cancer in a multi-institutional setting [88, 89].

Summary

Decades of clinical research have resulted in a variety of multimodality treatment paradigms for rectal cancer patients providing unprecedented local tumor control and patient survival. Although this represents a significant achievement in oncologic outcome, multimodality therapy can be associated with significant morbidity and long-term sequelae that can impair quality of life permanently. Identification of patients at

different risk levels for tumor recurrence and survival based on baseline tumor characteristics and response or resistance to therapy should enable us to tailor treatments accordingly and in certain cases omit radiation or surgery to decrease morbidity without compromising outcomes.

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29
Local Excision of Rectal Neoplasia

Mark H. Whiteford

Key Concepts

- When anatomically appropriate, local excision is the preferred over proctectomy for benign rectal polyps due to high success rates and lower morbidity.
- If local excision is to be utilized as definitive surgical therapy for rectal cancer, the depth of dissection should be full thickness of the rectal wall.
- Histologic predictors of lymph node metastasis in early rectal cancers include tumor depth, lymphatic and vascular invasion, poor differentiation, and tumor budding.
- Five-year disease-free survival after local excision of rectal cancer is lower than after proctectomy, although it is unclear whether overall survival is different.
- Survival and local recurrence rates for T2 rectal cancers treated with neoadjuvant chemoradiation and local excision appear to be similar to those of T1 cancers treated with local excision alone.
- Transanal endoscopic surgery may be associated with improved outcomes as compared to conventional transanal excision, although the quality of comparative studies is suboptimal.

Transanal Surgery, a Historical Perspective

The initial report of transanal excision (TAE) of a rectal tumor is attributed to Dr. Jacques Lisfranc in the early 1800s whereby a protruding and painful rectal tumor was excised via a prolapsing and incising technique [1]. There was no mention of anesthesia, no defect closure was attempted, and hemostasis was eventually maintained with serial intrarectal packing. Sir Alan Parks popularized the era of modern TAE in the 1960s [2]. This more familiar technique employed anesthesia, a self-retaining rectal retractor, epinephrine injection, a submucosal resection plane, use of stay sutures, and primary closure of the defect [2]. The appeal and benefits of TAE are obvious: direct endoluminal approach to the target pathology via the natural orifice; avoidance of a stoma; and avoidance of the morbidity associated with abdominal or transacral operations.

The goal of local excision is to completely remove the target pathology en bloc with negative margins. When applied to benign rectal polyps, this should be curative. When applied to rectal cancer, this has the potential to be curative if the tumor has not spread beyond the rectal wall. Due to technical limitations of the anus, rectum, and surgical instrumentation, conventional TAE has been limited to lesions within 8 cm from the anal verge, at or below the first rectal valve, ≤3 cm in size, and occupying ≤40% of the rectal circumference. Lesions that exceed these parameters are technically more challenging to remove.

In the early 1980s, Prof. Gerhard Buess, inspired by the poor visibility and limited reach of conventional TAE, ushered in the era of transanal endoscopic surgery (TES) when he invented a new technique and series of instruments for removal of rectal tumors [3]. His technique and instruments were termed transanal endoscopic microsurgery (TEM, Richard Wolf, GmbH, Knittlingen, Germany). TEM involves a 4×12 (or 20) cm cylindrical metal reusable operating rectoscope mounted to the operating table. The rectoscope has a sealed faceplate with multiple access ports that permit simultaneous pneumodistention of the rectum along with passage of a stereoscopic camera and modified laparoscopic instruments into the rectum. Stable pneumorectum is maintained with a dedicated TEM suction-CO_2 insufflation pump. TEM instruments could now remove larger lesions as well as lesions up to the rectosigmoid junction (~17 cm from the anal verge).

TEM proved to produce a specimen with less fragmentation and more negative margins and lead to a lower local recurrence than conventional TAE. Larger lesions and lesions up to the upper rectum could now be removed without the need for radical surgery. A similar reusable rigid proctoscopic transanal endoscopic operations (TEO®) system is also commercially

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available (Karl Storz, GmbH, Tuttlingen, Germany). The acceptance of TEM and TEO, however, was very slow due to the high capital cost of the equipment, requirement for specialized training, and complexity and technically challenging nature of the instrumentation and procedure. An additional obstacle was the lack of a category 1 CPT code for the procedure in the United States that made reimbursement problematic.

In 2010, Atallah first described the use of a commercially available single port laparoscopic platform placed transanally in conjunction with standard laparoscopic instruments and insufflators to perform transanal surgery [4]. This technique has been coined transanal minimally invasive surgery (TAMIS) and appears to show similar benefits as TEM [5]. This technique offers the promise of instrument simplicity and low upfront cost. Due to the similarities of the techniques and clinical results, TEM, TEO, and TAMIS are collectively termed TES.

Techniques

Technique for Conventional TAE

Patients undergo routine surgical history and physical examination with including evaluation of comorbidities, bowel function, and continence [6]. Examination should include digital rectal examination with proctoscopy to determine and document the longitudinal and circumferential location, extent of the lesion, and its proximity to the sphincter. Repeat or deeper biopsy can also be performed if colonoscopic biopsy was nondiagnostic. When concern for malignancy exists, then additional imaging studies such as endoscopic ultrasound, MRI, or CT scan may be considered.

The patient receives a full mechanical bowel prep and perioperative antibiotics. General anesthesia is the most common mode of anesthesia, but spinal anesthesia an acceptable option. Patient positioning is chosen such that the target pathology is placed dependently: lithotomy position for posterior lesions, prone jack knife for anterior and lateral lesions. Exposure is obtained via the surgeons preferred method of self-retaining anal retractor, lighted anoscope, operating proctoscope, Lone Star® retractor (Cooper Surgical, Inc, Trumbull, CT). A headlight provides ideal illumination in the tight confined operating field. Electrocautery is then utilized to demarcate a 5–10 mm margin around the lesion. Stay sutures may be placed laterally for retraction and improved visibility. Dissection progresses distally, laterally, then proximally with sharp or electrocautery dissection. Depth of dissection is in the submucosal plane for benign appearing lesions or to avoid sphincter injury, and full thickness dissection for biopsy-proven malignant lesions or lesions with gross features of malignancy. Additional stay sutures may be placed as one progresses proximally in order to maintain control of the proximal edge. Most authors advocate for primary transverse closure as longitudinal closure is thought to predispose to stricture. At times, there may be too much tension to close the defect. These can then either be partially closed or left open to heal by secondary intention if the defect is extraperitoneal (Figure 29-1).

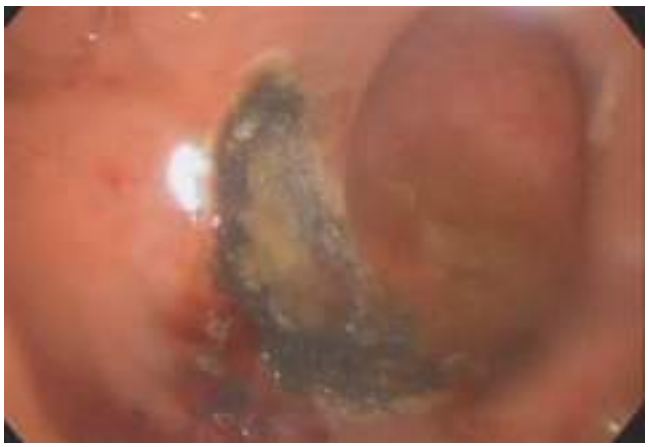

FIGURE 29-1. Open wound following local excision.

Technique for TEM and TEO [7]

Bowel preparation, anesthetic choice, and positioning are the same as TAE. Gentle digital dilation is performed to accommodate the 4 cm diameter proctoscope, which is then inserted and attached to the table mount. Both 12 and 20 cm lengths are available. The faceplate attached and tubing connected to the suction insufflator unit. Pneumorectum is established and the proctoscope adjusted to view the target lesion through the stereoscopic microscope or the laparoscopic video monitor. Three 5–9 mm instrument ports are available for use of the modified angled TEM laparoscopic instruments. Needle tip electrocautery is utilized to demarcate a 5–10 mm margin around the lesion. Submucosal or full thickness dissection is then initiated. This is most easily started in the distal right corner of the lesion with progression towards the proximal left corner. Partial en bloc resection of the mesorectum has also been described for deeper malignant lesions [8]. Continuous suction functions to clear the cautery smoke during the procedure. The integrated suction-insufflation unit prevents loss of pneumorectum from the suctioning. Following specimen removal, the defect is closed transversely using a running absorbable suture. A metal clip is locked at each end of the suture in lieu of intracorporeal knot tying. With the increased proximal reach of TEM, intraperitoneal entry occasionally occurs, and in experience hands, can safely be closed via the TEM instrumentation [9, 10]. TEM does suffer from technical limitations of the rigid proctoscope causing significant instrument conflict and has a longer learning curve for both technique and instrument troubleshooting than compared to other transanal techniques (Figures 29-2, 29-3, and 29-4).

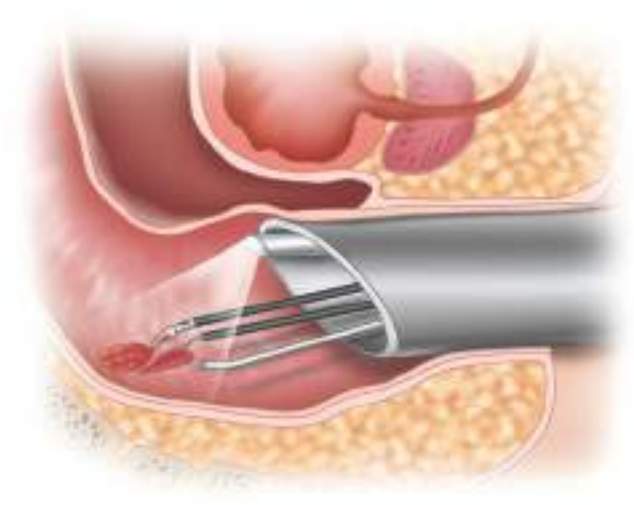

FIGURE 29-2. Transanal endoscopic microsurgery.

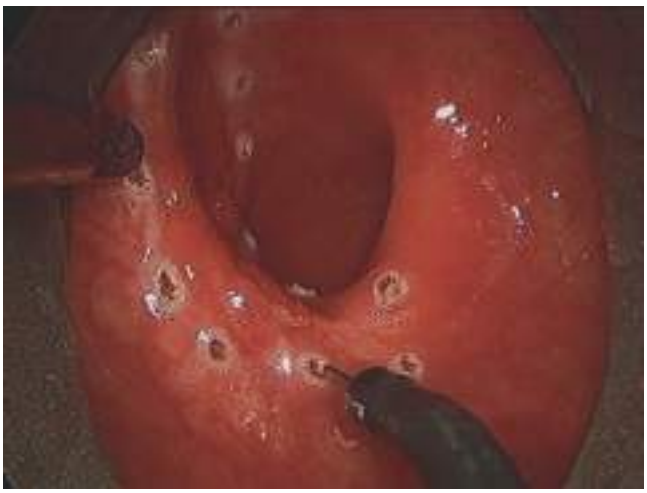

FIGURE 29-3. Margin around sessile polyp demarcated with monopolar cautery during TEM. *Courtesy Mark Whiteford, MD*.

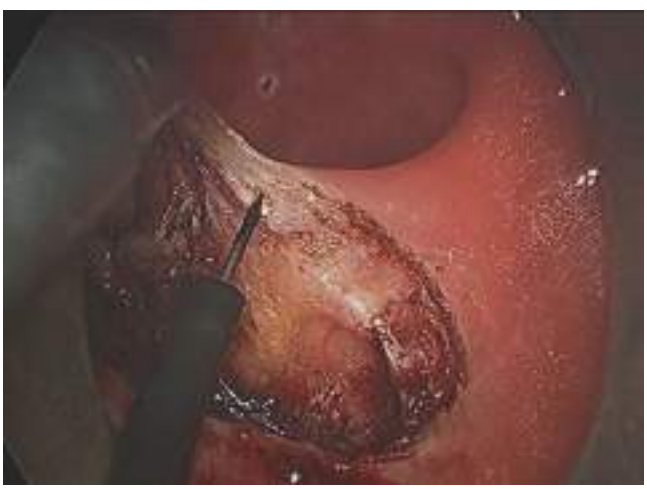

FIGURE 29-4. Full thickness depth of excision during TEM. *Courtesy Mark Whiteford, MD*.

Technique for TAMIS

TAMIS is a modification of TEM whereby the reusable rigid 4 cm diameter operating proctoscope is replaced by a flexible, disposable single port laparoscopic platform. Standard laparoscopic insufflators, camera, instruments, and vessel sealing devices are also utilized. Patient selection and preparation is similar to TAE and TEM. The shorter length and flexible platform of the TAMIS technique more easily permits operating on the non-dependent (downward) wall of the rectum, as is required with TAE and TEM. For this reason the majority of cases can be done in the lithotomy position. Dissection is performed in a similar fashion as with TEM. Laparoscopic suctioning must be done judiciously as not to lose pneumorectum and exposure. A more liberal use of laparoscopic vessel sealing devices provides improved hemostasis over that of monopolar cautery, thereby reducing the need for suctioning. Defect closure techniques vary among authors and include use of different laparoscopic suturing devices or barbed sutures [5]. Intraperitoneal entry during TAMIS is more likely to require laparoscopic assistance for defect closure due to loss of rectum and visualization of the defect via the transanal device [11]. Since the TAMIS devices rely on radial fixation to the top of the sphincter complex, low-lying rectal polyps become partially obscured by the transanal device and require a hybrid TAMIS and TAE resection technique. This involves dissection of the proximal portion of the lesion utilizing the TAMIS technique, and then removal of the TAMIS device followed by the conventional TAE technique to complete the distal dissection and defect closure.

All forms of TAE techniques have limitations such as the potential for incomplete resection or the requirement for conversion to an alternate technique, such as staged transanal procedures or need for an abdominal approach to complete the resection or defect closure. These events are more likely when the tumor is too bulky to permit adequate working space, the proximal extent of tumor cannot be visualized around a fold or sigmoid bend, uncontrolled bleeding is encountered, or there is an inadequate bowel preparation. Fortunately these situations are uncommon and or can be avoided with proper preoperative patient selection and preparation.

Transcoccygeal (Kraske) and transsphincteric (York-Mason) approaches to locally excise rectal neoplasia have largely been supplanted by these purely transanal techniques. If interested, the reader is directed to the previous addition of ASCRS textbook for an excellent overview of these topics [12].

TAE of Benign Rectal Polyps

The ideal indication for TAE is for the complete removal of benign lesions in the rectum. Radical surgery, in the form of proctectomy, which includes a complete regional lymphadenectomy, provides no clinical benefit over TAE in the setting of benign disease, yet subjects the patient to considerable perioperative morbidity and significant long-term risk of urinary, sexual, and defecatory dysfunction. Local excision has

the advantage of acting as a "total biopsy" to assess for completeness of resection and presence of otherwise occult cancer.

Most rectal polyps are detected on screening colonoscopy in asymptomatic patients. Occasionally rectal polyps produce symptoms such as rectal bleeding, blood or mucus on the stool, change in stool caliber, or tissue prolapse symptoms. While most small polyps are readily removed using colonoscopic polypectomy, larger polyps that would generally require piecemeal snare polypectomy are better served with TAE which provides a higher chance of complete polyp removal and a resultant lower chance of polyp recurrence.

Larger rectal polyps, particularly villous adenomas, have a higher incidence of harboring an occult cancer despite benign appearance and biopsies. For this reason preoperative assessment with endoscopic ultrasound is always reasonable to further assess tumor and nodal staging. Interpretation of endoscopic ultrasound performed soon after a full-thickness excision may be more challenging due to scar tissue, cautery artifact, and difficulty in differentiating between reactive and potentially malignant lymphadenopathy. These factors may result in overstaging of patients.

Benign polyps can be removed using either a partial thickness (submucosal plane) or full-thickness technique (deep to muscularis propria). Partial thickness dissection is facilitated through the use of submucosal injection of saline with or without epinephrine to help raise the polyp and mucosa off the muscularis propria. A non-lifting sign is worrisome for invasive cancer and is an indication for consideration of conversion to full-thickness excision for complete histologic assessment. A true submucosal dissection does not require defect closure provided there is no concern for full-thickness intraperitoneal entry. Alternatively, the mucosa is usually fairly mobile, and most defects can be closed primarily.

It should be noted that the submucosal plane is much more likely to be scarred or obliterated if the patient has undergone prior piecemeal hot snare polypectomy or multiple attempts at endoscopic excision. Full-thickness excision may be required in this situation if the layers of the rectal wall are fused by scar [7].

Results

Local excision with TAE, TEM, and TAMIS is typically performed in the outpatient setting. The goal of TAE is complete en bloc removal of the target pathology with minimal morbidity and mortality. Numerous case series and several comparison trials demonstrate a low perioperative complication rate (10–17%) and a less than 1% mortality rate following TAE and TEM [13–15]. There are some non-randomized studies that suggest that the quality of TEM excision, however, is better than TAE with the incidence of specimen fragmentation (1–6% vs. 24–35%), positive margins (10–12% vs. 29–50%), and local recurrence (5–6% vs. 27–29%) favoring TEM [14, 15]. Long-term recurrence data following TAMIS is not yet available.

Unfortunately, the quality of the studies of outcomes following local excision is distressingly suboptimal. Heterogeneous study populations (mixing benign and malignant pathology of various T stage), lack of appropriate time-to-event analysis, retrospective study design, and selection bias plague much of the published literature on the topic. It should also be remembered that, as of this writing, there have been no prospective, randomized comparisons of local excision techniques. Thus, although a few non-randomized retrospective analyses favor transanal endoscopic microsurgery vs. traditional local excision [16], it is unclear whether any surgical technique is truly superior to any other, especially for lesions in the distal rectum.

Some newer advanced colonoscopic techniques, endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), are being utilized for excision of benign colorectal polyps. EMR is usually a piecemeal resection whereas ESD attempts a single en bloc resection. These techniques are primarily utilized in Asia with limited North American and European experience. In early comparisons between TES and EMR, EMR shows a slightly lower complication rate (3.8% vs. 13%) but a higher local recurrence rate (11.2% vs. 5.4%) [17]. In comparisons between TES and ESD, TES shows higher percentage of en bloc excision (99% vs. 88%) and negative margins (89% vs. 74%) while maintaining similar rate of complications (8.0% vs. 8.0%) [18].

While there are no guidelines that mandate a recommended follow-up strategy following TES for benign rectal polyps, many institutions performed endoscopy every 6–12 months for 2–3 years. Routine endoscopic ultrasound and imaging are not recommended for benign disease.

TES for Rectal Cancer

Curative surgery for rectal cancer aims to maximize the oncologic clearance of the primary tumor as well as the mesorectal lymph nodes. Proctectomy is the accepted gold standard surgical procedure for rectal cancer with 5-year local recurrence rates in the 5–10% range. The procedure, however, comes with significant risk of perioperative complications, long-term defecatory, urinary, and sexual dysfunction, and frequent need for temporary or permanent ostomies [19–21].

Local excision has long been an appealing option for rectal cancer because of its low risk of morbidity and mortality, relative paucity of long-term functional sequelae and the potential for curative treatment of disease limited to the bowel wall. The ideal candidate for local excision is a patient who has no lymph node metastasis and has a primary tumor can be excised with negative margins. In such a situation local excision should be curative. The great controversy, however, is that our ability to predict lymph node metastases are disappointingly poor and local recurrence following TAE remains much higher than with radical surgery.

Local excision can be utilized as a tool to gain additional information regarding tumor biology and risk of lymph node metastasis. This may help guide clinical judgment in deciding whether or not a patient can be spared radical surgery. It is wise to clarify this concept with the patient preoperatively. The local excision will be utilized as a "total biopsy" to help guide treatment recommendations and that if this total biopsy reveals high risk histologic features then a recommendation for subsequent radical surgery will be made. However, if no high-risk features are identified and the priorities and values of a patient are such that they accept a potentially higher risk of local recurrence than with proctectomy, local excision may be considered acceptable treatment. Local excision remains most appealing in patients who are unfit or unwilling to undergo radical surgery.

Lymph node status dramatically effects patient prognosis as well as our treatment decisions and recommendations. Current efforts to predict lymph node status consist of identifying high-risk histopathologic features from biopsy specimens. This is complemented with selected imaging modalities. When considering patients for local excision, it is imperative to choose those with the lowest risk of harboring locoregional metastatic disease.

Predicting Risk of Lymph Node Metastasis

Prediction of lymph node metastasis for rectal cancer is an imprecise science. No single histologic feature can solely predict risk of lymph node metastasis nor is there any currently available genetic or molecular marker that is predictive. Through a combination of histopathologic characteristics and imaging modalities the surgeon and the patient try to roughly generate a risk-benefit calculation to guide clinical strategies related to local excision vs. radical surgery. Colonoscopic biopsies alone sample but a small portion of the tumor, whereas an excisional full-thickness biopsy allows the fullest examination of the tumor histology, death of invasion, and margin status. Unfavorable histologic features are not only independently predictive of lymph node metastasis, but multiple unfavorable features also have an additive risk [22].

Depth of Invasion

Depth of tumor invasion into the wall of the bowel has traditionally been one of the best predictors of lymph node metastasis and is assessable variable in nearly all complete excisions. T1 tumors, which are limited to the submucosa, are associated with a 10–15% incidence of occult lymph node metastases detected at the time of radical surgery. T2 tumors, which invade into but not through the muscularis propria, are associated with a 20–26% risk of lymph node metastasis [22–25]. Kikuchi further identified the importance of depth of submucosal invasion on lymph node metastases and local recurrence amongst T1 cancers. They analyzed a large series of patients subdivided by the cancer depth of invasion into the upper, middle, and lower thirds of the submucosa (SM1, SM2, SM3) and demonstrated an incremental increase in risk of lymph node metastasis or local recurrences with deeper depth of invasion. Tumors invading to the SM3 level were shown to have a similar risk of lymph node metastasis and local recurrence as T2 cancers [26].

Lymphovascular Invasion

Lymphovascular invasion is found in 12–32% of T1 rectal cancers [22, 27] and is a strong predictor of lymph node metastasis with an odds ratio between 3.0 and 11.5 reported on multivariate analysis [22, 24, 28]. Bach reviewed 487 rectal cancer subjects tracked prospectively in a national proctectomy database. The incidence of local recurrence based on depth of invasion, lymphatic invasion, and tumor diameter is shown in Table 29-1 [28].

Table 29-1. Local recurrence rates (percentage) at 36 months following TEM excision of rectal cancer

	Lymphatic invasion	Maximum tumor diameter (cm)					
Depth of invasion		≤1	1.1–2	2.1–3	3.1–4	4.1–5	≥5.1
pT1 sm1	No	3.0	3.6	4.4	5.4	6.6	8.1
	Yes	5.2	6.4	7.7	9.4	11.4	13.7
pT1 sm2–3	No	10.5	12.7	15.3	18.5	22.1	26.4
	Yes	17.8	21.4	25.5	30.3	35.7	41.8
pT2	No	9.8	11.9	14.3	17.3	20.7	24.7
	Yes	16.7	20.0	23.9	28.5	33.7	39.5
pT3	No	19.7	23.6	28.0	33.2	39.0	45.4
	Yes	32.2	37.9	44.1	51.0	58.3	65.7

pT = pathological tumor stage; sm1 and sm2–3 = Kikuchi submucosal stage

With permission from Bach SP, Hill J, Monson JR, Simson JN, Lane L, Merrie A, Warren B, Mortensen NJ. Transanal Endoscopic Microsurgery (TEM) Collaboration. A predictive model for local recurrence after transanal endoscopic microsurgery for rectal cancer. Br J Surg. 2009;96(3):280–90. Copyright © 2009 John Wiley & Sons, Inc. [29]

Poor Differentiation

Poorly differentiated histology also predicts for lymph node metastases in rectal cancer [22–24, 29]; however, this trait is seen infrequently, present in only 2–4% of early rectal cancers [22, 28, 30]. Odds ratio for probably of poorly differentiated tumors having lymph node metastasis is 4.8–6.1 [31, 32].

Tumor Budding

Tumor budding, defined as small nests of five or more, usually poorly differentiated, cancer cells along the invasive front, is a histologic trait not routinely mentioned on biopsy reports in the North America, but has been extensively reported in the Asian gastroenterology literature [27, 30, 32] as a strong predictor of lymph node metastasis in colon and rectal cancer. Tumor budding is present in 16–25% [27, 33] of T1 cancers and multivariate analysis has demonstrated an odds ratio of 5.1–5.8 in predicting lymph node metastasis [31, 32].

Location of the cancer within the rectum may also be a risk factor for lymph node metastasis. Nascimbeni reported 8 and 11% risk of lymph node metastasis for high and mid rectal cancers, and 34% for low rectal tumors [29]. Mucinous histology and gender have not consistently been associated with increased risk of lymph node metastasis [29]. Molecular markers are not yet able to reliably predict nodal status (Figure 29-5) [31].

Imaging for Early Rectal Cancer Staging

Imaging is a standard recommendation for the staging of rectal cancer [34]. Despite innumerable technological advances in medicine, however, imaging remains an unreliable and inadequate measure of lymph node metastasis for rectal cancer. At present, endoscopic rectal ultrasound (EUS) is the imaging modality of choice to distinguish between T1 and T2 rectal cancers. CT scan and MRI do not have adequate resolution to differentiate between layers of the bowel wall in T1 and T2 rectal cancers, but are better than EUS at determining deeper T3 and T4 tumors.

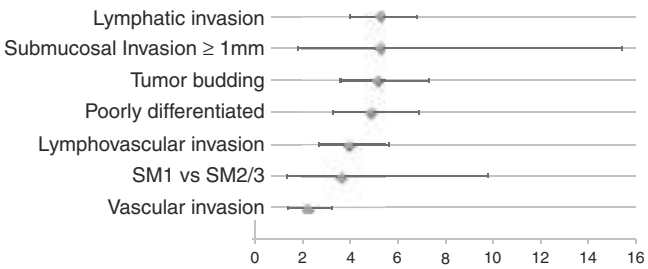

FIGURE 29-5. Relative risk (95% confidence intervals) of lymph node metastases in pT1 rectal cancers. (SM1 = invasion into superficial third of submucosa. SM2/3 = invasion into middle and deep third of submucosa). *With permission from Bosch SL, Teerenstra S, de Wilt JH, Cunningham C, Nagtegaal ID. Predicting lymph node metastasis in pT1 colorectal cancer: a systematic review of risk factors providing rationale for therapy decisions. Endoscopy. 2013 Oct; 45(10):827–34* [30].

Imaging features that are suspicious for malignant lymph nodes include presence of a round shape, internal heterogeneity, irregular border, and to a lesser extent, size. Lymph node size alone is not a reliable indicator of node positivity, but nodes greater than 8 mm are considered highly suspicious on EUS, CT, and MRI. MRI and EUS are the more reliable modalities for assessing lymph node metastasis in early rectal cancer [35, 37]. CT and MRI are more accurate than EUS in the setting of locally advanced and metastatic disease. There is some promise for improved lymph node accuracy through the use of gadofosveset-enhanced MRI [38].

Oncologic Results Following Local Excision of Rectal Cancer

As noted above, the methodology of many reported series of local excision for rectal neoplasia is suspect. In addition to the problems noted above, trials of local excision for rectal cancer suffer from additional issues. One is inclusion of patients who have cancer in a polyp that is completely or mostly removed by endoscopic polypectomy, and local excision is performed for unclear margins. Many of these patients will have no residual tumor in the local excision specimen and have an extremely low risk of local pelvic failure, biasing the results of the series in favor of local excision. Another is retrospective subgroup analysis, in which patients are only included in the analysis after review of the histology. This allows for exclusion of patients who have positive margins of resection, greater than T1 stage, or other unfavorable histologic features. This obviously biases the analysis in favor of local excision, but fails to replicate the true clinical situation in which margins and T stage cannot be known with certainty preoperatively. Nonrandomized comparative trials of local excision vs. proctectomy suffer from lack of information regarding mesorectal nodal status in the local excision group, which would most likely favor proctectomy. Although this bias can be mitigated by inclusion of patients in each group based on T stage alone, it cannot be completely eliminated as there may be hidden selection bias. It is thus difficult to make firm conclusions regarding the optimal place for local excision in our armamentarium of therapies for patients suffering from rectal cancer.

Local Excision for T1 Cancer

Local excision of T1 rectal cancer is a widely available and technically feasible procedure with low risk of short-term morbidity and mortality. Approximately 15% of all rectal cancers present at stage 1 with no metastatic lymph nodes and tumor confined to the bowel wall. In theory, these patients will gain no clinical benefit from the lymphadenec-

tomy associated with a low anterior or abdominoperineal resection. Therefore there is great controversy over whether the decrease in short-term morbidity is worth the long-term oncologic compromise. As discussed in the previous section, the unmet challenge is the inability to predict with high reliability, which patients have no cancer in their regional lymphatics. The reported rate of local recurrence following TAE varies considerably in the literature, but is universally higher than for proctectomy. For these reasons, proctectomy remains the oncologic gold standard for rectal cancer surgery.

The CALGB 8984 study reported a phase 2 trial in patients with adenocarcinoma of the low rectum less than 10 cm proximal to the dentate line and less than 4 cm in diameter who underwent local excision. Fifty-nine patients with T1 rectal cancers were followed for median a 48 months. Local recurrence occurred in three patients, two local only, one local and distant recurrence. Six-year disease-free survival was 83% [38]. However, approximately one-third of the patients initially enrolled were excluded from analysis, most for positive margins of resection. Several subsequent single institution case series within the United States demonstrated local recurrence rates from 7 to 18%, cancer-specific survival rates ranging from 89 to 92%, and overall survival 72–75% [39–42]. You reported the largest cohort study comparing TAE ($n=601$) and proctectomy ($n=493$) for excision of T1 rectal cancers tracked in the National Cancer Database with a median follow-up of 3.7 years [43]. Local recurrence rates were higher for TAE compared to proctectomy (12.5% vs. 6.9%, $p=0.003$) with concomitant lower 5 year disease-specific survival (93.2% vs. 97.2%, $p=0.004$) but similar 5 year overall survival (77.4% vs. 81.7%, $p=0.09$).

A meta-analysis by Kidane reviewed 1 randomized controlled trial and 12 observational studies comparing local to radical resection in adults with T1N0M0 rectal adenocarcinoma [44]. This showed a significantly lower 5-year overall survival with local excision as compared to radical resection (relative risk (RR) 1.46, 95% CI 1.19–1.77). This difference was not present in the TEM excision subgroup. Five year local recurrence was significantly higher for local excision (RR 2.36, 95% CI 1.64–3.39) including both the TAE and TEM subgroups. With regards to postoperative complications, local excision is associated with significantly lower perioperative mortality (RR, 0.31:95% CI, 0.14–0.71), postoperative complications (RR 0.16:95% CI, 0.08–0.30), and lower need for permanent ostomy (RR 0.17:95% CI, 0.09–0.30) when compared to radical surgery. Meta-regression analysis showed that when local resection and radical resection were compared only in distal rectal cancer, then there was no significant difference in between overall survival (RR 1.13, 95% CI 0.93–1.37). This supports the observation that distal rectal cancers have a higher risk of local recurrence than mid and upper rectal cancers [29]. The authors of this meta-analysis concluded that based on low to moderate quality evidence, TEM is the preferred surgery for T1N0M0 rectal cancer because of its low risk of complications, mortality, and permanent stoma compared to radical resection without sacrificing 5 year overall survival. However, as noted above, it is impossible to know whether a patient is truly "T1N0" prior to embarking on local excision.

There exists a concern that performing local excision for cancer may oncologically contaminate the embryonic surgery planes and make subsequent restorative radical proctectomy prohibitively difficult or result in a high incidence of local recurrence. This concern did not appear to be founded in a study of 63 local excision patients identified as having high-risk histology who soon thereafter underwent radical proctectomy. Fifty-three (84%) had restorative procedures. Local recurrence occurred in 1 patient whom had a T3 tumor found following TEM. No local recurrences were seen in the T1 or T2 patients [45]. No data exists to determine if immediate proctectomy results in a higher rate of permanent colostomy.

Local Excision for T2NX Cancer

The deeper T2 rectal cancers invade into the muscularis propria permitting them greater access to the lymphatics. As a consequence, the incidence of lymph node metastasis and local recurrence is double that of T1 cancers. Even more so than for T1 cancers, proctectomy is the oncologic procedure of choice. That said, as with T1 cancers, organ sparing options have been explored but in conjunction with the supplemental use of radiation therapy. The CALGB 8984 trial included 51 patients with T2 rectal cancer whom underwent post-op chemoradiation (5400 cGy with 5-fluorouracil). Local recurrence occurred in seven patients. Six year overall survival and failure-free survival was 85 and 71%, similar to historical data for radical surgery from the National Cancer Database [38].

Neoadjuvant chemoradiation prior to radical resection of locally advanced rectal cancer has been shown to downsize and downstage rectal cancers. Read et al. reviewed 649 consecutive rectal cancer patients and found a robust pathological response of the primary tumor to chemoradiation (ypT0-1) in 87 (23%) patients. Lymph node metastasis were identified in only 3% (3 of 87) of these patients indicating that response to neoadjuvant therapy may help predict low risk of lymph node metastasis in rectal cancer [46]. Rullier reviewed data from nine studies of preoperative radiotherapy followed by local excision in cT2-T3N0 rectal cancer. Local and distant recurrence occurred in 28/365 and 24/302, respectively. Complete responders had an 87% disease-free recurrence compared with that of 64% for partial or incomplete responders [47]. These data suggest that a robust primary tumor response to neoadjuvant chemoradiation can be utilized as a surrogate marker for a patient to have low risk lymph node metastasis and, hence, a candidate for organ

sparing local excision. This selection factor was included in the GRECCAR 2 multicenter, phase 3, randomized controlled trial for uT2-3 N0 low rectal cancers. Patients underwent neoadjuvant chemoradiation and the clinical response was reassessed. Good responders ($n=120$) were randomized to local excision or radical proctectomy surgery. Poor responders were not randomized and went directly to radical proctectomy as they were considered high risk for nodal metastasis. Study endpoints include operative mortality, recurrence, major morbidity, and severe side effects after randomization. This trial has completed accrual and its follow-up and data collection phase [48].

The ACOSOG Z6041 trial was a phase 2 trial of 84 patients treated by neoadjuvant 5400 cGy radiation with capecitabine and oxaliplatin followed by local excision of uT2N0 rectal cancers in the low rectum (≤8 cm from the anal verge). Complete pathologic response was seen in 44% of patients and down staging to ypT0-1 was seen in 64% of patients. Thirty-nine percent of patients experienced grade 3 toxicity, high enough for the capecitabine and radiation doses to be reduced mid trial [49]. After an average 4.2-year follow-up in 72 patients who underwent local excision for ypT0-2 cancers, local recurrence developed in 2 patients, distant metastasis in 5 patients. Disease-free and overall survival was 87 and 96% at 3 years and 97% of patients had rectal preservation [50]. While this study and other studies are encouraging, inadequate evidence exists to demonstrate the equivalence of neoadjuvant chemoradiation followed by local excision for uT2N0 rectal cancers. A single center, randomized control trial compared radical surgery to TEM following neoadjuvant chemoradiation in 70 patients with clinical T2N0 low rectal cancer [51]. Forty-nine percent of patients in each arm were down staged to ypT0-1. After a median follow-up of 84 months, the local recurrence rate was 6% in the TEM group, and 3% in the radical surgery group. Five-year survival was 94% in both groups. At present, this combination therapy should be reserved for patients unfit or unwilling to undergo the accepted standard therapy of proctectomy.

Surveillance and Salvage Following Local Excision of Rectal Cancer

Surveillance following local excision is recommended to assess for early identification of local recurrence. No formal guidelines are in place but a summary of several retrospective series suggests a follow-up strategy of proctoscopy or flexible sigmoidoscopy with high resolution rectal MRI or endorectal ultrasound every 3–6 months for 3 years, then q 6–12 months through year 5, colonoscopy at years 1, 4, and 9, and CT of abdomen and chest annually.

Median time to recurrence ranges from 13 to 47 months with most occurring between 12 and 24 months. The addition of radiation therapy often delays identification of local recurrence an additional 1–2 years [28, 52–55]. Despite close follow-up, recurrences have a relatively poor prognosis. Patients with local only recurrences who were candidates for resection had an R0 resection in 79–96% of cases resulting in a 53–58% disease-free survival [53, 54, 56]. These poor results of salvage therapy should provide a sobering reminder that the best chance of curing a patient suffering from rectal cancer is with initial treatment. Trying to "mop up" after local pelvic or distant failure has occurred is often futile. In addition, it should be remembered that patients undergoing local excision are typically those with the smallest, early stage lesions, those most easily cured by proctectomy.

Complications of TAE

Complications following local excision of rectal polyps and cancers occur in 5–25% with mortality rates in the 0.3–0.6% range [16, 57, 58]. Major intraoperative bleeding is a rare event. Bleeding is usually addressed with monopolar cautery, sutures, injection of epinephrine solution, or laparoscopic vessel sealing devices. Intraperitoneal entry during TEM was initially discouraged due to the concern for intraabdominal injury or leakage at the closure site. Gavagan reported their small case series that demonstrated the safety of intraperitoneal entry and closure during TEM [9], results that have been confirmed by other groups [10, 59]. The current TAMIS platforms do not have the rigid TEM operating proctoscope which stents open the operative field during the loss of pneumorectum into the peritoneal cavity during intraperitoneal entry. In this instance, closure of the full thickness defect is more likely to require combined transanal and laparoscopic assistance or conversion to open [11].

The most common complication with local excision is postoperative urinary retention. This occurs in up to 11% of patients and is thought to be due to a combination of direct pressure on the urethra, anal stretch, local edema, and pain. This is almost always self-limiting and can be treated by intermittent straight catheterization or short-term indwelling catheter placement. Postoperative bleeding is rare and tends to occur several days post-op corresponding to a suture line dehiscence, sloughing of a scab, or reinstitution of anticoagulant medication. Minor episodes are often self-limiting but frank hemorrhage warrants evaluation with volume assessment and resuscitation followed by endoscopic evaluation and treatment. Suture line dehiscence is more common in lower rectal excisions and in irradiated fields. The patient may report feeling well for a few days post-op followed by a constellation of dark blood and mucous with bowel movements, throbbing rectal pain, fevers, and night sweats. In the absence of sepsis, treatment is usually non-operative and based on symptom control. Symptoms should slowly resolve over 2–3 months.

The concern over potential sphincter damage during TES has been raised. While mild fecal incontinence has been reported immediately post-op, return to preoperative baseline function and quality of life typically occurs within 6 weeks of surgery [60, 61].

Conclusion

Local excision of benign rectal polyps and highly selected early rectal cancers is technically feasible and is associated with a markedly reduced morbidity and mortality when compared to radical surgery. Local excision techniques include conventional TAE and TES. Local excision of early rectal cancers does not remove or adequately sample the regional mesorectal lymph nodes. Preoperative prediction of lymph node positivity is an imprecise science. Increased risk factors for lymph node metastasis and local recurrence include depth of invasion, lymphatic or vascular invasion, poor differentiation, tumor budding, and abnormal lymph nodes identified on imaging. Because of imprecise staging and possibly greater chance of positive resection margins, local excision results in a higher incidence of local recurrence when compared to radical surgery. Patients who are unfit or unwilling to undergo radical surgery may choose an oncologically less sound local excision option in order to avoid the increased short- and long-term complications related to radical surgery. The decision to perform local excision must be individualized, the patient's values and personal preferences regarding cure vs. quality of life.

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30
Rectal Cancer: Watch and Wait

George J. Chang

Key Concepts

- Pathologic complete treatment response following neoadjuvant chemoradiation therapy and surgery for rectal cancer is associated with favorable prognosis.
- Pathologic complete treatment response is observed in approximately 15–20% of rectal cancer patients following chemoradiation therapy.
- Clinical and radiographic assessment of neoadjuvant therapy treatment response is suboptimal, and remains a primary challenge for safe implementation of watch and wait strategies.
- Approximately one in three patients exhibiting clinical complete response will develop tumor regrowth.
- At present, watch and wait should be offered to patients only in the context of a clinical trial.
- Local excision following neoadjuvant chemoradiation therapy is associated with significant risk for pain and poor wound healing.

Introduction

Over the past few decades, the management of rectal cancer has become increasingly complex. What was once a disease with high mortality and limited treatment options that typically necessitated a permanent colostomy has become a model for multidisciplinary evaluation and treatment and surgical advancement. For over a century, surgical resection has remained the cornerstone of curative treatment of rectal cancer. The principles of treatment include complete *en bloc* resection of the tumor-bearing rectum and mesorectum with clear margins along with clearance of pelvic lymphadenopathy and, when possible, restoration of intestinal continuity [1]. However, because of the historically high risk of local failure after surgery alone, clinicians have utilized neoadjuvant radiotherapy or chemoradiation therapy (nCRT) which has improved the rate of local tumor control [2]. Now the oncologic outcomes following treatment of rectal cancer in the modern era can equal outcomes following treatment of colon cancer [3]. Despite these advances, the multimodal treatment for rectal cancer is associated with a significant impact on long-term functional and quality of life outcomes including risks for bowel, bladder, and sexual dysfunction, pain, and potential need for permanent colostomy. Therefore there is great interest in strategies to decrease the toxicity of treatment, including strategies that employ the selective use of radiation, chemotherapy, or even surgery.

The modern concept of selective use of surgery following chemoradiation therapy for patients with rectal cancer are based on the fact that pathologic complete response (pCR) is observed in approximately 10–20% of patients following long course chemoradiation therapy. In 2004, Habr-Gama and her group first reported outcomes for selective surgery with a nonoperative (a.k.a. "watch and wait" or "wait and see") strategy in select patients who achieved a clinical complete response (cCR) following chemoradiation therapy [4]. In the decade since that initial report, a number of other investigators have attempted to bring further light to understanding the potential for a selective surgical approach. They have also highlighted a need for considering a number of important factors including assessing and improving the effectiveness of neoadjuvant therapy, predicting pCR prior to pathologic evaluation, determining the true risk for locoregional failure following a watch-and-wait approach, and understanding the potential for salvage surgical treatment and subsequent long-term survival outcome following treatment failure. While definitive surgical resection remains the standard of care for all patients with non-metastatic rectal cancer, a growing number of studies are providing supportive evidence for a watch and wait, organ-preserving approach in highly selected patients with rectal cancer.

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Neoadjuvant Chemoradiation Therapy

For patients with locally advanced rectal cancers, traditionally considered as clinical stage II and III, neoadjuvant therapy has been administered to improve local control. Building upon the demonstrated oncologic benefit of total mesorectal excision (TME) surgery by Heald, the Dutch Colorectal Cancer Group randomized patients to preoperative radiotherapy (5×5 Gy) followed by immediate TME surgery to TME surgery alone [5, 6]. This demonstrated that preoperative radiotherapy, when compared to TME surgery alone, was associated with a significant reduction in local recurrence although no improvement in overall survival could be demonstrated [7]. Meanwhile, the EORTC 22921 and FCCD 9203 studies demonstrated that addition of concurrent chemotherapy administered over a 5–6 week duration followed by delayed surgery demonstrated improvement in local recurrence free survival when compared to preoperative radiotherapy alone [8, 9]. However, the landmark study of the German Rectal Cancer Study Group definitively established the superiority of preoperative (neoadjuvant) vs. postoperative chemoradiation therapy, followed by surgery 6–8 weeks later, with improved local control and sphincter preservation [2].

Preoperative chemoradiotherapy is typically administered in "long course" fashion, with radiotherapy and a radiosensitizing chemotherapeutic agent administered over a 5–6 week period with a 6–10 week treatment break prior to proctectomy. This extended period of time allows for tumor regression, if the tumor is sensitive to the therapy [10]. This may facilitate more optimal surgery, including sphincter preservation, by reducing the tumor bulk and permitting surgery to be safely conducted in previously uninvolved but inaccessible adjacent tissue planes [11]. It also provides potential clearance of microscopic tumor spread, safely permitting a closer distal margin at resection with subsequent restoration of intestinal continuity [12, 13]. The surgeon should be cautious, however, not to leave tissue in situ that was previously involved with tumor, as radiotherapy does not induce tumor kill in a "wave front," and residual nests of tumor cells can be found spread throughout the initial volume of tissue involved by the tumor. Lastly, studies demonstrating improved sphincter preservation must be taken with a grain of salt, as estimation of whether a surgeon will be able to perform restorative proctectomy or not based on initial clinical examination is subjective.

As one would expect, similar responses to pelvic short-course preoperative therapy were previously not observed, as proctectomy was typically performed within a week or 2 of short-course radiotherapy, prior to the development of radiation induced inflammation, and too short a time to allow for significant tumor regression [14]. More recent trials in which proctectomy was delayed 4–8 weeks after short course radiotherapy reveal that tumor regression and relatively high rates of complete pathologic response do occur [15]. In addition, oncologic outcomes following short course radiotherapy and long course chemoradiotherapy for patients with locally advanced rectal cancer have been demonstrated to be similar in prospective randomized trials [14, 16]. Thus, it is likely that significant tumorcidal effect can be achieved with either regimen, but the added time delay prior to proctectomy with long course chemoradiotherapy results in more tumor involution seen on histologic evaluation of the proctectomy specimen. Furthermore, the potential systemic effects of the concurrent chemotherapy are not well understood.

Response to treatment has been an important observation, and following completion of CRT up to 50% of patients will experience a cCR as defined by replacement of the tumor bed by scar or normal appearing mucosa on clinical and endoscopic examination [17]. Pathologic complete response (specimen without evidence of residual tumor cells) or pathologic near-complete response (specimen with only single or small groups of tumor cells) can be observed in 10–40% of patients following neoadjuvant chemoradiation therapy (nCRT) [18, 19]. Complete clinical response, however, is not necessarily predictive of pathologic response. It is now widely recognized that tumor regression in response to neoadjuvant treatment is an important prognostic indicator of long-term outcome. It can be associated with tumor volume reduction, down-staging and nodal sterilization and a number of pathologic grading systems now exist to describe the extent of response (Table 30-1). It is a pathologic biomarker of the effectiveness of local and systemic tumor control and major response with complete or near complete resolution is

Table 30-1. Tumor Regression Grading Systems

TRG	Mandard [22]	Dworak [23]	Rödel [10]	Ryan [24]	CAP [25]
0		No regression	No regression		No residual tumor cells
1	No residual cancer cells	Dominant tumor mass with obvious fibrosis and/or vasculopathy	Fibrosis <25% of tumor mass	No residual cancer cells or single cells	Single or small groups of cancer cells
2	Rare residual cancer cells	Dominantly fibrotic changes with few tumor cells or groups	Fibrosis 25–50% of tumor mass	Residual cancer outgrown by fibrosis	Residual cancer outgrown by fibrosis
3	Fibrosis greater than residual cancer	Very few (difficult to find microscopically) tumor cells in fibrotic tissue with or without mucous substance	Fibrosis >50% of tumor mass	Significant cancer outgrown by cancer or no fibrosis with extensive residual cancer	Minimal evidence of fibrosis
4	Residual cancer greater than fibrosis	Complete regression	Complete regression		
5	No regression				

highly associated with a favorable prognosis [20]. In a large study of 725 patients treated with neoadjuvant chemoradiation and total mesorectal excision for locally advanced rectal cancer at The University of Texas, MD, Anderson Cancer Center, local recurrences were virtually absent and systemic recurrences occurred in fewer than 10% of patients exhibiting complete response or major downstaging to ypT0-2 N0 disease [21]. In fact in the modern era of TME surgery, distant, rather than local, disease recurrence has emerged as the primary concern.

Surgery for Rectal Cancer

The principles for surgical curative treatment for rectal cancer have been established since the beginning of the twentieth century with Ernest Miles' description of abdominoperineal excision (APE) with end colostomy for carcinomas of the rectum and pelvic colon [26]. Since then, a number of surgical and multidisciplinary advances as outlined above have improved treatment outcomes, reduced operative mortality, and offered the potential for sphincter preservation. However, for patients with distal rectal cancer, the excellent oncologic outcomes of nCRT and surgery can be associated with the need for permanent colostomy or with significant risk for bowel dysfunction including fecal incontinence and soiling following coloanal reconstruction.

Quality of life among rectal cancer patients undergoing surgical resection with or without a permanent colostomy was compared in a systematic review of 5127 patients from 35 non-randomized studies. Fourteen of the studies reported that APE was not associated with poorer quality of life measures than low anterior resection among patients with rectal cancer. The remaining studies found some difference, although it was not always in favor of non-stoma patients. These results may in part reflect underlying bowel dysfunction among patients undergoing TME surgery with sphincter preservation, so-called low anterior resection syndrome (LARS) [27]. In a long-term follow-up study at 14 years of patients randomized to preoperative radiotherapy followed by proctectomy with TME to proctectomy with TME alone in the Dutch trial, 56% of the patients randomized to preoperative radiotherapy followed by proctectomy and 35% of the patients randomized to proctectomy alone reported major LARS [28].

Finally the prevalence of male and female sexual dysfunction is high after surgery for rectal cancer and up to one-half of the patients undergoing surgery with rectal cancer will report a deterioration in sexual function, and a third of patients will report the development of urinary dysfunction [29, 30]. While some of these effects may be attributed to pelvic autonomic injury from radiation therapy, the majority of the effect is caused by nerve injury at surgery. This is a particular concern among distal rectal cancer patients undergoing APE. While the case can be made that these effects are exacerbated when surgery is performed by less experienced surgeons, these issues remain significant problems that impact quality of life following even among patients undergoing sphincter preserving rectal cancer surgery. Thus there is a need for approaches to treating rectal cancer that can also safely preserve functional and quality of life outcomes.

The Watch and Wait Approach

Based on these concerns, the appeal of a watch and wait, organ preserving, nonoperative approach is obvious. If radical surgery to resect rectal cancer could be avoided, then patients would not be subject to the associated surgical morbidity and potential long-term effects on quality of life. However before such a strategy can be more broadly applied, it is important to ensure that oncologic outcomes are not being compromised, particular for this group of patients who are expected to have excellent outcomes, with an extremely low risk for either local or distant disease recurrence, with proctectomy. What is also unknown is if response to chemoradiotherapy is just a biologic response indicator of favorable tumor biology, or if similarly good outcomes can be achieved by increasing the rate of pCR. In light of the fact that nCRT has been associated with improvement in pelvic control, but not overall survival suggests that the former may be true. However, the body of evidence regarding the prognostic value of even an intermediate response indicates that tumor behavior is a continuum from favorable to poor. Moreover, it is now recognized that the interval from the completion of chemoradiation therapy to clinical or pathologic assessment can impact the rate of complete response as ongoing regression can be observed well beyond the traditional 6–8 week interval to assessment.

Following Habr-Gama's original report, other investigators initially reported a wide range of success with an initially nonoperative approach, including a locoregional treatment failure rate of up to 50–60%, much higher than the 3% failure rate initially reported by Habr-Gama [31, 32]. While not fully explained, the reasons for this discrepancy may have included differences in initial tumor burden, selection of patients for a watch and wait approach following neoadjuvant therapy, method and timing of assessment, or the neoadjuvant treatment regimen. In addition the method of selection of patients for nonoperative therapy in Habr-Gama's initial report may have played a major role [4]. Specifically, patients were not included in the study (observation) group until they had been followed for 12 months following chemoradiotherapy. Put another way, patients initially selected for nonoperative therapy who failed in the first 12 months were excluded from analysis. This has the potential to bias the results heavily in favor of the observation group.

Recent data, including from an updated report by Habr-Gama, indicates that the true risk for locoregional treatment failure is approximately 30% [17, 33]. This suggests that a

Table 30-2. Comparison of selected modern studies

Series	Number of patients observed	Number of patients operated	Median follow-up (months)	cCR	Local regrowth	Outcome
Mass 2011 [36]	21	20	15 (observed)	100%	1 patient	2-year OS 100%
			35 (operated)			2-year DFS 89%
Dalton 2012 [31]	12	37	25.5 (mean)	24%	50%	Disease free at follow-up
Habr-Gama 2014 [17]	93	90	60	49%	31%	5-year OS 91%
						5-year LRFS 69%
						5-year DFS 68%
Smith 2015 [34]	73	72			26%	4-year OS 91% (obs) vs. 95% (surg)
						4-year DSS 91% (obs) vs. 96% (surg)
Smith 2015 [37]	18	30	68.4 (mean)		1 patient	Alive with pelvic disease at 54 months

number of patients initially thought to have a pCR based on clinical assessment of complete response actually had undetected viable tumor, highlighting one of the major challenges and pitfalls of the watch and wait approach. One potential solution to the challenge of clinically identifying patients with a pCR is to ensure a close follow-up strategy. This will only be effective, however, if salvage treatment is proven to be effective. We recommend that patients be monitored with digital rectal and endoluminal examination every 3 months along with carcinoembryonic antigen level determination and biopsy of any suspicious lesions. The majority of tumor regrowth will be detected within the first 12 months, in which case patients may be eligible for curative resection with the possibility for coloanal reconstruction for tumors without anal canal involvement precluding partial sphincter resection with anastomosis. There is concern that a longer delay to surgery will result in making the salvage resection more difficult. Although it has been reported that salvage surgical resection after nonoperative management is feasible, longer delays in identification of regrowth has been associated with more than a 50% decrease in the ability to perform sphincter preserving salvage surgery [17, 33]. Tumor regrowth occurring deep to the mucosa may be difficult to identify before more extensive sphincter involvement and the addition of radiation-induced posttreatment fibrosis along the pelvic floor or anal sphincter complex may also preclude subsequent sphincter-preserving resection.

Thus when tumor regrowth occurs, subsequent sphincter preservation cannot be assured. In fact this is quite understandable and reasonable if patients are indeed selected for a watch and wait approach based on distally located tumors. Finally, what remains to be settled is if leaving the rectum containing residual viable tumor in patients with cCR but not pCR increases the risk for distant failure. Recent data regarding 73 patients from Memorial Sloan Kettering suggest that there is the potential for increased risk of distant metastasis among patients undergoing watch and wait when compared to those with pCR, but the sample size was relatively small and the difference did not achieve statistical significance ($p = 0.09$) [34].

Despite these concerns the evidence in support of a watch and wait approach is growing. A limited number of prospective series have reported on nCRT followed by observation (Table 30-2). A review of the wait and see approach published in 2012 identified 30 publications from 9 series including 650 patients. While demonstrating proof of principle, significant heterogeneity of the studies in staging, inclusion criteria, study design, and follow-up rigor limit our ability to draw firm conclusions [35].

Clinical Assessment of Treatment Response

The clinical assessment of treatment response is difficult and is perhaps the greatest challenge and limiting factor for safe implementation of the watch and wait approach. A number of different strategies have been considered including clinical assessment, full-thickness local excision, metabolic imaging, and high-resolution pelvic MRI imaging.

The concordance between clinical and pathologic evaluation has traditionally been poor both in terms of sensitivity (~25%) for detecting pCR, and specificity (~60–90%) for excluding residual disease [38, 39]. Moreover, there has not existed a standard method for the clinical evaluation of complete response. Investigators have advocated for a combination of digital rectal examination and endoluminal visualization to identify residual mass, ulceration, nodularity, or stenosis, all of which may suggest persistent tumor [40]. Findings in support of a complete response include regular and smooth mucosa, and changes such as whitening or presence of telangiectasias. However, in a recent study, the false-positive rate for pCR based on preoperative clinical assessment was 27% [41]. Improvement in the clinical detection of pCR may be possible with a higher pretest probability of complete response, as demonstrated by the ACoSOG Z6041 trial of nCRT with concurrent capecitabine and oxaliplatin followed by local excision for cT2N0 rectal cancers that observed a sensitivity of 85% for detection of pCR based on

digital rectal examination and proctoscopy. However even in the setting of a prospective trial with a primary endpoint of pCR, the false positive rate was 33% [42]. These data suggest that while the detection of pCR can be improved, the risk for false-positivity remains a significant concern.

Given the challenges for clinical assessment of residual disease within the bowel wall, a number of investigators have considered local excision of the tumor bed as both a diagnostic test to assess pathologic treatment response and a therapeutic maneuver to excise any residual tumor cells residing within the bowel wall. Endoscopic biopsy alone has the obvious limitation of being able to provide only a superficial sampling of the tumor bed that can miss residual disease that may be present more deeply within the bowel wall or away from the site of biopsy. Among 39 patients exhibiting clinical response to nCRT but not meeting clinical criteria for pCR, endoluminal biopsies were associated with a negative predictive value of only 11% [43].

Full thickness excision of the entire tumor bed may be performed through a variety of approaches including transanal excision, transanal endoscopic microsurgery (TEM), or transanal minimally invasive surgery (TAMIS). However, while complete pathologic assessment of the bowel wall can be performed, it still cannot provide information regarding the status of the unresected lymph nodes, which may contain viable tumor in up to 9.1% of patients who achieve ypT0 status and 17.1% of patients with ypT1 disease [18, 44, 45]. However, the presence of ypN+ status may be influenced by pretreatment patient selection and ypT0 status among patients with earlier stage initial disease may be associated with a relatively low risk for ypN+ disease [46]. Another major limitation of full-thickness excision following nCRT is that it is associated with significant treatment associated toxicity including poor healing and pain. In fact the risk for wound dehiscence has been reported to be 26–70% following nCRT [47, 48]. Consistent with these single institutional findings, the multicentered ACoSOG Z6041 study reported a 54% overall rate of perioperative complications following local excision [42]. Moreover, local excision following nCRT is still associated with a significant risk for anorectal and sexual dysfunction. In a study of 44 patients, 51% and 46% reported incontinence of flatus and loose stool, respectively, and 59% reported clustering and 49% reported urgency. In addition, 19% of men and 20% of women reported negative impacts on sexual quality of life [49]. Finally, the watch and wait strategy may perhaps have the greatest appeal for patients whose tumors involve the anal sphincter for whom sphincter preservation would be impossible. Full-thickness excision in this circumstance would necessitate at least partial resection of the internal sphincter. Thus the role for full-thickness excision in a watch and wait approach remains limited.

Two primary approaches to radiologic imaging for the assessment of treatment response have been investigated. Despite its utility in signaling response to systemic therapy for a variety of malignant diseases, metabolic imaging with ^{18}fluorodeoxyglucose positron emission computed tomography (PET) has not been shown to be reliable for the identification of complete responders (AUC 0.57–0.73) [50]. Although comparing the change in baseline with 12-week posttreatment standardized ^{18}FDG uptake values may provide some improvement in test performance [51].

Table 30-3. MRI tumor regression grade (mrTRG) [54]

mrTRG	Description
1	Tumor bed with low signal intensity signaling fibrosis with no residual intermediate tumor signal
2	Tumor bed with predominance of fibrosis with minimal residual intermediate tumor signal
3	Substantial intermediate intensity tumor signal present, but does not predominate over low intensity fibrosis
4	Minimal fibrosis
5	No change from baseline

Perhaps one of the most useful imaging tests is high-resolution MRI. Areas of treatment response and fibrosis are characterized by low signal intensity on T2 weighted imaging. The presence of uniform low signal intensity with the absence of areas of intermediate signal intensity within it is suggestive of a pCR. Based on these findings and a comparison to pretreatment MRI, a tumor regression grade has been proposed by the Mercury Study investigators (Table 30-3) [52]. The so-called mrTRG of 1–3 correlated with better survival outcomes when compared to mrTRG 4–5, comparable to the difference in survival observed when comparing ypT0-3a vs. ypT3b or greater [52]. There is currently great interest in the potential for the addition of diffusion weighting or functional dynamic contrast enhanced MRI to improve the detection of response, and other technologies may still be on the horizon [53]. In the meantime, MRI may play an important role in identifying patients with significant treatment response and more favorable prognosis who may be eligible for a watch and wait approach. Such a strategy was employed by a group from Maastricht University in the Netherlands to identify 21 patients for a wait and see approach that were compared to 20 matched control patients exhibiting pCR treated with surgery. They utilized strict selection criteria requiring evidence of cCR, including by posttreatment high-resolution magnetic resonance imaging (MRI) and then MRI-based follow-up every 3 months for the 1st year and biannually thereafter. With their approach, 75% of the pCR patients who had undergone resection were classified by MRI incomplete responders. After a median follow-up of 15 months (vs. 35 months in the surgery group), only 1 patient experienced a local recurrence in the study arm [36]. The TRIGGER trial lead by investigators at the Royal Marsden and the Pelican Cancer Foundation in the United Kingdom will randomize patients to deferral of surgery with watch and wait for good (mrTRG 1–2) and systemic therapy for poor (mrTRG 3–5) responders based on MRI with an opportunity for the poor responders to be converted to complete response vs. immediate surgery in the control arm.

Increasing the Rate of Complete Response

Based on the presumption that patients with pCR are eligible for an organ-preserving watch and wait approach, a number of investigators have tried to improve the rate of PCR with neoadjuvant therapy. These can broadly be categorized as (1) radiotherapy dose intensification including contact radiation; (2) utilization of more active chemotherapeutic regimens; (3) increase in the time interval from chemoradiotherapy to surgery; and (4) a combination of these approaches.

Perhaps the most common strategy for radiotherapy dose escalation is local boost therapy to the tumor volume. This approach has the advantage of increasing the delivered dose to the tumor volume without increasing toxicity to uninvolved surrounded bowel and can be achieved through IMRT or contact therapy [55]. In a randomized trial of external beam radiotherapy to 39 Gy in three fractions with endocavitary boost to 85 Gy compared to external beam radiotherapy alone, there was significant increase in complete or near-complete sterilization (57% vs. 34%, respectively) [56]. Unfortunately, while boost therapy to the primary tumor bed can increase the rate of response within the bowel wall, the lymph nodes may remain unaddressed; however these strategies appear to be well tolerated and remain the subject of further investigation.

A number of studies have attempted to increase the treatment response by incorporating more highly active concurrent chemotherapy regimens. Indeed, it has been reported that systemic chemotherapy alone may be associated with pCR in up to 25% of patients with relatively early rectal cancers [57]. Unfortunately, after several randomized studies of concurrent fluoropyrimidine-based oxaliplatin containing regimens, an increase in pCR has been observed only in the German CAO/ARO/AIO-04 randomized trial at the cost of increased toxicity as demonstrated in NASBP R-04 and STAR-01 [58–61].

The time interval between nCRT and surgery is another important factor associated with pCR. The Lyon R90-01 trial randomized patients to an interval of 6–8 weeks vs. <2 weeks and found a higher rate of complete response (26% vs. 10.3% $p = 0.005$) following the longer interval [62]. However, subsequent long-term follow-up after a median 6.3 months demonstrates no difference in local recurrence or survival [63]. Thus while it is well recognized that a longer treatment interval is associated with a higher rate of pCR, it has not been demonstrated that patients exhibiting pCR after a longer treatment interval have the same good prognosis of those who were more rapidly sterilized. Thus tumor cell death is initiated immediately (during neoadjuvant therapy), but the pCR rate can be manipulated by changing the duration of delay prior to proctectomy. Therefore, one cannot assume that one neoadjuvant therapy regimen is superior to another based on pCR rate if proctectomy occurs at different intervals following neoadjuvant therapy.

Additional strategies for improving treatment response while providing systemically active therapy include induction and consolidation chemotherapy. Induction chemotherapy has the potential to improve survival outcomes by improving tumor regression and the ability to deliver systemic chemotherapy with a lower rate of associated toxicity. The EXPERT and EXPERT-C phase II studies of pretreatment capecitabine with oxaliplatin and with cetuximab in patients with high-risk rectal cancers showed that a high rate of R0 resection could be achieved although there was not a remarkable increase in the rate of pCR [64]. The addition of the EGFR inhibitor resulted in greater rates of radiographic response, although not in the rate of pCR [65].

Capitalizing on the potential for improved tumor regression with increased time interval to surgery, the Timing of Rectal Cancer Response to Chemoradiation trial, delivering up to six cycles of mFOLFOX6 after standard CRT was associated with an increase in pCR to 38% vs. 18% with standard nCRT alone [66]. The rate of surgical complications was not increased and no increased risk for progression was observed. Others have reported have provided supportive evidence for consolidation chemotherapy, but its potential role in improving durability of treatment response for patients undergoing a watch and wait strategy is unknown [67]. And the Rectal cAncer and Preoperative Induction therapy followed by Dedicated Operation (RAPIDO) trial is currently randomizing patients to short-course (5×5 Gy) pelvic radiation followed by six cycles of capecitabine and oxaliplatin and TME vs. standard nCRT and TME with the goal of improving disease-free and overall survival without compromising local control [68]. There is also an ongoing randomized study of induction vs. consolidative chemotherapy for patients with rectal cancer undergoing nCRT that is intended to improve disease-free survival when compared to standard CRT (NCT02008656). While these studies are not designed to investigate a strategy of watch and wait, it may shed new light on the role of consolidative chemotherapy in patients with high-risk rectal cancer.

Finding the Way Forward

The management of rectal cancer has become increasingly complex. While currently most patients with clinical stage II or III disease are treated with neoadjuvant chemoradiotherapy or short course radiotherapy followed by proctectomy, there is increasing recognition of the potential to avoid radiation therapy associated toxicity, as excellent results can be achieved with high-quality resection in appropriately selected patients without high-risk features on initial evaluation [69]. We also continue to learn about the role of neoadjuvant chemotherapy alone for treatment of intermediate-risk mid-rectal cancers [57]. Patients with intermediate-risk dis-

tal rectal cancers in whom a permanent colostomy will be required may be the optimal candidates in whom to study a watch and wait approach. These patients with small tumors close to or involving the sphincters are most likely to both require permanent colostomy at surgery and to achieve a complete response to chemoradiation therapy.

However a number of unresolved questions remain. The long-term oncologic efficacy of the watch and wait approach still requires validation, especially given the high cure potential associated with definitive surgery in this patient population. While it appears that surgical salvage for tumor regrowth is feasible, it is unknown if the delay can lead to lost window of opportunity for patients with distal cancers who were otherwise candidates for coloanal reconstruction. The potential that the risk for distant recurrence may be increased with a nonoperative approach must also be examined. Finally, there exists no reliable method for identifying patients with pCR who may then be eligible for a watch and wait approach and local tumor excision still carries significant morbidity risk without providing complete information regarding the status of the regional lymph nodes. Currently, the most objective method for identifying potential candidates for a watch and wait approach seems to be comparison of pre- and posttreatment high-resolution MRI imaging to assess response. Using MRI response to clinical response criteria with a strict protocol for follow-up may be the most reliable way of implementing a watch and wait strategy but it is far from a perfect test. Systemic chemotherapy, either as induction or consolidation, is another approach to increasing the likely of achieving pCR and identifying the low-risk in whom selective surgery can be considered and may play a role in reducing the risk for distant recurrence [66]. Finally, while there is great interest in molecular analysis that should be incorporated into all future trials, as of yet there are no molecular signatures that can predict the likelihood of achieving a pCR.

Until recently, most surgeons would have been reluctant to consider a nonoperative approach for rectal cancer, but the increasing emergence of data may have turned the tide on opinion [70]. As of yet there is no evidence from randomized controlled trials to support nonoperative strategies for patients with rectal cancer. Questions regarding patient selection, optimal method for inducing pCR, methods for assessing treatment response, and adequacy of follow-up remain unanswered.

Given the infrequent primary outcome of recurrence in this patient population, a randomized non-inferiority study is likely not feasible. But there is a critical need for evidence, perhaps through well-conducted prospective cohort studies, so that the watch and wait strategy can be safely incorporated into the overall management strategy for patients with rectal cancer. For now, radical surgery should remain standard treatment for rectal cancer, and watch and wait should only be performed in the context of clinical trials.

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31
Proctectomy

Emmanouil P. Pappou and Martin R. Weiser

Key Concepts

- A proper proctectomy with sharp dissection along the visceral and parietal layers of the endopelvic fascia facilitates margin-negative resection, reduces local recurrence, and limits nerve injury associated with sexual dysfunction.
- Precise understanding of pelvic anatomy including fascial planes, autonomic nerves, and pelvic floor musculature is critical in performing a proper proctectomy.
- The quality of mesorectal excision and the distance of the circumferential radial margin are associated with local pelvic control.
- Proctectomy can be performed using open, laparoscopic, and robot-assisted techniques.

Background and History

At the beginning of the twentieth century, the majority of patients diagnosed with rectal cancer in Europe and the United States underwent perineal proctectomy—the preferred operation of the day. While this operation was an improvement over previous surgeries, it was highly morbid, with poor oncologic results. In 1908, William Ernest Miles of St. Mark's Hospital in London recognized that nearly all of his patients suffering from rectal cancer died of recurrent disease within 3 years after perineal proctectomy. On autopsy, he noted that most recurrences were identified in the part of the mesorectum that had been left in place and/or within lymph nodes situated near the left common iliac artery. Miles termed these areas the "zone of upward spread." He concluded that perineal proctectomy was inadequate because it failed to address the ultimate cause of local recurrence: incomplete excision of the mesorectum, including its lymphovascular supply.

Based on his observations, Miles devised a different procedure, which he described as abdominal perineal excision (APE) or, as it came to be called, abdominoperineal resection (APR). APR soon became the surgical procedure of choice for treatment of carcinoma of the rectum [1]. As Miles described it, APR actually comprised two procedures performed during the same operation: an abdominal operation and a perineal operation. The abdominal part of the APR includes dissection of the rectum and mesorectum and creation of a colostomy; the perineal part includes detachment of the rectum, anus, and levator muscles from the genital/urinary organs and the ischiorectal fat. Describing the perineal approach in 1910, Miles stressed that the levator muscles should be "divided as far outwards as their origin from the white line so as to include the lateral zone of spread" [2]. Compared with perineal proctectomy, long-term outcomes following this new operation improved considerably.

Miles' emphasis on the necessity of removing the mesorectum in its entirety would become the guiding principle of what is now known as total mesorectal excision (TME). Today, TME remains the gold standard in rectal cancer surgery. TME entails sharp—rather than blunt—dissection of the visceral and parietal layers of the endopelvic fascia, resulting in intact removal of the rectum and mesorectum [3]. In Miles' time, however, most surgeons continued to perform traditional blunt dissection, limiting the benefits of APR and resulting in a 25% rate of positive resection margins, with high rates of recurrence and mortality.

The absolute necessity of sharp dissection in every rectal cancer operation—i.e., meticulous removal of the entire mesorectum along the areolar plane outside of the rectal fascia propria—was reemphasized in 1982 by Bill Heald. Heald defined TME as an "optimal dissection plane around the cancer which must clear all forms of extension and circumscribe predictably uninvolved tissue," in other words, sharp mesorectal excision along definable tissue planes. He described this as the "holy plane" of rectal cancer surgery [4]. The aims of TME are to excise the rectum and surrounding mesorectum, including its blood vessels and pararectal lymph nodes, within an intact visceral fascial "envelope"; to complete en

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bloc resection of the lymph nodes along the superior rectal and inferior mesenteric arteries; and to achieve clear resection margins.

Advocates of "total mesorectal excision" have focused attention on two critical components of oncologic proctectomy: the lateral (radial) margin and the distal margin of mesorectal excision. Sharp dissection in the avascular plane surrounding the mesorectum, so as to remove the mesorectum in its fascial envelope and achieve a wide circumferential radial margin (CRM), has been demonstrated to be essential in avoiding local recurrence of tumor in the pelvis [5–7]. Although this concept is not novel [8, 9], it has served to refocus attention on surgical technique during proctectomy, which is warranted, given the widely divergent local recurrence rates reported in the literature [10]. In 1985, Quirke and colleagues showed that pelvic relapse was the result of residual tumor at the CRM, and they were among the first to describe a systematic assessment of the CRM [7]. Since the original publication of this paper, numerous studies (including prospective trials) have confirmed that CRM involvement is a strong predictor of local recurrence, as well as distant metastasis and poor survival [11].

The second component of TME, as advocated initially by Heald et al., is the removal of the entire mesorectum distal to the tumor. However, the necessity of removing mesorectum more than 4–5 cm distal to a proximal rectal tumor is not supported by pathologic studies of lymph node involvement in the mesorectum [9, 10, 12–16]. Furthermore, it may have contributed to a high anastomotic leak rate (17%) in early series [17] and has not been shown to be of benefit in a large clinical review [18]. At present, many advocates of "total mesorectal excision" limit mesorectal resection to 4–5 cm distal to proximal rectal tumors [6, 19–21], although some authors still refer to this technique as "total" mesorectal excision [19–22], which has caused confusion. Other groups have termed the concept of tailoring the mesorectal excision to the position of the tumor "tumor-specific mesorectal excision" [6], which may be more accurate.

In summary, for all patients with rectal cancer, it is critical that the primary tumor is removed in its entirety. In addition, mesenteric tissue at greatest risk for nodal metastases should also be resected. For patients with mid and distal rectal cancers, appropriate proctectomy technique will involve removing the entire mesorectum. For patients with proximal rectal cancers, it is important to remove the mesorectum for a distance of approximately 4–5 cm distal to the tumor, although resecting the mesorectum distal to that point does not appear to confer benefit.

Anatomy of the Mesorectum/Rectal Fascia

Chapter 1 has an in-depth look at the anatomy of the colon, rectum, and anus; however, surgical anatomy as it relates to proctectomy will be covered here. The proctectomy technique is based on an understanding of the anatomy of the rectum and the mesorectal fascia. The rectum is located at the end of the large intestine, where the taeniae coalesce to form a complete lineal muscular layer. This is surrounded by a recognizable annular envelope: the rectal fascia (or mesorectum, as it is better known to surgeons). The mesorectum contains the lymphovascular supply of the rectum and upper anal canal. It encloses the branches of the superior rectal artery and the perirectal lymph nodes, which drain in a caudal direction toward the inferior mesenteric artery. Around the rectum is an avascular plane, surgically recognizable as a cobweb of areolar tissue.

The mesorectum is asymmetrically distributed. The bulk of it sits posterior to the rectum, identified by two protruding bulges (the "mesorectal cheeks"); anteriorly and laterally, the perirectal tissue is thinner. Similarly, the mesorectal fascia is most developed on the posterior aspect. Anteriorly, the mesorectum is thinner and bordered by the recto-genital septum known as Denonvilliers' fascia. In men, Denonvilliers' fascia separates the rectum and mesorectum from the prostate and seminal vesicles. In women, the thinner rectovaginal fascia separates the rectum from the vagina. Ligaments below and lateral to the peritoneal reflection connect to the parietal fascia on the pelvic sidewall.

An extensive autonomic nervous system of sympathetic and parasympathetic fibers supplies the rectum and genitourinary tract, controlling continence and sexual function. The sympathetic autonomous system is responsible for urinary continence and ejaculation, whereas the parasympathetic system controls micturition, as well as genital erection and lubrication. Precise knowledge of the anatomy of this pelvic autonomic network is essential in rectal surgery, as injury to these nerves during proctectomy can lead to sexual dysfunction and incontinence. The sympathetic autonomic plexus arises from lumbar sympathetic nerves originating in the T12–L2 spinal junction, which pass anterior to the aorta and form a network in close proximity to the origin of the inferior mesenteric artery. This is known as the superior hypogastric plexus. The superior hypogastric plexus enters the pelvic cavity anterior to the sacral promontory and splits into fairly well-defined left and right hypogastric nerves (Figure 31-1). Damage to this sympathetic plexus during ligation of the inferior mesenteric artery, or damage to the hypogastric nerve trunks during mesorectal mobilization, can lead to urinary incontinence and retrograde ejaculation. The hypogastric nerves course posterolateral to the mesorectum and ultimately join parasympathetic nerves—also known as the pelvic plexus, pelvic splanchnic nerves, or nervi erigentes—to form the inferior hypogastric plexus. The parasympathetic nerves that join the sympathetic system originate from the S2–S4 sacral spinal nerve roots, lying posterolaterally along the mesorectal fascia. Preservation of the pelvic splanchnic nerves and the inferior hypogastric plexus, and careful separation of these from the rectum, is one of the most challenging aspects of proctectomy. The inferior hypogastric plexus forms an extensive network of interlocking fibers of the sympathetic

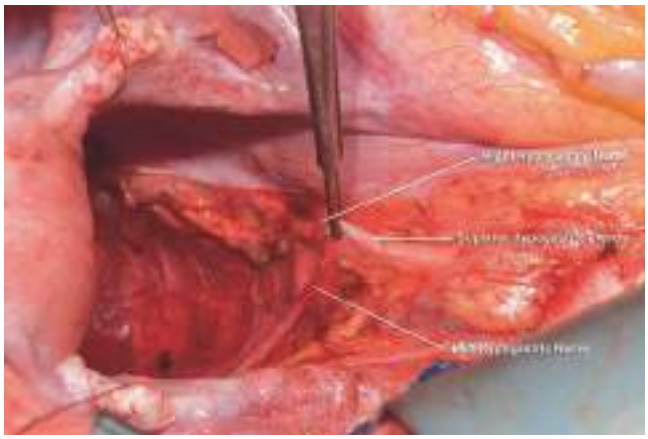

FIGURE 31-1. The superior hypogastric plexus splits into the *right* and *left* hypogastric nerves as it enters the pelvic cavity. Parasympathetic pelvic splanchnic nerves, also known as nervi erigentes, arise from sacral spinal nerves S2–S4 and pierce the presacral fascia on the *left* and *right side* to join the hypogastric nerves, forming the inferior hypogastric plexus (not shown). *With permission from Lee-Kong et al.: Autonomic nerve preservation during rectal cancer resection. J Gastrointest Surg 2010;14:416–422. © Springer* [104].

left and right hypogastric nerves, and parasympathetic pelvic splanchnic nerves are situated on the pelvic sidewall. Various nerves leave the inferior hypogastric plexus to enter the rectal wall, while the remaining neurovascular bundles extend anterolaterally to the seminal vesicles, distal ureters, vasa deferentia, urinary bladder, prostate and cavernous bodies in men, and in the similar anatomic area in women, for whom the lower portion of the inferior hypogastric plexus runs along the lower lateral wall of the vagina.

Laterally, the mesorectum is sometimes not completely covered by a layer of fascia and is penetrated by the middle rectal vessels (coming from the internal iliac vessels, present in about 10–20% of patients) and autonomic nerves from the inferior hypogastric plexus. The mesorectum is tethered inferolaterally to the inferior hypogastric plexus, necessitating a more challenging dissection that is best achieved with precise monopolar diathermy and subtle traction and countertraction, in order to draw the autonomic nerve fibers controlling urinary continence and sexual function carefully away from the surface of the mesorectum.

Posterior to the mesorectum is the presacral fascia, which follows the concavity of the sacrum. The presacral fascia is a thickened parietal fascia that covers the presacral veins and fat, extending laterally to join Denonvilliers' fascia anteriorly. Inferiorly, between the levels of the third and fourth sacral vertebra, the mesorectum and the presacral fascia fuse. The thick connective tissue bridging these two separate fascias is also known as the rectosacral fascia or Waldeyer's fascia. Waldeyer's fascia is an important surgical landmark during posterior rectal mobilization, because of its close relationship to the sympathetic hypogastric nerves and the inferior hypogastric plexus. Inaccurate dissection at this level can lead anteriorly to breach of the mesorectum and posteriorly to tearing of the fascia, resulting in considerable bleeding from the presacral veins. At the most distal part of the rectum, the mesorectum thins out as a recognizable structure so that it is virtually absent over the final 1 cm of the rectum. Distal rectal cancers are thus at greater risk of invading surrounding structures than proximal rectal cancers, particularly the pelvic floor/external anal sphincter, vagina, or prostate, because of the relative paucity of mesorectum at this level.

Surgical Principles of Proctectomy for Rectal Cancer

The basic principles of proctectomy are as follows [23]:

1. Sharp dissection circumferentially around the mesorectum in an avascular areolar plane between the visceral and parietal layers of the endopelvic fascia (Figure 31-2a)
2. Identification and preservation of the autonomic nerve plexus that controls bladder and sexual function (Figure 31-2b)
3. Achievement of a circumferential margin that is macroscopically and microscopically clear of tumor
4. Preservation of the anal sphincter complex and pelvic floor, with restoration of gastrointestinal continuity when appropriate

Pathological Assessment

In addition to assessment of proximal, distal, and CRMs, pathologists can grade the quality of the mesorectal specimen. This has been demonstrated to have prognostic significance. Quirke et al. described a grading system which classifies rectal cancer specimens according to whether the surgeon has dissected outside the mesorectal fascia, in the correct plane (the mesorectal excision plane), or has violated the mesorectum, leaving mesorectal tissue behind in the pelvis by following a plane within the mesorectum (intramesorectal plane) or directly on the muscularis propria (muscularis propria plane) [24]. This mesorectal grading system has been evaluated in subsequent studies and has been found to be an independent predictor of local pelvic control [25, 26]. One study reported a significant association between plane of surgery and survival—even in patients with an uninvolved CRM [27]. However, these studies also showed that the surgical plane was related to CRM positivity rates, with the lowest rates of positive CRM in surgery that achieved sharp dissection along the mesorectal plane.

Pathological analysis of the excised proctectomy specimen provides important prognostic information on the stage and biology of the tumor. It is also a means of assessing the

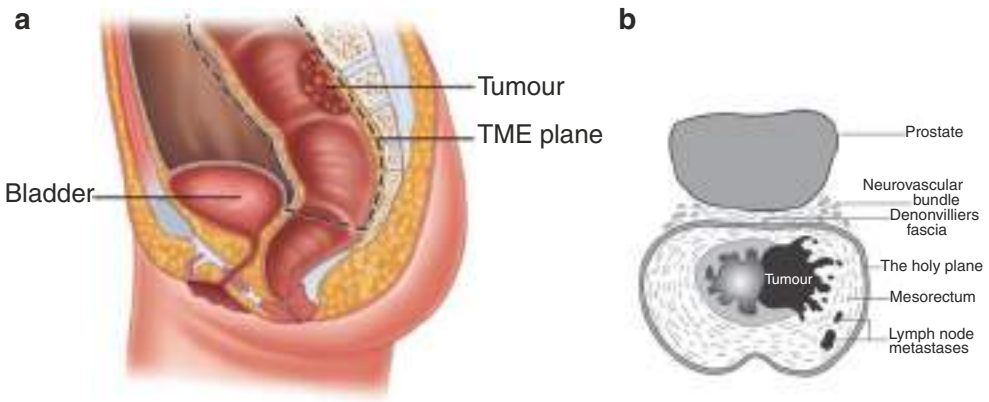

FIGURE 31-2. Total mesorectal excision. (**a**) Dissection follows the *dotted line*. Tumor deposits are often present within the lymphovascular tissue surrounding the rectum (mesorectum). Incomplete resection leaves residual deposits which are most likely the origin of local treatment failure. *With permission from Janjua AZ, Moran B, Heald RJ. Open surgical management of rectal cancer. Patel HRH, Mould T, Joseph JV, Delaney CP. (Eds). Pelvic Cancer Surgery: Modern Breakthroughs and Future Advances. Springer, New York, 2015: pp: 531. © Springer 2015* [105]. (**b**) The plane of total mesorectal excision allows complete removal of regional lymph nodes while sparing the neurovascular bundles. *With permission from Heald RJ et al.: Embryology and anatomy of the rectum. Semin Surg Oncol. 1998 Sep; 15(2):66–71. © John Wiley and Sons* [106].

quality of surgery, because margin status and quality of mesorectal excision can be used as surrogates for oncologic outcome assessment. The College of American Pathologists (CAP) has implemented standardized assessment of rectal cancer specimens [28]. The surgeon or pathologist should ink the non-peritonealized radial margin of the fresh resection specimen to help guide this analysis. A standardized synoptic report should include a subjective assessment of mesorectal grade and quantitative measurement of CRM in millimeters. A margin is considered positive if the primary tumor or involved lymph node extends to within 1 mm of the resection margin.

Preoperative Preparation

All patients undergoing rectal cancer surgery require preoperative preparation aimed at optimizing the technical success of the procedure and avoiding perioperative complications. Oral mechanical bowel preparation with polyethylene glycol, to reduce the bacterial load and risk of intraoperative fecal spillage, has been considered an axiom in colon and rectal surgery. However, a number of prospective trials have failed to demonstrate any benefit from mechanical bowel cleansing in preventing surgical site infections (SSIs) [29, 30]. These results were confirmed by a Cochrane systematic review of 5805 patients, in which the authors concluded that there is no statistically significant benefit from mechanical bowel preparation or the use of rectal enemas [31]. Another recent systematic review by the Agency for Healthcare Research and Quality reached similar conclusions [32]. Oral mechanical bowel preparation appeared to be protective, compared to no preparation, for peritonitis or intra-abdominal abscess, but the evidence was weak. The study could not draw any conclusion on potential harms, such as dehydration and electrolyte imbalances, related to use of oral mechanical bowel preparation.

Despite the lack of solid data regarding the impact of bowel preparation on wound infection, there are other valid reasons for preoperative cathartic bowel preparation prior to proctectomy. It is preferable to have the rectosigmoid cleared of stool, in order to accurately assess the position of the tumor intraoperatively. In addition, division of the colon and rectum is more easily accomplished if the lumen is free of stool. Lastly, if the patient is to undergo a temporary diverting proximal stoma, it is preferable to have the intervening colon free of stool, in case of anastomotic leak. Although it is theoretically possible to have patients clear stool from the rectosigmoid with preoperative enemas, in practice this is often difficult to accomplish due to the rectal tumor itself and physical disabilities associated with the advanced age of many patients. In addition, enemas do not clear the proximal colon of stool, mitigating the benefit of proximal fecal diversion if anastomosis is performed.

High-quality evidence indicates that preoperative antibiotics covering aerobic and anaerobic bacteria, delivered orally, intravenously, or both, reduce the risk of postoperative surgical wound infection by as much as 66% in elective colorectal surgery [33]. Oral neomycin- and erythromycin-based antibiotics are typically administered the day before surgery, in combination with oral mechanical bowel preparation. For patients without penicillin allergy, a second-generation cephalosporin (cefotetan or cefoxitin) is administered intravenously within 60 min of the surgical incision, with re-dosing

during the procedure as required, according to the half-life of the drug and the duration of surgery. For penicillin-allergic patients, metronidazole or clindamycin combined with either ciprofloxacin or gentamicin is acceptable, as are aztreonam and fluoroquinolones [34]. Ertapenem, a long-acting carbapenem active against gram-negative anaerobe, is an accepted alternative to second-generation cephalosporins for prophylaxis. Other measures that prevent SSI include tight glucose control in diabetic patients, smoking cessation, clipping rather than shaving the skin of the abdominal wall, and maintaining normothermia and adequate oxygenation during anesthesia [35]. Patients undergoing rectal cancer surgery are also at risk of deep venous thrombosis and pulmonary embolism and should have thromboembolic prophylaxis with unfractionated heparin or low molecular weight heparin during the perioperative and postoperative period [36].

As the incidence of rectal cancer increases with age, many patients also have cardiovascular or respiratory conditions requiring medical clearance before surgery. While technical advances have made rectal cancer operations safer, optimal outcomes require special effort to ensure that the patient's overall health is acceptable at the time of surgery. Many patients with other comorbid conditions such as diabetes, hypertension, and coronary artery disease require medical evaluation before undergoing surgery. Comorbidities can impact decision-making and affect short- and long-term outcomes. Patient's clinical and performance status should be optimized to reduce the risk of perioperative complications. Fertility options should be discussed with all individuals of childbearing potential. In the setting of Lynch syndrome, discussion regarding oophorectomy and hysterectomy is appropriate. Patients who may require a stoma should be seen before surgery by an enterostomal therapist. Adequate marking of the stoma site improves outcomes. Preoperative teaching shortens the time required by patients to gain proficiency in managing their stoma and reduces length of hospital stay [37].

The enhanced recovery after surgery (ERAS) protocols were introduced in open colorectal surgery in the 1990s, with the aim of speeding patient recovery, improving patient outcomes and satisfaction, shortening hospitalization, and reducing healthcare costs [38]. ERAS protocols span the entire perioperative period and attempt to minimize surgical stress and postoperative ileus through patient education, preoperative hydration and carbohydrate loading, goal-directed intraoperative fluid management, narcotic sparing for intraoperative and postoperative pain control, and early mobilization and oral feeding in the postoperative period. A number of prospective trials and reviews have indicated that the implementation of ERAS protocols reduces length of hospital stay, compared to conventional recovery in patients undergoing open or minimally invasive surgery for CRC [39, 40].

Operative Approaches

Optimal resection of rectal cancer according to the oncologic principles of TME can be achieved by open or minimally invasive (laparoscopic or robotic) surgical techniques. Herein, we describe methods for both open and minimally invasive approaches. General concepts such as nerve preservation are detailed in the "open" section but apply to minimally invasive approaches as well.

Open Low Anterior Resection

The patient is placed in a modified lithotomy or supine split-leg position. A variety of incisions can be utilized; however, it is important to keep the incision line away from the area of potential stoma and stoma appliance, so as to not interfere with management of the stoma postoperatively. The abdominal cavity is explored thoroughly, especially the liver and the peritoneum, to identify signs of distant metastatic disease. If unresectable distant metastatic disease is encountered, then the surgeon should carefully consider whether low pelvic anastomosis is warranted. Patients with unresectable distant metastatic spread often undergo prolonged treatment with chemotherapy, and the presence of a temporary diverting ileostomy may increase the severity of chemotherapy-induced enteritis. In addition, the added risk of colorectal or coloanal anastomotic leak may not be warranted because, if leak occurs, systemic chemotherapy may be delayed. In addition, chemotherapy must be stopped temporarily to close the ileostomy; if complications ensue from this second procedure, systemic chemotherapy may again be delayed. Lastly, the functional derangements associated with low pelvic anastomosis will only be exacerbated if the patient receives cytotoxic chemotherapy, which may produce enteritis. In sum, it may be preferable to simply perform a Hartmann's resection for mid and distal rectal adenocarcinoma that does not invade the pelvic floor or anal sphincter, in patients with unresectable distant metastatic disease. For patients with proximal rectal cancer who may not require temporary fecal diversion and are at low risk for anastomotic complications, it is reasonable to perform anterior resection with primary anastomosis, even in the setting of unresectable distant metastatic disease (if this was the original plan).

Our preferences regarding the technical aspects of restorative proctectomy are described as follows: The small bowel is carefully packed and retracted to the right, providing access to the pelvis. The sigmoid and left colon is mobilized by dissection laterally to medially along the white line of Toldt. The sigmoid colon is retracted medially. In this loose connective tissue plane, first the gonadal vessels and then, more medially, the left ureter are encountered. Dissection is continued in this plane, and the left colon is dissected away

from Gerota's fascia. At the base of the sigmoid mesocolon, the retrorectal avascular plane is entered. While the sigmoid colon is elevated from the left lateral side, gonadal vessels, the left ureter, and the left hypogastric nerve are preserved in the embryologic avascular plane, and the mesorectal dissection plane is reached. The sigmoid is retracted in the right lateral direction. Then, from the right side, the sigmoid mesocolon is entered through a window over the surgeon's hand at the pelvic brim. Through this window, the inferior mesenteric artery is liberated, and separate ligations of the artery and vein are performed. The superior rectal artery (just distal to the left colic artery) or inferior mesenteric artery, at its origin 1–2 cm from the aorta, is ligated and divided to preserve the sympathetic plexus. High ligation of the IMA is useful when bulky adenopathy is present at the base of the vessel or when a coloanal anastomosis is necessary and maximal length of the left colon is required. When the inferior mesenteric artery is ligated, care must be taken to preserve the marginal artery, which provides the blood supply from the middle colic vessels to the left colon and anastomosis.

The inferior mesenteric vein is ligated at the paraduodenal (ligament of Treitz) location just inferior to the pancreas and again adjacent to the ligation site of the inferior mesenteric artery. Dividing the vein at the ligament of Treitz is critical in order to accommodate full mobilization of the splenic flexure, which is then allowed to rotate into the pelvis for maximal length. Splenic flexure mobilization is performed by continuing the lateral dissection of the descending colon superiorly, retracting and dissecting the descending colon off Gerota's fascia. Colonic attachments to the pancreas are then taken down, and care is taken to avoid aggressive retraction on the colon, which can tear the splenic capsule. Omental attachments are then taken down from the distal transverse colon to complete the mobilization.

The sigmoid mesentery is divided to the bowel wall, which is stapled and divided. The left colon is packed superiorly, facilitating visualization of the pelvis. The stapled sigmoid is retracted anteriorly, which opens the perimesorectal planes. A sharp dissection is carried out under direct vision, circumferentially around the mesorectum. The presence of the superior hypogastric plexus posteriorly must be kept in mind throughout the dissection (Figure 31-3a). Starting the dissection in the posterior and then the lateral plane, in a stepwise manner, facilitates identification of the correct mesorectal plane (Figure 31-3b). If bleeding is encountered in one area, it is reasonable to proceed to the opposite circumference, so that pressure is applied while progress continues. The key to this phase is the recognition of the areolar tissue on the back of the mesorectum, through which the dissection should proceed when the areolar tissue is on stretch. Once there is sufficient space, a St. Mark's Pelvic Retractor is introduced behind the specimen. Traction and countertraction are critical to the pelvic dissection and are optimized by use of the retractor. The lateral dissection is carried out by extending the posterior plane of dissection anteriorly and around the sidewalls of the pelvis. At this point in the dissection, the inferior hypogastric plexuses curve around the surface of the mesorectum and are vulnerable to inadvertent injury. While retracting the divided rectosigmoid forward, the tangentially running hypogastric and pelvic parasympathetic nerves are carefully identified and dissected away from the mesorectal surface on each side (Figure 31-4a). This area of adherence between the nerves and the mesorectum is one of the most challenging and critical in proctectomy. As the lateral dissection moves deeper into the pelvis, one or two middle rectal arteries may be encountered. Middle rectal arteries are present in less than 20% of patients and, if encountered, can be easily divided with cautery. Dissection anteriorly progresses along Denonvilliers' fascia down to the pelvic floor (Figure 31-4b). Forward retraction with the help of the St. Mark's Retractor facilitates the development of the space anteriorly. Anterior tumors require resection of Denonvilliers' fascia, which puts the parasympathetic nerves at risk, as they extend anteriorly toward the prostate. For posterior tumors, dissection can pro-

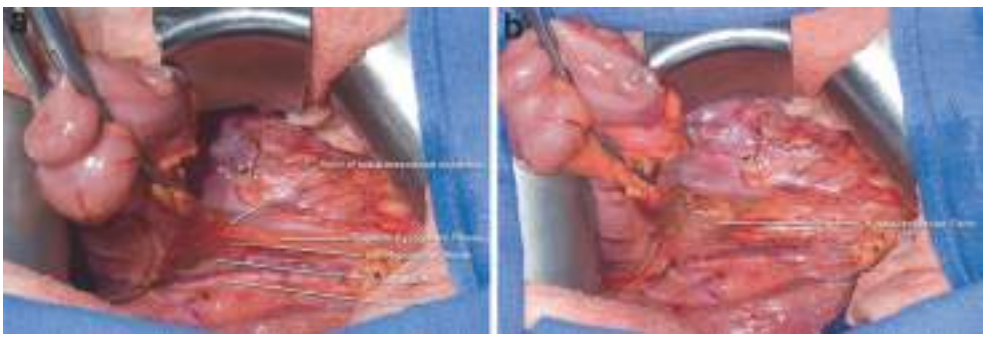

FIGURE 31-3. (**a**) The distal sigmoid/proximal rectum is elevated anteriorly, exposing the aortic bifurcation and sacral promontory, with identification of the left ureter, left iliac vein, and superior hypogastric plexus. The hypogastric nerves may appear as an obvious discrete band of tissue or as multiple smaller bands. (**b**) Careful dissection of the sigmoid mesentery distally results in an avascular, areolar plane separating the mesorectal fascia propria from the presacral fascia. *With permission from Lee-Kong et al.: Autonomic nerve preservation during rectal cancer resection. J Gastrointest Surg 2010;14:416–422. © Springer* [104].

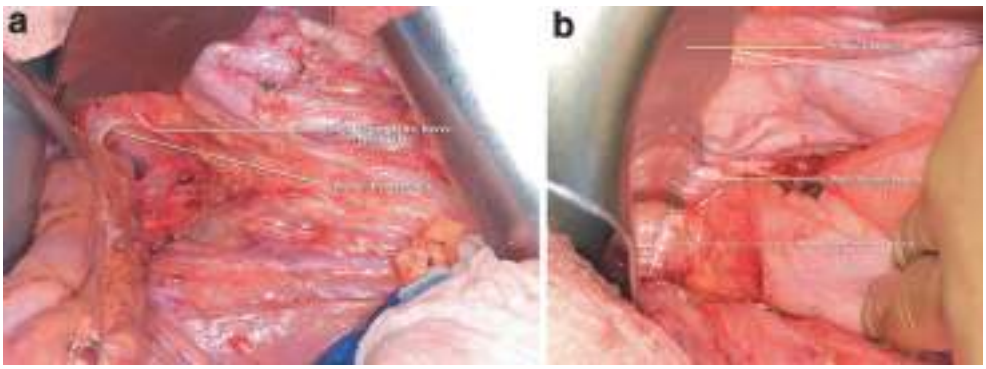

FIGURE 31-4. (**a**) Caudal dissection in the posterior midline, while lifting the rectum "toward the ceiling" may cause the hypogastric nerves to "tent up," as they often adhere to the mesorectal fascia. (**b**) Anterior dissection during TME. *With permission from Lee Kong et al.: Autonomic nerve preservation during rectal cancer resection. J Gastrointest Surg 2010;14: 416–422. © Springer* [104].

ceed below Denonvilliers' fascia. Adequacy of the dissection distal to the lower edge of the tumor is examined by palpation and/or endoscopy to ensure a proper distal margin. When mesorectal mobilization down to the pelvic floor is considered complete on both anterior and posterior sides, the rectum is elevated above the pelvic floor and cross-clamped. At this point, washout of the anorectal stump can be performed with saline solution or water. Following this, the rectum is transected with a linear stapler (TA-45), and the specimen is removed. The anastomosis between the colon conduit and the rectal stump is constructed with a circular EEA™ Stapler (Figure 31-5a). The serosa and mucosa are visually evaluated for adequate vascular supply. Intraoperative anastomotic air testing of the colorectal anastomosis is performed by filling the pelvis with saline solution and insufflating the rectum with air through a sigmoidoscope. A handsewn coloanal anastomosis is shown in Figure 31-5b and is discussed separately below.

Laparoscopic Low Anterior Resection

The patient is placed in a modified lithotomy position. A 5-trocar technique is generally utilized, with an umbilical camera port, two left-sided and two right-sided working (Figure 31-6). This allows the surgeon and second assistant to stand on the patient's right, with the first assistant standing on the left. The dissection is performed in a medial-to-lateral fashion, first dissecting the vessels, followed by takedown of the splenic flexure, and then the lateral colonic attachments before entering the pelvis for rectal resection. With the patient in head-down and right-sided tilt, enabling the surgeon to move the small bowel mesentery out of the pelvis and away from the colonic mesentery, dissection begins at the sacral promontory. The superior rectal vessels are lifted ventrally, and a plane is developed beneath the sigmoid mesentery. Dissection is carried out just beneath the vessels, in order to sweep the sympathetic nerves toward the retroperitoneum. Dissection proceeds medial to lateral beneath the mesentery and along Toldt's fascia, preserving the ureter and gonadal vessels. The root of the IMA is exposed by creating an additional window on the superior border of the IMA. The IMA is ligated, taking care not to injure the aortic nerve plexus, either just below the left colic branch or at the origin of the vessel. The IMV is subsequently divided along with the sigmoid mesentery. The left mesocolon is further mobilized along with the splenic flexure. The IMV is divided adjacent to the pancreas to allow full mobilization and rotation of the left colon, so as to reach the pelvis for a tension-free anastomosis. Again, in a medial-to-lateral fashion, dissection continues along the ventral plane of the pancreas, with entry into the lesser sac. Often, the lateral attachments of the splenic flexure can be divided in a medial approach, exposing the spleen. The transverse colon is then retracted caudally, and the omentum is dissected off the transverse colon, meeting the prior dissection place. Lastly, the remaining lateral and splenic attachments are divided by retracting the colon medially.

For pelvic dissection, it may be necessary to position the patient in a more head-down position, often with less rotation to the right. The rectum is retracted anteriorly and the retrorectal space is identified. Sharp dissection is carried out posteriorly along the areolar plane that defines the junction of the visceral and parietal layers of the endopelvic fascia. Care must be taken to sweep the hypogastric nerves laterally, and dissection proceeds posteriorly along the mesorectum. Once posterior mobilization is completed, dissection continues in the same perimesorectal plane on the lateral sides of the pelvis. The rectum is mobilized circumferentially, applying standard open TME surgical principles. Dissection can be performed with cautery, ultrasonic dissector, or vessel-sealing devices. After TME dissection is completed, the level of rectal transection is confirmed with digital rectal and endoscopic examinations. The rectum is irrigated and then stapled and divided with endoscopic staplers. The specimen is extracted via a wound protector at the umbilical camera port or the future diverting ileostomy site. The proximal sigmoid/left colon is divided, and the anvil is secured for laparoscopic circular anastomosis. An air leak test confirms the integrity of the anastomosis, and a diverting ileostomy is fashioned selectively.

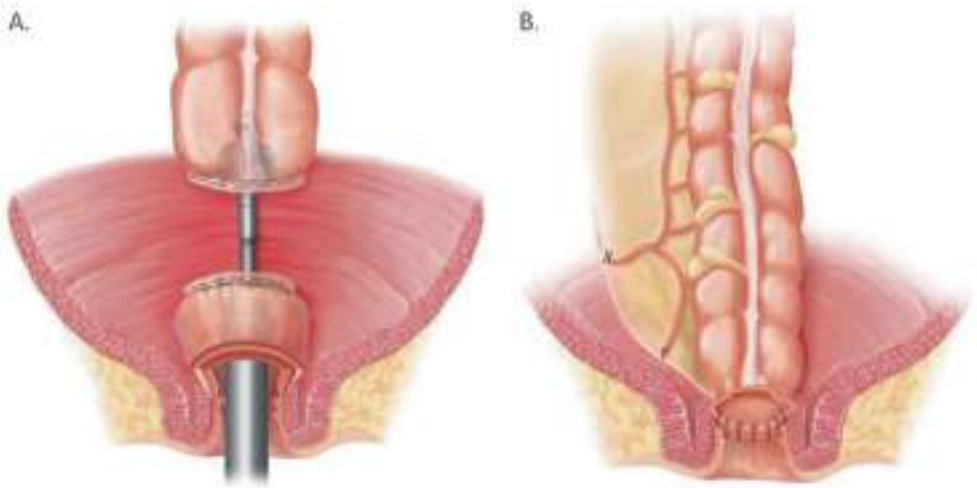

FIGURE 31-5. (**a**) Stapled end-to-end colorectal anastomosis. (**b**) Handsewn end-to-end coloanal anastomosis. *With permission from Wexner SD, Fleshman JW, editors. Colon and Rectal surgery: Abdominal Operations, Master Techniques in Surgery. Philadelphia: Lippincott Williams & Wilkins; 2012* [107].

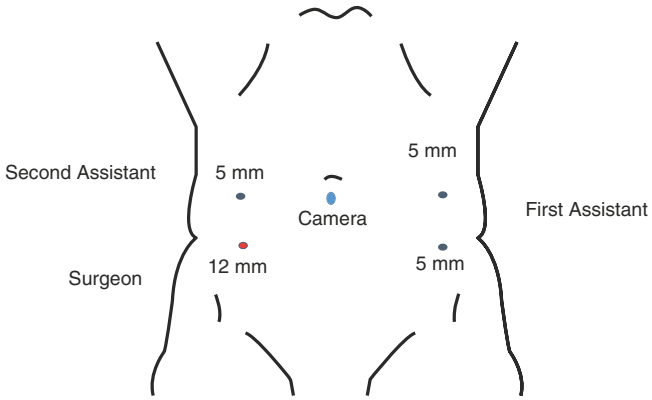

FIGURE 31-6. Preferred port placement for laparoscopic LAR with TME.

In patients with a narrow pelvis or elevated body mass index, pelvic dissection can be challenging. In such cases, a lower midline or Pfannenstiel incision may be utilized to allow open pelvic dissection, rectal division, and restoration of intestinal continuity. A combination of laparoscopic and open surgery in this manner is often referred to as a "hybrid" approach.

Robotic Low Anterior Resection

Robotics has emerged as a useful technology in pelvic dissection and may have advantages for the surgeon with respect to manual dexterity, versus standard laparoscopy. The straight laparoscopic instruments make dissection within the confines of the narrow, bony pelvis difficult and subject the surgeon to ergonomic stress. The robotic platform allows for stable retraction; enhanced three-dimensional (3D), high-definition visualization; and articulating instruments. There is some indication that use of the robot has been associated with a reduced rate of conversion to laparotomy during proctectomy as compared to standard laparoscopic surgery (although many of the studies on this topic are plagued by selection bias) [41].

A single-docking technique using the da Vinci® Si™ robot is first described. This entails single docking of the robot for the entire procedure, from colon mobilization to pelvic dissection. The patient is placed in a modified lithotomy position. Pneumoperitoneum is established with a Hasson technique through a supraumbilical incision. The abdominal cavity is examined using the robotic camera. Four additional robotic ports are inserted, along with an assistant port, as shown in Figure 31-7a. The greater omentum and the small bowel are retracted out of the pelvis. The patient is placed in Trendelenburg position, with right-side down. The robotic cart is brought to the left lower quadrant. The robotic arms are first docked, with robot arm 1 in the right lower quadrant using monopolar curved scissors or vessel sealer, robot arm 2 in the right upper abdomen using a fenestrated bipolar forceps, and robot arm 3 in the left mid-abdomen using a ProGrasp™ or Cadiere forceps for retraction. Arm 3 begins on the left side of the robot, on the same side as arm 1. Dissection proceeds in a medial-to-lateral fashion, as in standard laparoscopic dissection. Following division of the IMA and IMV, splenic flexure mobilization, and division of the left colic mesentery, robot arm 3 is repositioned (Figure 31-7b). The robot does not need to be moved, and patient position can be maintained. On occasion, a slightly more accentuated head-down and minimal tilt is utilized for the pelvic dissection, in order to keep the small bowel out of the pelvis. This configuration ensures that all instruments can reach the pelvic floor without conflict. Proctectomy proceeds, as described above for standard laparoscopy, but with a few exceptions. Care is taken to maintain dissection along the mesorectal plane laterally and avoid dissection into the pelvic sidewall. This is facilitated by early anterior dissection, which is easily visualized with the camera setup, as described, and use of articulating instruments. We often use a tie around the rectum

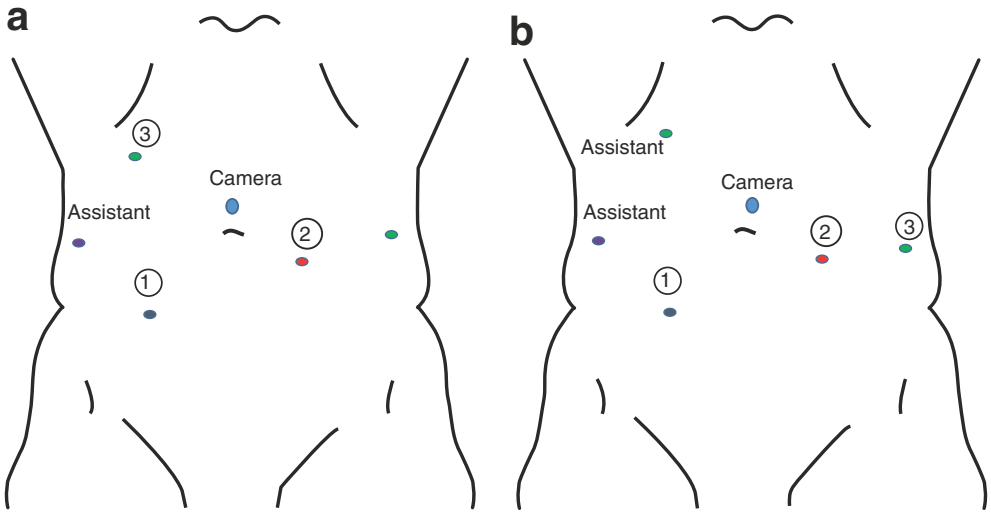

FIGURE 31-7. Trocar placement for robotic LAR using the da Vinci® Si™ robot with the two separate phases of the operation: (**a**) pedicle ligation, splenic flexure mobilization; (**b**) pelvic dissection.

(such as thin vaginal packing) to facilitate rectal retraction. During pelvic dissection, the bedside assistant utilizes the lateral assistant port and the right upper quadrant robotic port (which was used for pedicle ligation and flexure takedown). Intraoperative endoscopy, with picture-in-picture technology, allows the operating surgeon to visualize the rectal tumor at the robotic console and optimize the distal resection margin. We use cautery and the Vessel Sealer, along with the robotic stapler (EndoWrist® Stapler 45), to achieve low pelvic stapling. Superior visualization and retraction, along with articulating instruments, greatly facilitates deep pelvic dissection along the prostate and in the intersphincteric groove for coloanal anastomosis. When the distal rectum has been divided, the robot is undocked, and the rectum is extracted via a wound protector at the umbilical port or future stoma site. The descending colon is divided, the anvil secured, and the laparoscopic anastomosis performed.

A similar setup is utilized with the da Vinci® Xi™ robot. This system has more flexibility, as the camera is 8 mm and can be used in any port. This is referred to as "port hopping" and is useful if dissection becomes difficult and a new vantage point is needed. The da Vinci® Xi™ robot instruments are longer, eliminating problems related to reaching the splenic flexure and the deep pelvis. Port setup is shown in Figure 31-8a, b.

Abdominoperineal Resection

APR is necessary for very low rectal tumors that invade the external sphincter or the levator muscles. The relative indications for APR include external sphincter involvement at any time in the patient's workup. Relative indications include patients with poor preoperative baseline bowel function who are not candidates for a Hartmann resection. Furthermore, care should be taken when planning surgery in patients with bulky low tumors that show minimal response or progression on neoadjuvant chemoradiation. This portends aggressive tumor biology with extension along lymphovascular and perineural spaces, making complete margin-negative resection more challenging. Wide resection, including APR, should be considered in such cases.

During APR, left colon/splenic flexure mobilization is not required. Dissection is generally taken down to the pelvic floor, and then the perineal phase is begun. Perineal dissection can be performed in lithotomy or prone position. Some assert that the prone dissection is more comfortable for the surgeon and facilitates anterior dissection but requires abdominal closure and stoma maturation prior to repositioning the patient facedown. When beginning the perineal phase, additional Betadine® preparation is utilized, and the anus is sutured to reduce contamination. A wide elliptical incision is created to encompass the sphincter complex, and dissection proceeds into the ischiorectal space. Care is taken to dissect just superior to the coccyx, where the pelvic floor is divided and the perineal dissection meets the anterior dissection. The lateral pelvic floor musculature is divided widely, and the anterior dissection is then performed, carefully avoiding injury to the vagina or membranous portion of the urethra. Following specimen removal and pelvic irrigation, the perineum is closed in multiple layers to eliminate the dead space. Pelvic drains are used liberally to reduce fluid buildup in the contaminated pelvis.

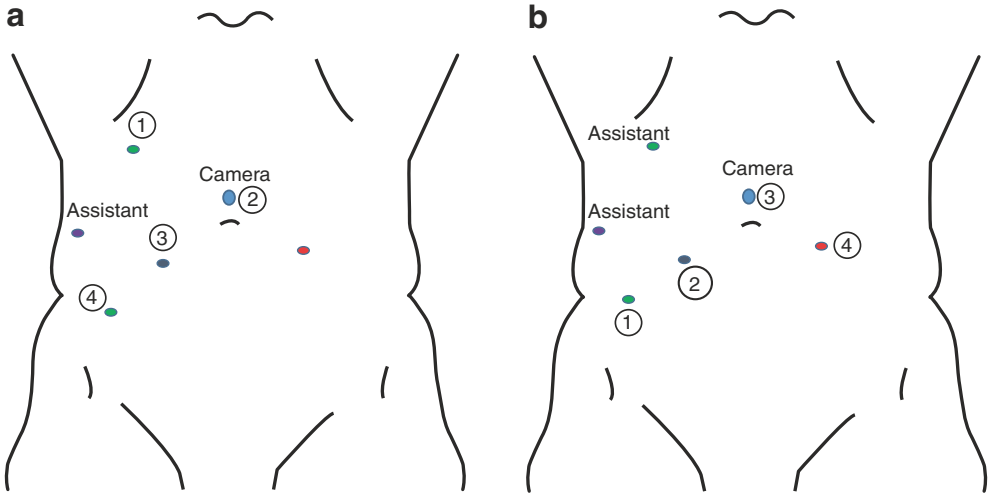

FIGURE 31-8. Trocar placement for a robotic LAR using the da Vinci® Xi™ robot. (**a**) Configuration used for pedicle ligation, splenic flexure mobilization. (**b**) Configuration used for pelvic dissection.

Extralevator or "Cylindrical" APR

In recent years, several authors have shown that oncologic outcomes after APR have not improved to the same degree as those seen after low anterior resection (LAR). In fact, compared with patients undergoing LAR during the same time period, patients undergoing APR have higher rates of local recurrence and poorer survival [42, 43]. The difference in oncologic outcomes may be explained to a substantial degree by the increased risk of tumor-involved margins (CRM) and inadvertent bowel perforations associated with APR, as both of these factors are significantly related to local control and survival. It is important to keep in mind that the distal rectum is devoid of surrounding mesorectum; therefore, tumor extension beyond the muscularis propria can invade surrounding tissues, resulting in positive CRM with standard resection. Higher rates of CRM were highlighted in a 2005 study from the UK and subsequently verified in a joint study of specimens from the Dutch trial [42, 44]. In the latter study, Nagtegaal and colleagues assessed 846 LAR and 373 APR specimens. They found that the plane of resection was within the sphincteric muscle, the submucosa, or lumen in more than one-third of the APR cases, resulting in a positive CRM rate of 30.4% in APR versus 10.7% in LAR and a perforation rate of 13.7% versus 2.5%, respectively. Others have reported improved outcomes with wide anatomic resection [45, 46].

An approach to reduce CRM involvement and specimen perforation, proposed by the Karolinska Institute in Stockholm and termed extralevator or "cylindrical" APR, involves wide resection of the levator muscles en bloc with the sphincter muscles, anal canal, and mesorectum. The abdominal component of the procedure terminates higher in the pelvis, and the levator ani muscle is divided along its attachments to the sidewall to avoid a "waist" in the specimen (Figure 31-9). The perineal phase widely resects the ischiorectal space and completes the dissection. In a report comparing cylindrical to conventional APR specimens, Holm and colleagues demonstrated a marked reduction in CRM involvement and perforation with cylindrical APR [47]; however, flap closure is usually required, and perineal wound complications, as well as chronic pain, were significantly increased in the extralevator group [48, 49]. Many advocate "selective extralevator dissection" in areas of

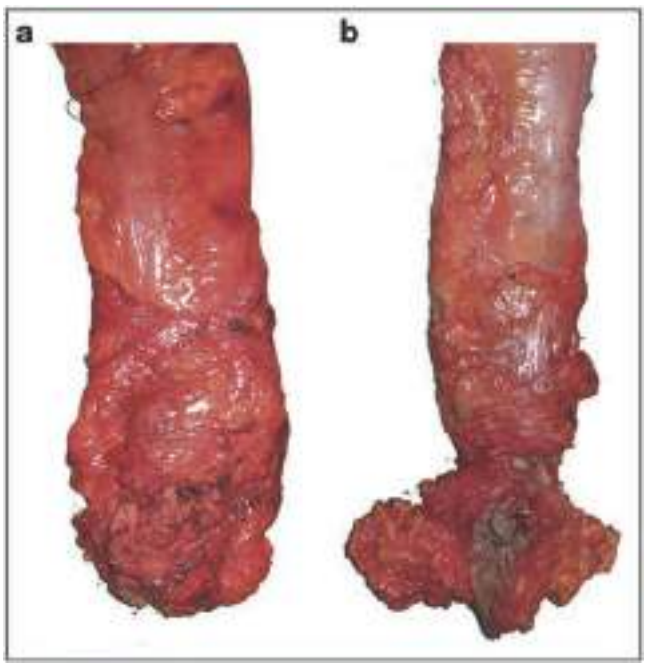

FIGURE 31-9. Abdominoperineal resection specimens. Dissections from above and below meet above the anal canal. (**a**) APR specimen with a waist. Courtesy of Eric K Johnson, MD. (**b**) Specimen with a cylindrical resection and no waist (intact mesorectum). Courtesy of Conor Delaney, MD.

tumor, stressing the need for accurate preoperative imaging and examination [50]. Prone positioning for the perineal phase is not mandatory, and minimally invasive approaches are feasible [51–53]. Appropriate patient selection, methods of closing the pelvic floor to reduce wound complications and perineal hernias, and an optimal approach (open versus laparoscopic or robotic) are pertinent issues warranting further investigation in extralevator APR.

Special Considerations

Rectal Washout

It has been suggested that implantation of exfoliated malignant cells is a possible mechanism of luminal tumor recurrence in colorectal anastomoses. Intraoperative rectal washout with saline solution or water theoretically decreases the amount and viability of these cells. A study from Sweden reported a reduction in local recurrence from 10.2% with no washout to 6% with washout. However, there is no conclusive evidence regarding the effect of rectal washout on local recurrence after rectal cancer surgery. Although it may be merely a surrogate marker for attention to detail, we routinely use intraoperative rectal washout. It is a simple procedure, with minimal morbidity and with potential benefits [54].

Distal Margin

The distal resection margin is an important consideration in rectal cancer surgery. Although lymphatic drainage of the rectum generally occurs in a cephalad direction toward the major lymph node stations, pathological studies have shown distal mesorectal spread as far as 2–3 cm below the lower palpable edge of the tumor. Thus, for upper rectal cancers, mesorectal resection should include mesorectum at least 4–5 cm distal to the lower edge of the tumor, and the mesorectum is divided perpendicular to the longitudinal access of the rectum for a tumor-specific mesorectal excision. It is critical not to "cone in" and leave mesorectum behind when performing this maneuver. For mid to low rectal cancers, dissection 4–5 cm below the tumor generally ends at the pelvic floor. Thus, as long as the entire mesorectum can be removed and negative margins of resection obtained for the primary tumor, it is reasonable to consider restorative proctectomy with coloanal anastomosis for patients with distal cancers [55–58]. The exact distance that constitutes an adequate distal mural margin in this situation is the subject of debate, but an attempt to achieve 1 cm seems reasonable.

Coloanal Anastomosis

In carefully selected cases in the setting of an ultra-low rectal cancer, continued dissection along the intersphincteric plane (which is an extension of the muscularis propria of the rectum) may facilitate sphincter preservation. A handsewn anastomosis is commonly performed, with good oncologic outcomes, especially in patients with a significant response to preoperative chemoradiotherapy [53, 58]. Patient selection and counseling are critical, as patients with coloanal anastomosis have worse bowel function and potentially poorer quality of life than those with a standard stapled colorectal anastomosis [59].

Options for Reconstruction of the Gastrointestinal Tract

Following rectal resection, patients often describe frequent bowel movements, incomplete evacuation, clustering, urgency, and, at times, incontinence. In order to mitigate these symptoms, which are collectively known as LAR syndrome, various techniques have been attempted to recreate the reservoir function of the resected rectum. These are known as colonic neorectal reservoirs and include the colonic J-pouch and the end-to-side (or "Baker-type") anastomosis.

A colonic J-pouch is constructed in similar fashion to an ileal J-pouch; however, the colonic J-pouch is much smaller, about 6–8 cm in length. Randomized trials, a meta-analysis, and Cochrane review have all concluded that a colonic J-pouch results in improvement of symptoms (decreased frequency, urgency, and nocturnal bowel movements) and a better quality of life for at least 1 year after surgery, compared to an end-to-end anastomosis [60–62]. Coloplasty, longitudinal colotomy closed transversely, was proposed for patients with a narrow pelvis for whom J-pouch was not technically feasible; however, this has not been shown to be an improvement over straight anastomosis. The additional suture line has a risk of leak that can be difficult to treat, and generally coloplasty has fallen out of favor. It is difficult to interpret the results of some trials, given the variation in surgical technique: specifically, the use of either sigmoid colon or descending colon for construction of the neorectum. The use of the sigmoid colon for construction of the neorectum in patients with significant muscular hypertrophy or diverticular disease may negatively impact postoperative function.

An end-to-side or Baker anastomosis, first described in 1950, has recently been revisited as another option for improving postoperative bowel function. This side-to-end anastomosis appears to confer many of the functional advantages of the colonic J-pouch. Compared to a straight anastomosis, it is associated with significantly fewer anastomotic leaks, and overall it is safe, easier, and faster to create than the colonic J-pouch. A 2008 Cochrane review of four randomized trials comparing colonic J-pouch to the side-to-end anastomosis, as well as a more recent meta-analysis of six randomized trials, found similar functional outcomes between the two groups [63]. In many instances, there is insufficient bowel length, or the pelvis is too narrow to permit creation of a reservoir. Ensuring sufficient length of the bowel to adequately sacralize in the pelvis is crucial to

healing and function. Some experts prefer to avoid the multiple staple lines associated with reservoirs and the risk of anastomotic leaks, which are difficult to remedy.

Fecal Diversion

Anastomotic leakage following proctectomy occurs in up to one-quarter of patients. Creation of a defunctioning stoma following restorative proctectomy may decrease the sequelae of anastomotic leak and pelvic sepsis. However, the value of a protective stoma has been a subject of controversy for many years. A randomized controlled trial in 2009 reported a reduction in leak rate from 28% without to 10% with a stoma [64]. A 2009 meta-analysis comparing defunctioning stoma to no stoma after rectal resection concluded that the defunctioning stoma resulted in lower rates of leak and reoperation [65]. This meta-analysis included data from four randomized controlled trials and 21 non-randomized studies, involving 11,429 patients in total. A recent meta-analysis of 13 studies published between 2004 and 2014, pooling data on 8002 patients, reported similar conclusions [66]. However, diversion does require a second operation, may result in dehydration, entails an increased risk of bowel obstruction, and is not popular with patients. Therefore, most centers divert selectively, based on anastomotic height, patient-related factors such as diabetes and previous pelvic radiation, and the results of intraoperative leak test.

Extended Resection

Up to 10% of patients with rectal cancer present with tumor invading adjacent structures, necessitating en bloc resection of the affected organ(s) [67]. En bloc resection of adjacent pelvic organs has been associated with good oncologic outcomes when pathologically negative microscopic (R0) margins can be achieved [68, 69].

Involvement of the uterus and vagina in women is best treated with en bloc resection of the rectum with the uterus and the posterior vaginal wall, in order to achieve R0 resection. Closure can be done easily after partial vaginectomy by flap reconstruction or primary closure, preserving sexual function.

Involvement of the seminal vesicles on one or both sides in men can be managed by dissection anterior to the vesicles, removing them en bloc with the rectum. The neurovascular bundles arising from the inferior hypogastric plexus, which control urinary and sexual function, are at risk during this dissection—as are the distal ureters, which should be identified and preserved. Involvement of the prostate by rectal cancer usually requires urologic consultation and is usually treated either with a partial prostatectomy or a pelvic exenteration, depending on the extent of tumor invasion. It should be noted that en bloc resection of the seminal vesicles only, with preservation of the bladder and prostate, is a challenging operation, often much more difficult than pelvic exenteration.

Involvement of the distal ureters by a locally advanced rectal tumor is rare. However, if encountered, it is best managed with en bloc resection of the ureter, with primary ureteric anastomosis over a stent or a psoas hitch, depending on the length of the ureteric defect. Rectal cancers that adhere to the urinary bladder require partial or total cystectomy, especially when the trigone is involved.

Lateral pelvic sidewall lymph node involvement has been reported in up to 20% of T3/T4 rectal cancer cases [70]. In general, pelvic sidewall lymph node involvement is associated with low-lying tumors and worse prognosis [71]. In Japanese studies, selective use of lateral pelvic lymphadenectomy has reportedly led to good outcomes. A meta-analysis of 20 studies demonstrated no improvement in survival or local recurrence when an extended lymphadenectomy was performed compared to standard proctectomy [72]. However, in selected cases where lymphatic spread is suspected clinically or radiographically, an extended lymphadenectomy is warranted in order to obtain an R0 resection.

Intraoperative Radiation Therapy

Intraoperative radiation therapy (IORT) has been used in patients with locally advanced primary rectal cancer and an involved or threatened CRM following surgical resection. The goal of IORT is to sterilize any microscopic foci of tumor, thus decreasing the risk of local recurrence. During IORT, the radiosensitive bladder and bowel can be excluded from the radiation field, allowing a higher dose to be delivered to the tumor bed. In the United States, IORT is most commonly administered by two different techniques: intraoperative electron-beam radiation therapy (IOERT) or high-dose-rate (HDR) brachytherapy. IOERT is delivered by means of a linear accelerator over the course of a few minutes; it can be used in any operating room because electrons do not penetrate the tissue as deeply as conventional radiation. The radiation is delivered through a cone, usually toward the tumor bed. HDR treatment, however, can be administered only in adequately shielded rooms. It is delivered through parallel catheters in a flexible plastic flap, which can be cut to fit the region at risk and packed onto the curving pelvic surface. HDR brachytherapy may take up to an hour.

IORT has been used in locally advanced rectal cancer for more than 30 years, yet there is no convincing evidence that it decreases local recurrence or improves survival. The only multicenter randomized trial to date included 142 patients with locally advanced rectal cancer, who had received preoperative chemoradiation and were randomly assigned to either surgical resection alone or surgery plus IORT [73]. After a 5-year follow-up, the trial did not demonstrate any significant improvement in local recurrence or disease-free survival. Observational studies have reported conflicting results with respect to the efficacy of IORT. A recent systematic review of 15 individual studies, including the previously mentioned randomized trial, with 1929 patients in the IORT

group and 2343 in the non-IORT group, concluded that IORT resulted in no definite improvement in overall survival or rate of recurrence for patients with R0 resections or for the total group (including R0, R1, and R2 resections) [74]. In the setting of locally advanced primary rectal cancers, we recommend having IORT available for patients if a close or threatened CRM is highly suspected, based on preoperative imaging. IORT is more commonly utilized in resection of recurrent rectal cancer if tissue planes have been previously disrupted, and discontinued foci of tumor may be present.

Flap Closure Following APR

Special attention to perineal closure is required after APR. The bony confines of the pelvis prevent tissue collapse, leading to significant dead space. Pelvic infection requiring opening of the perineum, prolonged wound healing, and chronic perineal sinuses are not uncommon. Multilayered closure to reduce dead space and liberal use of drains are common. However, in some cases rotating a well-vascularized omentum [75] or a mucocutaneous flap [76] into the pelvis should be considered, in order to reduce dead space and facilitate perineal healing after APR, especially in patients who have received pelvic radiation. A properly designed omental pedicle graft can be easily devised by dividing the gastrocolic omental attachments, detaching the left omentum from the spleen, and ligating the left gastroepiploic pedicle and the short gastric vessels. Care is taken to avoid injury to the right gastroepiploic, which allows the bulk of well-vascularized left omentum to rotate into and fill the pelvis. Rotation of the right omentum, based on the left gastroepiploic, is also feasible. In cases of exenteration, sacrectomy, extensive perineal skin loss, or requirement of vaginal reconstruction, a myocutaneous (vertical rectus abdominus myocutaneous, gracilis, or gluteal) flap is utilized.

Functional Outcomes

High rates of postoperative sexual and urinary dysfunction were a well-known phenomenon in the early years of rectal cancer surgery, ranging from 20 to 40% [77]. For example, registry data from Norway demonstrate that less than 50% of sexually active male were able to achieve erection 2 years after rectal resection. The rate fell to less than 20% in the cohort undergoing pelvic radiation and surgery [78].

Along with the advent of sharp dissection and precise technique emphasized in TME came the goal of identifying and preserving the autonomic pelvic nerves. As an integral part of the procedure, autonomic nerve preservation resulted in improved functional outcomes.

In an early study of 42 men undergoing sphincter-preserving operations for treatment of rectal cancer, Enker and colleagues reported high rates of potency (87%) and normal ejaculation (88%) after nerve-preserving proctectomy [79]. In a comprehensive study assessing sexual and urinary function in both women and men, through retrospective questionnaires, Havenga and colleagues reported the results of 136 patients undergoing nerve-sparing proctectomy [80]. They found that the ability to engage in intercourse was maintained by 86% of patients younger than 60 years and by 67% of patients 60 years and older. Eighty-seven percent of men maintained the ability to achieve orgasm. Type of surgery (APR compared to LAR) and age greater than 60 years were significantly associated with male sexual dysfunction. Women had similarly good results: 85% were able to experience arousal with vaginal lubrication, and 91% could achieve orgasm. The majority of patients had few or no complaints related to urinary function. Serious urinary dysfunction, such as neurogenic bladder, was not encountered.

The importance of autonomic nerve identification and preservation during proctectomy is also highlighted in a study by Shirouzou and colleagues, who assessed outcomes in 403 patients undergoing proctectomy, with or without autonomic nerve preservation, over a 20-year period [81]. In male patients who had proctectomy with nerve preservation, urinary function was preserved in greater than 80%, erection was preserved in 79%, and ejaculation in 65%; when proctectomy was performed without nerve preservation, urinary disorders were found in more than 90% and sexual dysfunction in virtually all patients, even those younger than age 60.

However, in patients with extensive pelvic disease, autonomic nerve preservation may not be feasible or oncologically sound. Involvement of the autonomic nerves by tumor, or lymphadenopathy in the pelvic sidewall, generally requires a resection that will affect nerve function permanently.

Despite suffering micturition and defecation problems, quality of life has consistently been shown to be better following an LAR compared an APR. This has been confirmed by comparative studies and in a meta-analysis of several studies [82–84]. Body image is consistently higher in patients undergoing an LAR versus APR, which may contribute to the inferior sexual function associated with APR.

In patients who undergo LAR, poor bowel function has been associated with the level of the anastomosis and the administration of pelvic radiotherapy. Low anastomoses (<3 cm) and coloanal anastomoses are associated with more incontinence of gas and solid stools compared to higher anastomoses [85]. Neoadjuvant radiation therapy causes fibrosis, leading to reduced compliance of the rectum and damage to the myenteric (Auerbach's) plexus, and has been associated with higher rates of urgency, frequency, and fecal incontinence [86]. Some of the most telling data emanates from the prospective Dutch rectal cancer study, in which patients were randomized to proctectomy or neoadjuvant short-course radiotherapy plus proctectomy. Daytime incontinence was noted in 38% of patients in the surgery alone

group and 62% of patients in the surgery plus radiotherapy group. Of even more concern is the finding that bowel dysfunction increased over time (studied at 2 years and 5 years after proctectomy) in the radiation cohort [87].

Oncologic Outcomes

Attention to detail during proctectomy, especially with regard to appropriate mesorectal excision, has been associated with improved local control and survival rates. Local pelvic failure rates following proctectomy at centers of excellence are now in the single digits [19, 21, 22, 88–91]. This is a substantial improvement compared to the local pelvic failure rates following proctectomy in the past, which were 3–5 times higher.

The importance of proper proctectomy technique is also reflected in a study from the Karolinska Institute reporting that in more than half of local recurrences in Sweden, evidence of residual mesorectal fat was identified on cross-sectional imaging, suggesting that incomplete mesorectal excision was the principal cause of local recurrence [92]. The same study claimed that extra-mesorectal lateral lymph node involvement accounted for only 6% of all locoregional recurrences.

The impact of training in proper proctectomy technique has been well documented. Surgical TME educational programs in Sweden, Norway, and the Netherlands have been shown to markedly reduce local recurrence, improve survival, and reduce the rate of permanent stomas [93–96]. In an observational national cohort study of 3319 patients in Norway, implementation of TME resulted in a decrease in local recurrence from 12 to 6% [96]. Survival rates were 73% after TME and 60% after conventional surgery—an overall improvement of 10–14%. In the Netherlands, the widespread adoption of TME led to a reduction in local recurrence of 16–9% [93]. In Sweden, implementation of specialized proctectomy training, utilization of neoadjuvant short-course radiotherapy, and referral of patients with rectal cancer to specialists has led to a fall in local recurrence rates: from 15% in the control group of the Stockholm I trial, and 14% in the Stockholm II trial, to 6% [97]. Cancer-related deaths fell from 15% to 16–9%. During the same period, the proportion of APR procedures performed in Sweden decreased by more than 50%. Along with participation in workshops and the increase in surgeons' expertise, case volume directly influenced patient outcomes; when surgeons with high operative volume were compared to those with low volume, local recurrence was additionally reduced (from 10 to 4%), and there were fewer deaths from rectal cancer (18% vs. 11%) [94].

Another factor associated with oncologic outcome is the training and experience of the operating surgeon. Studies have shown that subspecialty training, surgeon experience, volume of cases, and treatment in high-volume tertiary care centers influence and enhance patient outcomes with respect to postoperative morbidity and mortality, local recurrence, and long-term survival [98–100].

Multidisciplinary Rectal Cancer Care

There is increasing evidence that multidisciplinary team management is associated with improved clinical decision-making, superior outcomes, and better patient experience in several types of cancer, including rectal cancer [101]. Cancer centers of excellence have been successfully established in several European countries over the past decade to address variability and disparity in the quality of rectal cancer care. Similar efforts in standardizing care to improve outcome have begun in the United States. The OSTRiCh (Optimizing the Surgical Treatment of Rectal Cancer) Consortium, founded in 2011, comprises a group of healthcare institutions across the United States, dedicated to improving delivery of rectal cancer care by relying on evidence-based and standardized care [102].

Variability in care was recently demonstrated in a study analyzing data from the National Cancer Data Base, which examined adherence to neoadjuvant chemoradiotherapy in 30,994 patients with clinical stage II and III rectal cancers [103]. The use of neoadjuvant radiation therapy and chemotherapy varied significantly by type of cancer center, with the highest rates of adherence observed in high-volume centers compared with low-volume centers (78% vs. 69%; adjusted odds ratio = 1.46; $P<0.001$). This variation was mirrored by hospital geographic location, with little improvement observed over the last 5 years. These results further support the implementation of standardized care pathways for patients with rectal cancer.

Conclusion

The impact of optimal proctectomy technique in reducing the incidence of recurrence and improving long-term survival in rectal cancer is well established. The associated improvement in disease-free, recurrence-free, and overall survival, and increased improvement in bowel, bladder, and sexual function postoperatively, make proctectomy—with appropriate mesorectal excision and autonomic nerve preservation—the standard of care and a required part of colorectal surgical training. Complete surgical resection of the tumor and draining lymph nodes using sharp dissection are the basic principles of TME. Attention to preservation of the autonomic nerves can reduce the morbidity of this operation, improve functional outcomes, and provide a more acceptable quality of life. The use of multidisciplinary disease management teams, and implementation of centralization for the treatment of rectal cancer, has a strong potential to provide efficient delivery of evidence-based care.

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32
Rectal Cancer Decision-Making

W. Donald Buie and Anthony R. MacLean

Key Concepts

- Sound decision-making requires a full assessment of the primary lesion, the presence of metastatic disease, the patient's surgical risk, and goals of care.
- A submucosal excision may be used as a radical biopsy to assess a polyp for adverse features without compromising future radical excision.
- Following endoscopic excision of a malignant polyp, the pathology should be rereviewed and strict criteria adhered to regarding the need for radical surgery.
- While cT2 (clinical stage T2) lesions can be treated with radical excision alone, neoadjuvant treatment can be selectively given to patients with cT3 lesions, based on preoperative staging by MRI and multidisciplinary discussion.
- Pretreatment staging can be inaccurate, especially with regard to mesorectal nodal status. Treatment planning should include a discussion of what will be recommended if stage changes based on histologic analysis. This is especially true if patients are assumed to be node negative, undergo up-front proctectomy, and are found to be node positive or if patients undergo local excision and are found to have higher T stage than anticipated.
- Most operative decisions should be made prior to entering the operating room. The patient and the surgeon must be prepared for all eventualities. In some situations the ultimate surgical decision may depend on intraoperative findings.
- Patients with potentially curable Stage IV disease require multidisciplinary discussion with early involvement of hepatobiliary surgeons and medical oncologists to determine the optimal sequence of treatment.

By three methods we may learn wisdom: First, by reflection, which is noblest; Second, by imitation, which is easiest; and third by experience, which is the bitterest.
Confucius

Introduction

While a comprehensive knowledge base and consummate operative skill are required for optimal management of rectal cancer, sound decision-making is essential. Poor decisions whether preoperative, intraoperative, or postoperative may have a profound and irreversible affect on both short- and long-term patient outcomes. Thus, it is important to understand not only what you can do but what you should do.

The aim of this chapter is to examine common clinical situations encountered by the colorectal surgeon who treats rectal cancer and analyze the decision points. This includes identification of the variables that affect treatment decisions, the potential treatment options including the advantages and disadvantages of each, and finally the logic behind specific treatment decisions. The chapter is organized to include early rectal cancer, endoscopically removed cancers, locally advanced lesions, synchronous metastatic lesions, and special situations. While no chapter can cover all clinical situations, it is hoped that the principles outlined below can also be used as a guide in more unusual circumstances.

Assessment

Each situation like each patient is unique. Knowledge and a comprehensive understanding are paramount to making good surgical decisions. When first encountering a patient with a rectal neoplasm, our first step is to gather information. We assess the lesion in terms of size, location (distance from anal verge, distance from the superior aspect of the anorectal muscular ring, and circumferential position—anterior/posterior/lateral), morphology, fixation (fixed, tethered, mobile), and general appearance. Additional information is needed with respect to the presence of metastatic disease [1, 2]. Finally we assess the patient for surgical risk including anesthetic risk, procedural risk, and patient risk [3, 4]. As the surgeon you are responsible for ensuring that each patient is

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fully evaluated and optimized for the required treatment; the right procedure at the right time as safely as possible [5].

An important part of assessment includes goals of care. Oncologic surgery is a balance of cure versus morbidity, mortality, and quality of life. Patients with significant comorbidity or those who are elderly may place greater emphasis on quality rather than quantity of life and make decisions accordingly. You must facilitate this discussion and provide information to help each patient make a decision (s)he is comfortable with. The risk-benefit profile of each potential treatment should be outlined and discussed thoroughly.

The final part of assessment is a firm understanding of your own strengths, skills, and limitations. Utilizing senior colleagues for a second opinion or as an intraoperative assist is a sign of good judgment. The management of rectal cancer is multidisciplinary, and you must cultivate strong relationships with your colleagues in the associated disciplines of diagnostic radiology, radiation oncology, medical oncology, pathology, and hepatobiliary surgery to provide optimal patient care. Ideally rectal cancer patients should be discussed at regular multidisciplinary conferences which have been shown to enhance care and outcomes. In a study by Snelgrove et al., multidisciplinary conference resulted in a change in management plan in 29 % of patients, due in a large proportion to reinterpretation of the MRI [6].

Early Rectal Cancer

Local Excision

For rectal lesions that appear early (benign or cT1 cancers), we would typically arrange for local staging, most commonly with endorectal ultrasound to examine the depth of invasion as well as a pelvic MRI, for staging regional nodes, and to document the baseline appearance of the pelvis going forward [7–10]. If the lesion has a malignant appearance or is a proven cancer on biopsy, we also arrange systemic staging with a CT scan of the chest, abdomen, and pelvis.

As long as there are no features on biopsy or imaging that are high risk for nodal disease, we would offer local excision as a "radical biopsy." We typically use the transanal endoscopic microsurgery (TEM) technique for most lesions, although TAMIS is a good alternative [11–13]. For distal lesions below 7 cm from the anal verge, conventional transanal excision can be considered, though there are data suggesting a higher rate of specimen fragmentation and subsequent local recurrence [14].

We believe it is critical to have a thorough discussion with the patient prior to performing a local excision. While the prevailing opinion described in most textbooks advocates for full-thickness excision in all cases, we tend to be more selective in our approach.

For lesions that appear benign on biopsy and imaging or at worst T1, we try to gauge the patient's thoughts on what their wishes would be in response to the biopsy results. If the patient decides that he or she would want a radical excision for anything other than the most early, most favorable cancer, we feel that a partial thickness excision is a very reasonable option, as it provides definitive histology and allows assessment of high-risk features, including differentiation, lymphovascular invasion, tumor budding, and depth of invasion in microns (Table 32-1). For lesions invading to <1000 μm with no adverse pathologic features, particularly with no evidence of high-grade budding, local excision alone is felt to be an acceptable treatment, with close follow-up [16–18]. Additional reasons to consider a partial thickness excision also include less perioperative risk and no significant change in the perirectal fat that can affect the difficulty of (and complications from) subsequent radical excision in cases with unfavorable histologic features. Importantly, if the lesion is proven to be benign, then excision in the submucosal plane should be curative and will avoid the added morbidity of full-thickness excision.

Table 32-1. Risk of nodal involvement

	# Tumors	Nodal involvement (%)	Odds ratio	*P*-value
Tumor grade				
Favorable	176	5.7		
Unfavorable	75	29.2	2.9	0.023
Vascular invasion				
Absent	176	5.7		
Present	75	30.7	2.7	0.039
Cribriform pattern				
Absent	192	7.3		
Present	59	32.2	3.9	0.002
Tumor budding				
Negative	213	8		
Positive	38	42.1	3.7	0.008

With permission from Ueno H, Mochizuki H, Hasiguchi Y, et al. Risk factors for an adverse outcome in early invasive colorectal carcinoma. Gastroenterology 2004; 127:385–394 © Elsevier 2004 [15]

On the other hand, if the patient is more strongly in favor of avoiding radical surgery and would tolerate a slightly higher risk of local recurrence, we feel that a full-thickness excision is warranted for lesions that are proven on biopsy to be adenocarcinoma preoperatively or have gross features of malignancy, which again allows for histologic evaluation but also provides a wider deep margin for more significant lesions.

Once the histologic information is available (for which we also typically request a second opinion from an experienced GI pathologist), we have a thorough discussion with the patient about the results and define their risk of lymph node disease. For patients with T1 adenocarcinoma with high-risk features and/or depth of invasion greater than 1000 μm (or Kikuchi level SM2) [15, 18, 19], we recommend radical excision. However, in situations where the patient understands the risks and prefers to avoid radical excision, close follow-up is an acceptable alternative. For patients who are frail or have significant comorbidity that would preclude a radical excision, we consider extending our indications for local excision to more significant lesions.

Our follow-up depends somewhat on the characteristics of the lesion excised and the patient's age and comorbidity but, in general, would include sigmoidoscopic examination at 3–4 month intervals for the first 2 years when the risk of recurrence appears to be highest, then at 6-month intervals for an additional 2 years with colonoscopic evaluation as indicated for surveillance at year 1 and year 4. Additionally, we survey the pelvis with pelvic MRI scans at 6-month intervals for the first 2 years to look for nodal recurrence. Lastly, we typically arrange yearly CT scans of the chest, abdomen, and pelvis for the first 3 years to look for metastatic disease.

Endoscopically Excised Malignant Polyps

Occasionally we will be referred a patient who has had endoscopic excision of a malignant rectal polyp. In these situations, we obtain a pathologic review and then try to determine the risk of intraluminal recurrence as well as the risk of nodal disease and systemic recurrence. We examine the polypectomy site with sigmoidoscopy and, if not already done, mark it with a tattoo especially if completely excised. The patient is staged as in the early rectal cancer section above. However, it is important to remember that imaging can be affected by the thermal injury to the bowel wall from a large polypectomy. Occasionally lymphadenopathy related to local inflammation will be seen, that can be confused for nodal metastases. The risk of intraluminal recurrence is dependent on the margin of excision—while many textbooks advocate a 2 mm minimal margin, current evidence suggests that in the absence of other high-risk histologic features, a 1 mm margin is adequate [15, 20]. In terms of the risk of nodal disease, important factors include differentiation, lymphovascular invasion, tumor budding, and depth of invasion (see Table 32-1). When all histologic features are favorable and the margin is greater than 1 mm, close follow-up is recommended. When all histologic features are favorable, but the margin is <1 mm, we discuss re-excision transanally versus radical excision. When high-risk features for nodal metastases are present, we typically recommend radical excision assuming the patient is a suitable candidate. In high-risk patients where radical excision is not an option, we extend our indications for observation.

Operable and Locally Advanced Lesions

For lesions that are not amenable to local excision, our approach is to again assess the lesion as described above but also perform local staging with pelvic MRI and systemic staging with a CT of the chest abdomen and pelvis. We do not routinely advocate the use of PET scan in the preoperative staging of rectal cancer, except to help resolve an indeterminate lesion identified on CT or MRI.

For lesions that are T2 on imaging, we typically advocate a radical excision. We do not currently feel that there is sufficient evidence to recommend local excision in association with neoadjuvant [21] or adjuvant chemoradiation [22], though there is ongoing interest in this approach and further evidence could possibly change that opinion in the future.

The current standard of care for all clinical stage 2 and stage 3 rectal cancers is to receive neoadjuvant therapy followed by radical surgery when diagnosed on preoperative imaging and to receive postoperative chemoradiotherapy when final pathology unexpectedly demonstrates stage 2 or 3 disease [23]. However, it has become clear that some of these patients derive very little benefit from chemoradiotherapy and do suffer potential long-term complications from the administration of postoperative radiotherapy, including fibrosis/stricture of the anorectum and other issues with bowel, bladder, and sexual function [24–26]. It is also clear that receiving postoperative radiotherapy is less effective than neoadjuvant radiotherapy. Thus identifying those who are likely to derive the most benefit is important [27].

Current staging modalities are very accurate at determining T stage and distance to the expected mesorectal margin but are much less accurate in determining N-stage. TRUS, CT, and MR all suffer from a lack of sensitivity and specificity when queried to predict mesorectal nodal status [7, 28–31]. All the techniques suffer from the inherent limitation that they do not detect tumor but rather the size and morphology of the node. Tumor deposits in lymph nodes do not reliably produce lymphadenopathy greater than 1 cm; in fact more than 50 % of all positive nodes will be less than 5 mm in size. In addition, the inflammatory reaction from previous biopsies, or from the tumor itself, can result in nodal enlargement without tumor involvement, resulting in false positives. Metabolic imaging with 18-fluorodeoxyglucose positron emission tomography (FDG-PET) may not be effective in

detecting mesorectal nodal status because emission from the primary tumor may obscure adjacent nodal signal or because of the small size of some of the nodal metastases.

Given the limitations of preoperative staging, locally advanced lesions require a considerable amount of careful thought when deciding on the most appropriate course of treatment. One can decide that all patients with stage 2 or 3 disease require chemoradiotherapy and mandate that all patients with clinical stage 2 and 3 tumors receive neoadjuvant therapy and that all unsuspected stage 2 and 3 tumors receive postoperative chemoradiotherapy. An alternative strategy is to be more selective, trying to select those patients who are more likely to derive benefit from chemoradiotherapy, while avoiding the negative consequences of radiation in more favorable patients. We generally use the Mercury study group criteria [32, 33] to help decide which patients should be referred for neoadjuvant therapy. cT3a tumors with less than 5 mm of intrusion into the perirectal fat and predicted negative resection margins generally behave more as T2 lesions and thus can be spared the negative consequences of radiation therapy (Figure 32-1) [34]. For cT3 lesions with a close but predicted negative (>2 mm) margin based on staging MRI, neoadjuvant therapy is warranted. In this situation, both short-course radiation and long-course chemoradiation can be considered. For cT3 lesions with a predicted positive margin and for cT4 lesions, long-course neoadjuvant chemoradiation is required for tumor downstaging.

However, preoperative staging alone should not drive all treatment decisions with regard to neoadjuvant therapy. Pelvic morphology and tumor position may have a significant effect on decision-making. For example, a proctectomy in an obese man with a narrow pelvis and an anteriorly based tumor of the mid or distal rectum can be very challenging. Such a patient should be considered for neoadjuvant therapy and should be discussed in a multidisciplinary setting, ideally with radiologic review. Alternatively, proctectomy in a thin woman with a wide pelvis and a posteriorly based tumor should be relatively straightforward with little chance of positive margin if the tumor does not extend beyond the mesorectal fascia on preoperative imaging.

The inability to predict nodal status before embarking on a treatment course is of particular concern for the subset of patients staged as cN0 who undergo proctectomy as a first step in treatment and are upstaged to pN1+(2) following histologic review of the operative specimen. Prior to simply recommending postoperative radiotherapy because of N+status, it should be remembered that postoperative radiotherapy is not as effective as preoperative radiotherapy, must be administered at a higher dose with concurrent chemotherapy to achieve similar oncologic benefit, and has the downside of higher toxicity [35].

One strategy to avoid the issue of radiating patients postoperatively who are found unexpectedly to have node positive disease at proctectomy is to radiate all patients preoperatively regardless of pretreatment imaging results. Short-course radiotherapy is probably the best regimen for patients with non-fixed tumors if this strategy is adopted, as the oncologic results are equivalent to long-course chemoradiotherapy. In addition, short-course radiotherapy can be administered more quickly (shortening the time to full-dose cytotoxic chemotherapy in appropriate patients), is less costly, and is associated with less toxicity in the neoadjuvant period. The main downside of this approach is the large number of patients who would be treated and exposed to the

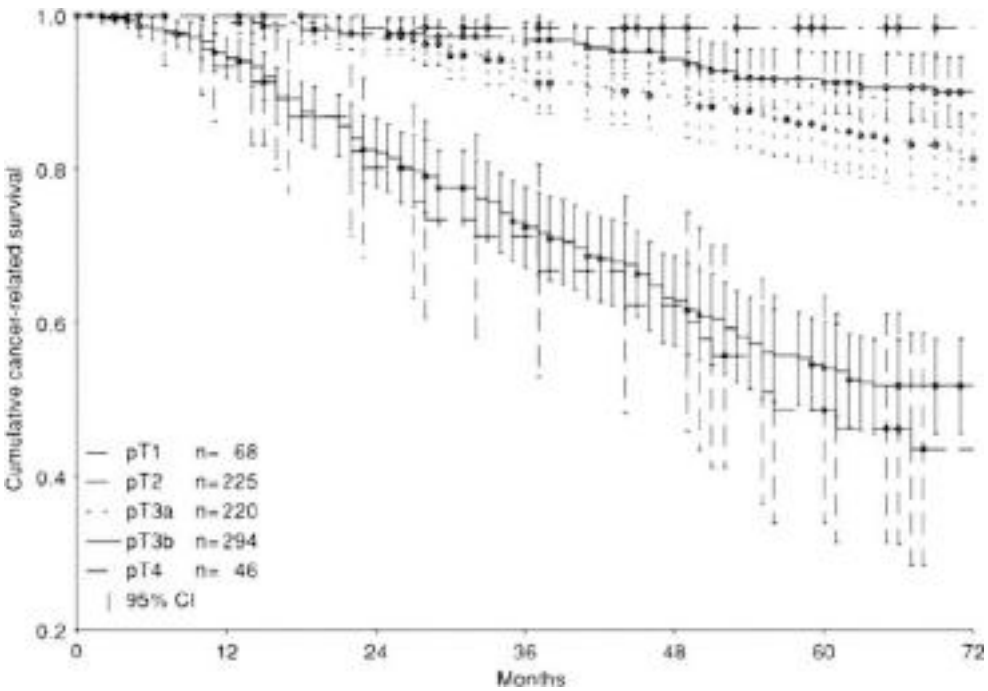

FIGURE 32-1. Cancer-related survival in relation to extended pT classification based on depth of invasion: pT1 submucosa, pT2 muscularis propria, pT3a<5 mm extramural disease, pT3b>5 mm extramural disease, and pT4 other organs. *With permission from Merkel S, Mansmann U, Siassi M, Papadopoulos T, et al. The prognostic inhomogeneity in pT3 rectal carcinomas. Int J Colorectal Dis 2001:16:298–304 © Springer 2001* [34].

long-term consequences of radiotherapy without deriving any significant benefit.

Another approach is to agree at the initial multidisciplinary conference that patients recommended for up-front proctectomy will not be considered for postoperative radiotherapy unless margins of resection are positive, and will be treated with chemotherapy alone if they are found to be node positive and resection margin negative. This strategy will also shorten the time to full-dose cytotoxic chemotherapy and avoid the toxicity of postoperative radiotherapy, which can be substantial. The argument that this is not "standard of care" is based on recommendations from decades past, when trials were conducted without surgery or pathology quality control, radial margins were not assessed, and chemotherapeutic agents were less effective. This is our current treatment approach for patients who are upstaged on pathologic review following proctectomy.

Lastly, there is continued interest in a "watch and wait" approach following neoadjuvant therapy with complete clinical response [36–38]. The issue remains that complete clinical response does not always equate with complete pathologic response. Except in situations of compromise due to patient frailty or comorbidity, we feel that this approach should be relegated to participation in a clinical trial [39]. This opinion may change as additional information becomes available.

As one may see from the above discussion, decision-making for patients with rectal cancer is complex and nuanced. Unfortunately, this complexity cannot be easily transformed into simple treatment guidelines.

Surgical Considerations

Intraoperative Decisions

Most operative decisions should be made prior to entering the operating room. There is no substitute for advance preparation having thought through the potential problems and solutions away from the OR when planning and reflection can occur without distraction and emotion. In difficult situations we will seek the advice of a colleague and plan to have a second surgeon available intraoperatively should the decision have far-reaching consequences or should the unexpected arise.

Despite the surgeon's best intentions, there are occasions where the final decision can only be made at the time of surgery. The surgeon must be flexible and have very precisely articulated goals of care; know why you are there and what you are trying to accomplish. In exceptional cases, this may include backing out if the situation requires more than what has been planned for. It is better to return on another day when the patient and surgeon are emotionally and physically prepared for the operation that is required.

Midrectal Cancers

As mesorectal spread can extend up to 3–4 cm distal to the gross tumor margin, a 5 cm mesorectal margin is required to ensure complete removal of at-risk nodal tissue [40, 41]. We advocate a tumor-specific mesorectal excision for tumors in the upper third of the rectum, preserving rectal length and function without compromising cure. When the tumor is located in the distal third of the rectum, 5 cm or less from the end of the mesorectum, we advocate a total mesorectal excision (TME) to remove all nodal tissue [40–43].

For tumors in the middle third especially in obese patients, it may be very difficult to perform a tumor-specific mesorectal excision and save 2–3 cm of viable rectum above the pelvic floor. We feel it is often technically easier and safer for the patient to extend the resection for an additional 2 or 3 cm to complete a TME. The decision is based primarily on the technical feasibility of dissecting through the distal mesorectum at that level while preserving the viability of the rectal stump.

Low Rectal Cancers

Surgical decision-making in low rectal cancer is complex balancing cure with function. In most situations, the decision to proceed with a sphincter-preserving procedure rather than an abdominoperineal resection is made preoperatively based on history, physical examination, imaging studies, response to chemoradiation, and the ability to obtain clear surgical margins. In addition patient factors including age, comorbidities, body habitus, continence, and patient wishes must be considered [44]. Good quality MRI with careful interpretation is important to identify any absolute indications for APR including involvement of the levators or external sphincter [45].

On rare occasions due to body habitus, tumor size, or pelvic shape, it may be difficult to predict preoperatively whether a tumor can be successfully resected with sphincter-preserving techniques. In this situation the patient must be fully informed and all options discussed in detail including the reasoning behind the decision, the expected outcomes, and potential complications. We consent the patient for "a low anterior resection-possible abdominoperineal resection" and emphasize that we are operating for local control and will proceed with sphincter preservation provided that cure is not compromised. The patient should be counseled and marked for both a colostomy and a loop ileostomy.

Preoperatively, all approaches that enhance distal dissection should be considered including a stapled coloanal anastomosis and a hand-sewn coloanal anastomosis with or without intersphincteric resection. Although a stapled anastomosis results in better function and less morbidity, an intersphincteric dissection provides additional distal margin length [46–48]. We restrict this technique to very low tumors

that are contained within the rectal wall, that do not invade the pelvic floor or anal sphincters, in patients who can tolerate and accept the functional compromise [44]. The functional results depend on preoperative sphincter function, the effect of neoadjuvant radiation, and the variable amount of residual internal sphincter left below the dentate line [49–52]. We feel it is critical that the surgeon carefully reviews and correlates the preoperative imaging and the findings on physical examination prior to considering an intersphincteric dissection, as it is essential that the tumor is well clear of the intersphincteric plane, to prevent a positive margin and consequently a high risk of local recurrence.

Generally speaking we will accept a 1 cm distal margin although a margin less than 1 cm may be acceptable following chemoradiation [53, 54]. Every effort should be made prior to rectal division to ascertain if the margin will be adequate. Once the rectum is divided and the specimen has been removed, it should be examined off table and if possible in concert with the pathologist. If the distal mural margin is inadequate, we would proceed directly with a completion proctectomy after repositioning in prone jack-knife position.

In the obese male with a bulky tumor and relatively small pelvis, distal mesorectal dissection under direct vision and thus sphincter preservation may be impossible using standard open or laparoscopic techniques such that an APR may be required to obtain clear margins. We discuss this situation with the patient preoperatively to ensure they are aware of the surgical limitations and the potential consequences. Transanal TME (taTME) with either TEM or TAMIS is a promising new technique to augment a technically difficult distal dissection. The distal margin and lower mesorectum are dissected transanally under direct vision and when combined with a laparoscopic or open TME extends the distal limits of dissection in these patients. While the initial case series are promising, this technique is not ready for universal adoption as the oncologic results are not mature, indications and contraindications remain to be refined, and the learning curve has yet to be established [55–57].

A clear circumferential margin is also critical to local control. Every effort should be made preoperatively in conjunction with your radiologist to identify potentially difficult areas of dissection where the margin may be compromised with steps taken to extend resection to an uninvolved plane as necessary. If, the decision to proceed with an APR is made intraoperatively, it should be made as soon as possible to maximize the circumferential tumor margin with a cylindrical dissection. The mesorectal plane leads the surgeon through the levator hiatus onto the bare area of the rectum with potential compromise to the circumferential margin in an ultralow tumor [58, 59]. All options need to be considered prior to entering this area of dissection. Intraoperatively, as we proceed distally, we frequently don an extra glove and bimanually palpate the tumor changing gloves prior to reentry into the operative field. If we feel that sphincter preservation will compromise the circumferential margin, we stop and proceed with a proctectomy in prone jack-knife position. We will often make this decision with a second surgeon present to ensure optimal care.

Low Hartmann's vs. APR

Patients with poor preoperative anal sphincter function who would normally have a low anterior resection with a coloanal anastomosis may also be treated with a low Hartmann resection. While this obviates the need for a perineal wound with its attendant risks of nonhealing and chronically draining sinus tract, a low Hartmann's is occasionally complicated by blowout of the stump and chronic pelvic sepsis [60]. We use this option primarily in the elderly in situations without preoperative radiation.

Special Situations

Obstructing Rectal Cancer

Obstructing rectal cancers present a challenging situation and require careful thought and planning to ensure that the patient's oncologic outcome is optimized. In the case of widely metastatic disease that is clearly not resectable, endoluminal stenting is a reasonable consideration provided that the bottom of the stent will lie clearly above the anorectal ring, to avoid causing pain and tenesmus [61, 62]. The tumor should be quite tight to ensure that the stent is held in place.

Alternatively, in patients with partial obstructive symptoms and without evidence of proximal colonic dilatation, administration of chemoradiotherapy will usually relieve the obstructive symptoms if instituted without delay.

In the case of curable disease, several scenarios can present themselves.

In cases requiring fecal diversion where an abdominoperineal resection will ultimately be required, we recommend using a loop colostomy for fecal diversion. At the time of the APR, the distal limb of the stoma can be divided, leaving the colostomy in situ if it is functioning well, or it can be revised to an end colostomy if needed. These patients are not good candidates for endoluminal stenting, because the stent will lie in contact with the anal canal and become symptomatic.

In cases requiring fecal diversion where an eventual reconstructive surgery is anticipated, decision-making can be more complex. In the "near-obstructing" but not clinically obstructed situation, and in situations where significant patient symptoms are a relative indication for fecal diversion, we select the type of stoma based primarily on the degree of stenosis. If the lesion can be passed by a colonoscope or gastroscope and the proximal bowel can be visualized, we would in general select a diverting loop ileostomy, which can be left in situ following the low anterior resection if needed. If the lesion cannot be passed with a colonoscope

or gastroscope, then we would generally construct a diverting loop colostomy. This prevents the possibility of a "closed loop" developing between the tumor and a competent ileocecal valve should the lesion swell and obstruct during neoadjuvant therapy. It also allows us to perform a colonoscopy preoperatively through the stoma to clear the rest of the colon. If fecal diversion is required following the reconstructive procedure, a loop ileostomy can still be brought through the previous left-sided loop colostomy site. A transverse loop colostomy is another option in these situations but is a more difficult stoma to manage for the patient and in general we avoid using them.

In cases presenting with a complete obstruction requiring emergency treatment, endoluminal stenting can be considered to relieve the obstruction and allow for semi-elective treatment of the cancer. The benefits of this approach include a rapid recovery from the procedure, that allows for prompt initiation of neoadjuvant chemoradiation if required, or to proceed on to radical surgery in the less common situation where neoadjuvant therapy is not indicated. The potential downsides of stenting include the risk of perforation and stent migration. The other main treatment option in the case of complete obstruction is a diverting loop colostomy. This strategy also provides relief of the obstruction and will reliably allow the patient to get through their neoadjuvant therapy, in addition to allowing for a preoperative colonoscopy prior to radical excision. The downsides include the fact that these cases do not always lend themselves to a laparoscopic approach (e.g., if there is loss of domain because of the distended colon) and therefore might require a longer period of recovery prior to initiation of neoadjuvant therapy. The open approach can also cause adhesions and make the future radical excision slightly more difficult. Our approach for these situations in general is to consider endoluminal stenting followed by semi-urgent radical excision (tumor-specific mesorectal excision) for the proximal rectal cancers and to use a diverting colostomy for most mid and distal rectal cancers, followed by neoadjuvant therapy, and radical excision.

Perforated Rectal Cancer

We tend to think of perforated rectal cancer in two ways: intraperitoneal perforations and extraperitoneal perforations.

For free intraperitoneal perforations, urgent surgery is generally required. The operation ideally should include an oncologic resection of the primary tumor. The decision on whether to perform a primary anastomosis (with or without and proximal diverting stoma) or a Hartmann procedure depends on several factors, including the overall health of the patient, their perioperative stability, the duration and extent of fecal contamination, and the anticipated intraoperative technical difficulties. Rarely should one simply divert these patients, as they risk having ongoing intraperitoneal tumor dissemination.

For contained intraperitoneal perforations, for example, those presenting with an abscess, we typically arrange percutaneous drainage, ensure that the patient is stable and fully staged, and then typically proceed with radical excision with or without an anastomosis.

For contained extraperitoneal perforations, we typically advocate proximal fecal diversion, drainage of sepsis, neoadjuvant chemoradiation, followed by radical excision, to include all tissues felt to have been contaminated by the perforation. This can require an exenterative procedure and/or an extrafascial dissection.

In the situation where a rectal cancer presents with perianal sepsis and fistulas, we generally ensure that the sepsis is well controlled, strongly consider fecal diversion with a laparoscopic loop sigmoid colostomy, and then arrange for neoadjuvant chemoradiotherapy. This is then followed by an APR with wide pelvic and perineal excision. These patients typically have large perineal wounds, and many benefit from a rectus abdominis myocutaneous flap for perineal reconstruction.

Synchronous Hepatic Metastases

Advancements in liver surgery and systemic chemotherapy have made it possible to consider alternative approaches to traditional primary tumor resection (PTR) in stage IV rectal cancer with synchronous hepatic metastases. These include synchronous resection (SR) and primary liver resection (PLR) [63]. No all-encompassing protocol exists for resectable stage IV rectal cancer as each alternative targets a different subpopulation [64]. SR and PLR should be used selectively and require multidisciplinary discussion with group ownership of the patients and the decisions.

Assuming that the patient is a surgical candidate, there are three overriding questions that need to be answered: is the primary resectable, is the metastatic liver disease resectable, and is there extrahepatic metastatic disease?

Prior to considering liver resection, the primary tumor must be staged and determined to be resectable, either primarily or following neoadjuvant therapy. We involve the hepatobiliary (HPB) surgeon very early to determine if the liver lesions are either resectable, potentially resectable with downstaging, or unresectable. It has been shown that resectability is best judged by an HPB surgeon [65].

Provided both the primary and hepatic metastases are resectable, then the decision is made to perform the rectal and liver resections either sequentially or in low-risk situations synchronously. We would typically consider PTR followed by liver resection for most patients [66]. Synchronous resection is offered to very selected patients to take advantage of a shorter overall recovery time accepting the increased risk of morbidity [67–69]. Generally speaking the magnitude of the two surgeries, the experience of the operating teams, the level of perioperative support and patient comorbidities/operative risk determines whether or not synchronous resections can

Table 32-2. Ideal criteria for liver-first protocol

1. Local regional control does not require downstaging with neoadjuvant therapy
2. Liver metastases are very clearly resectable for cure with adequate residual liver
3. Good overall operative risk patient with normal physiologic status and no known risk factors for perioperative infectious complications and major morbidity
4. Surgery can be performed in a high-volume liver unit with low-operative mortality and acceptable morbidity
5. Delays due to unexpected postoperative complications will not jeopardize local control or cure

and should be performed [70, 71]. For example, a high anterior resection can be combined with a nonanatomic resection in a low-risk patient with expected good results. On the other hand, an extended right hepatectomy and an extended low anterior resection should be done sequentially. The volume of resected liver is an important risk factor for postoperative complications. In a recent retrospective study, patients with postoperative complications averaged 350 g of resected liver tissue vs. patients in the non-complication group who averaged only 150 g [72].

When the rectal lesion is clearly resectable and the liver lesion is borderline or requires an extended resection, a PLR may be the best option [73]. In this situation the liver disease is the major determinant of survival. Because PLR is associated with a considerable increase in morbidity without the application of stringent selection criteria, it should be limited to very specific situations (Table 32-2) as a significant complication following liver resection may delay treatment of the primary [74–76]. Although it is tempting to push these limits, it is important to remember that it is the patient who takes on all the risk.

Patients with liver metastases and locally advanced primaries requiring neoadjuvant therapy are much more complicated. Most liver-first protocols exclude locally advanced rectal cancer patients due to the radiotherapy requirements of neoadjuvant therapy. In addition, the chemotherapy in long-course neoadjuvant therapy is relatively low dose; consequently liver metastases run the risk of growing and becoming unresectable. The presence of a borderline liver lesion further complicates the decision. In this situation, we typically use full-dose chemotherapy to downstage both lesions [77]. If there is a favorable response to several cycles of chemotherapy, then the patient may be treated with neoadjuvant chemoradiotherapy followed by either SR, PTR or PLR as determined by multidisciplinary discussion weighing the risks and benefits of each treatment course [77].

A promising new technique for this situation is the use of short-course radiotherapy to control margins followed by full-dose chemotherapy to allow time for tumor downstaging and systemic treatment for liver metastases. Prospective trials are currently underway to assess the efficacy of this pathway [78].

The presence of extrahepatic disease is generally a contraindication to hepatic resection for cure in stage IV disease. However, in select situations, in a good risk highly motivated patient, we will consider a lung resection following curative resection of the primary and all liver lesions. Surgery should be done sequentially at a reasonable time interval after recovery from the previous resections to ensure that the disease remains localized and the patient is fully optimized.

Conclusion

Nowhere in colorectal surgery are therapeutic decisions more complex or more important to long-term patient outcomes than in the treatment of rectal cancer.

As a young surgeon, decisions are made primarily by imitating our mentors. With experience we find that not all situations fit cleanly into algorithms, and we are forced to make decisions without a complete data set or in situations where there may not be a single correct answer only a best answer given the available information and the specific circumstances.

The treatment of rectal cancer is ever changing as new information is brought forward into practice. The surgeon must keep abreast of new developments, with a fundamental knowledge of all potential treatment options including the risks, benefits and alternatives. In addition to application of this knowledge set, each patient requires a full assessment of the primary lesion, the presence of metastatic disease, the patients' operative risk, and goals of care.

While skills and knowledge are important for optimal patient care, it is often a surgical decision that ultimately determines patient outcomes. Much like surgical skills, decision-making requires practice with continuous analysis and reflection for improvement to ensure the right care, at the right time as safely as possible for each patient.

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33
Colorectal Cancer: Postoperative Adjuvant Therapy

Stephen M. Sentovich and Marwan Fakih

Key Concepts

- Patients with stage III colon cancer should be considered for adjuvant chemotherapy.
- Oxaliplatin-based adjuvant chemotherapy regimens improve survival of stage III colon cancer patients by an absolute 20–25 % at 5 years versus no chemotherapy.
- Adjuvant chemotherapy has not been demonstrated to have significant impact on survival for stage II colon cancer patients, but it can be considered for patients whose tumors have high-risk features.
- In colon cancer patients, radiotherapy should be considered when tumors penetrate other fixed structures (T4) and can be guided by placing surgical clips at the time of operation.
- Patients with clinical stage II and III rectal cancers who undergo neoadjuvant chemoradiotherapy should be considered for postoperative adjuvant chemotherapy, regardless of the final pathologic staging, although the efficacy of adjuvant chemotherapy in this setting has not been firmly established.

While surgery remains the primary treatment for patients with colon and rectal cancer, adjuvant treatment with chemotherapy and radiotherapy plays an increasingly important role. For patients with stage III colon cancer, adjuvant chemotherapy has been recommended since 1990 [1]. More recently the National Quality Forum has endorsed metrics related to the administration of chemotherapy in stage III colon cancer patients in order to ensure that patients with stage III colon cancer not only are considered for chemotherapy but are given chemotherapy in a timely fashion [2]. For patients with stage I colon cancer, surgery alone is highly successful, and thus no adjuvant therapy is currently recommended. On the other hand, patients with stage II colon cancer may benefit from adjuvant treatment, although this is controversial and remains the focus of clinical trials. Finally, stage IV colon cancer patients are usually primarily treated with chemotherapy—this is the subject of a later chapter (see Chap. 36).

For patients with rectal cancer, adjuvant treatment has been recommended for both stage II and stage III disease. This treatment involves both chemotherapy and radiotherapy and usually begins preoperatively (see Chap. 28). After surgery, clinical stage II and stage III rectal cancer patients are recommend to undergo adjuvant postoperative chemotherapy regardless of the final surgical pathology. As with stage I colon cancer, surgery alone is highly successful for patients with stage I rectal cancer. This chapter will present the current recommendations regarding the use of postoperative adjuvant therapy for stage II and stage III colon and rectal cancer.

Colon Cancer

Stage III Colon Cancer

Adjuvant chemotherapy is recommended for all stage III colon cancer patients because it decreases recurrence and increases survival when compared to surgery alone [3, 4]. After surgery alone for stage III colon cancer, overall 5-year survival is 40–60 % [5]. Current chemotherapeutic regimens improve overall survival to 70–80 % [6]. Thus, 5-year overall survival of stage III colon cancer patients improves by an absolute 20–25 % with adjuvant chemotherapy. Table 33-1 summarizes the results of key clinical trials establishing the efficacy of adjuvant chemotherapy for nonmetastatic colon cancer [4, 6–11]. If all patients with stage III colon cancer receive adjuvant chemotherapy, roughly 1/3 to 1/2 of disease recurrences would be prevented.

Given the significant survival benefit of adjuvant chemotherapy, colon and rectal surgeons need to ensure that their stage III colon cancer patients are evaluated for chemotherapy after surgery. The National Quality Forum has endorsed two metrics regarding the treatment of stage III colon cancer patients [2]. The first metric estimates how many stage III patients are referred or treated with chemotherapy whereas the second metric looks at the timeliness of the administration

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Table 33-1. Key clinical trials establishing the efficacy of adjuvant chemotherapy for colon cancer

Trial	Tumor stage	Comparison	Results	Conclusion
INT 0035 1990	Stage III	Surgery alone vs. 5-FU/levamisole	3 Years survival 5-FU/levamisole 71 % Surgery alone 55 %	Postop adjuvant chemo improves survival for stage III colon cancer
IMPACT 1995	Stage III	Surgery alone vs. 5-FU/leucovorin	3 Years survival 5-FU/leucovorin 71 % Surgery alone 62 %	Postop adjuvant chemo improves survival for stage III colon cancer
QUASAR 2000	Stage III	5-FU/levamisole vs. 5-FU/folinic acid vs. 5-FU/placebo	Decreased survival and increased recurrence with levamisole compared with placebo	Postop adjuvant chemo with levamisole inferior to placebo
IMPACT 1999	Stage II	Surgery alone vs. 5-FU/leucovorin	5 Years survival = no difference 5-FU/leucovorin 82 % Surgery alone 80 %	Postop adjuvant chemo does not improve survival for stage II colon cancer
NSABP (CO-1, CO-2, CO-3, and CO-4) 1999	Stage II	Surgery alone vs. 5-FU +	5-Year survival improved with adjuvant treatment 30 % Mortality reduction with adjuvant treatment	Postop adjuvant chemo improves survival for stage II colon cancer
MOSAIC 2009	Stage II and III	FOLFOX vs. 5-FU/leucovorin	6-Year survival in stage III only FOLFOX 73 % 5-FU/Leucovorin 68 %	FOLFOX superior to 5-FU/LV for stage III colon cancer
XELOXA 2011	Stage III	XELOX vs. 5-FU/leucovorin	3 Year disease-free survival: XELOX 71 % 5-FU/Leucovorin 67 %	Capecitabine plus oxaliplatin superior to 5-FU/leucovorin

of chemotherapy. Specifically, the first metric (measure 0385) determines the percentage of patients ≥18 years old who are either referred for adjuvant chemotherapy, prescribed adjuvant chemotherapy, or have previously received adjuvant chemotherapy in the last 12 months. The other metric (measure 0223) determines the percentage of patients under the age of 80 for whom adjuvant chemotherapy is considered or administered within 4 months of the *diagnosis*. Thus, it is important for colon and rectal surgeons to promptly refer all stage III colon cancer patients for adjuvant chemotherapy.

For patients with stage III colon cancer, the National Comprehensive Cancer Network (NCCN) guidelines recommend adjuvant treatment with FOLFOX or CapeOx for 6 months [12]. FOLFOX has been found to be superior to 5-FU/leucovorin [6, 13], and CapeOx is superior to bolus 5-FU/leucovorin [14, 15]. While used frequently in patients with metastatic disease, biologic therapy with antibodies directed at VEGF-A (bevacizumab) and EGFR antibody (panitumumab, cetuximab) is not recommended for adjuvant therapy of stage III disease [16–19]. The current FOLFOX regimen, mFOLFOX6, and the CapeOx regimen are outlined in Table 33-2. These agents act in different ways on colon cancer cells. 5-Fluorouracil is a pyrimidine analog that incorporates into DNA to stop DNA synthesis. Capecitabine is an oral 5-FU prolog and thus works in the same way as 5-FU. Folinic acid (leucovorin) is a vitamin B derivative that increases the cytotoxicity of 5-FU. Oxaliplatin inhibits DNA synthesis by forming inter- and intra-strand cross-links in DNA preventing replication and transcription. Using FOLFOX, the survival benefit of adding oxaliplatin to 5-FU does come at a price, the added side effect of peripheral sensory neuropathy (PSN). While 40–50 % of patients given oxaliplatin will develop PSN, only 10–20 % of patients will have grade 3 PSN which is defined as severe symptoms limiting activities of daily living [20]. Fortunately only 1 % of patients will have grade 3 PSN at 12 months after treatment [6]. Since the benefit of the addition of oxaliplatin to 5-FU/leucovorin is unproven in patients over the age of 70, capecitabine alone or 5-FU/leucovorin should be considered in elderly patients with stage III colon cancer [12]. Capecitabine-based regimens can be particularly complicated by palmar-plantar erythrodyskinesia (hand-foot syndrome), but this side effect can be limited by symptomatic treatment and resolves after treatment is concluded [21].

Stage II Colon Cancer

The 5-year overall survival of patients with stage II colon cancer is 65–85 % with surgery alone [22]. Unlike stage III disease, the role of adjuvant chemotherapy in stage II disease remains controversial, with some studies showing a benefit [10] and others showing no benefit [23]. If there is a benefit to adjuvant chemotherapy in stage II colon cancer patients, the benefit does not improve survival by more than 5 % unlike the 25–30 % improvement for stage III patients receiving adjuvant chemotherapy [12].

Following surgery for stage II colon cancer, the current NCCN guidelines (February 2015) recommend observation (surgery alone), enrollment in a clinical trial or adjuvant chemotherapy [12]. To sort out these options, a detailed discussion with the patient is recommended to highlight the potential benefits and risks of chemotherapy. Any high-risk features should be identified and discussed (Table 33-3). Patients with or without high-risk features should consider observation,

Table 33-2. Current recommended adjuvant chemotherapy regimens for stage III colon cancer

Regimen	Agents and dosage	Frequency
mFOLFOX6	Oxaliplatin 85 mg/m^2 IV over 2 h, day 1	Every 2 weeks
	Leucovorin 400 mg/m^2 IV over 2 h, day 1	
	5-FU 400 mg/m^2 IV bolus on day 1, then 1200 mg/m^2/day × 2 days IV continuous infusion	
CapeOx	Oxaliplatin 130 mg/m^2 IV over 2 h, day 1	Every 3 weeks
	Capecitabine 850–1000 mg/m^2 PO twice daily for 14 days	

Table 33-3. High-risk factors for recurrence

- Poorly differentiated histology (exclusive of those that are MSI-H)
- Lymphatic/vascular invasion
- Perineural invasion
- Close, indeterminate, or positive margins
- Bowel obstruction
- Localized perforation
- Less than 12 lymph nodes examined

clinical trial or chemotherapy with capecitabine or 5-FU/leucovorin. Only those patients with high-risk features should be considered candidates for FOLFOX or CapeOx. It is important to remember that the addition of oxaliplatin has not been shown to improve survival in stage II colon cancer patients [6]. Finally, decision-making regarding the use of adjuvant chemotherapy for stage II disease may be aided by performing genetic testing of the tumor after surgical resection.

Genetic testing of stage II tumors has been shown to be independently predictive of prognosis. High microsatellite instability (MSI-H) or defective mismatch repair (dMMR) status has been shown to be associated with a lower recurrence rate (11 % vs. 26 %) after surgical resection alone [24]. In addition, MSI-H tumors do not benefit from 5-FU adjuvant therapy [24]. Thus, MSI/MMR testing is recommended in all patients with stage II disease in order to avoid giving adjuvant chemotherapy in patients who will derive no benefit from it. In addition to MSI/MMR testing, multigene colon cancer assays such as Oncotype Dx, ColoPrint, and ColDx are now available that can also predict prognosis and risk of recurrence. All three of these multigene assays predict recurrence independent from other factors such as TNM stage, MMR status, tumor grade, and nodes [25–31]. While these assays provide additional information regarding prognosis and recurrence risk, they are not predictive of the potential benefit of chemotherapy, and consequently are, to date, of limited clinical value.

Radiotherapy for Colon Cancer

Radiotherapy plays a limited role in patients with colon cancer. A few retrospective, single institution studies have shown that adjuvant radiotherapy improves local control for colon cancer patients at high risk of recurrence after surgery [32–34]. Unfortunately, the single randomized prospective trial comparing chemotherapy alone with combined chemotherapy and radiotherapy lacks sufficient power to draw valid conclusions [35]. Current NCCN guidelines recommend that radiotherapy for colon cancer be considered in patients with T4 tumors with penetration to a fixed structure [12]. The radiation field should include the tumor bed as defined by preoperative imaging and the placement of surgical clips at the time of operation. A dose of 45–50 Gy in 25–28 fractions is recommended and should be delivered with concomitant 5-FU chemotherapy [12]. Thus, the colorectal surgeon should always be ready to place clips in and around the tumor bed during operations involving the resection of a fixed T4 colon tumor in order to help direct postoperative radiotherapy. Neoadjuvant chemoradiotherapy can be considered for select patients with bulky tumors invading other structures.

Rectal Cancer

Treatment of patients suffering from rectal cancer is far more complex than treatment of patients with colon cancer, due to the multitude of therapeutic options and timing of those therapies. In addition, pretreatment staging is not always accurate, and this imprecision must be taken into account when planning treatment. Initial staging, neoadjuvant therapy, and surgical treatment are covered in other chapters, and thus we will focus on postoperative therapy.

Decisions regarding postoperative adjuvant treatment for rectal cancer are based primarily on tumor location, clinical stage, histologic stage, and history of neoadjuvant therapy. Proximal rectal/rectosigmoid tumors are located at least 12 cm proximal to the anal verge and are above the peritoneal reflection. Although somewhat controversial, non-advanced proximal rectal/rectosigmoid tumors are treated in the same fashion as tumors elsewhere in the colon, with surgical resection followed by postoperative chemotherapy for stage III and select stage II tumors. Tumors of the middle/lower rectum are located from 0 to 12 cm from the anal verge as measured by rigid proctoscopy [36]. They typically have a worse prognosis, stage for stage, when compared to more proximal tumors and thus treatment recommendations are slightly different.

Patients Who Did not Undergo Neoadjuvant Therapy

Like stage I colon cancer, 5-year survival after surgery alone for stage I rectal cancer exceeds 90 % [37]. Thus, no adjuvant treatment is recommended for patients undergoing proctectomy alone who are found to have T1-2N0M0 disease, assuming that margins of resection are negative for tumor. For those found to have stage II or III disease after proctectomy, decision-making

is more complex. Postoperative chemotherapy is indicated for patients with stage III disease, but the benefit for stage II disease is less certain. Postoperative radiotherapy should be considered for patients with stage II and III disease, but this recommendation is primarily based on data from the past, when there was little emphasis on surgical quality or assessment of circumferential radial margins. Postoperative radiotherapy is also associated with substantial long-term toxicity, most notable in patients undergoing restorative proctectomy. The recommendation for routine postoperative radiotherapy for patients with T3N0 disease with negative circumferential margins has thus been questioned, including in the most recent iteration of the ASCRS Practice Parameters for the Management of Rectal Cancer [38]. Even for patients with N+ disease, it is unclear whether the small benefit of postoperative radiotherapy in terms of local control is worth the risk of toxicity, which can be substantial.

If patients are to be treated with postoperative chemoradiotherapy, it is usually administered using a sandwich technique. This involves giving chemotherapy (FOLFOX or CapeOx) followed by chemoradiotherapy (Capecitabine + radiation or infusional 5FU + radiation) followed by more chemotherapy (FOLFOX or CapeOx). The radiotherapy dose is usually 45–50 Gy in 25–28 fractions using 3 or 4 fields. External iliac nodes should be included for T4 tumors involving anterior structures, and inclusion of the inguinal nodes should be considered for tumors invading the distal anal canal. In stage II and III rectal cancer patients, postoperative chemotherapy should be administered as soon as the patient has recovered from surgery as each 4 week delay in chemotherapy results in a 14 % decrease in overall survival [39].

Patients Who Underwent Neoadjuvant Radiotherapy/Chemoradiotherapy

After neoadjuvant radiotherapy/chemoradiotherapy, decisions regarding postoperative chemotherapy are more complex. Although a recent Cochrane review concluded that postoperative adjuvant chemotherapy after resection of rectal cancer was associated with improved survival regardless of stage [40], the data come from trials as old as 1975. Thus, it is difficult to draw any firm conclusions from this meta-analysis, given that some data are derived from trials in which patients were not given neoadjuvant therapy, nor was there surgical quality control or measurement of circumferential margins. Overall, there is a paucity of data on which to rely when making decisions regarding postoperative chemotherapy for patients with rectal cancer because neoadjuvant therapy regimens, surgical quality control, and pathologic processing have evolved so rapidly in the past 30 years. This evolution is ongoing, with different neoadjuvant regimens currently under investigation.

Traditionally, patients with ypT3 or ypN+ disease have been recommended to undergo postoperative chemotherapy [36]. However, a recent meta-analysis of published data found that adjuvant fluorouracil-based chemotherapy did not improve overall survival, disease-free survival, or distant recurrences, calling these recommendations into question [41]. If chemotherapy is utilized, it is also controversial as to which regimen to utilize. Two randomized clinical trials have reported a disease-free survival advantage to FOLFOX vs. fluoropyrimidine monotherapy in patients previously treated with neoadjuvant chemoradiotherapy followed by rectal surgery [42–44]. A summary of several key clinical trials regarding chemoradiotherapy for rectal cancer is shown in Table 33-4 [40, 42–44, 48–52].

Clinicians should be aware that current NCCN guidelines for clinical stage II and III rectal cancer recommend either (1) preoperative chemoradiotherapy, surgery then postoperative chemotherapy or (2) preoperative chemotherapy followed by preoperative chemoradiotherapy then surgery (see Table 33-5) [36, 45, 46]. The total duration of perioperative therapy (preoperative chemoradiotherapy and chemotherapy) should not exceed 6 months [36]. However, as noted above, these recommendations are based on incomplete and sometimes conflicting data.

Patients Undergoing Local Excision

Due to the oncologically inferior results of local excision as compared to proctectomy, even in highly select patients, many authors have recommended treatment with adjuvant chemoradiotherapy, either in the preoperative or postoperative period. The advantage of utilizing chemoradiotherapy in the postoperative period is that T stage can be known with certainty, and one can ensure healing of the wound prior to institution of radiotherapy. The advantage of utilizing neoadjuvant chemoradiotherapy is that ypT stage correlates more closely with ypN stage than T stage correlates with N stage [53] and there may be downsizing of the tumor prior to excision. The major downside of neoadjuvant therapy combined with local excision is that wound healing may be impaired, and patients may suffer substantial morbidity as a result.

For patients treated with neoadjuvant chemoradiotherapy followed by local excision, standard radiotherapy of 50.4 Gy over 28 fractions is typically given with either 5-FU or capecitabine chemotherapy. For clinical stage T2 tumors these standard neoadjuvant regimens result in complete pathologic response rates as high as 40–60 % [54, 55]. While overall 5-year survival data are insufficient, the current data suggests that there is a 90 % 5-year survival after a complete pathologic response but only a 75 % 5-year survival if there is residual disease (ypT1 or ypT2) [55]. Thus, in select stage I patients and patients with significant comorbidities that preclude an abdominal procedure, a non-standard approach using neoadjuvant treatment with or without subsequent transanal excision may be considered (see Chap. 28).

Table 33-4. Key clinical trials establishing the efficacy of chemoradiotherapy for rectal cancer

Trial	Tumor stage	Comparison	Results	Conclusion
Swedish rectal cancer trial 1993	Stage II and III	Surgery alone vs. preop short course XRT	Local recurrence: 27 % vs. 12 %	Preop XRT decreases local recurrence, improves survival (?)
			5 Years survival: 48 % vs. 58 %	
Dutch TME rectal cancer trial 2001	Stage II and III	TME alone vs. preop XRT + TME	Local recurrence: 11.4 % vs. 5.6 %	Preop XRT improves local recurrence even with TME
			Survival: no difference	Preop XRT no effect on survival
German CAO/ARO/AIO-94 2003/2004	Stage II and III	Preop chemo XRT vs. postop chemo XRT	Local recurrence: 13 % vs. 6 %	Decreased toxicity and local recurrence with preop chemo XRT
			Toxicity: 40 % vs. 27 %	Pre vs. post: no effect on survival
			Survival: no difference	
EORTC 22921 2006	Stage II and III	XRT vs. chemo XRT	Survival benefit for ypT0-2 responders	Chemo in addition to XRT can improve survival in the subgroup of responders
Cochran review: postop chemo 2012	Stage II and III	No postop chemo vs. postop chemo after neoadjuvant	Recurrence reduced 25 %	Postop chemo reduces recurrence and death rate after neoadjuvant
			Deaths reduced 17 %	
ADORE 2014	Stage II and III	FOLFOX vs. 5-FU/leucovorin after neoadjuvant	3 Year disease-free survival: 72 % vs. 62 %	Postop FOLFOX superior to 5-FU after neoadjuvant
German CAO/ARO/AIO-04 2012/2014	Stage II and III	Neoadjuvant and adjuvant FOLFOX vs. 5-FU/leucovorin	Complete pathologic response: 17 % vs. 13 %	Preop and postop addition of oxaliplatin improves survival and pathologic response
			3 Years survival: 76 % vs. 71 %	

XRT Radiation therapy, *TME* Total mesorectal excision, *preop* Preoperative, *postop* Postoperative, *chemoxrt* Combined chemoradiation therapy

Table 33-5. Neoadjuvant and adjuvant treatment of stage II and III rectal cancer

Option I	Capecitabine + Radiotherapy OR Infusional 5-FU + Radiotherapy	→	Surgery	→	FOLFOX OR Capecitabine + Oxalplatin	
Option II	FOLFOX OR Capecitabine + Oxaliplatin	→	Capecitabine + Radiotherapy OR Infusional 5-FU + Radiotherapy	→	Surgery	

Future of Adjuvant Treatment of Colorectal Cancer

While significant progress has been made in defining optimal cytotoxic regimens in the adjuvant treatment of colorectal cancer, several questions remain regarding the optimal duration of chemotherapy treatment, the role of radiotherapy in rectal cancer, the possibility of nonsurgical interventions for rectal cancer, and the emerging role of immunotherapy.

Clinical Trials in Stage II–III Colon Cancer

Prior studies have shown no benefit from extending adjuvant therapy beyond 6 months in patients with stage III colon cancer [56]. However, a shorter duration of chemotherapy has not been adequately investigated. CALGB 80702 is currently investigating 6 cycles (3 months) vs. 12 cycles (6 months) of FOLFOX chemotherapy in patients with resected

stage III colon cancer (NCT01150045). This will be one of 6 ongoing clinical trials evaluating 3 vs. 6 months of adjuvant oxaliplatin-based chemotherapy. A meta-analysis of these studies (IDEA) will test the non-inferiority of 3 months to a 6 months strategy. In addition to the investigation of the duration of adjuvant treatment in colon cancer, efforts are ongoing to define the role of COX inhibition on disease recurrence. Analysis of the Nurses' Health Study (NHS) and Health Professional Follow-up Study (HPFS) has shown a decreased recurrence rate in patients with a diagnosis of colon cancer with regular aspirin intake [57]. The benefit appeared to be limited to patient with COX-2 overexpressing tumors [58]. These analyses were limited by their retrospective nature and require further support from prospectively conducted trials. CALGB 80702 randomizes all enrolled subjects to celecoxib vs. placebo in order to investigate the role of COX-2 inhibition in the adjuvant treatment of colon cancer. Similarly, the ASCOLT clinical trial (NCT00565708) is randomizing patients with stage II or III disease to 3 years of aspirin vs. placebo to address the role of aspirin in preventing colorectal cancer recurrence. Finally, several studies are investigating immunotherapy as an adjuvant form of treatment in colon cancer. An ongoing phase III clinical trial is evaluating the role of cytokine-induced killer cell immunotherapy for stage III colon cancer following surgery and completion of adjuvant therapy (NCT02280278).

Clinical Trials in Stage II–III Rectal Cancer (Table 33-5)

Recent phase II and retrospective trials have investigated the role of FOLFOX as a neoadjuvant treatment for rectal cancer. These series have been associated with a remarkable complete pathological response rates and were associated with a low risk of local recurrence, questioning the role of adjuvant or neoadjuvant therapy in the era of effective combination therapy [59]. To test this question, the Alliance PROSPECT clinical trial (NCT01515787) is currently randomizing patients to neoadjuvant FOLFOX chemotherapy with selective use of chemoradiotherapy (in poor responders) vs. the standard approach of neoadjuvant chemoradiotherapy. Other studies are sequencing intense chemotherapeutic regimens followed by chemoradiotherapy in order to improve on DFS and OS. The NEOFIRINOX trial (NCT01804790) is randomizing patients with rectal cancer to intensive chemotherapy with irinotecan, oxaliplatin, and 5-FU (FOLFIRINOX) followed by chemoradiotherapy, surgery, and further adjuvant chemotherapy (capecitabine or FOLFOX) vs. a control arm of chemoradiotherapy followed by surgery and adjuvant chemotherapy (capecitabine or FOLFOX).

In order to maximize systemic therapy exposure, clinical trials are evaluating the administration of the all systemic chemotherapy prior to surgical resection. For example, the RAPIDO clinical trial (NCT01558921) is randomizing rectal cancer patients to 5×5 Gy of radiotherapy followed by 6 cycles of CAPOX and then surgery vs. standard chemoradiotherapy and further adjuvant therapy (at the treating physician's discretion). Finally, several studies are investigating nonsurgical approaches to patients with rectal cancer who have a complete clinical response to chemoradiotherapy. The Cancer Institute of San Paulo is leading a randomized clinical trial (NCT02052921) that randomizes rectal cancer patients with complete clinical response following neoadjuvant chemoradiotherapy to observation vs. surgical resection with a primary end point of 3 year DFS.

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34
Colorectal Cancer: Surveillance After Curative-Intent Therapy

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Key Concepts

- Liver metastases and locoregional recurrence are more likely to be amenable to curative-intent salvage resection when detected in asymptomatic patients. Therefore, active surveillance is indicated for patients who are candidates for liver and/or intestinal resection.
- Use of carcinoembryonic antigen testing and computed tomography (CT) scans is associated with increased detection of asymptomatic recurrence after curative resection for colorectal cancer. There is no evidence to support the use of any other laboratory testing or positron emission tomography (PET) scans in routine surveillance.
- Patients with advanced age and comorbidity, who would not be fit to undergo therapy for recurrence, should not be subjected to active surveillance. They should, however, receive evaluation and treatment for symptoms suggestive of recurrence.
- Patients with resected rectal cancers are at greater risk for locoregional recurrence. This risk is increased by omission of chemoradiotherapy for locally advanced tumors, close or positive margins, T4 and N2 histology. Consideration should therefore be given to local pelvic surveillance both endoluminally and extraluminally in these patients at highest risk.
- Surveillance after resection of Stage I colorectal cancer remains controversial. While the recurrence rates are low, in general, there are markers of relatively greater risk, including margin positivity, unknown lymph node status (e.g., local excision), inadequate lymph node sampling, lymphovascular invasion, poorly differentiated histology, and/or T2 disease. Active surveillance may be considered for patients with one or more of these risk factors.

Introduction

With improvements in screening, diagnosis, surgical technique, and adjuvant therapy for colon and rectal cancers, nearly two-thirds of patients who undergo surgical resection survive 5 years or more [1]. As a result, there is a rapidly growing population of colorectal cancer survivors, exceeding 1.2 million in the United States alone [2]. These individuals face varying risk for subsequent colorectal cancer throughout their lifetime, yet there is little consensus on optimal regimens for surveillance and survivorship care [3, 4].

The primary goal of colorectal cancer surveillance is to detect treatable recurrent, metastatic or metachronous colorectal malignancy and optimize the opportunities for potentially curative intervention. Thus, surveillance strategies must include not only evaluation for local recurrence and distant metastasis from the treated cancer, but also the increased personal risk for subsequent primary colorectal cancers. For patients with suspected or known genetic colorectal cancer syndromes, these strategies must also take into account the risk of other associated cancers, and the screening needs of potentially affected family members [5]. Ultimately, the success of colorectal cancer surveillance may be measured by improvements in overall survival, cancer-specific survival, disability or quality of life. Some studies have evaluated proxy measures, such as the rate of curative-intent metastasectomy or resection of colorectal neoplasia, but it is not clear to what degree these additional interventions benefit colorectal cancer survivors more broadly.

In order to demonstrate benefits from active surveillance, there must be evidence of improved detection of recurrence in patients amenable to curative-intent salvage therapy that itself is efficacious in improving outcome after recurrence. It has proven challenging to support with real data each of the steps in this chain of logic [6]. In addition, interpretation and synthesis of

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findings of published studies are complicated by the heterogeneity of the interventions and comparisons—the surveillance intervention in one trial may be no more intensive than the control group regimen of another—and the challenges of obtaining adequate power to detect meaningful differences in survival and other objective oncologic outcomes in such studies.

It is also important to consider the appropriateness of surveillance for patients who might not be eligible for, or willing to undergo, treatment for recurrence. Recognizing that older adults account for the majority of colorectal cancer patients [7], patient preferences, age, comorbidities, and functional status must all contribute to the decision to pursue active surveillance. There is little need, for example, to conduct surveillance for asymptomatic liver metastases for a patient unwilling or unable to undergo hepatic resection and/or chemotherapy. For such patients, symptom-driven evaluations may suffice.

At the same time, the landscape around both the detection and treatment of recurrence continues to evolve. Compared with two decades ago, when some of the first randomized trials of intensive surveillance were conducted, the sensitivity of radiographic surveillance has increased severalfold, allowing detection of earlier metastatic disease in the liver and lungs. The advent of pelvic and liver MRI, endorectal ultrasound, and PET scanning offers new modalities for the detection of recurrent disease. Meanwhile, second- and third-line chemotherapeutic regimens, and ablative techniques for liver and lung metastases, have increased the options for both curative-intent and palliative-intent therapy for recurrent disease. More than a third of patients with recurrence undergo salvage resection, with median survival among these highly selected patients in excess of 3–5 years [8–11].

Timing and Choice of Surveillance Modalities

Intensity of Surveillance

There are various clinical, laboratory, radiographic, and endoscopic methods available for surveillance after treatment of colorectal cancer. Recommendations regarding their application and frequency of use vary between agencies involved in scripting guidelines for colorectal cancer care, and are summarized in Table 34-1. Most guidelines include more intensive early surveillance, with diminishing frequency after 2–5 years, due to the recognition that 80% of recurrences are detected within 3 years after initial curative-intent surgical therapy, and at least 95% are evident within 5 years [10, 12–14]. After 3 years without evidence of disease, cancer-specific mortality declines significantly and conditional survival thereafter is very high [15].

There have been eight prospective randomized trials addressing outcomes of surveillance after curative resection [16–23]. Overall, there is a lack of high-level evidence to support specific choices among surveillance regimens [24], but their interpretation is complicated by the heterogeneity of surveillance regimens, changes in diagnostic and therapeutic technologies available at the times they were conducted, and limitations of sample size and duration of follow-up [25].

Older trials, without intensive radiographic surveillance, have tended to show less benefit. For example, Ohlsson et al. [16] randomized 107 patients from 1983 to 1986 to either no follow-up or a surveillance regimen including CEA, colonoscopy, and chest X-rays, and found no meaningful differences in survival or recurrence patterns. Makela et al. [17] randomized 54 patients from 1988 to 1990 to yearly barium enema versus endoscopic surveillance plus liver ultrasonography and annual CT, with both groups receiving CEA testing and chest X-rays. In the intervention group, recurrences were found earlier (median 10 vs. 15 months, $p=0.002$), but patients were not significantly more likely to undergo salvage resection (19% vs. 14%, $p=0.67$) and 5-year overall survival was not significantly different (54% vs. 59%, $p=0.50$). In study of nearly 600 patients from 1983 to 1994, Kjeldsen et al. [18] applied the same modalities (clinical examination, colonoscopy, chest X-ray, hemoglobin, sedimentation rate, and liver enzymes) to the treatment and control arms, but varied the frequency of exams (every 6 months versus every 5 years). Recurrences in the every 6 months group were more likely to be asymptomatic (50% vs. 16%, $p=0.02$), and were subjected to more salvage resections (22% vs. 7%, $p=0.15$), but there was no difference in overall survival (70% vs. 68%, $p=0.48$) or cancer-specific survival (79% vs. 79%, $p=0.9$) between groups. And Schoemaker [19] et al. randomized 325 patients to clinical evaluation only versus additional chest X-ray, liver CT, and colonoscopy annually, and found only three resectable, asymptomatic recurrences (one each in the colon, liver and lung), without significant improvement in 5-year survival ($p=0.20$).

In contrast, more recent trials, incorporating more frequent endoscopy and modern imaging techniques, have been more likely to demonstrate benefit. In a study of 259 patients between 1997 and 2001, Rodriguez-Moranta et al. [20] compared routine clinical examination, colonoscopy, and CEA alone versus intensive surveillance with the addition of semi-annual abdominal CT or ultrasound, annual chest X-ray, and annual colonoscopy. They found improved survival for patients with Stage II cancers and rectal lesions, primarily due to the detection of resectable metachronous and locally-recurrent tumors. Pietra et al. [21] compared a regimen of annual CEA, ultrasound, chest X-ray, and colonoscopy against more frequent CEA and ultrasound, annual chest X-ray and colonoscopy, and the addition of annual abdominal CT. They found no difference in recurrence rates, but a significantly higher rate of salvage resection in the intensive surveillance group (65% vs. 10%, $p<0.01$), which translated into improved survival at 5 years (73% vs. 58%, $p=0.02$), particularly among those with recurrence (38% vs. 0%, $p<0.01$). Secco et al. [22] stratified patients into high and low risk of recurrence (based on primary tumor location, T stage, differentiation histology, and preoperative CEA level) then randomized to minimal surveillance versus active surveillance, with frequency of abdominopelvic ultrasound,

Table 34-1. Summary of surveillance guidelines

Modality	American Society of Colon and Rectal Surgeons [37]	National Comprehensive Cancer Network [48, 49]	American Cancer Society, US Multisociety Task Force on Colorectal Cancer [70]	American Society of Clinical Oncology [55]	Cancer Care Ontario [51]	European Society of Medical Oncology [52, 79]	British Society of Gastroenterology, Association of Coloproctology for Great Britain and Ireland [72, 73]
History and physical exam	Every 3–6 months for 2 years, then every 6 months to 5 years	Every 3–6 months for 2 years, then every 6 months to 5 years	Not addressed	Every 3–6 months for 5 years	Every 6 months for 5 years	Every 3–6 months for 3 years, then every 6 months to 5 years	Not addressed
CEA	Every 3–6 months for 2 years, then every 6 months to 5 years	Every 3–6 months for 2 years, then every 6 months to 5 years	Not addressed	Every 3–6 months for 5 years	Every 6 months for 5 years	Every 3–6 months for 3 years, then every 6 months to 5 years	"Role of CEA is uncertain"
Other laboratory testing	Not recommended	Not recommended	Not addressed	Not recommended	Not recommended	Not recommended	Not recommended
Abdominal Imaging	CT scan annually for 5 years. Consider more frequent for highest risk[a]	CT scan annually for 5 years	Not addressed	CT scan annually for 3 years. Consider 6–12 months for high risk	CT scan annually for 3 years. US every 6–12 months may be substituted	CT scan or contrast-enhanced ultrasound every 6–12 months for 3 years for patients at higher risk of recurrence	"Reasonable to offer" CT of the liver within 2 years of resection
Pelvic imaging	CT scan annually for 5 years. Consider more frequent for highest risk[a]	CT scan annually for 5 years	Not addressed	CT scans every 6–12 months for 2–3 years, then annually up to 5 years	CT scan annually for 3 years for rectal cancers only	Not specifically recommended	Not specifically recommended
Chest imaging	CT scan annually for 5 years. Consider more frequent for highest risk[a]	CT scan annually for 5 years	Not addressed	CT scan annually for 3 years. Consider 6–12 months for high risk	CT scan annually for 3 years. CXR every 6–12 months may be substituted	CT scan every 6–12 months for 3 years for patients at higher risk of recurrence	Not specifically recommended
PET scan	Not recommended for routine surveillance	Not recommended for routine surveillance	Not addressed	Not recommended for routine surveillance	Not recommended for routine surveillance	Not recommended for routine surveillance	Not recommended
Colonoscopy	1 Year after resection (or within 6 months if previously incomplete). If normal, repeat in 3 years. If adenomas, repeat in 1 year. Annual colonoscopy for patients with suspected familial syndromes who have not undergone proctocolectomy	1 Year after resection (or within 6 months if previously incomplete). If normal, repeat in 3 years, then 5 years. If advanced adenoma, repeat in 1 year. Annual colonoscopy for patients with suspected familial syndromes who have not undergone proctocolectomy	1 Year after resection (or 1 year after colonoscopy that cleared synchronous disease before primary treatment). If normal, repeat in 3 years, then 5 years. More frequent if high-risk adenoma (s) or suspicion for Lynch syndrome	1 Year after resection, or upon completion of adjuvant therapy if previously incomplete. If normal, repeat in 5 years. Otherwise, according to endoscopic findings	1 Year after resection (or within 6 months if previously incomplete). If normal, repeat in 5 years	1 Year after resection, then every 3–5 years thereafter	Every 5 years after resection, until benefits outweighed by comorbidity

(continued)

TABLE 34-1. (continued)

Modality	American Society of Colon and Rectal Surgeons [37]	National Comprehensive Cancer Network [48, 49]	American Cancer Society, US Multisociety Task Force on Colorectal Cancer [70]	American Society of Clinical Oncology [55]	Cancer Care Ontario [51]	European Society of Medical Oncology [52, 79]	British Society of Gastroenterology, Association of Coloproctology for Great Britain and Ireland [72, 73]
Stage-specific recommendations	Stage 1: high risk only[b] Stage 2: all Stage 3: all Stage 4: when metastases are resected for cure	Stage 1: colonoscopic surveillance only Stage 2: all Stage 3: all Stage 4: when metastases are resected for cure, CT scan every 3–6 months for 2 years, then every 6–12 months to 5 years	Not addressed	Recommendations apply to Stage II and III disease only. Insufficient data to make recommendations for Stage I	Recommendations apply to Stage II and III disease only	Not addressed	Not addressed
Rectal surveillance	Proctoscopy every 6–12 months for patients with anastomosis, every 6 months after local excision, for 3–5 years. Endorectal ultrasound for high risk[c]	No additional testing specifically recommended	Proctoscopy, flexible sigmoidoscopy or endorectal ultrasound every 3–6 months for patients with anastomosis	Proctosigmoidoscopy every 6 months for 2–5 years for patients who did not receive radiotherapy, those with T4 or N2 tumors. Pelvic imaging for rectal tumors only	Proctosigmoidoscopy every 6 months for 2–5 years for patients who did not receive radiotherapy. Pelvic imaging for rectal tumors only	No additional testing specifically recommended	Not addressed

CEA Carcinoembryonic antigen, *CT* Computed tomography, *PET* Positron emission tomography

[a]Highest risk for systemic recurrence includes patients with N2 disease or after curative-intent metastasectomy

[b]High risk of recurrence in Stage I disease is to be defined by provider(s) according to features such as margin positivity, unknown lymph node status (e.g., local excision), inadequate lymph node sampling, lymphovascular invasion, poorly differentiated histology, and/or T2 disease

[c]High risk for local recurrence include local excisions with poor histology (T2+, poorly differentiated), positive margins, T4 or N2 disease

chest X-ray, and proctoscopy (for rectal cancers only) adapted to risk class. Recurrence rates were similar between regimens, but the likelihood of salvage reoperation for recurrence was higher with active surveillance among the high-risk (34% vs. 12%, $p<0.01$) but not low-risk (22% vs. 24%) patients. Survival at 5 years was improved with surveillance in both risk groups (both $p<0.01$, proportions were not presented in the manuscript).

In the Follow-up After Colorectal Surgery (FACS) trial, the only factorial-design randomized study to evaluate the role of CT scans of the chest, abdomen, and pelvis, Primrose et al. [23] compared four groups: minimum follow-up, CEA only (every 3 months for 2 years, then semiannually to 5 years), CT only (every 6 months for 2 years, then annually to 5 years), and both CEA and CT. Colonoscopy was performed at 5 years in the non-CT groups, and at 2 and 5 years in the CT groups. Between 2003 and 2009, they randomized over 1200 patients in 39 hospitals in the United Kingdom. Again, more curative-intent salvage operations were performed in the active surveillance groups (6.7% CEA alone, 8.0% CT alone, 6.6% CEA + CT) than the minimal follow-up group (2.3%, $p=0.02$), but there was no difference in survival (82% active vs. 84% minimal), and the addition of CT to CEA did not increase the detection of resectable recurrences.

Several meta-analyses have attempted to synthesize these and other non-randomized trials and have generally corroborated the findings of the trials described above. Tjandra and Chan [26] analyzed the seven pre-FACS studies above [16–20, 22, 27] and interim data from an ongoing study [4] and found that intensive surveillance resulted in more frequent and earlier detection of asymptomatic, resectable recurrence, with a small but statistically significant improvement in survival during follow-up (78% vs. 74%, $p=0.01$). Pita-Fernández et al. [28] evaluated 11 trials, including more than 4000 patients, randomized according to a variety of different protocols and regimens, and found a small improvement in overall survival with more intensive surveillance (74% vs. 71%, p value not reported). Survival was significantly improved among patients subjected to colonoscopy, chest X-ray, liver ultrasonography, CT, and clinical assessment. There was also improvement in survival associated with increased frequency of CEA testing, liver ultrasonography, and clinical assessment. Findings and conclusions were similar in a meta-analysis by Renehan et al. [29]. Further, a Cochrane Collaborative meta-analysis of the pre-FACS trials found that intensive surveillance more than doubled the odds of salvage surgery and was associated with approximately 27% reduced odds of mortality. Particular benefit was found in trails that increased frequency of testing and use liver imaging [25].

There are two ongoing randomized trials whose results have not yet been reported. The COLOFOL trial [30] in Denmark, Sweden, Poland, Ireland, and Uruguay is comparing semiannual CT or MRI against imaging performed at 12 and 36 months after resection. And the GILDA trial [4], in Italy, Spain, and the United States, evaluates increased frequency of colonoscopy, chest X-ray, liver ultrasound, and abdominopelvic CT (for rectal cancers only). As of 2004, GILDA had enrolled nearly 1000 patients and interim results demonstrated no improvement in mortality (7% in the intensive arms, 5% in the minimal surveillance arm).

Ultimately, high-level evidence to support each component of any of the guidelines included herein is lacking. Nevertheless, we can likely conclude that more frequent testing and the use of advanced imaging will result in more potentially curative surgery for recurrence and a measurable, but small, improvement in survival.

Physical Examination

Most of the major societies' guidelines include periodic clinical evaluation, including assessment of symptoms and physical examination. Findings suggestive of disease recurrence may include weight loss, fatigue, anemia, cough, abdominal pain, rectal bleeding, or changes in bowel habits. Physical examination should focus on the abdomen, including evaluation for wound implants, lymph nodes, and rectal exam (or perineal wound exam after abdominoperineal resection).

In addition to their role in colorectal cancer surveillance, these visits also serve an important survivorship role in overall health maintenance and management of physical and psychosocial function after colorectal resections. More than half of rectal cancer patients who undergo low anterior resection suffer bowel dysfunction [31, 32]. And high rates of depression persist among colorectal cancer survivors even more than 5 years beyond their diagnosis [33]. Additionally, health behavior promotion can improve cancer outcomes as well. High intake of red meat and saturated fat has been associated with worse survival after treatment of colorectal cancer [34, 35], whereas regular weekly exercise is associated with significantly increased disease-free survival [36]. Interventions to improve these preventive health-related behaviors may thus improve outcomes from both the cancer and comorbid disease.

American Society of Colon and Rectal Surgeons (ASCRS) recommends visits every 3–6 months for 2 years, followed by every 6 months until 5 years [37]. Recognizing that many patients who present with recurrence are symptomatic [18, 38], a detailed history and physical examination may be sufficient to detect recurrent disease in many instances. Symptomatic recurrences, however, are far less likely to be amenable to curative-intent therapy [38, 39].

Laboratory Testing

None of the major guidelines currently endorse the routine evaluation of complete blood count, liver function tests, fecal occult blood testing, or blood chemistries. However, most recommend checking levels of carcinoembryonic

antigen (CEA), an oncofetal protein that may be elevated in patients with recurrent colorectal cancer. CEA detects only about 30–60% of recurrences [10, 38, 40–43], the positive predictive value of CEA is only about 65% [44], and more than 15% of patients in surveillance have falsely elevated CEA in the absence of recurrence [40]. Yet, elevations in CEA may precede symptomatic presentation of metastasis [45], and the trials showing greatest benefit to intensive surveillance [21, 23] have included regular CEA evaluations. CEA elevations identify disease in the absence of abnormal imaging in up to 23% of patients with recurrent colorectal cancer [46], but may be more commonly elevated with metachronous liver metastases than with pulmonary metastases, luminal or locoregional recurrences [40, 42]. About a third of colorectal cancers do not produce CEA [47], but the significance of CEA elevation during surveillance seems to be independent of the preoperative CEA level [45]. Still, no studies have formally addressed the accuracy of surveillance CEA testing among patients with normal CEA at time of diagnosis.

Recommendations for management of asymptomatic CEA elevation are outlined in guidelines from both NCCN [48, 49] and ASCRS [37]. After confirmation of serial elevation in CEA level, a complete physical examination, endoscopy, and CT imaging of the chest, abdomen, and pelvis are performed. If these are all negative, consideration is given to PET-CT and/or repeat imaging every 3 months until levels decline or recurrence is detected.

Abdominal Imaging

The most common site of metachronous metastatic colorectal cancer is the liver [50]. Recommendations for routine imaging to detect liver metastases have, therefore, broadened substantially in the past decade. The Cochrane Collaborative meta-analysis [25] concluded that there was a survival benefit associated with liver imaging, with hazard ratio for mortality of 0.64 (95% confidence interval 0.49–0.85). This conclusion was derived from the results of five randomized trials [16, 17, 19–21], which used varying combinations of liver ultrasonography, abdominal CT, or both.

Observational studies have strongly supported the use of more frequent advanced liver imaging due to increased detection of resectable metastases. In a single-institution study, Fora et al. [14] reported results from their practice of CEA testing plus chest and abdominopelvic CTs every 6 months for the first 2 years, then annually to 5 years for patients with resected Stage II and III colorectal cancer. Among the 44 of 177 (25%) patients diagnosed with recurrence, CT detected the recurrence in 30 (68%). Half of patients diagnosed with recurrence had elevated CEA, but CEA was responsible for the diagnosis in only 8 (18%), and symptoms preceded diagnosis in only 3 patients (7%). Curative-intent salvage surgery was undertaken for 25 of the 44 recurrences (57%). Likewise, Arriola et al. [9] found that recurrences diagnosed by CT were far more likely to undergo curative-intent resection than those detected by CEA alone. In a meta-analysis of five surveillance trials, Renehan et al. [29] concluded that the regimens most consistently associated with improved survival included both CT scanning and frequent CEA testing.

Canadian [51] and European [52] guidelines provide the option of either CT or ultrasound, and as recently as 2004, ASCRS practice parameters for colorectal cancer [53] surveillance did not recommend routine liver imaging, because of the unclear survival benefit associated with salvage resection, the lack of evidence for incremental benefit of imaging in patients undergoing CEA testing, and the cost of CT. Since then, however, improvements in the detection and management of hepatic and pulmonary metastases have altered this calculus [54], and the current ASCRS practice parameter [37] and recommendations from other US-based agencies [48, 49, 55] recommend routine CT imaging, due to increased sensitivity for identifying early liver lesions, and the opportunity to evaluate the remainder of the abdomen and pelvis for other sites of metastasis (such as retroperitoneal lymph nodes and ovaries), and to identify local recurrence in the resection bed [37]. Despite a lack of controlled studies comparing different imaging intervals, the ASCRS guideline suggests consideration of semiannual imaging for patients at highest risk of recurrence, including those with resected N2 or Stage IV disease.

There is currently no organization that endorses routine use of PET-CT scans or liver MRI. One randomized trial compared addition of PET to a surveillance regimen including CTs at 9 and 15 months after surgery, and found shorter time to diagnosis (12.1 vs. 15.4 months, $p=0.01$) and a higher rate of resection for recurrence (44% vs. 10%, $p<0.01$) in the PET+CT group [56]. Nevertheless, a meta-analysis of the use of PET in surveillance regimens noted inadequate evidence to support its use in routine surveillance [57]. In the evaluation of unexplained CEA elevation, observational studies find that PET and PET-CT have sensitivity for detecting metastasis in excess of 90% despite somewhat lower specificity, from 70 to 80%, due to false positive findings [58–63]. In routine surveillance, however, PET does not improve sensitivity over CT due to its lower spatial resolution and the use of non-diagnostic quality CT imaging without contrast enhancement in combined PET-CT exams.

Chest Imaging

Whereas plain radiography was the mainstay of surveillance for pulmonary metastasis in the past, most of the major guidelines now recommend the use of cross-sectional thoracic imaging at least annually. This change has come with the recognition that pulmonary metastasis may present as a solitary site of disease recurrence [8, 50, 64, 65], and may

even represent the most common site of distant metastasis for distal rectal cancers [66, 67]. Unfortunately, among the published randomized studies, only the FACS trial [23] has included chest CT scans in the regimen, and this study did not find a statistically significant incremental benefit to CT scan over CEA alone (though the study was not powered to examine this comparison). In an observational study of 530 patients with resected Stage II or III colorectal cancers, Chau et al. [38] found that chest CT was responsible for 35% of the diagnosed metastases, and 73% of patients found to have isolated pulmonary recurrence underwent curative-intent resection. Thus, for now, chest imaging is recommended in spite of a lack of high-level evidence to support its effectiveness in practice.

Colonoscopy

Surveillance endoscopy after colorectal cancer resection can serve three important purposes: clearance of remaining colon when preoperative colonoscopy was incomplete, anastomotic surveillance for detection of local luminal recurrence, and detection of metachronous neoplasia. For patients who did not have complete colonoscopy before resection of the primary tumor (because of an obstructing tumor for example) complete colonoscopy should be performed within 3–6 months after surgery [37], because the estimated incidence of synchronous neoplasia exceeds 30% [68–70]. Anastomotic recurrence after resection of colon cancers is rare [29, 71], representing only about 4% of recurrences [65]. On the other hand, local recurrence is a common concern after low anterior rectal resections—local surveillance for rectal cancer is discussed in more detail below.

For patients who had complete colon evaluation before their primary resection, the primary goal of surveillance colonoscopy is the detection of metachronous neoplasia, or polyps that were missed on the preoperative evaluation. The BSG/ACPGBI guidelines suggest waiting until 5 years after resection [72, 73], whereas all of the other guidelines include a complete colonoscopy at 1 year, though the rate of clinically significant findings may be quite low. In a meta-analysis of 17 studies including nearly 8000 patients followed after curative colorectal cancer resections, there were only 57 metachronous cancers found with the first 2 years—an incidence of 0.7% [70], consistent with the incidence in other studies [74–76]. In a recent single-institution study, Cone et al. [71] found that 15% of patients had polyps on their 1-year colonoscopy, but only 3% of these were greater than 1 cm in diameter. Nevertheless, these detection rates, both for malignancy and for high-risk adenomas, are at least as high as those of average-risk screening exams. Combined with the recognition that more than half of metachronous cancers are detected in the first 2 years after resection [77, 78], these data have been considered reasonable justification for the recommendation for colonoscopy at 1 year in most guidelines [37, 48, 51, 52, 55, 70, 79, 80].

In a randomized trial, Wang et al. [75] evaluated even more frequent colonoscopy, comparing a regimen of exams every 3 months for 1 year, then every 6 months for 2 more years, then yearly to 5 years versus colonoscopy at 6, 30, and 60 months only. The overall incidence of anastomotic recurrence was 6.9% and metachronous cancers were found in 2.8%. There was a higher rate of asymptomatic recurrences and curative-intent salvage operations in the more frequent group, but no statistically significant difference in 5-year survival (77% vs. 72%, $p=0.25$). Likewise, in their meta-analysis of surveillance trials, Tjandra and Chan [26] concluded that there was an increase in the curative reoperation rate among studies with increased frequency of colonoscopy, but a mortality benefit to colonoscopy only when compared against no surveillance at all.

After the initial 1-year colonoscopy, patients with a personal history of colorectal cancer remain at increased risk for metachronous neoplasia for the rest of their lives. The annual incidence of a second primary colorectal cancer is about 0.3%, resulting in an incidence of 1.5–3.1% within 5–10 years [74, 78, 81, 82]. Up to half of patients develop metachronous polyps after resection of a primary colorectal cancer [83]. Thus, even after the first year, patients with a personal history of colorectal cancer still require more frequent endoscopic surveillance than average-risk individuals or those with a history of adenomas alone. The ASCRS guideline [37] recommends that the subsequent colonoscopy schedule be tailored to the findings at the 1-year examination, and to other patient specific risk factors and circumstances. Patients with high-risk adenomas (high-grade dysplasia, size greater than 1 cm or more than three adenomas) and those with a diagnosed or suspected hereditary colorectal cancer syndrome may require annual colonoscopy for more intensive surveillance [5]. On the other hand, patients with limited life expectancy are unlikely to benefit from the detection of an asymptomatic cancer, and may be selected for less frequent, or no, endoscopic surveillance [84–86].

Other methods of luminal surveillance are not formally recommended at this time. Air-contrast barium enema is a less effective means of surveillance after colonoscopic polypectomy [87], and would be expected to compare similarly among patients after cancer resections. CT colonography has been advocated elsewhere as a technique for simultaneous assessment of both luminal and distant disease [88, 89], but it has not been satisfactorily evaluated in the setting of colorectal cancer surveillance, and its sensitivity has not been satisfactory to replace optical colonoscopy in this setting [70, 90].

Stage I Disease

Most of the major guidelines for and studies of colorectal cancer surveillance pertain primarily to Stage II–III disease, and to Stage IV tumors that have been resected with curative intent. Stage I patients have been largely excluded from many of the randomized trials. As a *result*, there remains controversy regarding approaches to the surveillance of resected Stage I colon cancers (see Table 34-1). Several of the guidelines specifically recommend against routine imaging. For example, NCCN [48] and ASCO [55] recommend only endoscopic surveillance for anastomotic recurrence or metachronous cancers. Further, there is presumed to be low incidence of systemic recurrence, as 5-year colon cancer survival rates exceed 90%, and very few operations for metachronous metastatic recurrence occur in patients who initially presented with a Stage I tumor [91]. Thus, there is concern that surveillance will identify more incidental findings than treatable recurrences. Chao and Gibbs [92] estimated it would take nearly 200 patients with Stage I disease in surveillance to detect each curable metastasis, and cautioned against over-testing in this setting.

On the other hand, in a secondary analysis [8] of the Clinical Outcomes of Surgical Therapy trial [93], which compared laparoscopic and open colectomy for colon cancer, the 5-year recurrence rate was 9.5% for early stage patients (including Stage I and IIa), occurring at a median of 1.8 years after primary resection. More than a third of patients with recurrence underwent salvage resection, with no difference in salvage rates between initially early and late stage patients. Median survival after salvage surgery for early stage patients was 51 months. Finding equivalent rates of salvage and better survival for recurrences after resection of early stage disease, Tsikitis et al. [8] recommended active survival for these patients, though they did not distinguish between Stage I (T1-2, N0) and Stage 2a (T3N0) in the study. Accordingly, the most recent ASCRS [37] Practice Guideline recommends consideration of active surveillance for Stage I patients, but limits the recommendation to those designated at higher risk—for example, close or positive margins, unknown lymph node status (e.g., local or endoscopic excision), inadequate lymph node sampling, lymphovascular invasion, poorly differentiated histology, and/or T2 disease.

Local Surveillance for Rectal Cancer

Additional surveillance recommendations for rectal cancer are predicated on the greater risk of locoregional recurrence, compared with colon cancers [70], due to both anatomic and biologic differences between the tumors [94–96]. Locoregional recurrence of rectal cancer can occur either intraluminally, typically at the site of anastomosis, or extraluminally, likely associated with residual lymphatic disease, close radial margins, or tumor shed during resection. Although the use of total mesorectal excision (TME) and chemoradiotherapy for locally advanced rectal cancers have substantially reduced local failure after primary resection [97–100], between 4 and 22% of patients still experience local recurrence [98, 99, 101–103]. The resulting downstaging that may occur with the use of preoperative therapy for rectal cancer also may creates confusion about how to classify future risk of recurrence. In the ASCRS practice guidelines, it is recommended that pretreatment clinical staging be used to guide surveillance intensity unless the pathologic staging exceeds the preoperative assessment [37].

Early identification of local recurrence may offer the opportunity for curative-intent salvage resection. Therefore, surveillance of colorectal anastomoses and pelvic imaging are recommended beyond what is performed for colon cancer surveillance. Physical assessment including meticulous pelvic and groin examinations should be performed every 6 months. For patients with a low anastomosis or distal tumor with local excision or non-operative management, digital exam of the anastomosis or tumor site should be included. For patients who have undergone abdominoperineal resection (APR), careful palpation of the perineum and, in women, the posterior wall of the vagina is recommended. Special attention should be paid to areas of nodularity or changes over time. Any suspicious lesions should undergo biopsy as local recurrences after APR are frequently perineal or pre-sacral [100].

Proctosigmoidoscopy is recommended in the most recent ASCRS practice parameters [37] every 6–12 months for 3–5 years for those who have undergone a low anterior resection with anastomosis, and more frequently for those considered to be at higher risk of local recurrence. These higher risk patients and tumors might include men, distal lesions, close margins, incomplete TME, positive lymph nodes, lack of treatment response, lymphovascular invasion, and/or poor differentiation [98, 103–108]. On the other hand, in recognition of the substantially lower recurrence rate associated with TME and chemoradiotherapy, some guidelines have suggested limiting additional endoscopic surveillance only to patients who did not receive guideline-concordant multimodality therapy [51, 55]. To date, however, there have been no high-quality trials evaluating the effect of proctosigmoidoscopy on detection of recurrence, salvage resection, or survival after low anterior resection.

Recognizing that proctosigmoidoscopy only evaluates endoluminal surfaces, and thus may not detect early disease in residual mesorectum or other extraluminal tissues, the most recent ASCRS [37] and ACS/MSTF [70] guidelines also suggest consideration of endorectal ultrasonography (ERUS) for patients considered to be at high-risk for local recurrence. In three studies, ERUS identified asymptomatic rectal cancer recurrence that was otherwise undetected by digital exam, endoscopy, CT, or CEA in about 30% of cases [109–111]. Surgically resectable recurrences were more common in the ERUS-detected group, suggesting it may identify earlier

recurrent disease [111]. Further, ERUS-guided biopsy may provide the best opportunity to obtain histologic evaluation of extraluminal abnormalities [112–114]. Extraluminal pelvic disease may otherwise be evaluated by cross-sectional imaging. ASCO [55] and CCO [51] both recommend pelvic CT imaging for rectal cancers only, as a means of detection of local recurrence. MRI of the pelvis can also be used and is highly accurate for the diagnosis of pelvic recurrence [115], but its use in routine surveillance did not improve the detection of resectable recurrence in a single trial [116], and its cost-effectiveness has not been evaluated.

For rectal cancers treated by local excision, rather than radical resection, particular attention must be paid to both endoluminal and mesorectal surveillance. Even among the best candidates—those with T1 cancers and no high-risk histologic features—there is a significantly higher risk of local recurrence compared with resection with TME, ranging from 4 to 33% [117–119]. Outcomes of local excision for higher stage tumors are even worse [120]. Thus, at least semiannual endoscopic surveillance after local excision is highly recommended, and consideration may be given to the use of ERUS for these patients, especially.

As there is increasing interest in and application of non-operative approaches for patients who experience complete clinical response after chemoradiotherapy [121, 122], surveillance regimens for these patients will need to be defined as well. Because non-operative treatment is currently limited to clinical trials [123], none of the guidelines include formal recommendations for such patients. However, the non-operative trials reported to date have employed remarkably intensive surveillance, including very frequent physical examination, endoscopy, and imaging, often with pelvic MRI [122–125].

Compliance with Guidelines

Despite published recommendations for surveillance after resection for colorectal cancer, compliance with surveillance remains challenging both for patients and their physicians. There is evidence that patients who adhere to recommended surveillance have a greater likelihood of curative-intent reoperation for recurrence and improved overall and disease-specific 5-year survival [126, 127]. Yet anywhere from 25 to 42% of patients have poor completion of recommended surveillance, and 11–21% have no surveillance at all [126–129]. Studies in Canada [130], the Netherlands [131, 132], and Norway [133] have found substantial differences in the surveillance patterns between providers, and noted that routines are commonly inconsistent with published guidelines. Among US Medicare beneficiaries, there is substantial geographic variation in the intensity of surveillance, with about 60% of patients failing to complete recommended testing, while 23% undergo testing more intensive than recommended by guidelines [134]. Similarly, a survey of ASCRS membership revealed that colon and rectal surgeons employ a wide variety of surveillance approaches, and only 30% performed surveillance in accordance with a formal national or local guideline [135].

There is also little consensus regarding who should manage cancer surveillance—the operating surgeon, medical oncologist, gastroenterologist, or primary care doctor. This ambiguity may contribute to nonadherence in many patients, as responsibility for ordering and managing testing can be undefined [136]. In a survey of Canadian colorectal cancer specialists, Earle et al. found high levels of endorsement of recommended surveillance, and a belief that specialty physicians are more capable of effective surveillance. Similarly, in a Texas study, patients who saw a medical oncologist as part of surveillance were significantly more likely to exhibit compliance with minimal recommendations for office visits, CEA testing, and colonoscopy [128]. Two randomized trials have compared surveillance by general practitioners and surgeons. In both studies, surveillance by surgeons was associated with more costly and intensive diagnostic testing, but no difference in recurrence rates, time to diagnosis, survival, or quality of life [137, 138] Patients seeing general practitioners received more fecal occult blood testing, whereas those followed by surgeons had more ultrasounds and colonoscopies [137]. Patients followed by primary care doctors report that greater attention is paid to preventive health maintenance for comorbidities [139].

In a single-institution study, Standeven et al. [140] found that, compared with community-based primary care follow-up, the establishment of a formal surveillance program in a referral center improved adherence to surveillance guidelines. Strand et al. [141] trained specialty nurses to conduct surveillance and found similar patient satisfaction and detection of recurrence among patients randomized patients to visits with either the nurse or a surgeon. It remains unclear, however, whether such a model—a multidisciplinary team with a clinic dedicated to colorectal cancer surveillance—could be replicated more widely.

Quality of Life

Apart from the cancer-specific outcomes of surveillance, an essential question is the effect of intensive surveillance on psychological health and quality of life. While reassuring surveillance examinations may allay fears of cancer recurrence for some patients, there could be others for whom surveillance examinations create additional unwarranted worry and result in investigations for false positive or incidental findings.

Most patients in surveillance report, however, that these anxieties and inconveniences are outweighed by the reassurance and optimism imparted by negative results [142]. In the randomized trial by Kjeldsen et al. [143] patients randomized to more frequent evaluations reported greater confidence in

the surveillance process, and somewhat less worry about test results, even in this trial which showed no effect of surveillance intensity on survival. Likewise, Stiggelbout et al. [144] interviewed more than 212 patients undergoing surveillance for colorectal cancer and found generally positive attitudes toward surveillance, with relatively little worry regarding testing. Even when asked to consider the possibility that testing would not improve the detection of recurrence, 64% of patients in that study still expressed a preference for active surveillance.

Cost

As recommendations for surveillance imaging have expanded in recent guidelines, another important consideration will be the costs of surveillance. Total costs of the surveillance regimens in published studies vary 28-fold [145], without a clear correlation between cost and efficacy. Meanwhile, between 1999 and 2006, the use of CT and MRI scans in the follow-up of patients with colorectal cancer increased at an annual rate of more than 5%, and the use of PET scans more than tripled [146].

Among a cohort of Italian patients undergoing surveillance with clinical examination, CEA, abdominal ultrasonography, chest X-ray, and colonoscopy, the 5-year cost of surveillance averaged $5400 per patient, but more than $100,000 per detected case of potentially curable recurrence [147]. Similarly, in a meta-analysis of five randomized trials [16–19, 21], Renehan et al. [148] estimated the average costs of surveillance at almost £2500 per patient, or about £3000 per year of life saved—within the range of acceptable cost-effectiveness for the UK's National Health Service. And a comparative study in France estimated that intensive surveillance cost an additional 3144€ per quality-adjusted life year gained over a minimal surveillance strategy [149].

We can conclude from these limited data that the cost-effectiveness of colorectal cancer surveillance is likely to be within the range of other interventions considered acceptably costly. Caution must be taken, however, if an increase in the cost, complexity, and frequency of recommended testing is contemplated.

Conclusions

There continues to be substantial uncertainty about the magnitude of benefits from active surveillance and the content of optimal surveillance regimens after curative resection for colorectal cancer. With improved imaging technology and a growing array of management options for recurrence, however, active surveillance is recommended for patients eligible for treatment of recurrent disease. Although there is likely great value to standardization of surveillance regimens, optimal approaches will require tailoring of surveillance strategies to individual patient risk factors. Perhaps the introduction of biomarkers [150] or simulation models [151, 152] to estimate individual risk will inform choices about surveillance modalities in the future [153]. In coming years, the GILDA [4, 154] and COLOFOL [30] trials should contribute important data on the cancer-related outcomes of surveillance and will also report on health-related quality of life and the cost-effectiveness of intensive surveillance. For now, however, decisions must be based largely on clinicopathologic risk factors, preferences for intensity of testing, and willingness to pursue further investigation and active treatment for abnormalities detected by testing.

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35
Colorectal Cancer: Management of Local Recurrence

Eric J. Dozois and Dorin T. Colibaseanu

Key Concepts

- Patients with colorectal cancer at the highest risk for local recurrence are those who present with obstruction or perforation, higher-stage disease, and adverse pathologic features, or undergo an operation that does not adhere to standard oncologic principles.
- The most significant predictor of survival following surgery for local recurrence is the ability to achieve a negative-margin (R0) resection.
- The probability of achieving an R0 resection is much greater in patients with recurrences involving an anastomosis or urogynecologic structures compared with those involving para-aortic tissue, sacrum, or lateral pelvic sidewall.
- A dedicated multidisciplinary team at an institution experienced in the management of patients with local colorectal cancer recurrence can facilitate complex surgical decision-making and greatly enhance patient outcomes.
- A multimodality approach that includes chemotherapy and radiotherapy improves local control and improves 5-year survival in patients with local recurrence.

Introduction

The medical and surgical management of colorectal cancer has a rich history, and treatment paradigms have evolved significantly over the last 100 years [1–6]. Major advances have been made in our understanding of tumor biology, the role of chemoradiotherapy, and most importantly, the significance of precise surgical technique. These advances have dramatically decreased local recurrence and increased 5-year survival in patients with primary colorectal cancer [1, 6–9]. Despite these advances, local recurrence following surgery remains a significant problem [4, 10–18]. In addition to its impact on survival, major morbidity from local recurrence can have a dramatic detrimental impact on quality of life [19–21].

In the United States, approximately 90,000 patients are diagnosed with colon cancer each year, and in those that undergo surgery, somewhere between 8 and 12 % will develop a local recurrence [22, 23]. Of the 40,000 patients diagnosed with rectal cancer each year, approximately 5–30 % will develop a local recurrence [24–28]. Patients with colorectal cancer at the highest risk for local recurrence are those that have higher-stage disease, high-grade tumors, and lymphovascular involvement or present with obstruction, perforation, or a locally advanced tumor at the time of presentation [29–34]. Operations done by noncolorectal-trained surgeons, or by surgeons who perform less than 20 rectal cancer resections per year, have been reported to have higher local recurrence rates [30]. Recently, the importance of a threatened or violated circumferential margin as an independent predictor of future recurrence has reinforced the importance of meticulous surgical technique [15, 35, 36]. All efforts to reduce the risk of local recurrence should be made when managing primary colorectal cancer, and the best results are achieved when patients are managed by experienced teams [37, 38].

When patients with colorectal cancer develop local recurrence, surgery offers the best opportunity for cure [15, 24, 39]. In the last 20 years, surgery for local recurrence has become safer, indications have expanded, and better results are being achieved leading to meaningful survival for many patients [17, 18, 40–42]. This chapter will review all aspects of management in patients with local recurrence as well as outcomes of surgery. Due to the complexity of medical and surgical decision-making, in addition to the surgical expertise required to perform these technically challenging operations, the treatment of patients with local recurrence should preferentially occur at centers that have a dedicated and experienced multidisciplinary team.

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Preoperative Evaluation and Patient Selection

The majority of colorectal cancer relapses following surgery occur within 3 years of resection [7, 16, 26, 28, 43]. Most but not all patients will have symptoms from recurrent disease, and these will include pain, malaise, bleeding, and symptoms of partial obstruction [21]. In some patients, carcinoembryonic antigen (CEA) levels will be elevated, and this finding in the asymptomatic patient should trigger a workup for recurrence.

In patients with suspected local recurrence, every attempt should be made to obtain tissue for confirmation. Patients with luminal local recurrences can undergo endoscopy to obtain tissue. In patients with suspicious radiographic findings, obtaining tissue confirmation may be more challenging. Most patients with recurrent colon cancer will have obvious findings on imaging to confidently diagnose them with recurrence, and a transabdominal biopsy should be avoided. In contrast, every attempt should be made to obtain tissue confirmation in patients with suspected pelvic recurrence. One should be hesitant to undertake a major pelvic resection without tissue confirmation of recurrence. In our experience, computed tomography (CT)-guided percutaneous biopsy has been very useful to confirm or refute the presence of recurrence. In some cases, it may be very difficult to differentiate postoperative changes from recurrent tumor based on imaging alone. CT-guided percutaneous biopsy can confirm recurrence, but a negative result does not rule it out. In the absence of a tissue diagnosis, a rising CEA, with a notable change in the size of the lesion on serial imaging, and lesions that are positron emission tomography (PET) avid can be considered consistent with recurrent disease.

Patients with recurrent colorectal cancer being considered for curative-intent resection undergo imaging studies to assess the local-regional characteristics of the recurrence and to exclude metastatic disease [17, 18, 40]. Our protocol includes fusion PET-CT imaging of the chest, abdomen, and pelvis and magnetic resonance imaging (MRI) of the pelvis for recurrent rectal cancers. Several studies have confirmed that 18-fluorodeoxyglucose PET imaging has a high sensitivity for the detection of locoregional and distant recurrences in patients with colorectal cancer [44–46]. In the evaluation of 58 patients for advanced or recurrent colorectal cancer, Ogunbiyi et al. found that PET imaging had a sensitivity and specificity of 91 % and 100 %, respectively [47]. Chessin et al. showed that fusion imaging that combines CT and PET imaging has an enhanced sensitivity of 98 % as compared to 64 % with standard CT for the detection of rectal recurrence; in other studies, fusion imaging led to altered management in 58 % of patients [48, 49]. Moreover, PET retains its diagnostic ability even after irradiation, and because of this, we believe that all patients being considered for resection should undergo this study.

When seeing patients with local recurrence, it is important to obtain a complete history and physical examination. All records of previous treatments (surgical and chemoradiotherapy) should be reviewed. Pain and neurologic dysfunction may be a sign of advanced pelvic disease [15]. Bilateral lower extremity edema is an indicator of venous or lymphatic obstruction. A full colonoscopy should be done to rule out any synchronous lesions. If the rectum is intact, a digital rectal exam can assess the relationship of the recurrent cancer to the sphincter complex, prostate, or posterior vaginal wall. Cystoscopy may be useful to assess transmural invasion of the bladder.

Laboratory tests should be obtained by looking particularly for anemia and the nutritional state of the patient. The patient's albumin, prealbumin, and transferrin levels will give an idea of the protein reserves of the patient. If required, nutritional supplementation should be instituted to strengthen the immune system and optimize wound healing. A significantly elevated CEA should raise concern for occult metastatic disease [50].

Operations for local recurrence are often long and can be associated with significant blood loss, systemic inflammation, and tissue trauma, and the overall stress response associated with these big operations can pose significant risk to patients [51, 52]. Despite this, recent series have demonstrated a very low mortality following these major resections [17, 18, 40]. Patients with significant chronic obstructive pulmonary disease and cardiovascular conditions should be carefully evaluated and optimized preoperatively. Patients with ASA classifications of IV or V will be at the highest surgical risk and are generally not candidates for a major resection.

The decision to go ahead with a major, potentially morbid operation for local recurrence requires that the patient is fully informed regarding the risks and life-changing impact on quality of life. Ultimately, it should be the well-informed patient who decides what disability that might arise from surgery they are willing to live with. The likelihood of a stoma is high, and patients should be counseled by a stoma therapist preoperatively [53–55]. Patients undergoing multivisceral and musculoskeletal resections will require the most intense counseling regarding their postoperative recovery, limitations, and potential morbidity and mortality [14, 27, 42, 56].

The inclusion criteria for surgery in patients with recurrence have expanded significantly in the last 10 years [57]. In determining who should be offered surgery, one must consider the goals of the operation. If palliation is the goal, surgery must have a high probability of symptomatic relief and not be significantly morbid. If oncologic cure is the goal, the ability to confidently achieve a margin-negative (R0) resection must be highly probable. Based on multiple studies in patients with recurrent colorectal cancer, the number one determinant of oncologic benefit is the ability to achieve an

R0 resection. Multiple points of tumor fixation may limit the surgeon's ability to achieve an R0 resection, and this finding on evaluation has been associated with poor outcomes [15]. Patients operated for central recurrences that extend anteriorly (urogenital, gynecologic organs) have the best opportunity for an R0 resection and, therefore, good outcomes following surgery [15, 16, 58]. When a recurrence in the pelvis extends posteriorly to the sacrum or lateral to the pelvic sidewall, the ability to achieve an R0 resection becomes much less certain. In cases where there is significant lateral extension of the tumor, specifically through the sciatic notch, a positive margin is almost certain unless an extended resection such as a hemipelvectomy is done [41].

Contraindications to surgery will vary from institution to institution and from surgeon to surgeon. Local recurrences that involve major vascular structures, the high sacrum, or extensive pelvic sidewall disease were frequently listed in publications as contraindications to surgery in the past [16, 59, 60]. In the modern era, several well-recognized and respected centers have expanded their indications in light of increasing data demonstrating meaningful survival in patients undergoing extended resections [17, 18, 40, 42, 57]. In the author's view, contraindications to surgery should be based primarily on the inability to completely clear the tumor with the understanding that limited survival benefit is achieved if gross residual tumor remains.

Classification of Local Recurrence and Determining Resectability

Classification schemes for both recurrent colon cancer and rectal cancer have been proposed and are used not only to characterize patterns of recurrence but also to predict R0 resectability and oncologic outcomes [61].

Locoregional recurrence in patients with colon cancer can be classified as four distinct groups and include peri-anastomotic (mural disease), mesenteric (regional nodal disease), retroperitoneal or pelvic (drop metastases, distant nodal disease, or residual disease transmural disease), and peritoneal. In a study from the Memorial Sloan Kettering Cancer Center, Bowne et al. demonstrated that the most common site of recurrence was peri-anastomotic (36 %), followed by peritoneal (16 %), mesenteric (15 %), and retroperitoneal (12 %) [62]. In our experience, some cases of recurrence were directly attributed to inadequate mesenteric resections at the time of original surgery. However, most nodal-based relapses were found at nodal sites (iliac, para-aortic) not typically removed during standard oncologic resection [63].

Pelvic recurrences can be broadly categorized in terms of what resection would be necessary for complete tumor removal. With this in mind, the authors have generally classified recurrences as those requiring an anterior, posterior, lateral, or combined resection (Figure 35-1). In anterior resections, the rectum and urogynecologic structures are removed. A posterior resection involves removing the rectum and a portion of the sacrum. A lateral resection involves removal of the rectum and iliac vessels and/or components of the lumbosacral plexus. The term "combined resection" or "composite resection" includes any combination of anterior, posterior, or lateral structures.

For recurrent colon cancer, CT imaging is our study of choice to make decisions regarding resectability. For recurrent rectal cancer, MRI of the pelvis is our study of choice to assess neuromuscular and bony involvement and for surgical planning. We use a musculoskeletal protocol that is done with and without gadolinium and includes sagittal, axial, and coronal oblique views (Figure 35-2). MRI has highly detailed soft-tissue resolution, which is helpful in planning lines of resection as it pertains to adjacent structures. Specifically, for tumors with posterior and lateral extension, MRI can determine proximal sacral extent, involvement of lumbosacral nerves, and whether or not a margin can be obtained on the lateral pelvic sidewall. Computerized tomography or MR angiogram or venogram may add additional information regarding vascular involvement and indicate the need for a vascular surgeon to be a member of the multidisciplinary surgical team.

A major challenge from a surgical planning perspective in many cases of local recurrence is the fact that the borders of recurrences can be indiscrete and ill defined on imaging. Recurrences may be infiltrative and sheetlike and sometimes have islands of intervening normal tissue. This makes it difficult to preoperatively determine where the "true margins" are. Because of this, one must be prepared to alter the surgical plan intraoperatively as findings may differ significantly from what the preoperative imaging suggested. Intraoperative frozen section pathologic analysis can be very useful to ensure that further resection can be done if there is a persistent microscopic margin discovered at the time of surgery.

Another challenge in management of local recurrence is differentiating both postoperative and radiation-induced fibrosis from actual tumor. MRI with T2-weighted imaging can assist because fibrosis and tumor demonstrate different signal intensities [64]. Gadolinium-enhanced MRI is reported to have an 88 % and 95 % sensitivity and specificity, for the detection of pelvic recurrences in the setting of previous surgery and radiation [65].

Multimodal Therapy Including Intraoperative Radiation

Multimodal therapy in the management of locally recurrent colorectal cancer refers to a treatment approach that includes pre- and postoperative systemic chemotherapy, preoperative external beam radiotherapy (EBRT), and, in some protocols, intraoperative radiation therapy (IORT). The authors have used this approach very selectively in patients with recurrent

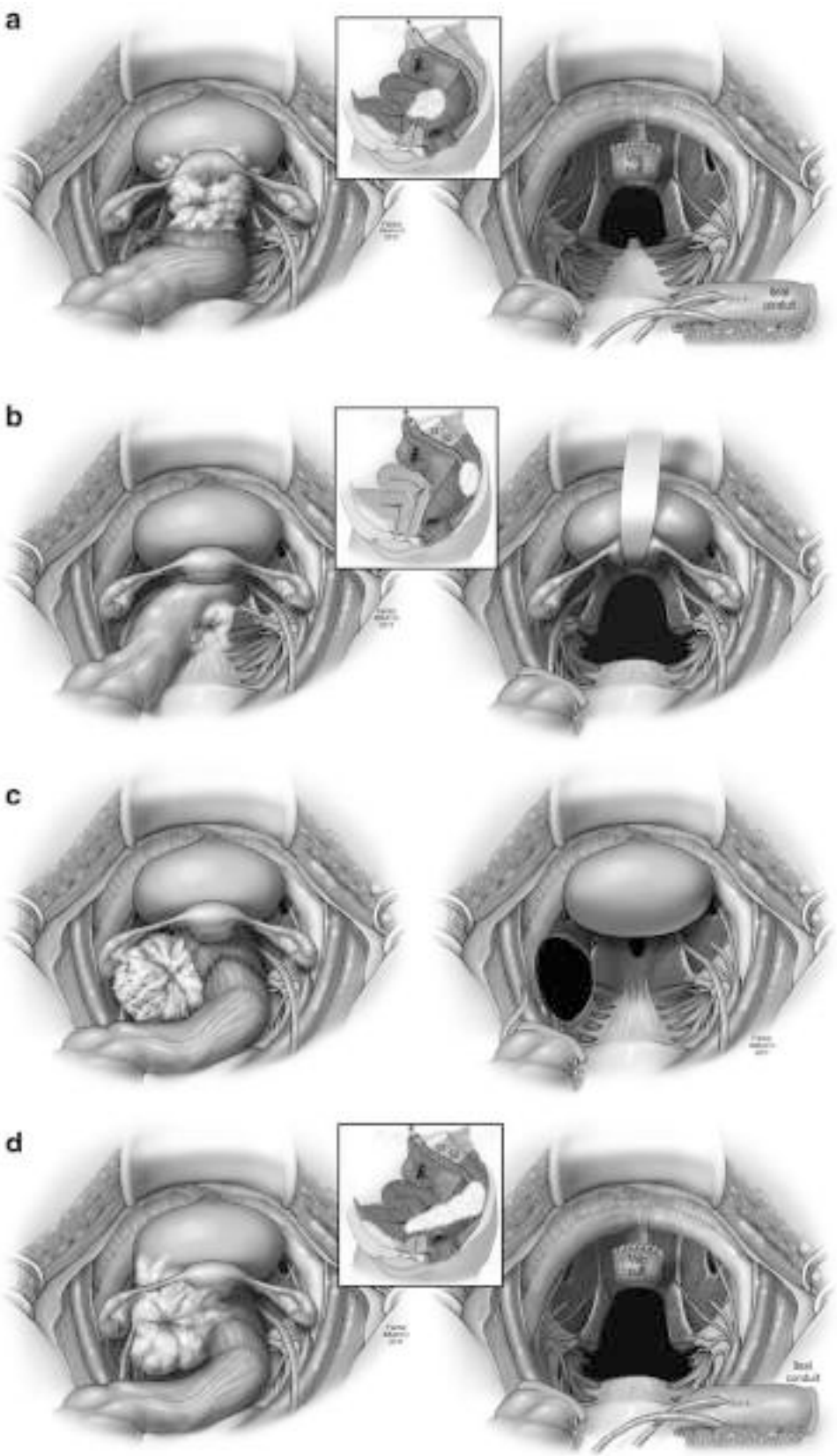

FIGURE 35-1. Classification of recurrence. (**a**) *Anterior*: involves structures anterior to the neorectum. (**b**) *Posterior*: involves structures posterior to the neorectum. (**c**) *Lateral*: involves pelvic sidewall and associated structures. (**d**) *Combined anterior-posterior*: tumor includes anterior and posterior structures.

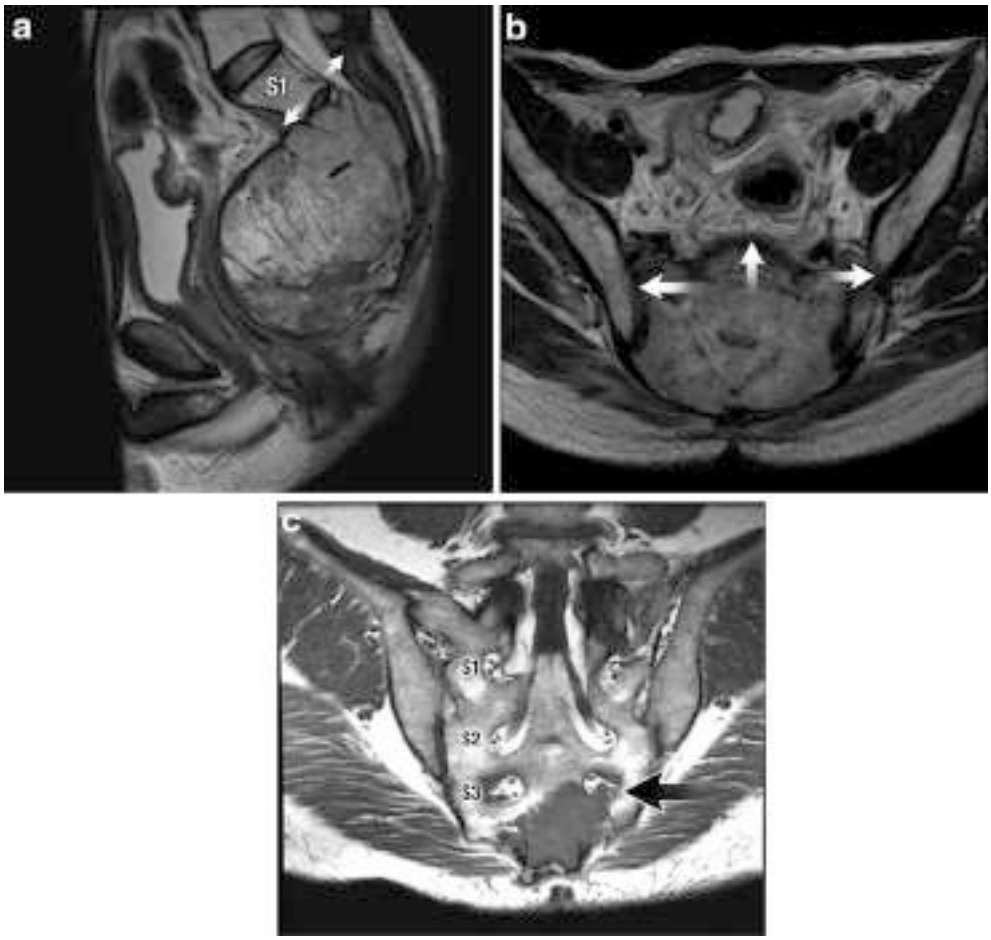

FIGURE 35-2. MRI assessing neuromuscular and bony involvement for surgical planning in recurrent rectal cancer. (**a**) Sagittal section showing cephalad and posterior extension of the recurrence to the first sacral body (S1). *White arrows* demonstrating lines of resection necessary for R0 resection; (**b**) coronal section demonstrating soft-tissue extension anteriorly and laterally, with viscera and bilateral iliac involvement (*white arrows*); (**c**) coronal/oblique view showing left nerve root involvement (*black arrow*).

colon cancer and in almost all cases of recurrent rectal cancer. In patients with locally recurrent colon cancer, there is usually less concern about the ability to get a wide surgical resection unless tumor abuts fixed critical structures (e.g., lumbar spine, aorta, vena cava). In these cases, we will employ a full multimodality approach that included IORT [63]. Since 1981, curative-intent therapy at our institution has included IORT for locally advanced and locally recurrent rectal cancer. Our protocol includes neoadjuvant chemotherapy and EBRT, IORT, and postoperative chemotherapy [13, 21, 66]. Patients who are radiation naïve receive 50.4 Gy of EBRT with concurrent five FU-based chemotherapies over 5 weeks followed by a 6–8-week recovery period before surgery. In patients who have received previous irradiation, we give 20–30 Gy with concurrent five FU-based chemotherapies, over a 3-week period followed by surgery within 7 days of the last dose of radiation. The amount of radiation given intraoperatively to the tumor resection bed depends on the margin status at the time of resection. For wide margins (500–750 cGy), R1 (1000–1250 cGy), <2 cm of gross residual (1500 cGy) and for >2 cm gross residual (1750–2000 cGy) [66]. Given that distant relapse of disease is the most common cause of death following surgery for local recurrence, systemic chemotherapy is part of our multimodality protocol. In a series of 607 patients with locally recurrent colorectal cancer treated at our institution with a multimodality approach that included IORT, the cumulative incidence of distant relapse was 53 % at 5 years. Distant relapse was less common in patients who had R0 vs. R1 or R2 resections and in those treated with postoperative chemotherapy [66]. Significant advances in chemotherapeutic regimens over the last 20 years have likely decreased the incidence of distant failures following surgery for local recurrence, but the optimal regimen and length of treatment are still debated.

Though there is a paucity of randomized data, many authors agree that a multimodality approach can significantly decrease local relapse and improve 5-year survival in

TABLE 35-1. Survival and local recurrence after intraoperative radiation therapy in patients undergoing R0 resection (adapted with permission from Ref [66])

Study	Patients (no.)	IORT dose (Gy)	EBRT dose (Gy)	5-year survival rate (%)	5-year local control rate (%)
Vermaas et al. 2005	17	10	50	45 (3 years)	35 (3 years)
Alektiar et al. 2000	53	10–18	45–50.4	36	43
Abuchaibe et al. 1993	8	15	40–50	29	50
Dresen et al. 2008	84	10–15	50.4 or 30.6	59 (3 years)	75 (3 years)
Lindel et al. 2001	25	10–20	50.4	40	56
Eble et al. 1998	14	12	41.4	71 (4 years)	79 (4 years)
Wiig et al. 2002	18	15	46–50	60	70
Valentini et al. 1999	11	10–15	45–47	41	80
Haddock et al. 2011	226	12.5 (median)	30.0–0.4	46	72

EBRT external beam radiation therapy, *IORT* intraoperative radiation therapy. EBRT generally was delivered only to patients not previously treated with radiation, except for patients in Dresen et al. (2008) [39] and the current series. Five-year rates are shown unless otherwise indicated. Lower doses were administered in previously irradiated patients

With permission from Haddock MG, Gunderson LL, Nelson H, Cha SS, Devine RM, Dozois RR, et al. Intraoperative irradiation for locally recurrent colorectal cancer in previously irradiated patients. International journal of radiation oncology, biology, physics. 2001;49(5):1267-74. [21] ©Elsevier 2001

TABLE 35-2. Survival and local control after intraoperative radiation therapy in patients undergoing R1 and R2 resection (adapted with permission from Ref [66])

Study	Patients (no.)	Surgical margins	IORT dose (Gy)	5-year survival rate (%[a])	5-year local control rate (%)
Vermaas et al. 2005	10	R1–R2	10	21 (3 years)	21 (3 years)
Alektiar et al. 2000	21	R1	10–18	11	26
Abuchaibe et al. 1993	19	R1–R2	15	7	16
Dresen et al. 2008	34	R1	12.5	27 (3 years)	29 (3 years)
	29	R2	15–17.5	24 (3 years)	29 (3 years)
Lindel et al. 2001	9	R1	10–15	11	33
	15	R2	15–20	13	12
Eble et al. 1998	9	R1	10–20	33 (4-year RFS)	67
	8	R2	10–20	25 (4-year RFS)	63
Martinez-Mong et al. 1999	39	R1	10–15	6	26
	41	R2	15–20	7	29
Wiig et al. 2002	29	R1	15	20	50
	12	R2	17.5–20	0	–
Haddock et al. 2011	224	R1	15 (median)	27	68
	156	R2	20 (median)	16	68

IORT intraoperative radiation therapy, *RFS* relapse-free survival

Five-year rates are shown unless otherwise indicated

With permission from Haddock MG, Gunderson LL, Nelson H, Cha SS, Devine RM, Dozois RR, et al. Intraoperative irradiation for locally recurrent colorectal cancer in previously irradiated patients. International journal of radiation oncology, biology, physics. 2001;49(5):1267-74 [21]. ©Elsevier 2001

colorectal cancer patients with local recurrence [15, 67, 68]. Several centers have shown good results with the use of IORT in patients with recurrent colorectal cancer, and 5-year survival rates range from 29 to 60 % in patients undergoing R0 resection (Table 35-1). Five-year survival rates after IORT in patients having R1 or R2 resection can be as high as 16 % and 27 %, respectively (Table 35-2). In most series where IORT is not included in the management of patients who had an R2 resection, no long-term survival is seen [66].

Radiation-induced toxicity is a significant concern in patients receiving multimodality therapy that includes IORT. In many cases, it may be hard to separate IORT-related complications from surgical ones. In a published series of 607 patients from our institution with recurrent colorectal cancer treated with EBRT and IORT, we attributed radiation specifically as the cause for some septic complications (wound related, enterocutaneous fistulas), small bowel and ureteral obstructions, as well as neuropathy [66]. Both the incidence and severity of neuropathy were related to IORT dose. Doses that exceeded 12.5 Gy were associated with a higher rate and severity. In total, 15 % of patients experienced some grade of neuropathy, with only 3 % of patients suffering from grade 3 neuropathy defined as severe weakness or intractable pain.

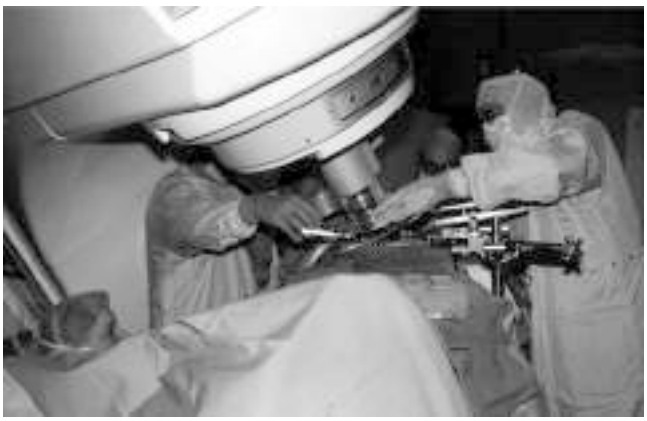

FIGURE 35-3. The IORT suite; the operating table is positioned under the linear accelerator by the radiation oncologist and the appropriate Lucite cone is affixed to direct the beam.

Technical Aspects of Surgical Resection

General Considerations

We use ureteral stents for all operations in patients with local recurrence in the pelvis. The Lloyd-Davies position is used to allow access to the perineum. Care is taken to protect the extremities from nerve injury with adequate padding of both the tucked arms and lateral lower extremities in the stirrups. An exploratory laparotomy is carried out through a midline incision to confirm absence of extra-pelvic disease and determine local resectability. Any lesions suspicious for metastatic disease are biopsied and sent for frozen section analysis. The presence of metastatic disease typically precludes resection for cure, and proceeding on to resection of the local recurrence has to be weighed carefully. All adherent tissue to the recurrence tumor should be resected en bloc. In general, the technical approach to local recurrence in the abdomen or in the pelvis is carried out by widely mobilizing normal surrounding tissues and organs in preserved embryologic planes when feasible and working toward the distorted anatomy and malignant pathology. This allows exposure of structures that are close to the recurrence but will be preserved if not invaded. In addition, vascular pedicles and collateral vasculature should be well delineated prior to ultimate mobilization of the recurrence and surrounding adherent tissue or organs, so that when significant bleeding is encountered, proximal and distal vascular control can be achieved safely.

Most cases for recurrence at our institution are done in a dedicated IORT operating room. This suite houses our linear accelerator and mobile anesthesia equipment that allows the patient to move into the optimal position for IORT (Figure 35-3). The radiation dose and field are selected based on tumor margin status. At our institution, Lucite cones are used to focus the beam of radiation delivered by the linear accelerator and protect the small bowel and other organs from radiation injury (Figure 35-4). The radiation oncologist and surgeon position the cone together for optimal radiation delivery.

Recurrent Colon Cancer

As previously stated, local recurrence in patients with colon cancer typically occurs in one of three patterns, luminal, locoregional, or para-aortic lymphatics, and in the resection bed of the previous index colectomy. Luminal and locoregional nodal recurrences are generally straightforward technically, and surgery involves resection of additional colon and adjacent mesentery. During operations in patients with retained mesentery from incomplete previous surgery, it is the author's experience that isolation and ligation of the vascular pedicles of the original tumor (that should have been removed during the index operation) is a good initial step to allow safe mobilization of the recurrence that lies within the retained mesentery. In cases where para-aortic or para-iliac nodes are involved, major vascular reconstruction may be necessary in addition to en bloc resection of surrounding structures (Figure 35-5) [69].

In cases where recurrence occurs in the previous resection bed, locoregional structures associated with the course of the colon are often involved (kidney, ureters, psoas muscle, stomach, spleen, duodenum, and pancreas). The most complex resections done for local recurrence after right colon resection are those that involve the duodenum and the head of the pancreas. When a Whipple operation is required, we involve a hepatobiliary surgeon to assist with resection and reconstruction. In cases where IORT will be used, radiation is delivered to the at-risk tumor bed just prior to closure.

Recurrent Rectal Cancer

Recurrences That Extend Anteriorly

After ruling out metastatic disease, the left colon is fully mobilized and transected at the appropriate level for subsequent end colostomy (in patients who have intestinal continuity). The entrance to the pelvis is cleared of loops of small bowel for optimal pelvic exposure. Dissection begins in the lower abdomen before entering the presacral space along the lower aorta and continues distally over the iliac vessels and ureters. Vasiloops are used to retract the ureters and vascular structures. In the re-operative pelvis, dense fibrosis and distorted anatomy require careful, meticulous dissection to avoid inadvertent injuries and major bleeding complications. In the author's experience, the most at-risk region for significant bleeding occurs during mobilization of the left common iliac vein, and this dissection should proceed with caution. Posterior lumbar branches, if not identified and injured, can lead to significant blood loss if avulsed.

The anterior and lateral lines of resection (decided upon during preoperative review of imaging) are delineated and confirmed, and the involved structures and organs are mobilized widely for subsequent en bloc resection. The presacral space is further developed, and the dissection is

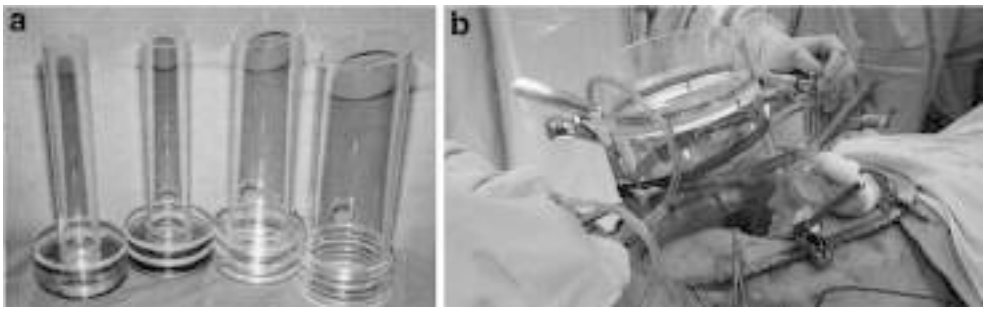

FIGURE 35-4. (**a**) Assortment of Lucite cones of different size used to direct the IORT field, (**b**) in situ placement of the Lucite tube.

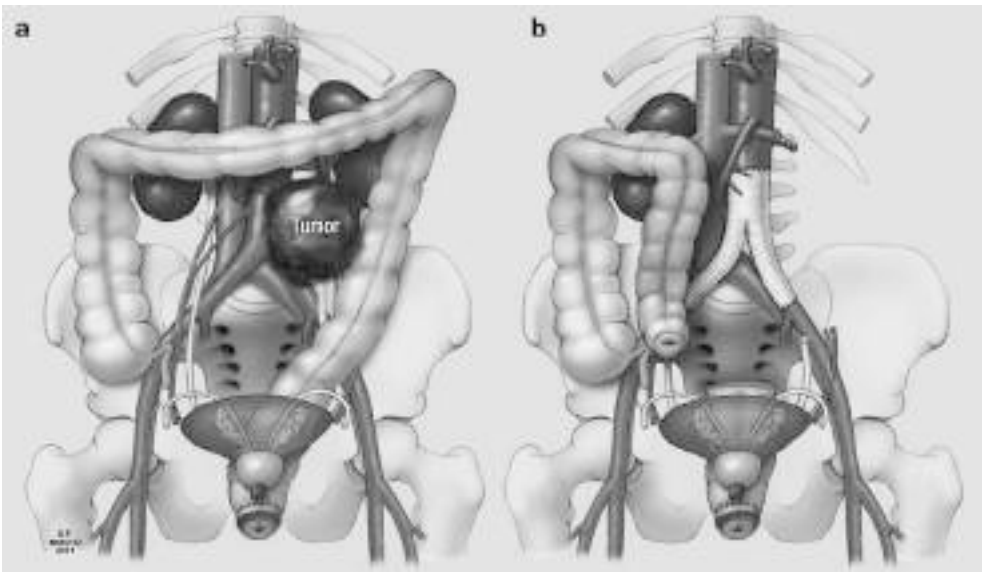

FIGURE 35-5. (**a**) Illustration of a local recurrence involving the aortic bifurcation, colon, kidney, and ureter, (**b**) en bloc resection with aortoiliac reconstruction.

carried down along the anterior sacrum being careful to stay anterior to Waldeyer's fascia to avoid the presacral venous plexus. The dissection is then carried laterally along the pelvic sidewall on each side with careful protection of the lumbosacral plexus and internal iliac vessels. The deepest part of the pelvic dissection will be the pelvic floor musculature, which can be incised during the abdominal portion of the procedure. When the transabdominal portion reaches this point, a combined transperineal approach facilitates final tumor removal. The transperineal portion begins with purse-string closure of the anus (if present), and then a wide, elliptical incision is made to include the sphincter complex and as much pelvic floor musculature as possible. With a surgeon working above, the two dissection planes can be joined safely and with careful attention to the tumor margins.

In women, anterior involvement may require resection of the posterior wall of vagina, and this portion of the operation is approached transvaginally and transabdominally simultaneously. In men, anterior fixation often requires cystoprostatectomy due to invasion of the trigone and prostate. Partial cystectomy may be sufficient in rare cases. When a urinary conduit is necessary, the ureters are mobilized as close to the bladder as possible to provide adequate length to reach the conduit. To mobilize the bladder, the space of Retzius is entered to fully mobilize the anterior portion of the bladder. The blood supply to the bladder (superior and inferior pedicles) is taken serially along the pelvic sidewall off the internal iliac vessels. The wings of peritoneum to the bladder are then taken down until the bilateral vasa are identified and clipped. The endopelvic fascia is opened bilaterally. The dorsal venous complex is subsequently ligated. The urethra is then delivered into the wound and transected.

Once the tumor is out, the surgeon orients the specimen for the pathologist and frozen section margins are assessed. If margins are not clear, further resection is undertaken when safe to achieve an R0 resection. At this point, IORT is given to the at-risk resection bed. Creation of end colostomy and urinary conduit completes the procedure. In women in whom a large portion of the posterior vaginal wall is removed, a vertical rectus abdominis flap (VRAM) is used for vaginal reconstruction.

Resection That Includes Sacrectomy

Stage I: Anterior Component

This dissection begins as outlined above for anterior recurrences. Once the deep pelvic portion of the operation begins, the anterior, lateral, and superior (along the spine) lines of resection are delineated, and the involved neuromuscular structures and organs are mobilized widely for subsequent en bloc resection. Frozen section biopsies are taken as needed to establish that final margins will be negative.

Vascular exposure often requires mobilization of the lower aorta and vena cava, in addition to the iliac arteries and veins. If vascular structures need to be resected en bloc with the tumor, the decision to do so is made here. If the resection does not require aortoiliac reconstruction, circumferential mobilization of the common and external iliac arteries will facilitate exposure of the veins. The internal iliac artery branches are ligated and divided first, distal to the takeoff of the posterior division superior gluteal artery branch, to preserve blood flow to the gluteal muscles and soft tissue of the perineum. Multiple internal iliac vein branches are then ligated after control of the main trunk(s) of the internal iliac vein has been achieved. The branches are ligated and divided before ligation of the main trunk to avoid venous distention of the branches, which can lead to troublesome bleeding (Figure 35-6). Lateral and middle sacral vein branches, which drain into the posterior aspect of the left common iliac vein and caval confluence, are ligated and divided. Suture ligature is preferable for short, broad-based internal iliac vein branches. The vascular dissection is carried along both sides of the sacrum onto the pelvic floor. In general, the internal iliac vessels are taken at their confluence as part of any sacrectomy above the third sacral body. For sacrectomy at or below the third sacral body, we generally preserve the internal iliac vessels.

Once the most proximal lumbosacral level of transection is determined, unicortical anterior osteotomies are performed at the bony level of resection (Figure 35-7). Prior to closing the abdomen, a thick Silastic mesh is placed anterior to the sacrum and posterior to the ureters, aorta, iliac vessels, and soft-tissue structures to protect against injury when blind osteotomies are performed during the second stage of the procedure, at which point the patient is in prone position. A titanium screw is also placed at the level of the osteotomy site to facilitate performing the posterior osteotomies by using intraoperative fluoroscopy (Figure 35-8).

During the anterior stage of the operation, IORT may be delivered prior to final tumor resection if orientation of the Lucite cone in the prone position will not be feasible to radiate the at-risk tumor bed. A colostomy and ileal or colonic urinary conduit are fashioned as needed, and a VRAM flap is then elevated for subsequent perineal reconstruction.

Stage II: Posterior Component

The second stage of the procedure is typically carried out 2 days after the anterior portion. With the patient in the prone position, a posterior midline incision is made along the middle

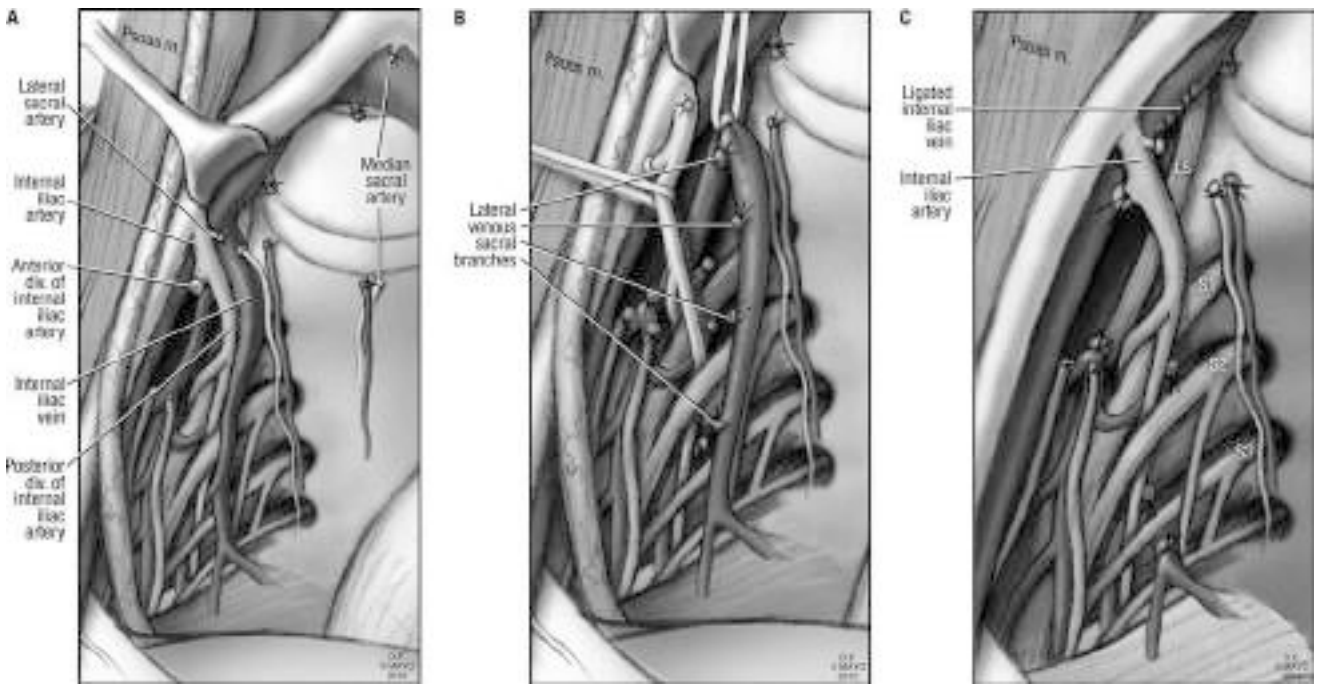

FIGURE 35-6. (**a**) Pelvic vascular anatomy. Ligation of anterior division of internal iliac artery, lateral sacral arteries and veins, and sacral artery and vein. (**b**) Ligation of lateral venous sacral branches. (**c**) Ligation of internal iliac vein.

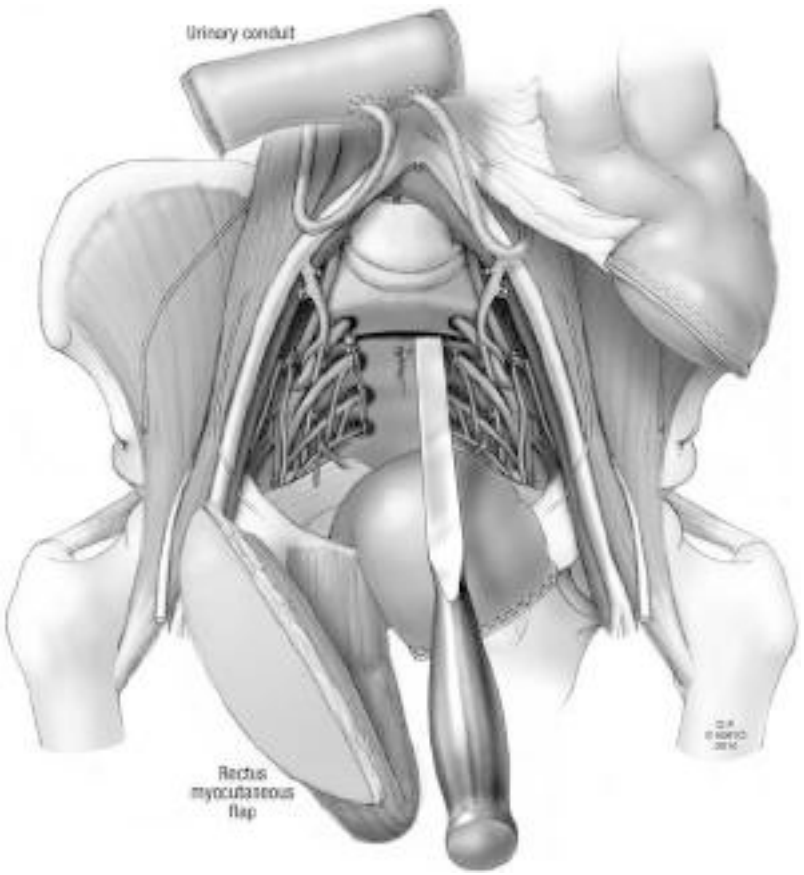

FIGURE 35-7. Unicortical anterior transverse osteotomy.

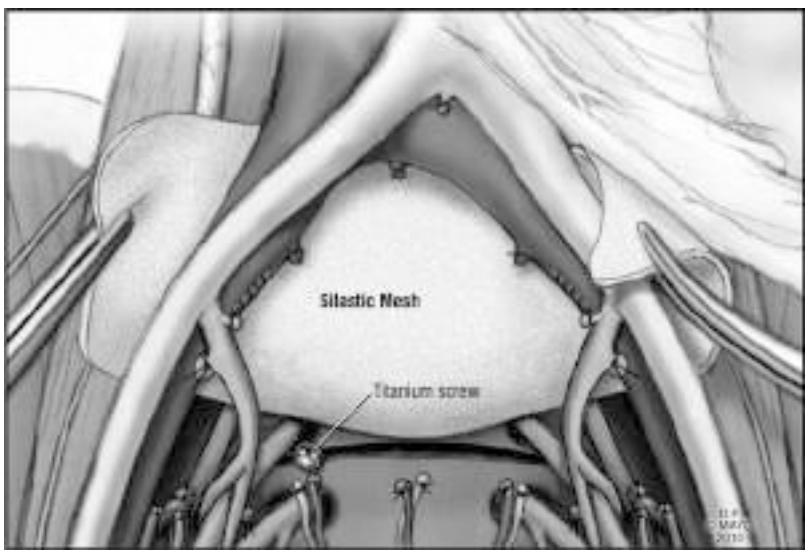

FIGURE 35-8. Placement of Silastic mesh to protect pelvic vasculature during the posterior osteotomies. Titanium screw marks the level of the anterior osteotomy to guide fluoroscopic identification of anterior osteotomy level when performing posterior osteotomy.

portion of the sacrum, and the gluteus maximus muscles are dissected away from the sacral attachments. The sacrospinous and sacrotuberous ligaments are divided to access the pelvic cavity posteriorly. The piriformis muscles are divided while protecting the sciatic and pudendal nerves. Laminectomy, dural sac ligation, and posterior sacral osteotomies are then carried out (Figure 35-9). Final osteotomies are performed based on the preoperative MRI imaging studies and intraoperative fluoroscopy to identify the anterior positioned titanium screw. After resection, the surgical team meets with the pathologist to accurately orient the specimen, and together they assess the completeness of resection. If frozen section analysis demonstrates an R1 or R2 margin, wider resection is undertaken as it can be done safely. Before soft-tissue wound reconstruction is done, IORT is given (if not given during stage I) and the dose is based on tumor margin status, as discussed above.

Stage III: Spinal Reconstructive Component

In cases where the lumbosacral line is transected, spinopelvic stability is compromised and patients will require instrumented reconstruction. For resections above the level of the S1 neuroforamen but below the lumbosacral junction, clinical experience and biomechanical studies have shown that in situ spinopelvic stabilization is beneficial to avoid collapse of the residual sacrum [70]. In these cases, an instrumented posterior spinopelvic fusion is made from the lower lumbar spine to the remaining pelvis.

Resections done through the lumbosacral junction, or higher, disrupt spinopelvic continuity. These patients undergo reconstruction using a combination of dual fibula grafts and instrumented stabilization from the lower lumbar spine to the remaining pelvis (Figure 35-10) [71]. The decision to use fibula allo- or autografts is individualized.

A concurrent hemipelvectomy is considered if the local extent of disease leads to sacrifice of both the femoral nerve and the lumbosacral plexus/sciatic nerve or the hip joint and the femoral or sciatic nerves. Resections of this magnitude would otherwise leave a nonfunctional limb. In addition, patients will have such a large soft-tissue defect that a pedicled quadriceps apron flap is necessary for closure. In these cases, the fibula from the amputated limb can be preserved on a pedicle at the end of the quadriceps flap for reconstruction. This is then used to restore spinopelvic continuity.

Soft-Tissue Reconstruction

Nonhealing perineal wounds following an abdominal perineal approach to complex pelvic tumors are reported to occur in 7–66 % of patients [72]. We, as well as others, have found that the use of a VRAM flap is associated with fewer perineal wound complications [72, 73]. The VRAM provides a well-vascularized, bulky tissue paddle that not only fills dead space but also can be used to reconstruct the perineal skin defect. Our technique is described elsewhere, but in essence, the VRAM is mobilized en bloc with the overlying fat and

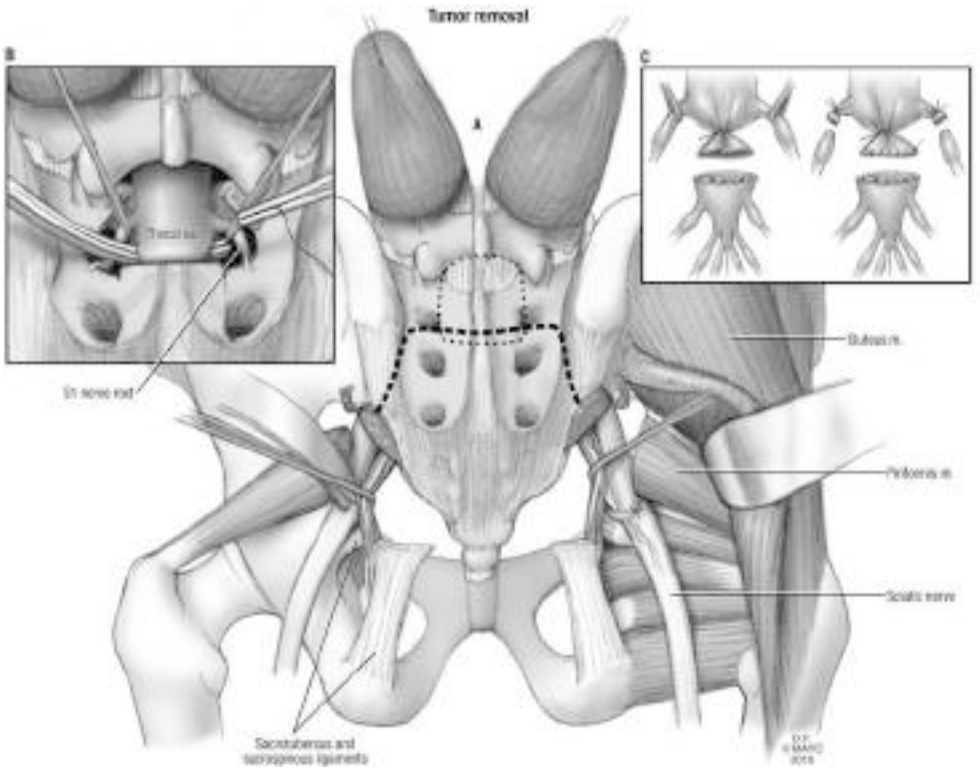

FIGURE 35-9. (**a**) Posterior transverse osteotomy (*thick dotted black line*). Sacrospinous and sacrotuberous ligament transection. The gluteus maximus muscle is reflected laterally to expose obturator vessels and the sciatic nerve. (**b**) Laminectomy to identify thecal sac, (**c**) dural sac, and sacral root ligation.

FIGURE 35-10. Intraoperative photograph of fibula grafts and instrumented spinopelvic reconstruction following total sacrectomy.

skin [74]. Particular attention is paid to the blood supply, especially the deep inferior epigastric artery and vein. Once mobilized, it is rotated transabdominally in the perineum keeping the overlying skin and fat intact, which helps bridge the significant defects that these resections leave behind. In cases where the rectus is not available, a pedicled omental flap can be a good second choice if it is robust. It can fill the pelvic dead space providing vascularized tissue and has been shown to decrease risk of pelvic sepsis following surgery [75]. Moreover, the omentum can line the raw surfaces of the pelvis, preventing the small bowel from getting trapped in the deep pelvis, which is a common cause of small bowel obstruction following exenteration.

Thigh fillet flaps are used after hindquarter amputation and are based on the superior and inferior gluteal vessels. This flap allows one to take advantage of the bulky gluteal muscle, which can cover large defects after the ipsilateral pelvis has been resected. Long anterior hemipelvectomy flaps are based on the vascular muscle distribution supplied by the superficial femoral artery. This flap includes the bulk of the quadriceps femoris and—like the posterior hemipelvectomy flap—can provide significant coverage of very large pelvic and soft-tissue defects.

Results of Surgery

Recurrent Colon Cancer

Limited data exists on surgical and oncologic outcomes in patients with locally advanced recurrent colon cancer. Few centers have published their experience, and patient groups are small and heterogeneous, making definitive conclusions regarding management difficult. In a series from the Mayo Clinic, 73 patients underwent a multimodality approach that included IORT for recurrent colon cancer [63]. In this cohort, an R0 resection was achieved in 52 % and led to a 5-year survival of 37 %. In a series from Leeds, Harji et al. reported on 42 patients with recurrent colon cancer [76]. An R0 resection was achieved in 64 %, and mean survival did not differ between R0 vs. R1 resected patients (29 months vs. 26 months). Survival outcomes were dependent on location of recurrence, and median survival after resection was 33 months for anastomotic, 26 months for pelvic, and 19 months for abdominal recurrences. In the largest series published, Bowne et al. from the Memorial Sloan Kettering Cancer Center reported on 100 patients operated on for curative-intent resection for locally recurrent colon cancer [62]. Fourteen patients were found to have unresectable disease at the time of surgery and 65 % had an R0 resection. Multivisceral resection was common, and the best oncologic outcomes were achieved in patients undergoing R0 resection. Actuarial 5-year survival was 35 % for their entire cohort but was 58 % in those undergoing R0 resection.

In all three of these series, surgery could be performed safely, but multivisceral en bloc resection was required in many patients in attempts to reach a negative-margin resection. Margin status and location of recurrence appear to be the most important predictors of outcome in patients with recurrent colon cancer.

Recurrent Rectal Cancer

In the past, published series of surgery for locally recurrent rectal cancer were limited by small numbers and heterogeneous patient groups. In 2015, we now have robust data that confirms that an R0 resection, the ultimate goal for these operations, is achievable in 70–93 % [17, 18, 42] and overall 5-year survival can be as high as 40 %. Moreover, in series published where IORT is a component of multimodality therapy, meaningful survival can also be achieved in patients who have R1 or R2 resections [40]. Aggressive surgery that includes more lateral pelvic resections (pelvic sidewall tumors) and higher sacral resection (above the third sacral body) is increasingly reported by experienced centers with good results [17, 18, 56, 57].

In a Mayo Clinic series, Hahnloser et al. reported outcomes in 394 patients that underwent a curative-intent resection for locally recurrent cancer [15]. Operative mortality was 0.3 % (1 patient with uncontrolled hemorrhage), and significant morbidities were seen in 26 % of patients (most common was pelvic sepsis). Margin status for this cohort was R0 (45 %), R1 (9 %), and R2 (46 %). Survival was clearly impacted by margin status, 37 % for R0 and 16 % for R1/R2 patients. Other significant findings in this study were that symptomatic pain at presentation and >1 fixation point of the recurrence was associated with margin-positive resection and therefore a poor outcome. Patient demographics, factors related to the initial rectal cancer, and extended vs. limited resection did not impact overall oncologic outcomes. In a series from the Leeds General Infirmary, Boyle et al. reviewed outcomes in 64 patients with locally recurrent rec-

tal cancer, 57 of which underwent curative-intent resection [39]. Pelvic exenteration or sacrectomy was required in 32 %. An R0 resection was achieved in 37 %, perioperative mortality was 1.6 %, and morbidity was 40 %. Overall median survival was 34 months, and R0 resected patients had a significantly longer survival compared to R1 or R2 patients (median survival for R2 was 8 months). In a recent report from Denmark, Nielsen et al. published results on early and late outcomes of surgery for locally recurrent rectal cancer [77]. In their series, 115 patients underwent curative-intent resection. 30-day mortality was 0.8 % and an R0 resection was achieved in 61 %. The 3- and 5-year survival rates for R0 resections were 55 % and 42 %, respectively. No patients with R2 resection lived past 3 years.

Local excision for early rectal cancers has gained wider acceptance in the last 10 years [78]. The risk of local recurrence following local excision remains elevated, especially for high-risk T1 and T2 cancers. When local recurrence occurs following local excision, surgical salvage is the only treatment that has the potential to achieve meaningful survival. In a recent report, Bikhchandani et al. found that R0 resection was possible in 93 % and 5-year survival rate and DFS were 50 % and 47 %, respectively [79]. Metastatic disease following salvage surgery was the most common cause of death in this cohort. You et al. from the MD Anderson Cancer Center reported on 40 patients undergoing surgical salvage following local excision for rectal cancer [80]. A multimodality approach was used and R0 resection was achieved in 80 %. Multivisceral resection was required in 33 % and perioperative morbidity was 50 %. The 5-year overall and 3-year recurrence-free survival was 63 % and 43 %. Pathological stage at initial local excision, receipt of neoadjuvant chemoradiotherapy before local excision, pathological stage at salvage, and R0 resection at salvage significantly influenced re-recurrence-free survival.

The importance of an R0 resection in patients undergoing surgery for recurrent rectal cancer cannot be overstated. A recent meta-analysis of survival based on resection margin status following surgery for recurrent rectal cancer was published by Bhangu and colleagues [81]. In their analysis, they reviewed 22 studies that included 1460 patients and found that 57 % underwent R0 resection, 25 % R1, and 11 % R2. The range of median survival was 28–92 months for R0 resections, 12–50 months for R1, and 6–17 months for R2. Patients undergoing an R0 resection survived on average for 28 months longer than those undergoing R1 resection and 53 months longer than those undergoing R2 resection.

Surgery for Re-recurrent Disease

In the author's view, a second colorectal cancer recurrence is not a contraindication to curative resection as long as the principles of determining resectability for primary recurrence are followed. In a study by Colibaseanu et al., 47 patients underwent surgery for locally re-recurrent colorectal cancer [40]. An R0 resection was achieved in 60 % and 30-day mortality was nil. Overall 2- and 5-year survival was 83 and 33 %. Disease-free survival at 2 and 5 years was 55 and 27 %. In another study by Harji et al., 30 patients underwent resection for a second-time locally recurrent rectal cancer [82]. In their series, an R0 resection was achieved in 30 %, and they achieved a 1- and 3-year survival rate of 77 % and 27 %, respectively. It was the conclusion of both studies that in patients where R0 resection was possible, surgical resection for re-recurrent colorectal cancer had comparable oncologic outcomes than those patients undergoing surgery for first-time recurrences.

Resection That Includes the Aortoiliac Axis

The safety and feasibility of aortoiliac axis reconstruction in the course of complex tumor resections has been well described [83]. Small series have been published that specifically evaluate outcomes following resection in patients with locally recurrent colorectal cancers that involve the aortoiliac axis. In a study by Abdelsattar et al., 12 patients underwent major vessel resection that included the internal and external iliac arteries and veins and in some cases the aorta [69]. An R0 resection was achieved in 7 patients and R1 in 5. No graft complications were seen in long-term follow-up and 30-day mortality was nil. Overall survival and DFS at 4 years were 55 and 45 %. In another study by Austin et al., en bloc vascular resection was done as part of pelvic exenteration for pelvic malignancies in 36 patients (69 % were rectal cancers) [84]. An R0 resection was achieved in 60 % of the locally advanced primary and recurrent rectal cancer cases. For the overall cohort, 46 % of patients were disease-free with the average disease-free interval being 30 months. Both studies concluded that despite the complexity of the technique, the surgery can be performed safely when done by expert multidisciplinary teams, and overall survival and DFS are comparable to outcomes seen with locally advanced disease to nonvascular structures.

Sacropelvic Resections

Owing to the complex anatomical relationships of the pelvic structures, some local recurrences involve multiple fixation points and will require both multivisceral and neuromusculoskeletal resection to achieve a negative-margin resection. Operations for recurrences involving the lateral pelvic sidewall or high lumbosacral skeletal components are among the most technically challenging to perform. In the past, limited data existed regarding both the safety and the oncologic benefits of surgery in these patients. Once thought to be a common contraindication to surgery for recurrent colorectal cancer, high sacral and other complex sacropelvic resections are being done by an increasing number of centers around the world [57]. In most recent series from

specialized centers, authors have shown that surgery in these complex patients can be done safely and with meaningful oncologic outcomes.

In a small series of 9 patients who had sacral resection at the level of the second sacral body or higher (up to fifth lumbar space), Dozois et al. reported an R0 rate of 100 %, no 30-day mortality, and an overall median survival of 31 months [41]. Three patients were long-term survivors at 40, 76, and 101 months. In another study from the same institution, Colibaseanu et al. reviewed 30 patients that had undergone curative-intent extended sacropelvic resections [17]. Four patients in this series underwent hindquarter amputations and over 50 % had sacral resections above the third sacral body. There were no 30-day mortalities and R0 resection was achieved in 93 %. Overall survival and DFS at 2 and 5 years were 79 and 43 %. Overall survival in this series was not different in patients undergoing high (>3rd sacral body) vs. low sacral resection.

In a study from the Royal Prince Alfred Hospital in Sydney, Australia, Milne et al. reported on 100 patients undergoing sacropelvic resection for advanced pelvic malignancies, of which 18 were primary rectal cancers and 61 were recurrent rectal cancers [18]. In the entire cohort, an R0 resection was achieved in 72 %, no 30-day mortality was seen, and overall survival and DFS were 38 % and 30 %, respectively. In a study by Sagar et al. from the Leeds General Infirmary, 40 patients underwent composite sacropelvic resection [56]. An R0 resection was achieved in 50 %, and the mean disease-free interval was 55.6 months for R0 and 32 months for R2 patients.

Postoperative Complications and Quality of Life

Despite the complex nature and magnitude of surgery for local recurrence, several recent series have demonstrated that these cases can be done with an operative mortality rate that ranges from 0 to 3 % [17, 18, 40, 42]. When it does occur, 30-day mortality is usually a result of uncontrolled sepsis. This is a dramatic improvement compared to series published 20 years ago, where operative mortality could be as high as 8.5 % [14]. Several factors are responsible for the significant decrease in operative mortality, better patient selection, improved surgical technique by experienced specialists, better anesthesia, and better postoperative ICU management.

Early and late complications following surgery for local recurrence remain a significant challenge. Most series report intra-abdominal/pelvic sepsis and wound-related complications as the most significant causes of morbidity [17, 18, 56, 60, 67, 85]. Other common complications are postoperative bleeding requiring transfusion, voiding dysfunction, prolonged ileus, delayed small bowel perforation, and late fistulas. Universally, higher complications are associated with extended resections such a sacrectomy and exenteration [15, 17]. Urologic complications both early (ureteral obstruction, leak) and late (ureteral stricture) are reported in many series. In a study by Rahbari et al., risk factors associated with postoperative complications were analyzed [86]. In their series, 92 patients underwent curative-intent surgery for recurrent rectal cancer. To identify predictors of complications after resection, univariate and multivariate analysis was done. On univariate analysis, partial sacrectomy ($p=0.0001$), intraoperative blood loss ($p=0.005$), amount of transfusion ($p=0.02$), and operating time ($p=0.006$) were associated significantly with surgical complications. Multivariate logistic regression analysis of ASA score, BMI, partial sacrectomy (yes or no), blood loss, operating time, and the use of IORT (yes or no) revealed that partial sacrectomy is the only independent predictor of surgical morbidity. It is the author's perspective that careful surgical planning, reducing blood loss, reducing operating time, and the judicious use of soft-tissue flaps can significantly decrease postoperative morbidity.

Little information exists about the impact of major surgical intervention on quality of life in patients with recurrent colorectal cancer. While oncologic outcomes remain the most important outcome measure for patients and physicians deciding on an aggressive surgical approach, quality of life after surgery must be considered and discussed with patients so that they are well informed. In the modern era, advances in surgical technique and expertise allow surgeons to perform increasingly more complex operations, and how these operations impact quality of life is a relevant and growing area of interest to both patients and surgeons.

In a study by Austin and colleagues at the Royal Prince Alfred Hospital in Sydney, Australia, quality of life in 75 patients undergoing pelvic exenteration for advanced rectal cancer was assessed using the Short Form 36 version 2 (SF-36v2) and Functional Assessment of Cancer Therapy-Colorectal (FACT-C) instruments [87]. They found that FACT-C scores in survivors were good and comparable to those of patients who had low anterior resections or abdominal perineal resections. Though the summary scale of the SF-36v2 form was lower in exenteration patients than the general Australian population, the mental component summary scale was high and comparable. In a systematic review of health-related quality of life (HRQoL) in patients with locally recurrent rectal cancer, Harji et al. reviewed a total of 14 studies compromising 501 patients [88]. This study (the first published study to focus exclusively on HRQoL in patients with locally recurrent rectal cancer) identified several consistent themes. There are few studies of variable quality, reporting on a large number of HRQoL domains. Moreover, the heterogeneous treatment approach and patient population make study comparisons difficult. Harji and colleagues conclude that a disease-specific, validated, and reliable outcome measures are both lacking and required to provide meaningful data in patients who undergo surgery for locally recurrent rectal cancer. This tool, once developed,

could then be used to prospectively measure HRQoL. This data would be very useful in assisting in surgical decision-making for both the physician and the patient.

Palliative Approach

Patients with an asymptomatic recurrence which is unresectable, either due to the presence of concurrent metastases or because of local factors, do not warrant surgical intervention [89]. In symptomatic patients, EBRT can sometimes relieve obstruction, decrease bleeding, and reduce pain [90]. Endoscopic stenting is especially helpful with malignant obstructions and can in some cases be used to palliate malignant fistulas that are inoperable [91, 92]. Patients not candidates for stents may need a colostomy for symptomatic relief.

Chemotherapy has been shown to prolong survival and palliate symptoms in patients with primary metastatic colorectal cancer, and in large, the treatment of unresectable recurrent colorectal cancer is based on extrapolations from this data. FOLFOX and FOLFIRI are the most commonly used chemotherapy protocols in patients with unresectable metastatic disease. The three most prominent trials comparing the two regimens did not distinguish which is superior, though both regimens prolong survival [93–95]. Newer agents such as bevacizumab, cetuximab, and panitumumab have and continue to be studied as monotherapy or as part of multidrug regimens [96–98].

Patients in whom a palliative approach is taken will benefit greatly by meeting with a palliative medicine team to discuss treatment goals and assist with end-of-life decisions. In addition, a cancer pain specialist can assist in reducing suffering through optimal pain management, and this should be the goal in patients undergoing a palliative approach.

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36
Colorectal Cancer: Management of Stage IV Disease

Glenn T. Ault and Kyle G. Cologne

Key Concepts

- Multidisciplinary evaluation is of paramount importance in the treatment of metastatic colorectal cancer.
- Positron emission tomography (PET) scan should be used in the evaluation of metastatic disease prior to potentially curative surgical therapy, or in cases of equivocal disease, but not for routine detection of metastatic disease.
- Patients with incurable metastatic disease and asymptomatic primary tumors should be considered for initial treatment with chemotherapy.
- For metastatic colorectal liver lesions, synchronous resection, liver-first, or colon-first strategies are all acceptable means of surgical treatment.
- Resection, ablation, or a combination of ablative and resection techniques can be used to minimize parenchymal liver resection and preserve function when treating metastatic colorectal metastases.
- Cytoreduction and hyperthermic intraperitoneal chemotherapy (HIPEC) may be considered in appropriately selected patients treated at specialized centers with expertise in this technique, although it has not been demonstrated to be superior to modern systemic chemotherapy.
- Metastases to organs other than the liver, lung, ovary, or peritoneum are uncommon and commonly occur in conjunction with widely metastatic disease. Thus, resection rarely has an impact on overall survival and should only be undertaken in select circumstances after multidisciplinary evaluation.
- Treatment of metastatic disease in the elderly requires consideration of the performance status, frailty, and impact of various treatments on quality of life.

Introduction

Despite screening protocols, approximately 20% of colorectal cancer patients present with established distant metastasis [1]. Computed tomography (CT) scan or magnetic resonance imaging (MRI) generally detects this metastasis at the time of the initial staging of the cancer. Once the diagnosis of stage IV disease is made, a multidisciplinary team should plan appropriate curative or palliative therapy. Unfortunately for the clinician, there is enormous heterogeneity with respect to sites of disease, extent of disease and symptoms, performance status, and comorbidities in these patients. Stage IV patients have a range of presentation from the asymptomatic patient with a single metastatic lesion to the rapidly deteriorating patient with colon obstruction and advanced multiorgan metastases. While treatment algorithms may exist for some forms of metastatic disease such as a solitary liver lesion, others, especially for those with multiple sites of metastases, are still being defined. This chapter aims to provide a reference source for colorectal surgeons managing patients who present with metastatic stage IV colorectal cancer.

While there has been considerable progress in the treatment of advanced colorectal cancer, the vast majority of stage IV patients are unfortunately not curable by current treatment protocols. An evaluation of data from the SEER population-based database estimates that the 5-year survival rate for stage IV patients diagnosed between 1991 and 2000 was 8% [2]. Even with this low overall cure rate, there are treatment options available to extend survival and enhance quality of life. Oncologic teams have several tools to utilize including systemic chemotherapy, radiotherapy, endoscopic treatments to palliate obstruction, surgical diversion, and surgical resection, all of which can play important roles in the treatment of these patients. Treatment approaches must be individualized based on the extent of resectability of local and distant disease, the presence or absence of bowel obstruction, performance status, and comorbidities. For patients with good performance status and minimal symptoms from the primary site of the cancer, standard treatment is systemic chemotherapy, which has been proven to prolong survival and quality of life [3, 4]. Surgical resection of the primary tumor and, if indicated, of the metastatic lesions can provide excellent palliation and in a limited number of cases can provide lasting cure.

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First-line therapy with either FOLFOX or FOLFIRI now has been shown to yield major responses in up to 50% of previously untreated patients and achieves minor responses or stable disease in an additional 20% of patients [5]. Multiple effective drug combinations are available as well, and second and third line chemotherapy is becoming more effective and more likely to impact survival. Over the past 15 years, the median survival for patients with metastatic disease who are treated with chemotherapy has improved from 9 to 12 months and is currently greater than 24 months and may be as long as 36 months [6–8]. Although cure from chemotherapy alone remains extremely rare, effective chemotherapy combined with aggressive surgery may be increasing the overall cure rate. In this setting, the care of patients with advanced disease has become quite complex. In this chapter the aim is to provide a reference source for colorectal surgeons managing patients who present with metastatic stage IV colorectal cancer.

Biology of Metastatic Disease

Metastasis is defined as the spread of malignant cells from a primary tumor to a distant organ. It is estimated that 90% of all cancer deaths are the result of metastatic spread [9]. The biologic process of metastasis is poorly understood. Numerous clinical and laboratory studies have attempted to define the complex process of metastasis formation. The process relies on properties of the tumor cells, as well as the microenvironment of the primary and secondary sites [10, 11]. A series of major events must occur (Figure 36-1).

The first step is tumorigenesis, which occurs after the initial malignant transformation. The tumor proliferates into a small mass of heterogeneous cells that are of varying metastatic or malignant potential. These tumor cells undergo multiple and sequential genetic changes, characterized by the appearance of oncogenes and a decrease in tumor suppressor genes. As a tumor grows beyond 1 mm in diameter and becomes relatively hypoxic, angiogenesis is initiated. The process of tumor angiogenesis is tightly regulated by pro- and antiangiogenic factors secreted by both the tumor and its environment. As tumors successfully grow, suppressors of angiogenesis are inhibited, and proangiogenic factors predominate, resulting in neovascularity and further growth of the tumor [12]. Some tumors may grow by utilizing other existing blood vessels in nearby tissues.

In the next step, some cells will develop an invasive phenotype. Most researchers believe that there is a selection process resulting in the clonal expansion of certain cell subpopulations with growth advantage and invasive properties. Whether this process represents a property of the whole tumor cell mass or true clonal selection of more invasive cell subpopulation is not known, and it is a subject of intense research [13]. Malignant invasion is characterized by down-regulation of cell adhesion, resulting in detachment of the cell from the primary tumor mass and the extracellular matrix. Stromal invasion is accomplished through interactions with the basement membrane, including adhesion,

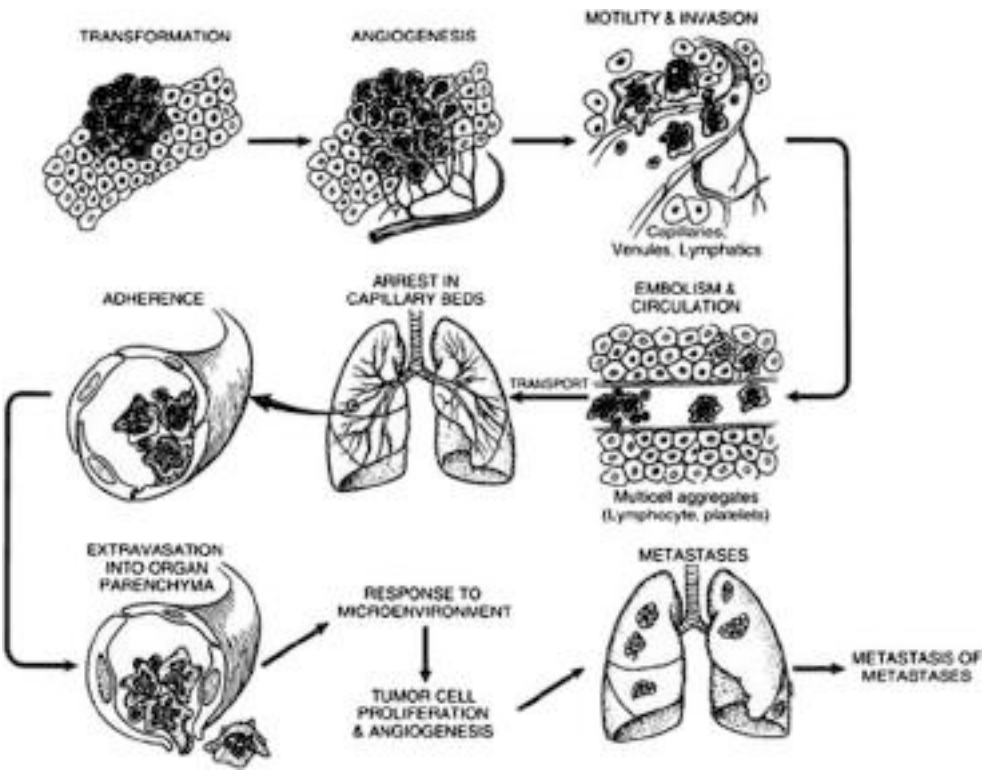

FIGURE 36-1. Schematic illustrating the multistep process involved in the development of metastasis. With permission from DeVita VT Jr., Hellman S, Rosenberg SA. Cancer: Principles and Practice of Oncology, 6th ed., Lippincott Williams and Wilkins, copyright 2001 [303].

proteolysis, and migration, ultimately resulting in detachment and invasion through the basement membrane. This invasive phenotype also enables these cells to enter thin-walled lymphatics and vasculatures, allowing access to systemic circulation [14, 15]. Once inside the vascular system, cells or cell clumps (emboli) are circulated and must survive hemodynamic filtering as well as immune surveillance. They must then arrest in distant organ. There is likely a complex interaction between the malignant cell and the endothelium or exposed basement membrane, allowing cell arrest. Once arrested in a tissue bed, the cells extravasate into the tissue, enabling formation of the metastatic focus. These metastatic cells can become dormant or proliferate; what determines this fate is not fully understood. Growth in the distant organ after deposition is a major limiting factor in the formation of metastasis. Some metastatic cells can remain dormant while others proliferate and must again go through tumor genesis, angiogenesis, and evasion of the immune system. This complex multistep process of metastasis formation is related to multiple genetic changes among malignant cells. Recent studies have shown differences in the genetic fingerprints of matched primary tumors and their lymph node metastasis suggesting that tumors may undergo continual mutagenesis. The metastatic tumor cells may genetically look very different from its parent primary cells [16]. This finding appears to confirm that there are genes specific to tumorigenesis, invasion, angiogenesis, and other steps. A number of genes have been identified that suppress metastatic potential and, by their downregulation, affect a cell's ability to metastasize without affecting tumorigenicity [16].

These discoveries provide a sense of the future challenge in elucidating the multiple, stepwise, and specific changes that regulate a cell's ability to metastasize. Advances in this field will have obvious and profound implications for the treatment of cancer.

Diagnostic Strategies

Part of the evaluation of newly diagnosed colorectal cancer includes systemic staging with cross-sectional imaging of the chest, abdomen, and pelvis. Rectal cancers will also include additional local staging with an endorectal ultrasound or pelvic MRI [17]. Twenty to thirty percentages of patients will present with evidence of metastatic disease on this staging workup [17, 18]. Increased suspicion should be given to the presence of metastatic disease when the CEA level is greater than 20 ng/mL [19].

There is the potential for some diagnostic uncertainty, as some lesions detected on staging workup may represent entities other than metastatic cancer (such as cysts, hemangiomas, granulomatous or infectious lesions, focal nodular hyperplasia, etc.). Hemangiomas have a prevalence of 7–21% and have characteristic imaging findings including a hyper-enhancing ring. Focal nodular hyperplasia is present in up to 3% of patients [18]. There are several imaging modalities that can be used to help identify true metastatic disease from other possibilities in the differential diagnosis, and each has unique characteristics. None is infallible, and in cases of uncertainty, multiple imaging modalities or tissue biopsy may be required to confirm the diagnosis, as it dramatically changes the prognosis and perhaps the treatment strategy as well. Consultation with a radiologist specializing in these imaging techniques is also helpful.

Computed Tomography

Computed tomography has been the mainstay of distant staging workup for colorectal cancer. Technology now allows high resolution, subcentimeter slice thickness with multiplane reformatting. This allows vascular reconstruction and volumetric analysis, which can be particularly important for operative planning for large liver resections [20–22]. Triple phase scans allow improved delineation of hepatic metastases (Figure 36-2). Though enhancement characteristics differ, most metastatic lesions are hypoattenuating on portal venous phases of an abdominal CT. Numerous studies have failed to gain significant value in routine use of four-phase CT to detect hepatic metastases, and portal venous phases are the most important to detect hypoattenuating liver lesions suggestive of metastases [23–25]. Despite this, up to 25% of hepatic liver metastases may be missed on high-quality CT, due mostly either to size or confusion with other disease processes [26, 27].

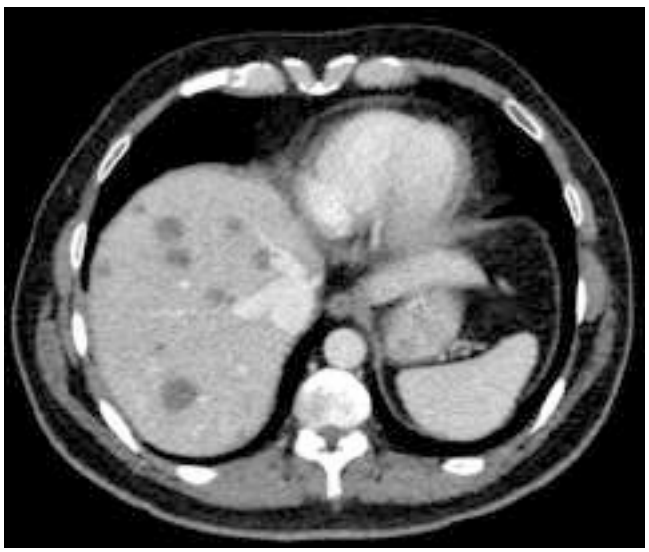

FIGURE 36-2. CT of the abdomen demonstrating liver metastases involving multiple segments of the liver. Treatment of these requires advanced planning and input in a multidisciplinary setting involving hepatobiliary, interventional radiology, oncology, and other specialties to determine planned interventions and timing.

Positron Emission Tomography

PET and PET-CT scans are a modality used both for initial staging and for follow-up imaging. The technology has dramatically improved recently and can now provide very clear pictures of tumor deposits in distant locations (Figure 36-3) [28]. Sensitivity of PET-CT for detecting metastatic lesions ranges from 87 to 100%, which compares favorably with regular CT (where sensitivities range from 52 to 69%) [29]. Specificity of PET-CT is also good and ranges from 94 to 100% (compared with 80–94% for regular CT). Limitations include a size resolution of about 1 cm and limited ability to detect mucinous tumors. Some studies suggest that the ability of PET-CT to detect subcentimeter lesions may be less than 50% [30–32]. Most protocols include a lack of intravenous contrast, which may limit the ability to evaluate some smaller lesions. National Comprehensive Cancer Network (NCCN) guidelines do not recommend routine use of PET-CT to evaluate metastatic lesions except in equivocal findings or in cases where patients are allergic to IV contrast which would otherwise limit the usefulness of regular CT [33]. In cases where patients are being considered for liver resection of metastatic tumor, there is some evidence that PET-CT can detect extrahepatic disease that is missed in up to one third of patients evaluated by CT scan alone. This changed management strategy in 8–21% of patients [34].

Magnetic Resonance Imaging

While MRI is used to perform the initial staging of rectal cancers, it can also be useful for characterizing equivocal lesions of the liver, as it is particularly good at soft tissue characteristics, especially those that fall below the resolution of PET [35, 36]. The soft tissue delineation is also better than CT scan and can help with tumor identification [34]. MRI of the liver with contrast using a liver-specific protocol can help define lesions that are potentially resectable. Sensitivity of MRI at detecting response of liver lesions to neoadjuvant treatments may be better than PET [37]. MRI cannot be used in patients with pacemakers, implantable cardiac defibrillators, cochlear implants, and other orbital foreign bodies [18]. Cost remains a significant factor that also limits routine use of MRI in the evaluation of liver lesions.

Contrast-Enhanced Ultrasound

Contrast-enhanced ultrasound (CEUS) is the newest imaging modality to gain popularity. It is highly operator dependent but highly effective (one study demonstrated 97% of lesions seen on CT were also detected on CEUS) [38]. As centers gain expertise in this modality, its use may increase in the future. Another potential limitation is that chemotherapy-induced fatty infiltration of the liver may limit diagnostic accuracy.

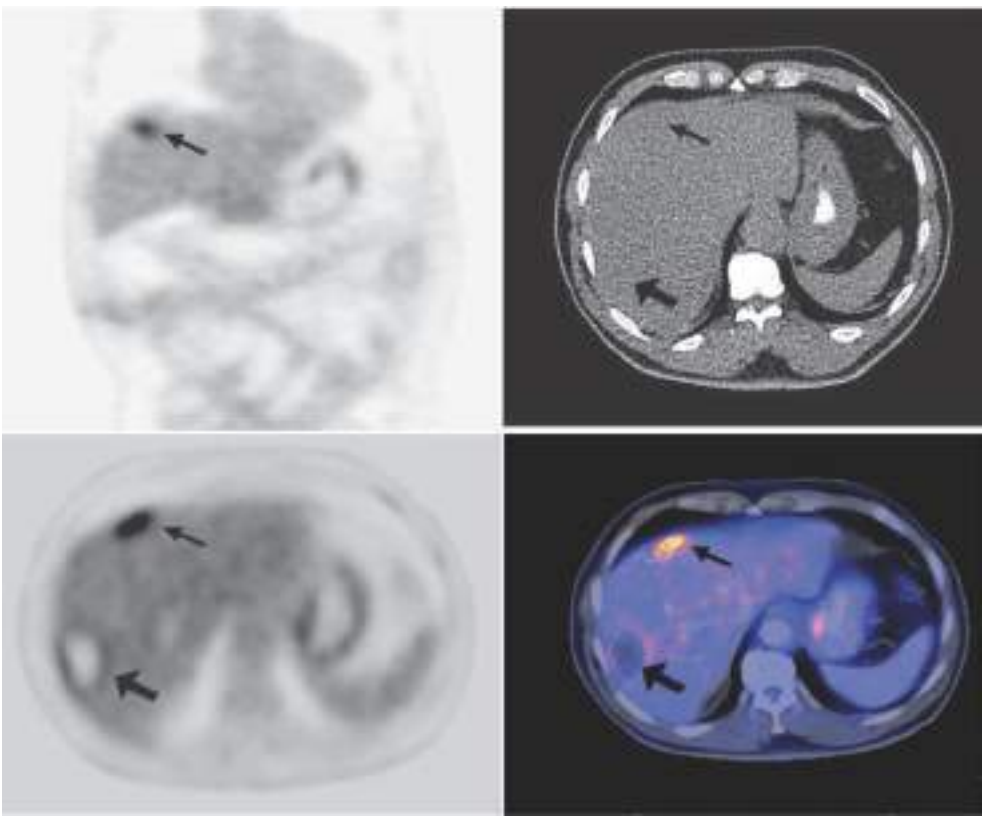

FIGURE 36-3. PET-CT scan and various phases. Lesions may not always show up or appear active on all phases of imaging.

Biopsy

In equivocal cases where imaging characteristics are not suspicious of colorectal metastases, tissue biopsy confirmation remains an option. A small percentage of patients will have a histologic process other than the primary malignancy [39, 40].

Multidisciplinary Evaluation

Multidisciplinary evaluation is of critical importance to caring for patients with metastatic disease. As there is often no one agreed-upon absolute treatment strategy, it is important to have consensus from treating oncologists, radiation oncologists, and various surgical disciplines such as colorectal, hepatobiliary, thoracic, and gynecology [41, 42]. Of particular value is whether or not an organ can be rendered disease-free. This allows surgery for cure, which has a different end point than surgery for palliation [43]. It is estimated that only 20–30% of patients with identified metastatic disease will have potentially resectable disease [44]. Goals of multidisciplinary evaluation should include relief of symptoms and quality of life improvement and determine the best means of prolonging life expectancy. In some cases, this may include chemotherapy alone. Consideration must be given to multiple variables including performance status, tumor burden, patient's expectations of treatment, and overall care goals.

If disease is determined to be resectable, common considerations are whether to perform sequential or simultaneous resections, use of chemotherapy or radiation in a neoadjuvant or adjuvant setting, and whether or not to perform an anastomosis. If the disease is not resectable, there are a few common scenarios that deserve some additional attention. A typical algorithm can be found in Figure 36-4.

Surgical Emergency

Tumors at the primary site may cause a surgical emergency, even in the setting of metastatic disease. In these cases, surgical intervention should be undertaken to relieve the immediate, life threatening issue, such as perforation with peritonitis, lower GI bleeding, or large-bowel obstruction. If possible, and if it can be performed with limited morbidity, an oncologic surgical resection should be performed [17, 45]. A primary anastomosis can be performed in select, low risk patients, but carries the potential it may delay chemotherapy and other life-sustaining treatments if an anastomotic leak should occur [46]. This should be weighed very carefully when performing surgery in the emergent setting.

Palliative Management of Primary Cancer: Laser, Fulguration, and Stents

Incidence and Presentation

Approximately 8–29% of patients with colorectal cancer initially present with symptoms of partial or complete bowel obstruction [47]. In a review of 713 obstructing carcinomas, 77% were left-sided and 23% were right-sided cases [48]. The majority of patients with obstructing colorectal carcinomas have either stage III or stage IV disease [49]. Acute malignant colon or rectal obstruction is an indication for emergent surgical intervention. However, these emergency operations are associated with a mortality rate of 15–34% and a morbidity rate of 32–64% despite advances in perioperative care [49, 50]. Therefore, alternative palliative endoluminal strategies aimed at relieving obstruction have gained increasing popularity over the past decades.

The initial symptoms of bowel obstruction may include mild discomfort and a change in bowel habits. With disease progression and luminal narrowing, the symptoms may worsen ranging from crampy abdominal pain, abdominal distension, nausea, abdominal tenderness, and obstipation. Vomiting is a late symptom unless there is an associated small bowel obstruction. Leukocytosis is a concerning finding and may indicate near or complete obstruction. Without treatment, the process can progress to complete obstruction, ischemia, and perforation. The risk of cecal perforation is greatest in patients who have a competent ileocecal valve that does not allow decompression of the large intestine into the proximal small intestine.

In the setting of metastatic cancer, the clinician must first answer the following critical question, "is the colon or rectal

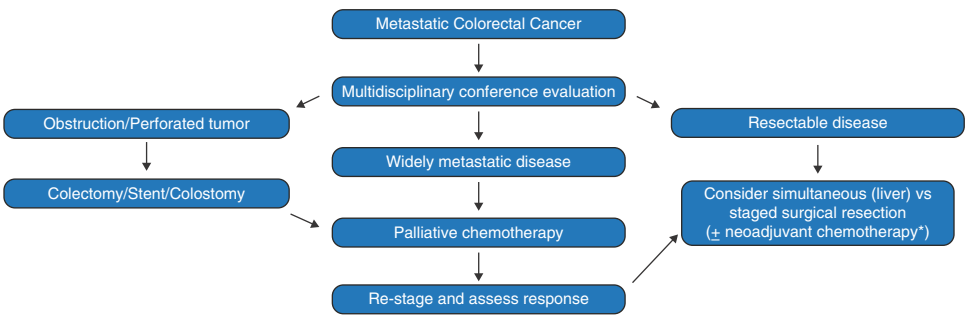

FIGURE 36-4. Treatment algorithm for metastatic colorectal cancer.

obstruction a contraindication for system chemotherapy or radiotherapy?" The degree of obstructive symptoms and endoscopic and radiographic findings are key elements to consider when answering this question. If the patient has minimal symptoms and there is no radiographic evidence of high-grade obstruction, many patients with partially obstructing colon and rectal cancers will tolerate aggressive chemotherapy as described previously in this chapter. In those patients with partially obstructing rectal cancers, the addition of radiation therapy is also well tolerated and can be highly effective. Patients must be instructed to monitor their symptoms closely and to report any signs of worsening obstruction immediately. A liquid diet or pureed diet with adequate protein and calorie intake taken in small portions may help reduce obstructive symptoms. For patients with advanced obstruction, nonsurgical palliative options include laser therapy, fulguration, and colonic self-expanding metal stents. If less-invasive endoluminal strategies are not successful in patients with nonresectable malignant obstruction of the colon and rectum, surgical creation of palliative proximal diverting stoma or intestinal bypass should be performed.

Laser Therapy and Fulguration

Laser therapy has been utilized for palliation of obstructing rectal cancers [51–54]. In a large series of 272 patients who underwent palliative laser therapy for rectosigmoid cancers, the immediate success rate in treating obstructive symptoms was 85% [55]. Other studies have shown similar success rates in the range of 80–90% [53, 54]. However, laser therapy is practical only for treating cancers of the distal colon and rectum and is rarely used to treat proximal lesions. In addition, multiple sessions are often required in order to achieve lasting relief of symptom. Serious complications like bleeding, perforation, and sever pain have been reported in 5–15% of patients, especially those undergoing multiple treatment sessions [52, 54–56]. While laser therapy has been shown to be practical and feasible to other palliative treatment modalities in the management of these unfortunate stage IV patients and has low morbidity and mortality [57], it does not affect overall survival of stage IV patients.

Surgical fulguration of rectal cancers is another method of opening the rectal lumen and relieving obstruction [58, 59]. Fulguration, in combination with endoluminal debulking, can remove a large volume of tumor. However, unlike laser therapy, fulguration and debulking require hospital admission and regional or general anesthesia. Both fulguration and laser therapy have given way to stenting.

Self-Expanding Metal Stents

Since their introduction in 1991, colonic stents have become an effective method of palliation for obstruction in colorectal cancer patients, especially those with unresectable metastatic disease, or used in an effort to decompress an obstructed patient preoperatively [60]. Especially in nonoperative stage IV patients or those that have significant comorbidities, these self-expanding metallic stents can potentially dilate the lumen to a near-normal diameter, providing quick relief of symptoms. Stents can be placed in patients using minimal sedation in the endoscopy suite with the aid of fluoroscopy. Moreover, these stents can be placed across relatively long lesions by overlapping stents in a "stent-within-stent" fashion. Laser therapy has also been used in certain situations, in conjunction with colonic stents, to recanalize and decompress large bowel or when tumor ingrowth occurs in patients who have had long-term stents in place. It should be noted the emergency surgery is recommended over stent placement in those patients with evidence of colonic obstruction and systemic toxicity. Presence of systemic toxicity may indicate the presence of ischemia and/or perforation which requires immediate evaluation and the potential for emergency surgery.

Stenting can achieve long-term palliation in patients who are not operative candidates. More than 75% of patients can achieve adequate palliation with stenting, although tumor ingrowth, stent migration, and perforation, especially those receiving bevacizumab, may occur [61]. If these stent-related complications occur, it may necessitate reintervention either with an additional stent or with other palliative measures such as laser or argon plasma coagulation therapy or surgery [62].

A systematic review from 1990 to 2000 of the published data on stenting of colorectal obstruction included 29 case series in the analysis [63]. The review evaluated technical and clinical success, complications, and reobstruction. Cases involving stent replacement for palliation and stent placement as a "bridge to surgery" were both assessed. Stent insertion was attempted in 598 cases. Stent deployment was technically feasible in 551 (92%) cases and clinically successful in relieving obstruction in 525 (88%) cases. Palliation of obstruction was achieved in 302 (90%) of 336 cases. Stent placement as a "bridge to surgery" was successful in 223 (88%) of 262 insertions of which 95% had a one-stage surgical procedure. There were three deaths (1%). Perforation occurred in 22 cases (4%). Stent migration was reported in 54 (1%) of the 551 technically successful cases. Stent reobstruction occurred in 52 (10%) of the 525 clinically successful cases and trended toward a higher incidence of reobstruction in the palliative treatment group. The reviewers concluded that "stent usage can avoid the need for a stoma and is associated with low rates of mortality and morbidity" [63]. A series of 52 patients with malignant obstruction secondary to either primary or recurrent colon or rectal carcinoma, who underwent stent replacement by colorectal surgeons, reported that 50 out of 52 were successfully palliated [64]. One patient had a perforation, and in another patient obstruction was not relieved because of multiple sites of obstruction. The overall complication rate in this series was 25%. Stent migration was the most common complication (15%), followed by reobstruction secondary to tumor ingrowth (4%), perforation (2%), colovesical fistula

(2%), and sever tenesmus (2%). Surgical intervention was required in 17% of cases due primarily to one of the above complications or recurrent obstruction.

There are limited data evaluating stent placement proximal to the splenic flexure. In a recent publication, colonic stenting was attempted in 97 patients with malignant large-bowel obstruction [65]. Sixteen (17%) patients had lesions proximal to the splenic flexure (eight ascending, eight transverse colon). Stenting was successful in relieving obstruction in 14 (88%) of these patients. Stenting was performed for definitive palliation in nine of these patients and as a bridge to elective surgery in the other seven patients. One patient developed gastrointestinal bleeding that was managed conservatively. No perforations or stent migrations were reported [65].

Complications reported in the literature for colonic and rectal stents include stent malpositioning, perforation, stent migration, tumor ingrowth (through the stent interstices), tumor overgrowth (beyond the ends of a stent), stool impaction, bleeding, tenesmus, and postprocedure pain (Figure 36-5). Perforation and stent migration occur with the highest frequency. The rate of perforation however appears to be decreasing overall as the technique and technology have improved and in experienced hands is now approximately 5% [66]. Stent migration has been described to occur in a median of 11% of patients in a systematic review [67]. Migrations tend to occur with stents that are too narrow or too short in relation to the obstructing lesion or in the presence of tumor shrinkage following therapy [68]. Stenting of cancers in the mid to low rectum may result in urgency, pain, and incontinence. While the complications associated with stents and other less-invasive endoluminal strategies should not be taken lightly, one must keep in mind that emergency operations for malignant colon and rectal obstruction have a significant mortality rate of 15–34% and a high morbidity rate of 32–64%. Taken in the correct context, these endoluminal palliative strategies provide increasingly effective and durable relief for patients with malignant obstruction.

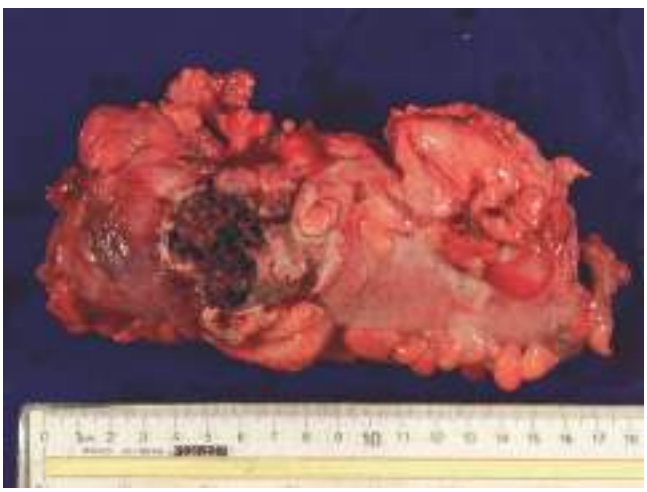

FIGURE 36-5. Perforation of the bowel in a colonic stent. Courtesy of Philip Y. Pearson, M.D.

The Challenge of Primary Tumor Management in Asymptomatic Stage IV Colorectal Cancer: To Resect or Not to Resect?

Optimal first-line therapy for patients who present initially with unresectable stage IV disease remains controversial. Some advocate initial resection of the primary, while others recommend initial chemotherapy if the primary tumor is asymptomatic.

In the era of modern chemotherapy, patients can experience increased length and quality of life with 5-FU-based multiagent chemotherapy [69]. Prophylactic resection of the primary tumor can provide long-term local control and may benefit select patients [70]. This must be weighed against the risk of surgical complications resulting in delay in chemotherapy and other palliative treatments. Particularly in rectal cancer, complications arising from surgery have been shown to delay initiation of chemotherapy beyond 8 weeks postoperatively. As these patients have worse overall survival, the risk of these complications may not be inconsequential [71]. As there are no randomized, controlled trials for this topic, some information on the natural history of the disease can aid management decisions.

Poultsides et al. [72] examined the natural history of patients receiving primary chemotherapy without surgical intervention for stage IV colorectal cancer. Left untreated, only 7% of primary lesions progressed to require emergency surgery for obstruction or perforation while receiving palliative multiagent chemotherapy. An additional 4% required a nonoperative intervention (e.g., stent or radiotherapy). The remaining 89% never required any further intervention on the primary tumor. Twenty percent responded well enough to undergo combined resection at the time of subsequent metastasectomy. Matsumoto et al. [73] reported that 75% of patients with unresectable disease could be spared primary tumor intervention. An endoscopically nontraversable primary lesion at the time of diagnosis was predictive of subsequent need for intervention (which occurred 64% of the time within the next year). Other studies suggest that 68–90.7% of patients will not require surgical intervention on the primary tumor [69, 74–76]. As there are some high-risk features that may predispose to perforation or obstruction, some oncologists will request initial surgical diversion for locally advanced, near-obstructing lesions or those that display signs of impending perforation or abscess on imaging.

Indeed, the argument for up-front primary tumor resection is based on the desire to avoid potential complications from the primary tumor during treatment. This concern may be greatest when the agent bevacizumab is utilized—which has led both surgical and medical oncologists to advocate primary tumor resection at the time of diagnosis prior to the institution of the drug [77, 78]. In fact, the majority of US patients presenting with stage IV disease will still undergo

noncurative primary tumor resection, perhaps partially for this reason. However, during the past decade, several highly active systemic agents, both cytotoxic and biologic, have become available for the treatment of patients with metastatic colorectal cancer. As a result the median survival of patients with unresectable metastatic disease has increased from 9 to 12 months with fluorouracil alone to up to 24 months with sequential modern cytotoxic and biologic treatments [8]. Therefore, it may be generally accepted that, in these stage IV patients, systemic chemotherapy with or without primary resection is the essential treatment modality to prolong survival. These modern agents also have increased activity on the primary tumor and can even induce a complete response [79–81]. Thus the old question of how best to manage the primary tumor continues to be debated. It is agreed upon that resection of a lymph node basin outside the primary vascular pedicle is rarely indicated [82].

While there was some initial evidence in the literature that resection of the primary tumor was associated with a survival benefit [83], this finding was most likely the effect of selection bias. Patients with less extensive disease, or better performance status, were selected for resection [74, 84, 85]. Currently, routine surgery for the asymptomatic primary tumor in the setting of unresectable metastatic disease is not recommended. This recommendation stems in part from a Cochrane review of 798 studies involving 1086 patients that suggests there is not enough evidence to justify routine resection of primary tumors. Furthermore, survival was not consistently improved with primary tumor resection, nor was morbidity of complications from tumor complications reduced by initial resection. However, further study was recommended as there is a paucity of randomized trials on this matter [17, 86].

Investigators from the National Surgical Adjuvant Breast and Bowel Project (NSABP) have reported results of a phase II prospective single-arm study or primary systemic chemotherapy with fluorouracil, oxaliplatin (mFOLFOX6), and bevacizumab for patients with asymptomatic primary intact unresectable stage IV colorectal cancer (NSABP C-10) [87]. The investigators aimed to directly address the concerns for both primary tumor-related complications associated with first-line systemic therapy in patients with asymptomatic disease and the risk of tumor complications with the use of bevacizumab in this setting. A total of 86 patients form 29 institutions were evaluated with the primary eligibility criteria being that the treating clinician identified the patient to be asymptomatic with respect to his or her primary tumor. After a median follow-up of 20.7 months, the majority of the patients could be successfully managed nonoperatively without the need for primary tumor intervention, meeting the study's primary end point. Median overall survival was 19.9 months, and the overall rate of major morbidity related to the intact primary tumor was 16.3% (95% CI, 7.6–25.1%) at 24 months.

The investigators concluded that the first-line combination therapy with mFOLFOX6 and bevacizumab did not result in an unacceptable rate of primary tumor-related complications and that noncurative resection of the asymptomatic primary tumor in these patients could be avoided. These findings confirm prior retrospective reports demonstrating low rates of intestinal complications with either fluorouracil-based or more modern systemic chemotherapies [72, 88, 89]. In their prospective evaluation, however, the NSABP investigators [87] have further demonstrated the safety of first-line chemotherapy with bevacizumab in patients with intact but asymptomatic tumors. Indeed, 73.3% of the patients still had not required primary tumor resection at the time of death or last follow-up.

This study has moved clinical treatment decision-making forward and provides prospective evidence that routine noncurative resection may be unnecessary. This relatively small study also highlights a key question in determining which patients may be eligible for this approach. Establishing a patient as "asymptomatic" was a key eligibility criteria. In this study, asymptomatic was defined as having no bowel perforation or obstruction and no active bleeding requiring a transfusion [87]. It was at the treating physician's discretion to define whether a patient exhibited signs of obstruction. The key issue of understanding which patients are eligible for this approach can also influence the true incidence of primary tumor-related morbidity (i.e., not all patients with asymptomatic disease are the same.) Despite some limitations of the study, the results were reassuring for the safety of first-line systemic chemotherapy with bevacizumab. There will remain a group of patients who will still require subsequent primary tumor resection. The challenge of identifying these patients for planned elective resection to avoid the higher mortality and morbidity risks of emergent resection while sparing the morbidity of resection still needs to be defined.

It also needs to be acknowledged that retrospective comparative studies, even in the era of modern systemic therapies, have demonstrated survival benefits associated with resection of the primary tumor, although the individual contributions of the multiple factors of patient selection, location and extent of tumor burden, tumor biology, ability to tolerate, and availability of systemic therapy and aggressiveness of surveillance are unknown. A comparative multi-institutional study of patients with stage IV cancer at diagnosis remarkably demonstrated a median survival of 30.7 months with primary tumor resection compared with 21.9 months ($p=0.031$), raising the question of whether primary tumor resection has the potential to further improve median survival beyond what can be achieve by even modern systemic therapy alone [90]. Perhaps there is a group of patients with putatively asymptomatic circumferential or locally advance primary tumors who might derive a survival benefit from either up-front or interval resection with the potential to avoid the need for emergent intervention or

permanent ostomy. Performing a randomized study in an unselected stage IV population may indeed prove to be difficult.

The NSABP C-10 trail is the only modern prospective multi-institutional study that specifically addresses the issue of primary tumor resection in patients with asymptomatic stage IV colorectal cancer. Current treatment patterns are influenced by strong patient and provider biases but with this trial there is no additional evidence supporting the safety of systemic chemotherapy as the initial primary treatment approach for carefully selected asymptomatic patients avoiding the need for and the morbidity risk of noncurative resection. Unfortunately more questions remain and additional study is needed to help us understand how best to select patients and optimize the available treatment modalities, including surgery to improve outcomes and prevent subsequent morbidity.

Surgical Therapy of Liver Metastases

Liver metastases are a common occurrence, and surgical resection represents the best opportunity for long-term cure. Approximately 20–30% of patients have potentially resectable lesions at the time of diagnosis. With appropriate selection, 5-year survival has been reported around 30% (range 15–67%) [91–94]. Even with modern chemotherapy for colorectal cancer, surgery for metastatic cancer (if possible) has consistently been shown to improve 5-year survival and quality of life and should be considered when possible. This may require referral to a specialized center [92, 95, 96].

Untreated, potentially resectable liver lesions have a median survival of 8 months, with 5-year survival of <5% [43, 97]. With modern forms of chemotherapy, median survival can be extended to greater than 24 months and in rare cases can be up to 34 months [7, 8]. In addition, newer liver strategies may allow a staged resection, portal vein embolization, or a combination of resection, embolization, and other strategies to ablate or otherwise treat or downsize liver lesions, which may allow a greater percentage of patients to undergo some form of treatment [98]. This has allowed some centers to see overall 5-year survival rates among patients with metastatic colorectal cancer at the time of diagnosis to be as much as 19% [99]. This underscores the importance of multidisciplinary evaluation of these patients. The main reason for failure in treated patients is intrahepatic recurrence of the tumor, which occurs in 60–70% of patients, one third of whom die within 2 years of surgery for hepatic metastases [99].

For patients with resectable lesions, there are several strategies that can be utilized to treat these lesions. Each has its own merits and they will be reviewed here. Multidisciplinary evaluation and local expertise are again key to determining the appropriate strategy, as there is a paucity of data to evaluate the various treatment strategies.

Combination Liver and Colon Resection

Combination resection involves simultaneous resection of liver and colonic lesions. This allows a single operation to treat both disease foci without delay between procedures. There is evidence to suggest that this approach results in a similar long-term outcome when compared to those undergoing staged therapy. Similarly, simultaneous resection does not increase overall morbidity, though there is an inherent selection bias in trials examining this issue [92, 100–102]. This approach is typically done for relatively minor resections which can include lobectomy. Larger liver resections may result in increased morbidity when combined with other procedures and may not be appropriate candidates for this strategy [103, 104]. A meta-analysis of 2880 patients suggested that simultaneous resection was safe provided patients were less than 70 years old and did not have severe comorbidity [105, 106]. An additional meta-analysis of 18 studies including 3605 patients did not show a survival advantage to any strategy, though there is the potential for considerable selection bias toward smaller lesions in the patients undergoing a combined approach strategy [107].

Liver-First Strategy

In patients with liver metastases from colorectal cancer, it is the metastatic disease in the liver (particularly if >3 cm in size) that is the primary determinant of overall survival [108, 109]. This is a potential reason for addressing the liver disease first, particularly in the setting of larger metastatic lesions where the primary lesion is asymptomatic. As there is some evidence to suggest the primary lesion has a low chance of becoming symptomatic during follow-up, it is reasonable to proceed with treatment of the metastatic disease first [72]. This also may avoid unnecessary colorectal surgery (and its associated morbidity) in patients who go on to develop incurable metastatic disease. There is evidence to suggest that a “liver-first” strategy may still allow patients with potentially curable disease to undergo both liver and colon resection over time [109].

It is unclear whether the development of additional metastatic disease is stimulated by the liver metastases vs. the primary tumor [110–114]. This has generated considerable debate between hepatobiliary and colorectal surgeons as well as oncologists. As no randomized trials exist, this is a philosophic discussion that occurs at many tumor board interactions. The answer remains unclear, but it may affect the opinions of those involved in making recommendations.

The liver-first approach can be combined with neoadjuvant chemotherapy for borderline resectable lesions or to allow tumor biology to dictate those lesions that are likely to progress rapidly prior to surgery. While this has been recommended as standard of care by some, others have disputed this and still recommend surgical resection followed by adjuvant chemotherapy due to the effect of chemotherapy-associated steatosis

that can increase surgical morbidity [115–118]. The liver-first strategy has a particular advantage in the setting or rectal cancer, where the process of neoadjuvant chemoradiotherapy can potentially take up to 3 months. This may allow surgery on the metastatic disease while treatment for the primary lesion is still ongoing. Alternatively, radiotherapy on rectal lesions can be reserved for overall disease that responds favorably to initial treatments—particularly the short course variety. The data for the liver-first approach is limited and largely based on non-randomized data, but seems to remain a viable method with good long-term results [119–125]. An international multidisciplinary consensus conference [126] suggested the liver-first strategy is as good as the conventional approach. The recommendation is to perform resection as soon as technically possible with a course of chemotherapy (if used) as short as possible in the absence of tumor progression. Furthermore age and total number of hepatic metastases should not be an absolute contraindication to surgery. The importance of a multidisciplinary approach remains crucial to ensuring long-term survival.

Colon-First Strategy

Proponents of the colon-first strategy hypothesize that the colon or rectum acts as an ongoing source of seeding metastatic disease. Additionally, the primary tumor represents a potential source of bowel-related morbidity in the form of bleeding, obstruction, or perforation. Some authors suggest the rates of this can be as high as 20%, but others suggest it is much lower than this [72, 87]. Additionally, the risk of morbidity associated with a colorectal anastomosis may be increased by addition of a liver procedure, where anesthesia and surgical techniques may include a low flow state or temporary alteration in portal blood circulation (e.g., a Pringle maneuver), which may affect blood flow to the bowel [127, 128]. Along similar lines, removal of the colon or rectum first may allow subsequent, more advanced, or aggressive strategies such as portal vein embolization to be used without compromising a future bowel procedure. Finally, resection of the colon first may allow detection of new or occult liver metastases which can then be removed with definitive surgery [129, 130].

Evidence to support each of these strategies is very limited and largely based on small, single institution series. Survival analyses across multiple studies suggest there is little difference between simultaneous, colon-, or liver-first strategies [105, 131–133]. As such, the agreed-upon treatment strategy should depend on the local expertise at an individual institution. The colon-first strategy may allow removal of the primary lesion with subsequent referral to a higher level of care or specialized center for definitive hepatectomy/metastasectomy. In counseling patients on the risk of recurrence, there have been identified factors to help determine prognosis. The Fong score is a series of five factors identified to have the greatest influence on outcome based on an analysis of 1001 patients undergoing potentially curative hepatectomy [134]. These included size >5 cm, disease-free survival less than 1 year, more than one tumor, lymph node-positive primary, and CEA >200 ng/mL.

Margin Status

Excision to negative margins in hepatic resection results in improved disease-free and overall survival. One study revealed an overall survival of 46 months was reduced to 24 months in patients with positive margins [135]. Furthermore, recurrence rates were significantly higher (28% with R1 resection vs. 17% with R0 resection, $p=0.004$) in a study of 436 patients comparing margin status of hepatectomy specimens [136]. A consensus statement from the Society of Surgical Oncology concluded that while wide margins of >1 cm are desirable, a close margin should not preclude resection. Another study suggested that a margin <5 mm is a risk factor for local recurrence [137].

Ablation of Liver Metastases

There are a variety of techniques for ablation of liver metastases that do not require tissue resection. These include percutaneous ethanol ablation, radiofrequency ablation (RFA), microwave ablation, cryoablation, and irreversible electroporation (or NanoKnife). RFA is the most commonly employed technique, though all can be used successfully and also used in conjunction with other forms of therapy (e.g., surgical resection) [138]. As patients may develop a future recurrence, preservation of liver parenchyma may be important, especially with a larger burden of disease. This is the typical place for use of these ablative therapies. In selecting what treatment modality to use, the overarching goals of minimal morbidity with maximum treatment effect and prolongation of life remain a guiding principle during multidisciplinary evaluation. Several different treatments may be used simultaneously or in a staged approach. Recently, these combined ablation and resection (CARe) techniques have shown promising results. A four-center retrospective study showed disease-free 1- and 5-year survival rates of 87.9% and 78%, respectively [139].

RFA has been the most widely applied ablative technique, used primarily for metastatic liver tumors that are not amenable to surgical resection. Patients may not be candidates for surgery for various reasons including that the lesions are anatomically difficult for surgical resection (adjacent to the confluence of the hepatic or portal veins), the functional hepatic reserve after resection would be insufficient, there are significant comorbidities that preclude an operation, or extrahepatic metastases are present, further decreasing the likelihood of cure. RFA uses heat generated from high frequency alternating current (generally in the range of 350–500 kHz) to ablate diseased tissue. RFA can be performed with open, laparoscopic, or percutaneous approaches. Studies have reported that the approach by which RFA is

performed has an impact on tumor recurrence rates, with the fewest local recurrences after open RFA, followed by laparoscopy, and finally percutaneous RFA [140–143]. However, local tumor recurrence rates overlap broadly with each technique, and physician experience as well as the type of RFA equipment is also inversely related to local recurrence rates [144, 145]. An expert panel convened by the American Society of Clinical Oncology (ASCO) to review the evidence on RFA for colorectal cancer liver metastases concluded that there is insufficient evidence to resolve the issue of optimal approach [146].

The vast majority of published data on efficacy of RFA for colorectal cancer liver metastases comes from retrospective series, many of which have limited follow-up (20 months or less), and there are few published randomized trials [140, 147–152]. A systematic review of the literature reported a wide range of 5-year survival (14–55%) and local recurrence rates (3.6–60%) [146]. However, both the retrospective series and the limited number of prospective trials consist of a variable mix of patients with potentially resectable liver-isolated disease and unresectable liver metastases with or without extrahepatic disease involvement. Finally, few series provide data on the use of chemotherapy concurrent with or following RFA, and as outcome measures differ between studies, a comparison is not always possible.

How the timing and use of RFA play into the overall treatment strategy remains an unanswered question. While many retrospective comparative series suggest RFA has higher local recurrence rates and worse progression-free survival (compared with resection), there are inherent limitations in these studies [153–159]. Given the evidence from retrospective reports that resection improves overall survival, particularly in the absence of extrahepatic disease, a systematic review of the literature by an expert panel from ASCO concluded that there is not enough evidence to support the use of RFA over resection in patients with potentially resectable colorectal cancer liver metastases [146]. A similar conclusion was reached in a 2012 Cochrane review [160].

RFA is a relatively well-tolerated technique, with a mortality rate of 0–2% and the major complication rate between 6 and 9% in most studies [146]. Complications can include liver abscess, pleural effusion, skin burns, and pneumothorax from diaphragm injury [161]. In summary, the place of RFA in the management of colorectal cancer liver metastases is still evolving, particularly in patients who have extrahepatic disease involvement. It is a potential option for patients with potentially resectable isolated liver metastases who are not surgical candidates.

Other Liver Metastasis Strategies: Hepatic Intra-arterial Chemotherapy/Chemoembolization

Regional chemotherapy through the hepatic artery is a therapeutic option for patients with isolated liver metastasis that are not amenable to surgical resection or local ablation. This method can also be combined with other forms of treatment. This mode of therapy is based upon the fact that liver macrometastases derive more than 80% of their blood supply from the hepatic arterial circulation, while normal hepatocytes are supplied primarily by the portal circulation [162]. This allows selective delivery of drug to the tumor with relative sparing of the normal hepatocytes. There is also a marked increase in the local concentration of the chemotherapy that is achieved by injection into the hepatic artery. Regional administration of agents that are rapidly metabolized in the liver by a first-pass effect leads to higher levels of drug exposure and minimizes side effects [163].

Transarterial embolization with or without chemotherapy (transarterial chemoembolization, TACE) has been investigated in patients with colorectal cancer liver metastases using both conventional techniques and drug-eluting beads. Response rates vary from 29 to 88%, which is based on limited experience. Most reported studies lack a control group, and the results from the two small-randomized controlled trials had conflicting results [164–166].

Most series of colorectal liver metastases have studied infusional hepatic artery chemotherapy without embolization. While there has been extensive clinical investigation of hepatic infusional chemotherapy in the past 30 years, there are fewer studies evaluating modern chemotherapeutic agents. A number of strategies have been explored in an attempt to overcome treatment-limiting toxicity and to maximize the safety and efficacy of HIA treatment. The majority of reports have evaluated modifications of 5-FU-based therapy, while more recent studies have explored other agents such as irinotecan and oxaliplatin. It has been shown that both oxaliplatin and irinotecan can be safely delivered and result in a high response rate in patients with unresectable disease [167–171]. A review of trials in the 1990s demonstrated that while response rates of tumors may be improved over systemic chemotherapy, the effect on survival was modest (overall survival 22.7 vs. 19.8 months). Other randomized trials have not seen any survival advantage [172, 173]. With improvements in chemotherapy, there is a paucity of high-quality data on the effectiveness of this treatment methodology. A recent review of nine studies and 1057 patients [174] did demonstrate improved 5-year disease-free survival rates (hazard ratio 0.61) when compared with systemic chemotherapy alone. A modest improvement in overall survival was also seen. This suggests it may have a role in the treatment of patients at high risk for recurrence, but this will require corroborative studies and should at present be restricted to centers with expertise in the technical aspects of its use.

Pulmonary Metastasis

Approximately 10% of patients with colorectal cancer develop pulmonary metastasis. The vast majority of patients with metastatic colorectal cancer to the lungs have advanced

disease and are therefore treated with systemic chemotherapy or best supportive care. Due to differences in blood supply, pulmonary metastases may be more common after rectal (vs. colon) cancer due to the dual blood supply of the rectum (portal and systemic). A limited number of studies have reviewed the incidence of pulmonary metastases after resection of rectal cancer and have estimated that approximately 1–12% of patients develop isolated pulmonary metastases [175–178]. Of those patients with isolated pulmonary metastases, approximately 7–14% of patients would be considered as candidates for pulmonary metastasectomy [175, 178, 179].

There may be some tumor-related factors that give a predisposition to pulmonary metastasis. A recent study investigated predictive factors for pulmonary metastases after R0 resection of rectal cancer without preoperative chemoradiotherapy. Actuarial incidence of pulmonary metastases was significantly related to the number of risk factors present. Tumor depth (T2–T3), lymph node ratio >0.091, and tumor location in the anal canal were the independent risk factors for pulmonary metastases in patients with rectal cancer [180]. Another study demonstrated that adjuvant chemotherapy, extrapulmonary metastases, and prelaparotomy CEA value were independent prognostic factors for overall survival of patients with pulmonary metastases after a resection for colorectal cancer with curative intent [181].

Due to the retrospective nature of the reported information in the literature, clinical outcome data after metastasectomy for colorectal lung metastases must be interpreted with caution. Improved clinical outcome and survival data is more likely due to ideal patient selection and tumor biology rather than the surgical intervention in and of itself. In addition, there are no adequate control groups in these reports; therefore, survival statistics are difficult to interpret. However, there are patients who undergo pulmonary metastasectomy with no evidence of disease after long-term follow-up [179, 181]. In addition, long-term survival without complete resection is very rare, suggesting that select patients do occasionally benefit from pulmonary metastasectomy. Input on the resectability of lung lesions by a thoracic surgeon at multidisciplinary evaluation is essential.

Modern series of lung resection for metastatic colorectal cancer report operative mortalities of less than 2% (Table 36-1). Five-year survival rates range from 16 to 64%, but generally cluster around 30–40%. Most studies evaluate factors associated with outcome; however, given the limited number of cases, the statistical power of these studies to detect significant factors is limited. In general, the pathology of the primary tumor (grade, location, stage) has not been shown to impact clinical outcome. The most commonly cited significant factors associated with adverse outcomes include the number and size of pulmonary metastasis, short disease-free interval, elevated CEA, and incomplete resection.

A recently published series of 94 patients from a single institution who underwent complete resection of pulmonary metastases from colorectal cancer was analyzed for survival rates as well as prognostic indicators for long-term survival. The cumulative survival rate was 45.5% after pulmonary metastasectomy [182]. Multivariate analysis revealed that an elevated preoperative CEA level was an independent prognostic indicator as shown in other studies. The study concluded that surgical resection offers a chance to prolong survival in colorectal cancer patients with resectable pulmonary metastases. However, there was a high recurrence rate (69.1%) and careful postoperative follow-up was advocated by the authors. Critiques of this study include the lack of randomization, appopriate controls, and failure to address the role of adjuvant chemotherapy.

While a majority of series have evaluated metastatic disease limited to the lungs, several series have evaluated patients with both liver and lung metastases. The majority of studies that have analyzed synchronous liver and lung metastases report a uniformly poor outcome following combined resections. Long-term survival is very uncommon in this situation [182–185]. In the setting of isolated pulmonary recurrence after partial hepatectomy, pulmonary metastasectomy appears to have more favorable outcomes similar to those for the initial hepatectomy [183, 184, 186].

TABLE 36-1. Outcome of patients undergoing pulmonary metastasectomy for colorectal cancer

Study	*n*	Operative mortality (%)	5-year survival (%)	Significant risk factors
Mori et al. [293]	35	–	38	None found
McCormack et al. [294]	144	0	44	Margin
McAfee et al. [185]	139	1	31	Number of lesions, CEA
Yano et al. [295]	27	–	41	Number of lesions
Saclarides et al. [296]	23	–	16	Number of lesions
van Halteren et al. [297]	38	–	43	DFI
Shirouzu et al. [298]	22	–	37	Number of lesions, size
Girard et al. [299]	86	1	24	CEA, margin
Okumura et al. [300]	159	2	41	Number of lesions, LN status
Zanella et al. [301]	22	0	62	None found
Zink [302]	110	0	33	Size, CEA
Dahabre et al. [179]	52	–	33	None found

n number of patients, *yr* year, *LN* lymph nodes, *DFI* disease-free interval
Source: Adapted from Rizk et al. [186]

The surgical approach to patients who are potential candidates for pulmonary metastasectomy has been somewhat controversial. Based on older studies reported in the 1980s citing a 38% yield of contralateral thoracotomy in finding radiographically occult disease, routine bilateral thoracotomy had been advocated previously [187]. With modern-day imaging, routine bilateral thoracotomy is no longer justified. The use of video-assisted thoracoscopic surgery (VATS) has increased significantly and is often used in metastasectomy when a minimal parenchymal resection is necessary. Initially, VATS was deemed substandard to thoracotomy due to the inability to palpate the lung parenchyma; a prospective study evaluating confirmatory thoracotomy after VATS showed that 22% of lesions were missed [187, 188]. However, with improvements in modern imaging and VATS techniques, a minimally invasive approach can now be employed.

Radiation therapy for colorectal cancer pulmonary metastasis has been of limited utility in the past due to radiation-induced pneumonitis, rib and spinal fractures, and skin toxicities. However, these toxicities can be minimized with the advent of robotic-assisted Gamma Knife radiotherapy or "CyberKnife" [189]. Initial reports appear to have minimal toxicity associated with single-session lung radiotherapy using robotic image-guided real-time respiratory and tumor tracking. This is an exciting field of research and may become an additional therapeutic modality in the future. However, the outcome and efficacy data is limited at this time, and the associated cost of robotic image-guided radiotherapy will be a limiting factor in widespread availability.

While it appears that certain colorectal cancer patients would benefit from pulmonary metastasectomy even in the presence of liver metastases, no randomized controlled trials have been conducted and reported, and the effectiveness of pulmonary metastasectomy has been suggested mostly by results of retrospective analyses. A randomized trial to investigate the effectiveness of pulmonary metastasectomy in colorectal cancer is currently in progress [190], and we will need to look to those results which hopefully will give clear evidences on the benefits of and to establish standard guidelines for pulmonary metastasectomy.

Peritoneal Metastasis

Peritoneal carcinomatosis represents one of the most challenging aspects of metastatic colorectal cancer. The peritoneal surface is involved in approximately 10–15% of colorectal cancer patients at time of initial presentation (synchronous metastases) and in 20–50% of patients who develop recurrence (metachronous metastases) [191–193]. As a site of colorectal cancer metastasis, the peritoneal surface ranks second only to the liver. It is characterized by intraperitoneal spread of metastatic nodules. Peritoneal metastasis occurs by direct implantation of cancer cells via one of four mechanisms: (1) spontaneous intraperitoneal seeding from a T4 colorectal cancer that has penetrated the serosal surface of the colon, (2) extravasation of tumor cells at the time of colon perforation from an obstructing cancer, (3) iatrogenic tumor perforation through an area of serosal injury or enterotomy at the time of colon resection, and (4) leakage of tumor cells from transected lymphatics or veins at the time of colon resection [192]. The risk of peritoneal metastasis is therefore highest in the setting of locally advanced cancers, and, until recently, most oncologists viewed peritoneal carcinomatosis as a terminal condition, to be palliated only with systemic chemotherapy.

However, in a small set of cases, the peritoneal cavity is determined to be the only site of metastatic disease after a detailed workup of the lungs and liver. This has led some to hypothesize that in some cases, peritoneal carcinomatosis may represent a first site of dissemination and, therefore, not necessarily indicative of generalized disease [194–196]. This scenario appears to be rare overall. In a combined series of 2095 patients with metastatic colorectal cancer (CRC) who were enrolled in two chemotherapy trials, 364 (17%) had peritoneal carcinomatosis, but only 44 (2.1%) had peritoneal carcinomatosis as the sole presentation of metastatic disease [197].

A similar paradigm is hypothesized for appendiceal cancer, which also has a propensity to spread intraperitoneally. Radical surgical cytoreduction and intraperitoneal (IP) chemotherapy has gained acceptance for the treatment of diffuse peritoneal adenomucinosis (pseudomyxoma peritonei) and selected patients with peritoneal dissemination of an appendiceal adenocarcinoma (mucinous peritoneal carcinomatosis). This topic is covered in the chapter devoted to appendiceal neoplasms.

Peritoneal metastases are clinically important because of their frequent progression to malignant ascites and/or malignant bowel obstruction [193, 198–201]. When patients present with peritoneal metastases, the most frequent symptoms were ascites (29.7%) and bowel obstruction (19.5%). Preoperative detection of peritoneal metastases is not reliable. Noninvasive imaging frequently misses small peritoneal lesions, even when these are widely disseminated. The sensitivity of CT scanning for lesions smaller than 5 mm is only 28% as compared to 70% for lesions 2 cm or greater [202]. Thus, indirect signs such as bulky primary tumor, ascites, or bowel obstruction are important clues. The utility of MRI in diagnosis of peritoneal carcinomatosis beyond that of CT is largely unknown and PET scans are of limited value. Unfortunately, in the majority of cases, diagnosis is made at the time of primary resection [203]. There are several approaches to treatment if peritoneal involvement is discovered.

The extent of carcinomatosis is a major prognostic factor and is best assessed by either laparoscopic or open exploration. Two different peritoneal carcinomatosis staging systems (Gilly's classification and Peritoneal Cancer Index of Sugarbaker) can be used to assess the extent of carcinomatosis

[204, 205]. These staging systems have both shown utility in determining the prognosis and treatment of patients with peritoneal carcinomatosis. By Gilly's classification, carcinomatosis is classified principally by the dimensions of the peritoneal tumor implants: stage I, tumor nodules less than 5 mm in diameter localized in one part of the abdomen; stage II, tumor nodules less than 5 mm disseminated widely through the abdomen; stage III, tumor nodules 5–2 cm in diameter; and stage IV, tumor nodules greater than 2 cm. The Peritoneal Cancer Index scores the extent of carcinomatosis on the basis of tumor size and location within 13 regions of the abdomen and pelvis with the largest size in each abdominopelvic region is scored on a scale of 0–3 (0, no tumor; 1, tumor up to 0.5 cm; 2, tumor up to 5.0 cm; 3, >5 cm or confluence). The total score of the Peritoneal Cancer Index is shown to correlate with survival. Median survival and 5-year survival after surgical debulking and intraperitoneal chemotherapy were 48 months and 50% for peritoneal index <10, compared to 12 months and 0% for index >20.

Standard management of patients known to have peritoneal metastases at initial presentation (if known preoperatively) is systemic chemotherapy. Colon resection plays an important role for patients with obstructing primary cancers and also for patients with occult metastases that are first detected in the operating room. Historically, the median survival for patients with unresected peritoneal metastasis treated with 5-fluorouracil-based systemic chemotherapy was very poor (6–8 months) [194, 206, 207]. However, patient survival is highly variable, depending on the extent of metastatic disease and response to chemotherapy [194, 207]. Contemporary combination chemotherapy regimens have significantly greater efficacy and can produce long periods of disease control in certain patients.

Despite the grim prognosis for patients with peritoneal carcinomatosis from colorectal cancer, a subset of patients once thought unsalvageable are now being considered for surgery with curative intent. Pioneered by Sugarbaker, the goal of cytoreductive surgery and intraperitoneal (IP) chemotherapy is to remove all macroscopic disease with peritonectomy procedures and visceral resections followed by perioperative IP chemotherapy to destroy residual microscopic disease. IP delivery offers pharmacokinetic advantage over standard intravenous delivery by producing high regional concentrations of drug while simultaneously minimizing systemic toxicities [208–210]. For patients with isolated peritoneal carcinomatosis from colorectal cancer, radical surgery to achieve an R0 resection (if it can be accomplished) remains the mainstay of treatment. Benefit from cytoreductive surgery with heated intraperitoneal chemotherapy has been suggested in several retrospective case series, a multi-institutional registry review [211], two randomized trials, and a systematic review.

These randomized trials must be interpreted with caution as neither used modern combination chemotherapy as the control arm [212, 213]. In the first trial, 105 patients with established peritoneal carcinomatosis of colorectal ($n=87$) or appendiceal ($n=18$) origin were randomly assigned to (A) cytoreductive surgery and HIPEC (with intraoperative mitomycin C) followed by systemic chemotherapy (5-FU and leucovorin only) or (B) systemic 5-FU and leucovorin alone with palliative surgery as needed [212]. Despite the high postoperative mortality rate (8%), the median disease-specific survival in the IP treatment group was significantly longer (22 versus 13 months). At a median follow-up of 8 years, 45% of patients in the IP chemotherapy arm who underwent complete cytoreduction (no residual tumor nodules) were still alive [214]. It should be noted that the use of a modern systemic oxaliplatin or irinotecan containing regimens in the control arm could potentially have narrowed and even eliminated the survival difference between the groups, since median survival durations in contemporary reports approximate 20 months.

The second trial, which also randomly assigned patients following aggressive surgical cytoreduction to systemic therapy (5-FU-based) with or without hyperthermic IP chemotherapy, only accrued 35 of the planned cohort of 90 patients (30 CRC, 5 appendiceal cancers) [213]. Although the 2-year survival rate of patients undergoing IP chemotherapy was 60% (much higher than would be expected among patients treated with systemic 5-FU/leucovorin chemotherapy), the difference in survival between the experimental and control groups was not statistically significant.

A systematic review of published data of cytoreductive surgery and IP chemotherapy for peritoneal dissemination of colorectal cancer, including the two randomized trials described above [212, 213], one comparative study [215], a multi-institutional registry series (an earlier report than described above) [216], and several case series, came to the following conclusions [217]:

- Median survival varied from 13 to 29 months, and 5-year survival rates ranged from 11 to 19%.
- Patients who underwent complete surgical cytoreduction appeared to benefit the most, with median survival 28–60 months and 5-year survival from 22 to 49%.
- This survival benefit was achieved at a cost of overall treatment-related morbidity rates between 23 and 44% and mortality rates from 0 to 12%.

Although these results seem promising, many important unanswered questions remain, including which patients with colorectal cancer peritoneal carcinomatosis have a higher or considerably lower likelihood of long-term survival after cytoreductive surgery and HIPEC [218] (Figure 36-6) and whether results in any population are better than could be achieved using modern oxaliplatin and/or irinotecan-based systemic chemotherapy with or without biologic agents. These regimens have greater activity as compared with 5-FU and leucovorin alone. Median survival durations in unselected patients with metastatic disease are 22–24 months, and approximately 10% of patients remain alive at 5 years.

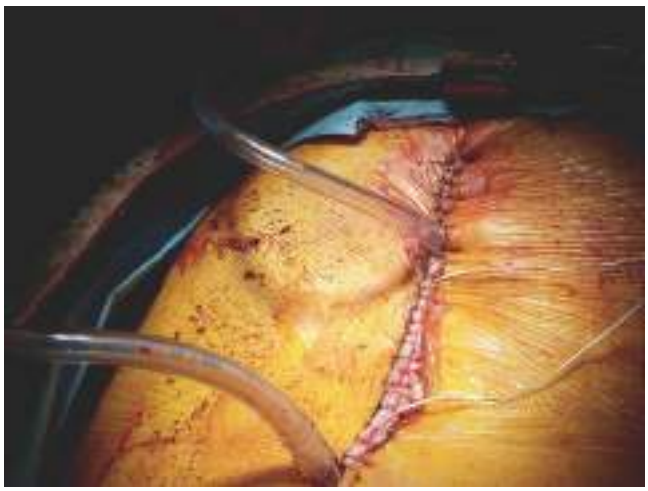

FIGURE 36-6. Hyperthermic intraperitoneal chemotherapy (HIPEC). Courtesy of Eric K. Johnson, M.D.

The only data that specifically address the efficacy of modern systemic chemotherapy in patients with isolated peritoneal carcinomatosis come from a retrospective analysis of 48 highly selected patients with peritoneal carcinomatosis from colorectal cancer who were treated with an oxaliplatin- or irinotecan-based palliative chemotherapy regimen at one of five French comprehensive cancer centers (where cytoreductive surgery and HIPEC were not available) over a 5-year period [219]. These patients were selected as the control group on the basis of their meeting clinicopathologic criteria defined as good prognostic factors for HIPEC [213]. The 2- and 5-year survival rates were 65 and 13%, respectively, and the median survival was 24 months. In contrast, the median and 2- and 5-year survival rates for a separate group of 48 patients who underwent cytoreductive surgery and HIPEC for colorectal cancer peritoneal carcinomatosis during the same time period at the Gustave Roussy Institute were 63 months and 81 and 51%, respectively. The authors concluded that, in appropriately selected patients with isolated peritoneal carcinomatosis, results with cytoreductive surgery and HIPEC are superior to those that can be achieved with modern combination chemotherapy regimens. The retrospective nature of this analysis and the inherent bias in comparing nonrandomly assigned patients limit the confidence with which this conclusion can be judged.

While patients who undergo complete cytoreduction followed by HIPEC seem to have a more favorable prognosis than can be achieved with systemic chemotherapy alone, there remains insufficient evidence to conclude whether the survival advantage is due to treatment or to biologic features that allow these patients to undergo complete cytoreductive surgery. Furthermore, the quality of the cytoreductive surgery is dependent upon the skills and level of experience of the surgeon. The favorable results (particularly with regard to treatment-related toxicity) [211, 220] achieved by international experts in the field may not be replicated in routine clinical practice. Finally, the independent contribution of HIPEC to the success of this approach has not been proven. Randomized trials are needed.

Based upon all of these issues, the NCCN believes [221] this approach should not be considered standard at present and only pursued in centers with demonstrated expertise [222], preferably in the context of a clinical trial. Such a trial, USMCI 8214/ACOSOG Z6091, in which patients with peritoneal carcinomatosis from colorectal cancer were randomized to standard systemic chemotherapy or surgical cytoreduction with heated intraperitoneal chemotherapy followed by systemic chemotherapy, was closed for lack of accrual. Another trial, Prodige 7, in which patients with isolated intraperitoneal metastases from colorectal cancer are randomly assigned to cytoreductive surgery with or without HIPEC, is underway in France.

In summary, the standard therapy for patients with peritoneal metastases is systemic chemotherapy. However, there is some evidence that aggressive surgical cytoreduction and IP chemotherapy may benefit highly select patients with limited peritoneal tumor burden. Additional clinical trials are needed to define optimal use of this aggressive treatment approach. As a result, if unexpected, diffuse carcinomatosis is found at the time of operative intervention, consideration should be given to referral to a specialized center prior to further operative intervention other than a possible proximal diversion or relief of any immediate surgical emergency.

Ovarian Metastases

Approximately 4–30% of ovarian neoplasms are metastatic cancers with the most common being colorectal and breast cancer [223]. A recent autopsy study demonstrated that of all women dying with colorectal cancer, between 6 and 14% were found to have ovarian metastasis at the time of death [224]. For those women with stage IV disease, the risk of developing ovarian metastases is substantially higher and approaches 90% for those with established peritoneal metastasis. Therefore, in a woman with a recent diagnosis of advanced colorectal cancer, any ovarian mass should be considered a metastasis from colorectal cancer until proven otherwise.

The pathogenesis of ovarian metastasis from colorectal cancer is multifactorial. While metastatic spread occurs primarily through the peritoneum, it can also occur by direct extension, hematogenously or lymphatically. It is imperative that careful intraoperative assessment of the ovaries is undertaken at the time of primary resection of the colon cancer. Depending on the study, synchronous metastases can occur in 0–8.6% of patients [225–228], while metachronous metastases develop in 1.4–6.8% of cases [223, 224], usually within 2 years after the primary resection [226–233]. At least half of the cases have bilateral ovarian involvement [234, 235], and 40% of these patients have associated extra-ovarian

pelvic metastasis [234] and if large enough can be palpated on physical exam or with peritoneal drop metastasis known as the "Blumer's shelf." It is extremely difficult to determine a primary ovarian tumor from a metastatic colorectal tumor by gross examination alone, but through the integration of pathologic, cytogenic, and immunohistochemical features, a correct diagnosis can be generally arrived at. Most metastatic colorectal lesions are CK20+/CEA+/CK7− on immunohistochemical staining, while primary ovarian neoplasms are CK20−/CEA−/CK7+ [235–238].

The decision to perform an oophorectomy at the time of surgery requires some in-depth reasoning. Primary en bloc resection of colorectal cancer with direct extension to the ovary (T4) or resection of macroscopic metastatic disease to the ovary with prophylactic bilateral resection has been suggested to offer survival benefit and should be performed with curative intent in the absence of other significant metastatic disease. However, the removal of macroscopically normal ovaries (prophylactic oophorectomy) in women with colorectal cancer is controversial and remains the subject of much debate. Proponents of removal argue that resection improves the cure rate by removing potential microscopic "undetectable" synchronous disease, eliminates the risk of ovarian cancer, and removes the risk of future metachronous ovarian metastatic disease. Others argue that the low incidence of ovarian metastasis, the small amount of supportive data, and few clinical correlations with predictive value make the additional resection of the ovaries unnecessary [224]. Clinical studies attempting to document the benefit of ovarian metastasectomy in patients with colorectal cancer are small and retrospective [225, 239, 240]. The majority of studies to date, however, fail to show any survival benefit for prophylactic oophorectomy, and most studies demonstrate that when ovarian metastases are present, it is a very poor prognostic sign [224]. Based on available information, it is reasonable to offer prophylactic oophorectomy to all postmenopausal patients, in particular to those women who have undergone pelvic radiation as part of their treatment for rectal cancer. For premenopausal patients, only those with established peritoneal metastases, those that are proven to have an increased risk of developing ovarian carcinoma (strong family history, known carriers of breast cancer (BRCA), or those with an HNPCC mutation), or those who have already completed their families should be considered for prophylactic oophorectomy.

Most ovarian metastases are asymptomatic and are only detected at the time of surgery; however, larger metastatic lesions can compress or invade adjacent organs, rupture, and on rare occasions bleed. Larger ovarian lesions are usually visualized on initial staging imaging and should be part of the decision-making regarding surgical resection and informed consent. Survival of women with synchronous ovarian colorectal metastases is significantly worse than that of patients without such metastases [223, 241]. Ovarian metastases are frequently resistant to systemic chemotherapy even when other sites of metastatic disease are responding, and therefore, resection of these synchronous metastases including bilateral oophorectomy and resection of gross disease should be performed at the index operation [242–245]. Reoperation for metachronous metastases should be considered in select patients with good performance status and limited tumor burden elsewhere. Discussion of these patients in a multidisciplinary fashion is imperative. To prevent local tumor progression, an aggressive surgical approach should be undertaken to achieve complete resection. The survival benefit of removing ovarian metastases had never been well documented, although complete metastasectomy is associated with significantly better outcome when compared to palliative debulking, especially in the setting of metastatic disease confined to the pelvis [246, 247]. It should be noted that complete resection is possible in 50% of these cases. The median post-resection survival for women with isolated ovarian metastases is 18 months [242]. Women with other sites have significantly shorter survival, and 5-year survival after resection of established metastasis is rare [243, 244]. In these cases, systemic chemotherapy should be strongly considered, particularly when residual disease is present. With the constant evolution and improvement of chemotherapeutic regimens, containing oxaliplatin, irinotecan, and/or bevacizumab, better survival can be expected [248–251]. See Figure 36-7 for an algorithm outlining the treatment of ovarian metastases.

Other Sites of Metastasis

Bone

Before the introduction of modern chemotherapy and targeted treatment options, bone metastases were reported in as high as 24% of cases [252, 253]. With modern therapies, bone metastases from colorectal cancer reportedly occur now in 7–9% of cases, and most often present in the context of widespread metastatic disease [254–257]. Routine diagnostic bone imaging is not indicated in colorectal cancer patients, unless there are specific bone-related symptoms. When bone metastases occur, they most commonly occur in the spine (65%), followed by hip/pelvis (34%) and long bones (17%). There are no curative modalities, but palliation of pain, fractures, or spinal cord involvement are important issues for these patients. Symptomatic relief from bony metastases can usually be accomplished with radiation, chemotherapy, as well as bisphosphonate therapy with zoledronic acid [253]. However, pathologic fractures are best treated by operative internal fixation. The systemic issues related to bone metastases are serious and include debilitation, immobility, hypercalcemia, and thromboembolic disease.

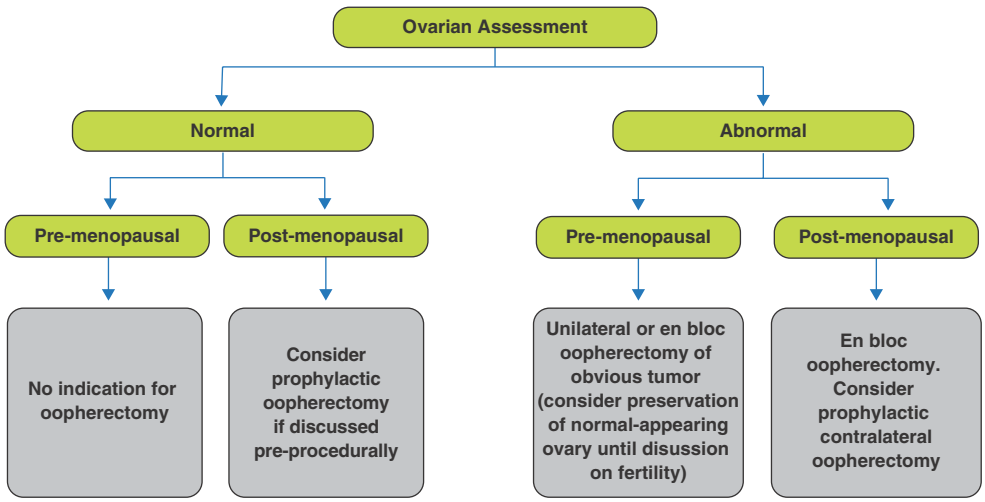

FIGURE 36-7. Treatment algorithm for ovarian metastases.

Brain

Cerebral metastases from colorectal cancer are uncommon, occurring in 1–4% of colorectal cancer cases [254–256]. Colorectal tumors account for approximately 3% of all metastatic brain tumors [257]. These are generally found in the context of widespread metastases to multiple organ sites, but on rare occasion can present as an isolated brain metastasis [258]. There is no role for routine brain imaging at primary presentation or at presentation with metastases elsewhere, unless there are specific neurologic symptoms. Once brain metastases occur, symptoms are common; palliative therapies include steroids to decrease swelling and anticonvulsants to control seizures. Definitive therapy of colorectal brain metastases usually involves surgery, radiation, or a combination of the two. For isolated, single brain metastases, resection can result in survival beyond 1–2 years; however, because brain metastases are infrequently the sole site of metastatic disease and because survival is dismal regardless of therapy chosen, craniotomy is rarely indicated [256–260]. As with pulmonary metastasis, there is increasing interest and data in the literature regarding Gamma Knife and CyberKnife radiotherapy for bone and brain metastasis [261, 262]. The outcome and efficacy data is limited at this time and the associated cost of robotic real-time image-guided radiotherapy may be a limiting factor in widespread applicability.

Pancreas

The pancreas is an uncommon location for solitary metastases from other primary cancers [263]. While the prevalence of pancreatic metastases has been described as high as 6–11% [264], reports of solitary resectable pancreatic metastases from colorectal cancer are extremely rare [265, 266]. Although long-term survival is rare, surgical resection can be performed safely in patients with isolated pancreatic metastases from colorectal cancer and in selected patients with extrapancreatic disease [265]. As with other sites of multiorgan metastases, a multimodality approach is strongly recommended and consideration for surgical resection should be taken in context with an overall treatment plan and chances for improving survival while maintaining quality of life.

Adrenal

Adrenal metastases are uncommon with 14% found in one autopsy series [267]. Isolated adrenal metastases are even rarer. Aggressive surgical resection for isolated adrenal metastases is described in only a few case reports or small series [268–273]. In the largest series of eight patients with apparently isolated adrenal metastasis from colorectal cancer, all of whom received adjuvant chemotherapy, or remained alive and disease-free 12 months after adrenalectomy, one was lost to follow-up and six died of their malignancy. The mean survival of patients who died was 32 (range 12–60 months) [268]. In contrast to the situation with isolated adrenal metastases, the development of adrenal metastases after liver resection for colorectal cancer is associated with a poor prognosis, and adrenalectomy is not warranted [274].

Retroperitoneal Lymph Nodes

Isolated retroperitoneal nodal recurrence occurs in less than 2% of patients following a colorectal cancer resection with curative intent [275–277]. Salvage surgery has been previously avoided due to the poor prognosis; however, this concept is being challenged [278, 279]. A retrospective review of nine studies including case reports, case series, and case-control studies reported a survival benefit and no operative mortality for 110 patients undergoing a salvage retroperitoneal nodal resection. The median disease-free survival was

17–21 months, and the duration of overall survival ranged from 19 months to 18 years with a median of 34–44 months [280]. These series were collective over a time when the newer chemotherapy regimens were evolving (e.g., oxaliplatin, irinotecan, cetuximab, bevacizumab). There is no current data addressing the benefit of chemotherapy after resection of isolated retroperitoneal nodal disease. As in the case in patients with resected colorectal cancer with hepatic and pulmonary metastases, it is unclear if the addition of chemotherapy improves the observed survival statistics.

Metastatic Disease in the Elderly

Colorectal cancer remains one of the most commonly diagnosed cancers in the world with 60% of patients being over 70 years old and 43% are over 75 [281, 282]. The world's population is aging and it is estimated that the number of Americans over the age of 65 will double by the year 2030 and will account for 20% of the total population [283]. The average 65-year-old person can expect to live another 15 years and remain functionally independent for the majority of that time [284]. Thus, the number of older cancer patients is expected to increase. It is estimated that 50% of all cancer and 70% of all cancer mortality occurs in this age group [285]. Therefore, multidisciplinary teams will increasingly see older patients with colorectal cancer, and management of this distinct group deserves special mention.

When considering surgery, comorbidity, functional dependency, and older age are associated with early postoperative mortality in patients with gastrointestinal malignancies, with 30-day postoperative mortality rates underestimating postoperative mortality in older patients [286]. In regards to chemotherapy, the data available indicates that older patients derive the same benefit and have the same degree of toxicity as younger patients. The clinical trial data however may not be reflective of the average elderly patient seen in practice that is often suffering from more comorbidities and has greater functional impairment [287]. For these reasons, the International Society of Geriatric Oncology (SIOG) previously recommended that colorectal cancer patients >65 years of age requiring surgery should undergo a preoperative whole patient evaluation of the most common physiological side effects of aging, physical and mental ability, and social support. Further for those patients assessed as having physical or psychological comorbidities, it was recommended that a geriatrician was involved in the patient management [288].

Since those original recommendations, there have been multiple frailty indices proposed to detect vulnerability in elderly patients with cancer so that treatment can be adjusted accordingly. The process of these assessments, however, can be time consuming, and prescreening is often used to identify fit patients who are able to receive standard treatment versus those in whom a full comprehensive geriatric assessment should be done [289, 290]. The four most common indices utilized appear to be the abbreviated comprehensive geriatric assessment (aCGA), the Vulnerable Elders Survey-13 (VES-13), the Groningen Frailty Indicator (GFI), and the Geriatric 8 (G8). Unfortunately, at present, there is no universal screening tool that adequately identifies frailty in at-risk older patients, and sensitivity and specificity for these indices ranged from 67 to 87% and 59 to 73%, respectively, which questions the value they may offer to the clinician [290]. There has been a study that has shown that the aCGA and G8 were the best screens for older patients with cancer that qualified for elective abdominal surgery; the G8 had the highest sensitivity and negative predictive value and the aCGA was a good overall assessment tool [291]. The American College of Surgeons NSQIP Risk Calculator (http://riskcalculator.facs.org) also uses degree of independence and other comorbidity variables that can be used to assess surgical risk in the elderly. In particular, it also gives an assessment of the risk of discharge to a long-term care facility in addition to the risk of common complications. Colorectal surgeons should be aware of the availability of these assessments and can use them as tools to aid them in evaluating the elderly population.

Because of the ever-increasing complexity and diversity of treatment options for elderly patients with colorectal cancer, SIOG reassembled their task force in 2013 to revise treatment recommendations. As a result of that group's work, it was recommended that the following outcomes need to be considered in relation to contemplating surgery in the elderly population: immediate postoperative morbidity, 30-day postoperative morbidity and mortality, length of stay, discharge to nursing home, 1-year mortality, short-term and long-term functional outcomes, quality of life, and survival. With regard to contemplating chemotherapy management in these patients, it was recommended that the following outcomes need to be considered: toxicity, completion of therapy, quality of life, functional status, progression, survival, and composite end points. Furthermore, it is important to recognize that embracing the concept of individualized treatment in a multidisciplinary setting is key to further improvements in the management of elderly patients utilizing some form of comprehensive geriatric assessment, involving patients in decision-making by providing them with tailored information and the potential for morbidities in advance of treatment, as well as the need for encouraging investigators to design trials using low-toxicity treatments that maintain efficacy of full-dose treatments and patient-centered assessments to expand the evidence base in the treatment of older patients with colorectal cancer [292].

Summary

This chapter has summarized the approach to patients with stage IV colorectal cancer. Throughout a variety of studies, the one overarching principle has been the

emphasis on multidisciplinary evaluation. No one prescribed treatment protocol has proved more successful than others, and a combination of therapies across multiple specialties is now possible and an individualized approach to treatment is important. Available options include modern chemotherapy in the neoadjuvant or adjuvant setting, metastatic surgical resection with a variety of timing options, and nonsurgical ablative techniques. The overarching goal in the use of these treatment strategies is to improve survival and quality of life. There have been dramatic improvements in recent years, and although some patients cannot be cured, they can be effectively treated or palliated. As the approach to tumors can be highly individualized, consensus agreement with expert multidisciplinary evaluation remains of paramount importance in the care of these patients.

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37
Appendiceal Neoplasms

Constantine P. Spanos and Andreas M. Kaiser

Abbreviations

AJCC	American Joint Commission on Cancer
DPAM	Disseminated peritoneal adenomucinosis
ENETS	European Neuroendocrine Tumor Society
HIPEC	Hyperthermic (or heated) intraperitoneal chemotherapy
LAMN	Low grade appendiceal mucinous neoplasms
PCI	Peritoneal carcinomatosis index
PMAC	Peritoneal mucinous adenocarcinomatosis
PMCA	Peritoneal mucinous carcinomatosis
PMP	Pseudomyxoma peritonei

Key Concepts

- Although appendectomy for appendicitis is the most common emergency operation performed by general surgeons, primary neoplasms of the vermiform appendix are rare, and each individual general surgeon will have limited personal experience in the management of such lesions.
- Most primary neoplasms of the appendix are not associated with specific signs or symptoms and are incidentally diagnosed after pathological analysis of the appendectomy specimen, or detected incidentally on imaging such as computed tomography (CT) done for other indications.
- Primary neoplasms of the appendix can generally be divided into epithelial, non-epithelial, and mixed lesions. Epithelial lesions include adenoma and adenocarcinoma. Non-epithelial tumors include neuroendocrine tumors (carcinoids), lymphoma, leiomyoma, leiomyosarcoma, and other even rarer rarities. Goblet cell carcinoids are mixed lesions with features of carcinoid as well as mucinous adenocarcinoma.
- Epithelial tumors, and specifically mucinous adenocarcinomas, are the most common primary appendiceal neoplasms.
- Pseudomyxoma peritonei is the result of a perforation and peritoneal dissemination of a mucin-producing epithelial neoplasm, most commonly originating from the appendix or the ovaries. In select patients, cytoreductive surgery with HIPEC should be considered.
- A mucocele is a morphologic cystic manifestation of an epithelial appendiceal neoplasm. Perforation leads to pseudomyxoma peritonei. Therefore, intact removal en-bloc is of utmost importance.
- Appendiceal carcinoids are rarely associated with carcinoid syndrome or multicentricity.
- The newest tumor staging guidelines distinguish appendiceal tumors from colon cancer, and separate between epithelial and non-epithelial lesions.
- The extent of surgical resection depends on the cell type, preoperative staging, the ability to achieve negative resection margins, and the probability of nodal disease.
- Surgery is the primary treatment for localized disease, whereas its role in metastatic disease needs to be individually analyzed and weighed against systemic chemotherapy.

Introduction

The appendix vermiformis is commonly regarded as the organ that will introduce a surgical trainee to the art of his or her chosen specialty. Inflammation of this organ, namely appendicitis, is the disease process which will be instrumental in "teaching" the fundamentals of history taking, physical examination and differential diagnosis of the acute abdomen to medical students and surgical residents. Appendectomy is the most frequent emergency operation

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Table 37-1. Clinical scenarios depending on type and timing of diagnosis of appendiceal neoplasms

Scenario	Acute symptoms	Presumptive preoperative diagnosis	Surgery	Pre-/intraop evidence of perforation (P) or dissemination (D)	Timing of tumor recognition	Impact/action in decision-making
1. Acute	Y	Appendicitis	N	–	N	Rely on indirect signs/risk factors for identification of affected individuals
						Re-imaging?
2. Acute	Y	Appendicitis	Y	P–	(a) Intraoperative	Primary or secondary evaluation for more extensive/oncological surgery/treatment
				D–	(b) Only on final pathology	
					(c) Not recognized at all (missed opportunity)	
3. Acute	Y	Appendicitis	Y	P+	(a) Intraoperative	Appropriate treatment for perforation with primary or secondary evaluation for more extensive/oncological surgery/treatment
				D–	(b) Only on final pathology	
					(c) Not recognized at all (missed opportunity)	
4. Acute	Y	Appendicitis	Y	P+	Intraoperative	Primary appropriate treatment for perforation
				D+		Secondary assessment for more extensive surgery/treatment
5. Acute	Y	Appendicitis	Y	P–	Intraoperative: evidence of localized mucocele or tumor involving the appendix/cecum	Intraoperative determination of appropriate extent of resection
				D–		Possible frozen section
6. Elective	Y/N	Localized mucocele/ tumor involving appendix/cecum—no signs of PMP	Y	P–	Preoperative	Oncological resection
				D+		Preparedness for HIPEC
7. Elective	Y/N	Localized mucocele/ tumor of appendix/ cecum AND signs of PMP	TBD	P–	Preoperative	PCI
				D+		Systemic treatment and evaluation for CRS/HIPEC
8. Elective	Y/N	PMP, but no obvious cecal pathology	TBD	P–	Preoperative	Evaluation for other potential primary tumor locations
				D+		PCI
						Systemic treatment and evaluation for CRS/HIPEC
9. Elective	Y/N	PMP+distant metastases	N	P–	Pre-treatment	Systemic treatment
				D+		

performed by general surgeons with close to 300,000 performed in the United States annually [1, 2], of which a substantial proportion are performed laparoscopically. On comparably rare occasion, the pathology of the appendectomy specimen incidentally reveals an appendiceal neoplasm ("incidentaloma"), which sometimes is recognized even before or at least during surgery, but more often only after the patient has already been discharged from the hospital. Paradoxically and despite the fact that abdominal surgeons at all levels are very frequently involved in treating appendiceal pathology, appendiceal neoplasms are quite infrequent but may cause rather complex intellectual, management and technical challenges in subsequent surgical interventions (Table 37-1) [3].

Epidemiology

Primary neoplasms of the appendix have an incidence of 0.12 cases per 1,000,000 person years and are found in 0.9–1.4% of appendectomy specimens [3, 4]. They can be asymptomatic, be associated with appendicitis, or cause noninflammatory symptoms. Preoperative diagnosis based on symptoms, imaging, and laboratory results is extremely rare. Even intraoperatively, less than 50% appendiceal neoplasms are recognized as such. A retrospective cohort analysis of the Surveillance, Epidemiology, and End-Results database suggested that the incidence of appendiceal neoplasms has increased significantly in the past few decades from 0.63 to 0.97 per 100,000 population [5, 6]. It is unclear

TABLE 37-2. Reported incidence over time of appendiceal neoplasms in SEER database [5, 6]

Subtype	1973–2001 (*N*=2514)	2000–2009 (*N*=4765)
Mucinous adenocarcinoma (%)	38	38
Non-mucinous adenocarcinoma (%)	26	27
Carcinoid tumors (%)	17	28
Goblet cell carcinoids (%)	15	
Signet ring cell tumors (%)	4	7

TABLE 37-3. Tumor classifications and manifestations

	Localized[a]	Disseminated	Pattern of dissemination[b]
Epithelial	Adenoma (B)		L, H, P
	Adenocarcinoma (M)	Adenocarcinoma	L, H, P
	Mucocele (B)	PMP: Mucinosis peritonei	P
	Mucinous cystadenoma (IM, LAMN)	PMP: Disseminated peritoneal adenomucinosis (DPAM)	P
	Mucinous (cyst-)adenocarcinoma (M)	PMP: Peritoneal mucinous adenocarcinomatosis (PMAC)	P, L, H
		PMP: Peritoneal mucinous carcinomatosis (PMCA)	P, L, H
	Signet ring cell carcinoma (M)	Advanced/metastatic signet ring cell carcinoma	DI, P, L, H
Mixed	Goblet cell carcinoid (adenocarcinoid)	Metastatic goblet cell adenocarcinoid	P, L, H
Non-epithelial	Carcinoid	Metastatic carcinoid	L, H
	<1 cm (B)		
	1–2 cm (IM)		
	>2 cm (M)		
	Lymphoma (M)	Disseminated/multicentric lymphoma	Systemic
	Leiomyoma (B)		
	Leiomyosarcoma (M)	Metastatic leiomyosarcoma	H, L
	Kaposi sarcoma (M)	Disseminated Kaposi sarcoma	Systemic

LAMN Low grade mucinous neoplasia, *PMP* Pseudomyxoma peritonei
[a]*B* Benign, *IM* Intermediate malignant potential, *M* Malignant
[b]*P* Peritoneal, *L* Lymphatic, *H* Hematogenous, *DI* Diffuse infiltrative

though whether this is a true increase or a simple reflection of higher awareness and reclassification as a separate entity. The increase appears to have affected all histological subtypes in an equal fashion (Table 37-2) [5, 6]. Historically, carcinoid tumors were considered the most frequent neoplasms originating within the appendix, and in 1955 a systematic evaluation of 50,000 appendectomy specimens revealed only 41 epithelial neoplasms (0.082%) [7]. More recent publications, however, demonstrate that epithelial neoplasms are more frequent and represent 58% of malignant appendiceal tumors [5, 8]. At the same time, a surge was also noted for the frequency of distant metastatic disease [5]. In contrast, however, appendiceal carcinoids have an incidence of 0.15/100,000/year but the relative frequency compared to other primary sites of neuroendocrine tumors within the gastrointestinal tract has decreased to 16.7% [9, 10]. Epithelial appendiceal neoplasms—paralleling colorectal cancer—usually develop in the sixth or seventh decade of life, whereas non-epithelial pathology including neuroendocrine tumors occur at a younger age, namely the fourth to fifth decade [2, 5, 7, 8, 11]. At the time of diagnosis, a total of 74% of appendiceal cancer cases have already spread, and developed regional or distant metastases in 39% and 35%, respectively [5].

Anatomical Pathology and Staging

The literature unfortunately has for a long time shown little consistency and used a variety of nomenclatures, classification systems, and descriptive terms when referring to appendiceal neoplasms. The many synonyms for lesions of such rarity undoubtedly has led to confounding terminology. From an anatomical point of view, the appendix in essence has a smaller diameter but otherwise a similar layered wall structure as the rest of the large intestine; however there is a higher representation of immunological tissue components (GALT, gut associated lymphoid tissue). The appendix does not participate in processing of intestinal contents but produces 2–3 mL of mucin per day and may participate in immunological functions. The arterial blood supply originates from the appendicular artery which branches off the ileocolic artery; the venous drainage is via the superior mesenteric vein to the portal vein system; the lymphatic drainage follows the vascular structures and due to variability may parallel the ileocolic, right colic, and right branch of the middle colic artery.

Appendiceal neoplasms should be categorized according to the tissue of origin as well as the pattern of growth, expansion, and spreading (Table 37-3). As for the latter,

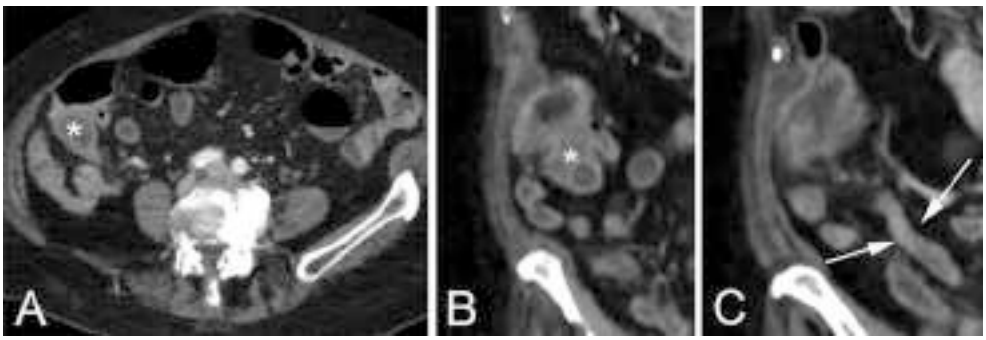

FIGURE 37-1. Appendiceal mucocele: the computed tomography shows the cystic enlargement at the base of the appendix (*asterisk*, panels (**a**) and (**b**)), as well as the moderately enlarged appendix (in-between *arrows*, panel (**c**)).

tumors may either metastasize via vascular, lymphatic, or transperitoneal route. A major distinction is made between epithelial and non-epithelial lesions, the latter of which includes among others neuroendocrine tumors such as carcinoid tumors.

Epithelial Neoplasms

Epithelial neoplasms are divided into mucinous and non-mucinous neoplasms [8]. Mucinous neoplasms of the appendix are classified according to the grade and aggressiveness of the tumor. Descriptively, these lesions characteristically can form mucoceles of the appendix, a morphologic term describing the dilation of the appendix with intraluminal accumulation of mucoid material (Figure 37-1). The obstruction can either be caused by the epithelial neoplasm itself, an independent tumor, or a benign process (retention cysts, mucosal hyperplasia). Rupture of a mucocele results in peritoneal spillage and spread of mucin and—depending on the malignant potential of the lesion—of cellular elements, which are the basis for mucinosis, pseudomyxoma peritonei, and carcinomatosis.

Low grade appendiceal mucinous neoplasms (LAMN) are well-differentiated neoplasms that morphologically resemble adenomas. LAMN has become the neutral term for a number of entities such as appendiceal villous or serrated adenoma, cystadenoma, borderline tumor of the appendix, and mucinous tumors of uncertain malignant potential. These lesions tend to grow slowly and grossly are characterized by a well-defined structure, cystic dilation, and mucinous content. The appendiceal wall is fibrotic and—as a sign of chronicity—may sometimes contain calcifications. Gross rupture (spontaneously or as a result of surgical manipulation) may be evident as mucin extruding on to the serosal surface or seeding of more distant peritoneal surfaces as evidenced by presence of mucin lakes. Histologically, the appendiceal mucosa is replaced by adenomatous proliferations of villous, papillary, serrated, or flat mucinous character. The columnar epithelial cells are mucin-rich and may have elongated (pencil-shaped), mildly hyperchromatic nuclei with nuclear pseudostratification, rare mitoses, and apoptotic nuclear debris. It is of note that the neoplastic epithelium on occasion may herniate through the muscularis propria and form "pseudodiverticula." One might speculate that these extensions represent a route by which such lesions perforate and disseminate to the peritoneal cavity [11].

Prognosis of LAMN depends on the presence or absence of epithelial cells outside the appendix. Tumors confined to the appendix generally have an excellent prognosis. However, LAMN may proliferate outside the appendix in a malignant fashion, producing pseudomyxoma peritonei and/or distant metastases. Pseudomyxoma peritonei (PMP) derived from perforation of a LAMN is characterized by abundant extracellular mucin, hyalinized fibrotic stroma, and harboring scant strips of low-grade mucinous epithelium [8]. The term is not strictly limited to appendiceal neoplasms but the condition can result from other tumor origins such as ovaries, gallbladder, and others. The prognosis of a ruptured LAMN is dependent on the amount and cellularity of mucin deposits, and recurrence rates increase when epithelial cells are present in the mucin. Most instances of PMP resulting from LAMN remain confined to the right lower quadrant. Even if the spread of PMP goes beyond the immediate vicinity, the lesion may pursue an indolent but progressive course. The superordinate term "PMP" has been categorized into disseminated peritoneal adenomucinosis (DPAM) and peritoneal mucinous (adeno-) carcinomatosis (PMAC or PMCA) [12]. The former reflects a low-grade pseudomyxoma arising from LAMNs, whereas the latter indicates peritoneal carcinomatosis. DPAM lesions contain scarce strips of low-grade mucinous epithelium with mild atypia and no significant mitotic activity; [12] these low-grade lesions usually cover but do not infiltrate the surface of the organs to which they adhere.

Appendiceal adenocarcinoma is also divided into mucinous and non-mucinous types. Mucinous adenocarcinoma of the appendix is characterized by a destructive growth pattern with tumor invasion of the appendiceal wall beyond the muscularis mucosae; infiltrating pools of mucin harbor cytologically malignant glandular epithelium arranged in strips, clusters,

and complex proliferations. Mucinous adenocarcinoma due to the increasing pressure of accumulating mucin is prone to rupture, spreading, and seeding into the peritoneal cavity, leading to formation of pseudomyxoma peritonei. Mucinous tumors spread along peritoneal surfaces, even in the absence of lymph node metastases. Peritoneal mucinous (adeno-)carcinomatosis (PMAC/PMCA) results from secondary peritoneal proliferation of appendiceal or intestinal mucinous adenocarcinoma nests that lead to invasion of parenchymal and visceral organs and the omentum, and potentially trigger secondary lymph node metastases at those sites.

Non-mucinous adenocarcinomas behave similarly to colonic adenocarcinomas, infiltrating the appendiceal wall and metastasizing to regional lymph nodes and the liver [11]. Non-mucinous adenocarcinomas show a spectrum of morphological features of the invasive component. In some cases the tumor is identical to colonic adenocarcinoma with malignant (pseudo-)glandular formations, increased stratification, and disorganization (compared to the regular columnar epithelium). In other cases, the malignant glands are tubular in shape, lined by cuboidal epithelium, associated with modest amount of extracellular mucin.

Signet-ring cell carcinoma is a rare but aggressive subentity of mucinous adenocarcinoma, characterized by dissolute growth and infiltration of mucin-containing cancer cells (signet rings); it almost never remains confined, may display an infiltrative growth below intact appearing mucosal surfaces as well as a rapid dissemination within the peritoneal cavity. Signet-ring cell carcinoma is typically associated with a poor prognosis.

Prognosis of appendiceal adenocarcinomas—similar to colon cancer—is primarily determined by the stage, but within stage IV also depends on the histological subtype and grading as well as the route of dissemination. Within each stage and histological subtype, poor differentiation is associated with unfavorable outcomes. Mucinous adenocarcinomas have a markedly worse outcome (reduced cancer-specific survival) than non-mucinous adenocarcinomas of the appendix (Table 37-4). This observation, which was based on published data analysis of the National Cancer Database (NCDB) [4], was recently implemented into the current staging guidelines by the American Joint Commission for Cancer (AJCC) [13]. Appendiceal carcinomas for the first time are classified separately from colonic adenocarcinoma, and distinction is made between mucinous and non-mucinous types; histologic grading for mucinous tumors is considered of particular importance for metastatic tumors (Table 37-5). Stage T4 is divided into T4a (penetration of visceral serosa) and T4b

Table 37-4. Cancer-specific survival for appendiceal adenocarcinoma stratified by stage and grade [4]

Subtype	Stages I–III (%)	Stage IV (%)
Mucinous adenocarcinoma ($N=1375$)		
Well differentiated	82	71
Moderately differentiated	64	51
Poorly differentiated	50	0
Non-mucinous adenocarcinoma ($N=860$)		
Well differentiated	69	48
Moderately differentiated	73	9
Poorly differentiated	55	5

Table 37-5. TNM staging by AJCC for appendiceal adenocarcinoma [13]

Stage	T	*N*	M
X	Primary tumor not determined, or any T	Regional lymph nodes not determined, or any *N*	Metastatic disease not determined, or any M
0	No evidence of primary tumor	No regional lymph node metastasis	No distant metastasis
Is	Carcinoma in situ: intraepithelial or invasion of lamina propria	–	–
1	Tumor invades submucosa	Metastasis in 1–3 regional lymph nodes	1a: Intraperitoneal metastasis beyond the right lower quadrant, including pseudomyxoma peritonei
			1b: Non-peritoneal metastases
2	Tumor invades muscularis propria	Metastasis in four or more regional lymph nodes	
3	Tumor invades through muscularis propria into subserosa or into mesoappendix		
4	4a: Tumor penetrates visceral peritoneum, including mucinous peritoneal tumor within the right lower quadrant		
	4b: Tumor directly invades other organs or structures		

Stage I: T1–2 N0 M0; stage II: T3–4 N0 M0; stage III: Tx N1–2 M0; stage IV: Tx Nx M1

(invasion of other organs). In mucinous tumors that penetrate the visceral peritoneum and cause mucin deposits confined to the right lower quadrant are still considered a T4a (that is a stage II if no lymph nodes are involved); when mucin has dispersed beyond the right lower quadrant, it is designated M1a (stage IV) [13]. M1 is divided into M1a and M1b to distinguish pseudomyxoma peritonei (M1a) from nonperitoneal metastasis (M1b) [13].

Neuroendocrine Appendiceal Lesions/ Carcinoid Tumors

The WHO classification utilizes the terms "neuroendocrine tumor" (NET), "neuroendocrine carcinoma" (NEC), and "mixed adeno-neuroendocrine carcinomas" (MANEC) [14]. Synonyms for NET include carcinoid tumors and well-differentiated endocrine tumors/carcinoma. Synonyms for NEC: poorly differentiated endocrine carcinoma and small cell/large cell endocrine carcinoma. Goblet cell carcinoids (now called carcinomas) are MANEC [14].

Carcinoids or carcinoid tumors represent NETs grade 1 and derive from a variety of dispersed neuroendocrine cells (formerly labeled as amine precursor uptake and decarboxylation cells, APUD cells). These cells and the resulting tumors are not only found in the appendix but also in the entire gastrointestinal tract and other organs and are therefore addressed more comprehensively in the next chapter. Nonetheless, appendiceal carcinoids are only extremely rarely associated with multicentricity, and there is no known association with multiple endocrine neoplasia (MEN syndrome).

Appendiceal carcinoids belong to the embryological and anatomical region of the midgut to include jejunum, ileum appendix, cecum, and right colon. More than foregut and hindgut carcinoids, these midgut carcinoid cells characteristically are hormone-active. Among other products (such as GH, GHRH, gastrin, calcitonin, substance P, insulin, and neurotensin), they produce serotonin from its precursor 5-hydroxytryptophan by means of the enzyme aromatic acid decarboxylase; serotonin is subsequently metabolized in the liver by monoamine oxidase to 5-hydroxyindoleacetic acid (5-HIAA), which is excreted in the urine.

On gross examination, carcinoid tumors of the appendix are yellow-tan firm nodules. 75% are located at the tip, 15% in the mid-appendix and 10% at the base of the organ. At the time of diagnosis, the majority (80%) is less than 1 cm, 14% measure between 1 and 2 cm, and 6% are greater than 2 cm in size [14]. Histologically, carcinoids are characterized by submucosal uniform cell conglomerates with a nested or insular pattern. The cytoplasm has a modestly eosinophilic, fine granularity, and the nuclei show the classic endocrine "salt-and-pepper" chromatin pattern. Tumors have positive reactions to silver stains (argentaffin/argyrophilic) and immunohistochemically to markers of neuroendocrine tissue, including neuron-specific enolase, synaptophysin, and chromogranin A [11]. Ki67 is used to determine the proliferative capacity of the tumor for grading according the current WHO classification [14, 15]. Under the electron microscope (which is not part of routine examinations), carcinoid tumors are typically found to contain numerous membrane-bound neurosecretory granules which store a variety of hormones and biogenic amines [16].

With increasing size of the lesion, the tumor may extend deeper into the wall and even reach the peritoneal surface or in up to 27% of cases infiltrate the mesoappendix. Hence, the AJCC staging for carcinoids is based on tumor size as it correlates with the incidence of metastases and represents the most important prognostic parameter, whereas depth of invasion, lymphatic, perineural, or serosal invasion lack prognostic power (Table 37-6). Lymph node metastases are

Table 37-6. TNM staging (by AJCC and ENETS) for neuroendocrine appendiceal tumors [15]

Stage	T (AJCC)	T (ENETS)	*N* (AJCC/ ENETS)	M (AJCC/ ENETS)
X	Primary tumor not determined, or any T	Primary tumor not determined, or any T	Lymph nodes not determined, or any *N*	Metastatic disease not determined, or any M
0	No evidence of primary tumor	No evidence of primary tumor	No lymph node metastasis	No distant metastasis
1	1a: Tumor ≤1 cm 1a: Tumor 1–2 cm	T1 Tumor ≤1 cm invading submucosa and muscularis propria	Lymph node metastasis	Distant metastasis
2	Tumor 2–4 cm or with extension to the cecum	Tumor ≤2 cm with invasion of submucosa or muscularis propria, and/or minimal invasion (up to 3 mm) of subserosa/ mesoappendix		
3	Tumor >4 cm or with extension to the ileum	Tumor >2 cm and/or extensive invasion (>3 mm) of subserosa/mesoappendix		
4	Tumor directly invades other adjacent organs or structures, e.g., abdominal wall and skeletal muscle[a]	Tumor invades peritoneum/other organs		

[a]Tumor adherent to other organs or structures grossly classified as cT4 but if microscopically negative adhesion as pT1–3 depending on depth of wall invasion

Stage I: T1 N0 M0; stage II: T2–3 N0 M0; stage III: T4 N0 M0 or Tx N1 M0; stage IV: Tx Nx M1

Table 37-7. Impact of appendiceal carcinoid size on lymph node metastasis and survival [11, 14, 18, 49]

Carcinoid size	LN metastases (%)	5–/10-Year survival rates (%)
<1 cm	<1.0–15.0	92–100
1–2 cm	3.0–47.0	81
>2 cm	20–86	31

rare for lesions of less than 10 mm diameter, but occur in 20–30% of patients with carcinoids greater than 2 cm in size (Table 37-7); distant metastases are comparably rare in appendiceal carcinoids. It should be noted that the staging system by the European Neuroendocrine Tumor Society (ENETS) differs from AJCC as it also takes into account depth of appendiceal wall and meso-appendiceal invasion with invasion greater than 3 mm representing more aggressive disease [17]. Five-year survival rates for patients with local, regional metastatic, and distant metastatic disease are 95%, 81%, and 31%, respectively [9, 15, 18].

Goblet Cell Carcinoids

This term may add confusion to the classification of appendiceal lesions. It is considered a hybrid between epithelial and NETs and is also referred to as mucinous adenoneuroendocrine carcinoma [19–21]. These tumors have a mean age of presentation in the fifth decade and behave more like adenocarcinoma than carcinoid. Clinically, goblet cell carcinoids in the middle third of the appendix may in fact cause appendicitis [22]. At surgical exploration, 10% or more of the tumors are found to have already widespread metastatic disease; two-thirds of goblet cell carcinoids are incidental findings on appendectomy and ileocecectomy specimens. Five-year survival rates are worse than for regular carcinoids and for stages I, II, III, and IV were 100%, 76%, 22%, and 14%, respectively, i.e., range from 50 to 80% for locoregional disease to less than 20% for patients with distant metastases [19, 20].

Rare Appendiceal Neoplasms

All other neoplasms are comparably rare and often represent a more systemic disease process. Among the rarities, primary lymphoma of the appendix is seen with some frequency; it affects patients of all ages but most frequently occurs in the second to fourth decade of life. In children and young adults, Burkitt's lymphoma is the most common subtype, whereas older patients are more likely to have diffused large B-cell lymphoma. Furthermore, the appendix has been reported as the site of relapse of several subtypes of lymphoma [11]. Any of these lesions may either present with acute appendicitis or through a palpable mass, intussusception, or lower gastrointestinal bleeding as rarer manifestations. Other even less common and therefore not further detailed lesions include Kaposi sarcoma, leiomyoma or leiomyosarcoma, or leukemic infiltrates.

Clinical Features

Appendiceal epithelial neoplasms are notorious for the absence of any specific signs or symptoms, especially at early stages. Complicating factor is that they escape detection by routine screening efforts such as colonoscopy [23]. If a tumor is concentric and causes obstruction of the lumen, clinical symptomatology of appendicitis may ensue. Red flags in patients with signs of "appendicitis" should include any age above 50, family history of colorectal cancer or inflammatory bowel disease, prolonged history, or anemia. At later stages, epithelial appendiceal neoplasms may present as a localized abdominal or pelvic mass, bowel obstruction, or as progressive, painless, abdominal distention when large volumes of mucin accumulate in the peritoneal cavity (pseudomyxoma peritonei) [2–5].

Even hormone-active tumors such as carcinoids remain silent and are only incidentally detected. Since they are frequently located at the tip of the appendix, they may not even trigger appendicitis. Carcinoid syndrome or "crisis" with flushing, wheezing, diarrhea, and eventually right-sided valvular heart disease results from the release of serotonin and other vasoactive substances. From appendiceal primary carcinoids, this is extremely rare (less than 5%) and requires presence of significant metastatic disease to allow these substances to escape the hepatic first-pass effect and be released into the systemic circulation.

Given the incredible variability of clinical circumstances under which an appendiceal neoplasm may be diagnosed, clinicians will have to develop concepts and algorithms to optimize and standardize their management (Table 37-1).

Diagnostic Procedures

Clinical examination is expectedly unreliable in detecting, confirming, or ruling out an appendiceal neoplasm. Tumor markers are limited and include nonspecific carcinoembryonic antigen (CEA) for epithelial lesions, or 5-HIAA metabolites in the urine for carcinoids. Neither marker is suited for screening or as a negative predictive test. Cross-sectional imaging (CT, MRI) is of greatest value in evaluating a suspected appendiceal neoplasm. Plain radiographs or contrast small bowel follow-throughs may suggest a mass effect when adjacent loops of bowel appear to be displaced, but are rarely definitive. Similarly, contrast enemas, even though rarely done, may provide a hint of an extrinsic impression on the cecum, terminal ileum, or sigmoid colon.

Ultrasonography in skilled hands may allow for identification of appendiceal abnormalities, including appendicitis, fecoliths, mucoceles (hypoechogenic structure), or on occasion a mass in the right lower quadrant. Cystic masses may have a heterogeneous appearance due to the combination of fine cellular framework with mucin-containing chambers with synchronously liquid, gelatinous, and viscous components. A lack of appendiceal wall thickening (>6 mm) suggests

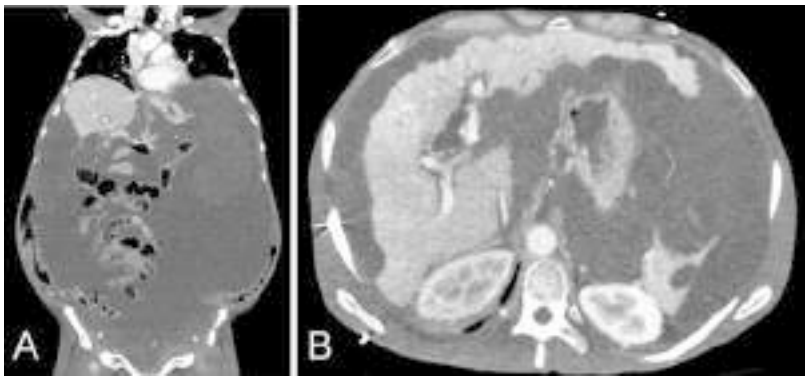

FIGURE 37-2. Pseudomyxoma peritonei: the computed tomography a coronal view (panel (**a**)) and axial view (panel (**b**)) of a patient with massive deposits of low attenuation mucin throughout the entire abdomen with scalloping of the liver contour and widening of the spaces between the compressed bowel loops.

absence of inflammation (appendicitis). A target sign either implies an enlarged and edematous appendix or an intussusception. To a limited degree, mucinous ascites can be detected and even quantified, but for comprehensive assessment of pseudomyxoma, ultrasound is not well suited.

CT or, less commonly used, MRI are the cross-sectional imaging modalities of choice as they provide reproducible, complete, and quantifiable evaluation of the whole abdomen [24, 25]. They are indicated for workup of right lower quadrant symptoms, or after the fact when diagnosed tumors (epithelial and non-epithelial) require lymph node and systemic staging, treatment planning, or evaluation of treatment response. Tumors of sufficient size can be demonstrated as a moderately enhancing soft tissue mass or a cystic dilatation of the appendix beyond 15 mm, which should raise suspicion if noted as an incidental finding [26]. Bowel displacement is an indirect sign of a pathological extraluminal process and is best visualized by adequate opacification of the terminal ileum and cecum by means of intraluminal contrast and differs from an abscess by the lack of inflammatory signs. Features of a mucocele include well-encapsulated and smooth lesions in the right lower quadrant with regular wall and low attenuation that depends on the amount of mucin in the tissue and the center of the lesion [27]. Presence of punctuate, curvilinear calcifications in a right lower quadrant cystic lesion are highly suggestive of a mucocele: they develop as a dystrophic response to a chronic inflammatory process. Myxoglobulosis is an anecdotal variant of an appendiceal mucocele with formation of multiple translucent or calcified mucin globules rather than a homogenous mucin lake.

Pseudomyxoma peritonei is characterized by low attenuation ascites and serosal implants which when not obvious are best seen as scalloping of the liver contour, at peritoneal reflections, or the pouch of Douglas (Figure 37-2). For treatment strategy and prognosis, it is important to quantify areas affected by PMP. The peritoneal carcinomatosis index (PCI) is a summary score with a maximum of 39 points from nine abdominal squares and 4 small bowel segments, whereby each area is scored between 0 and 3 when deposits are >5 cm [24]. Positron emission tomography (PET scan) may have a role for detection or monitoring of systemic metastatic disease but is notoriously ineffective in assessing pseudomyxoma peritonei.

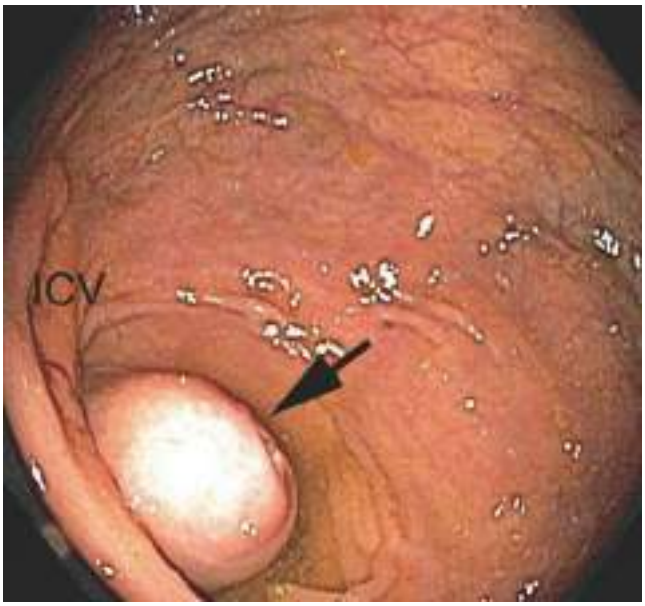

FIGURE 37-3. Colonoscopic appearance: even though appendiceal neoplasms frequently escape endoscopic detection, they occasionally lead to an extramucosal protrusion (*asterisk*) of the appendiceal orifice into the cecal lumen. ICV: ileocecal valve.

Since most carcinoids are surgical/pathological incidentalomas, most diagnostic investigations are performed after the initial operation. For the majority of incidentally diagnosed, well-differentiated appendiceal NERs of <10 mm, no postoperative diagnostic procedure is necessary [15]. After complete resection of 10–20 mm lesions, a single CT or MRI to rule out lymph node and distant metastases is recommended, but without level I evidence [15]. For lesions >20 mm, CT and or MRI of the abdomen is recommended; in addition a PET scan or a somatostatin receptor scan in combination with SPECT/CT (or Somatostatin Receptor PET with 3-phase CT scan) may be considered to detect or rule out distant tumor spread.

Appendiceal neoplasms typically evade detection by colonoscopy [23]. Occasionally, a protrusion of the appendiceal orifice or release of mucoid material may be recognized (Figure 37-3). However, colonic evaluation (colonoscopy, CT

colonography) is recommended prior to any elective intervention for a suspected or proven appendiceal neoplasm, because both epithelial and NETs may be multicentric and/or be associated with a synchronous lesion in up to 10–20% [28].

Medical Management

Management of localized appendiceal neoplasms is primarily surgical. Nonsurgical modalities come into play for locally advanced or metastatic lesions as well as for primarily systemic neoplasms such as leukemia or lymphoma. Pseudomyxoma of too significant extent (high PCI) may not benefit from cytoreductive surgery and HIPEC (see later). Adjuvant and palliative systemic chemotherapy are still largely based of 5-fluorouracil and typically combined with other conventional agents (oxaliplatin and others), or biological drugs such as bevacizumab [29]. Regimens and timings before, during and after surgery remain areas of research [30, 31]. Somatostatin is being used for metastatic and particularly symptomatic carcinoid tumors. Radiation treatment is not part of routine management of any appendiceal tumor and is reserved for special circumstances on an individualized basis.

Surgical Treatment of Appendiceal Lesions

Surgery is the primary treatment for localized disease with the goal to achieve a curative R0 resection; in metastatic disease, the role of surgery needs to be individually analyzed and weighed against systemic chemotherapy or best palliative care. Surgical decision-making should therefore take five questions into consideration as also alluded to in the previously listed clinical scenarios:

1. Has the primary tumor already been removed?
2. Was the clinical situation associated with possible tumor spillage?
3. For a given tumor, what entails an adequate margin?
4. What is the probability of nodal involvement?
5. In case of locally advanced or metastatic disease, is aggressive surgical intervention superior to conservative management?

Depending on the answers, there are four possible surgical responses (Table 37-8): (a) appendectomy only, (b) hemicolectomy or completion hemicolectomy, (c) cytoreductive surgery and peritonectomy with or without HIPEC, or (d) conservative management.

Appendectomy

Appendectomy alone should be reserved for premalignant lesions, carcinoma in situ (Tis), or carcinoids of less than 1 cm diameter provided that a sufficient margin can be obtained. Carcinoids of 1–2 cm represent a grey zone but may be associated with a higher than previously reported incidence of nodal disease [18], suggesting that appendectomy may not suffice. An appendiceal mucocele requires careful dissection to avoid perforation of the lesion. If the case is approached laparoscopically, placement of the whole appendix/cecum into a specimen bag prior to starting the dissection may be a strategy to avoid rupture and spillage or conversion to a laparotomy [32].

TABLE 37-8. Operations performed for appendiceal neoplasms

Appendectomy	Right hemicolectomy	Cytoreduction + HIPEC	Nonsurgical
Intact mucocele	Invasive adenocarcinoma	PMP with PCI ≤16 (–20):[a]	PMP with PCI > (16–)20?[a]
Adenocarcinoma tis		– Diffuse mucinous adenomucinosis peritonei	Adenocarcinoma with diffuse systemic metastases
		– Peritoneal mucinous (adeno-) carcinomatosis	Adenocarcinoma with peritoneal disease AND systemic metastases
		Perforated appendiceal neoplasm without visible PMP?	
Appendiceal carcinoid <1 cm, R0	Appendiceal carcinoid 1–2 cm, R0?		Carcinoid with diffuse systemic metastases beyond one organ
	Appendiceal carcinoid >2 cm		
	Any carcinoid with insufficient margin (R1, questionable R), multifocality, invasion of mesoappendix >3 mm		
	Any carcinoid with nodal involvement		
	Any carcinoid with systemic metastases to the liver only		
	Goblet cell carcinoid	PMP from goblet cell carcinoid	Widespread systemic metastases, or PMP from goblet cell carcinoid with systemic metastases

[a]*PMP* Pseudomyxoma peritonei, *PCI* Peritoneal carcinomatosis index

Right Hemicolectomy

For non-perforated appendiceal adenocarcinoma, carcinoids larger than 2 cm and any of the previously mentioned lesions with unfavorable features or whose margins are insufficient with an appendectomy alone, an oncological right hemicolectomy with a mesocolic lymph node dissection is indicated [15, 18]. Oncological resection for adenocarcinoma achieves better 5-year survival rates than appendectomy alone [33]. The incidence of lymph node metastases in appendiceal carcinoid tumors increases with size of the tumor (Table 37-7). There is controversy regarding the surgical management of patients in which perforation of a mucinous appendiceal neoplasm has occurred resulting in pseudomyxoma peritonei. Some argue that a right hemicolectomy is not necessary in this situation as the outcome is determined by the peritoneal disease rather than the lymph nodes [32, 34].

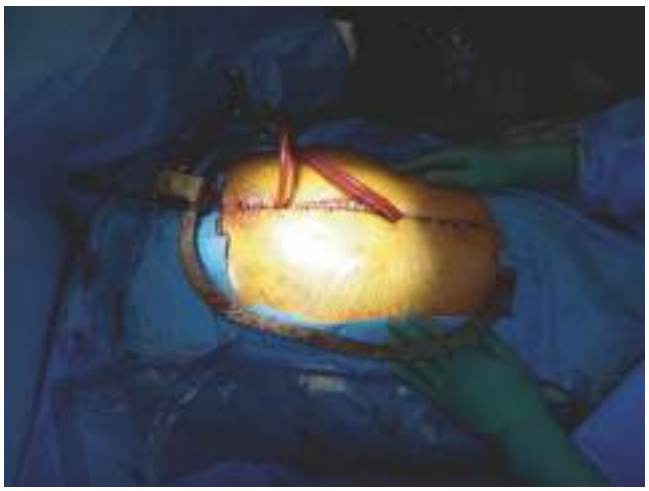

FIGURE 37-4. Hyperthermic intraperitoneal chemotherapy (HIPEC) (Courtesy of Eric K. Johnson, M.D.).

Cytoreductive Surgery and HIPEC

In cases of advanced peritoneal dissemination, cytoreductive surgery with HIPEC is performed in selected cases [15]. If pseudomyxoma peritonei is unexpectedly encountered during an operative exploration, the patient would be best served by careful retrieval and cytological analysis of any mucinous fluid present, and referral to a specialized center with expertise in cytoreductive surgery and HIPEC [35]. Minimization of surgical manipulation and mobilization of intra-abdominal viscera will facilitate the subsequent cytoreductive surgery performed later.

The mainstay of surgical treatment for disseminated peritoneal disease is the arduous operative task of cytoreductive surgery and heated intraperitoneal chemotherapy (HIPEC) (Figure 37-4). In retrospective series, this surgical modality has demonstrated favorable results in carefully selected patients [36], but at the same time was associated with a substantial morbidity and mortality; [37–41] in addition, most series note that incomplete cytoreduction was unable to achieve a relevant benefit as the recurrence rates were very high [37, 42, 43]. It seems rather obvious that the outcomes depend on the extent of the initial disease whereby a number of authors recommended to limit cytoreductive surgery and HIPEC to patients with a PCI of less than (16–)20.

In reviewing the evidence supporting the use of cytoreduction and HIPEC, it should be noted that the literature on the technique and outcomes continues to have significant limitations. On one hand, most series are retrospective and inconsistent in regards to inclusion criteria, extent of disease, concomitant treatment, protocols, and follow-up. Selection bias is inherent to their study designs. Furthermore, they are heavily dominated by Sugarbaker [44], who has advocated for the use of cytoreduction and HIPEC not only for appendiceal neoplasms, but also for peritoneal carcinomatosis arising from non-appendiceal cancers. Corroboration of his data by other groups is in process, but at the same time challenged by availability of more aggressive systemic chemotherapy regimens, the latter of which parenthetically has been found to increase the risk of complications after HIPEC [31]. Most importantly, however, there is a lack of prospective randomized data on direct comparison of HIPEC and cytoreductive surgery with systemic chemotherapy alone. The only prospective randomized trial to date that suggested improved outcomes with HIPEC compared to systemic treatment only was limited by a chemotherapy regimen (fluorouracil-leucovorin) that many feel was not representative of modern treatment standards [43]. A heated debate continues as to whether HIPEC should be considered the standard of care or still an experimental approach [45, 46].

In preparation for cytoreductive surgery and HIPEC, adequate staging and quantitative assessment using the PCI [24], colonic clearance, aggressive hydration, and bowel cleansing are essential. Considerations include provisions for stomas, timely prophylactic vaccination for splenectomy (against pneumococcus, meningococcus, and H. Influenza) and placement of a gastrostomy tube and feeding jejunostomy tube. Cytoreductive surgery aims at removing or reducing all visible tumor implants to less than 2 mm in size as only complete cytoreduction allows for adequate drug penetration into residual tumor deposits. It typically includes omentectomy and stripping of all parietal peritoneal surfaces, including the subdiaphragmatic spaces and the paracolic recesses (peritonectomy). However, it may also involve aggressive multiorgan resection including tumor-involved bowel (colon, small bowel) or other organs (gallbladder, spleen, uterus/ovaries, and others) or the posterior rectus sheath may be removed. For the HIPEC phase of the procedure, a number of open or closed techniques have been reported. We have typically used the closed technique to minimize heat dissipation, spillage of perfusate, and safety hazard to health personnel [47, 48]. The incision is temporarily closed to the size of a gel port through which large-bore afferent and efferent cannulas are placed to the peritoneal cavity. The heated chemothera-

Table 37-9. Selected series on cytoreductive surgery and HIPEC for appendiceal neoplasms

Institution	Year	*N*	Appendiceal origin (%)	Complete CR[a] (%)	M/M[b]	RR[c]	SV[d]
Washington Cancer Institute [50]	1999	200	75	n/a	27/2	n/a	n/a
University of Cincinnati College of Medicine [51]	2004	33	67	67	27/0	>33	(49)[e] (3 years)
Wake Forest University, NC [52]	2006	110	100	28	38/4	n/a	53.4 (5 years)
Istituto dei Tumori, Milan, Italy [53]	2008	96	100	67	27/1	61	71.9 (5 years)
Washington Cancer Institute [54]	2008	472	85	100	n/a	26	n/a
Mercy Medical Center, Baltimore MD [55]	2012	77	100	65	27/0	n/a	40 (3 years)
International Multicenter [36]	2012	2298	100	51	24/2	n/a	63 (10 years)
National Cancer Centre Singapore [56]	2013	100	20	90	55/0	74	50.9 (5 years)
Mount Sinai Medical Ctr, NY [57]	2014	170	29	37	52/4	40–79	30.6 (3 years)
Basingstoke/North Hampshire Hospital, UK [58]	2015	752	100	68	46/2	50	64.5 (5 years)
Wake Forest University, NC [59]	2015	430	100	44	28/3	n/a	53.4 (5 years)

[a]*CR* Cytoreduction
[b]*M/M* 30 Day morbidity and mortality
[c]*RR* Recurrence rate
[d]*SV* Survival
[e]Number calculated from graph by weighted average

peutic drugs are circulated throughout the abdominal cavity via pumps and heat exchangers (heart-lung machine). The most frequently used drug is mitomycin-c, which is administered for a duration of 60–120 min at a temperature of 41–43 °C. Other drugs have been used and are being tested without any increased benefit. Reconstructions and anastomoses are to be performed after the hyperthermic perfusion phase. Cytoreductive surgery and HIPEC are associated with formidable morbidity that may exceed 50% (Table 37-9). Apart from myelosuppression and nephrotoxicity with intensified diuresis, complications include sepsis, respiratory failure, ileus, anastomotic leak, abscess, enterocutaneous fistula, acute renal failure, thromboembolic events, and in the long run formation of hostile adhesions. The mortality rates in initial reports were approximately 10%, but could be reduced significantly in more recent series (Table 37-9). In the majority of reports, PCI score, PMCA tumor type and completeness of cytoreduction were significant prognostic factors. Perioperative or neo-adjuvant chemotherapy is currently a matter of debate and is not routinely used.

Conclusion

Appendiceal neoplasms are rare lesions. Most individual surgeons will encounter few, if any, during their career. Nevertheless, when a diagnosis of such a lesion is made, careful investigation of the histopathology and rational analysis of the various parameters are of paramount importance in order to finalize treatment and follow-up. There are numerous areas (e.g., incidentalomas, conservatively treated "appendicitis," perforated tumor without visible implants, and others) that await clarification of guidance which should be developed on preferably prospective data.

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38
Carcinoids, GISTs, and Lymphomas of Colon and Rectum

David J. Maron

Key Concepts

- Treatment of colonic carcinoids is segmental resection including mesenteric lymph nodes.
- Somatostatin analogues control the symptoms of carcinoid syndrome and help limit progression of disease.
- Rectal carcinoids less than 1 cm may be treated by local excision, while tumors greater than 2 cm require radical resection.
- Imatinib blocks activation of the KIT oncoprotein in gastrointestinal stromal tumors.
- Patients with colonic lymphomas that produce symptoms are best treated with surgical resection prior to chemotherapy.

The majority of neoplasms that arise in the colon and rectum are adenomas and adenocarcinomas; however, other tumors may present as well. It is important for the clinician to understand the biology of these tumors so that proper therapy may be offered. Tumors may develop from epithelial, mesenchymal, neural, vascular, or lymphoid tissue. While there are a number of rare colorectal tumors, this chapter will discuss three more commonly occurring non-adenomatous neoplasms.

Carcinoid Tumors

Carcinoid tumors were originally described in 1888 in two patients with multiple small tumors of the ileum by Otto Lubarsch, a German pathologist. In 1907, Siegfried Oberndorfer first used the term "Karzinoid," which translates as "carcinoma-like," hinting that these tumors behave differently from adenocarcinoma [1]. It was believed that although these tumors could metastasize like carcinomas, their clinical course was typically fairly benign.

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Histology

Carcinoids are slow growing tumors of the neuroectodermal origin and belong to the amine precursor uptake and decarboxylation (APUD) system. They originate from Kulchitsky or basogranular enterochromaffin cells located in the crypts of Lieberkuhn [2]. Microscopically, these tumors are composed of monotonous sheets of small round cells with uniform nuclei and cytoplasm. The cells contain very dense neurosecretory granules that contain various secretory peptides; these granules are similar to synaptic vesicles found in neurons. The cytoplasmic features are typically benign-appearing and mitotic figures are infrequent. Five histologic patterns of carcinoid tumors include insular, trabecular, glandular, undifferentiated, and mixed. Insular and trabecular patterns are typically associated with a more favorable prognosis. Distinguishing between benign and malignant carcinoids can be difficult; however, increased cellular atypia, high mitotic activity, or necrosis is often associated with more aggressive tumors.

Carcinoid tumors have specific staining patterns related to the amines and peptides they produce as well as cytoplasmic proteins they contain. Serotonin is capable of reducing silver salts to metallic silver, and therefore carcinoid tumors that produce serotonin and stain positive with silver stains are described as "argentaffin positive." Some tumors are capable silver uptake but not reduction, and these may be demonstrated by the addition of an external reducing agent; these tumors are referred to as "argyrophilic." Carcinoid tumors of the midgut are typically argentaffin positive, while those in the hindgut are often mixed (6–70% argyrophilic and 8–16% argentaffin positive) [3]. Silver staining has been abandoned in favor of immunohistochemical staining for cytoplasmic proteins, including chromogranin, synaptophysin, and neuron-specific enolase [4].

Carcinoid tumors have been shown to produce at least 30 bioactive compounds [5]. These compounds include amines such as serotonin and histamine, proteins (including various hormones and kinins), and prostaglandins. Serotonin is

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derived from the amino acid tryptophan in a two-step process and is stored and transported in platelets. As tryptophan is an essential amino acid important in the production of proteins such as niacin (vitamin B_7) and nicotinamide (vitamin B_3), deficiencies of these vitamins may occur if large quantities of tryptophan are consumed in the production of serotonin by carcinoid tumors. Metabolism of serotonin occurs first in the liver (monoamine oxidase) and then in the kidney (aldehyde dehydrogenase) to produce 5-hydroxy-indole-acetic acid (5-HIAA), which is excreted in the urine.

Incidence and Distribution

Carcinoid tumors may originate in the foregut, midgut, or hindgut. Foregut tumors arise in the thymus, respiratory tract, stomach, duodenum, and pancreas. Midgut carcinoids originate in the jejunum, ileum, appendix, and proximal colon. Hindgut tumors arise in the distal colon and rectum. The distribution of carcinoids varies among reports. In a series of almost 3000 carcinoid tumors, Godwin [6] found that the most frequent site of origin was in the appendix (38%), followed by the ileum, rectum, and bronchus (23%, 13%, and 11.5%, respectively). Modlin and Sandor [7] combined Godwin's series with an additional 5000 carcinoid tumors and reported the most common site as the small bowel (28.7%) followed by the bronchus, appendix, and rectum (25.1%, 18.9%, and 12.6%, respectively). A recent report noted that since the implementation of screening colonoscopy in the United States, the incidence of rectal carcinoids has surpassed that of small bowel carcinoids [8]. Carcinoid tumors are associated with an increased risk of synchronous colorectal and small bowel tumors, as well as metachronous lung, prostate, and urinary tract neoplasms [9, 10]. The reason for this association is unknown; however, it has been theorized that the various peptides secreted by carcinoid tumors may have tumorigenic properties [9].

Clinical Presentation

Approximately half of all gastrointestinal carcinoids are diagnosed following appendectomy for suspected appendicitis. Carcinoids of the appendix are discussed in detail in Chap. 37. Colonic carcinoids most commonly occur in the seventh or eighth decade of life and are more common in women than in men [11]. They may present as a polyp or as a mass that is indistinguishable from a colon carcinoma, both grossly and on radiographic visualization. Many patients with colonic carcinoids are asymptomatic or have symptoms from another condition that prompt an investigation that leads to the diagnosis [12]. Those tumors that are symptomatic produce symptoms similar to colonic carcinomas (bleeding, abdominal pain, and change in bowel habits).

Carcinoids may arise throughout the colon; however, they are more commonly found in the cecum. Ballantyne and colleagues reported 48% of colonic carcinoids were found in the cecum, 16% in the ascending colon, 6% in the transverse colon, 11% in the descending colon, and 13% in the sigmoid colon [13]. Murray et al. reported similar results, with 73% of tumors found in the cecum, 7% in the ascending colon, and 20% in the sigmoid colon [14].

Symptoms of rectal carcinoids, when present, are typically rectal bleeding or change in bowel habits. Most rectal carcinoids, however, are asymptomatic and are found at the time of colorectal cancer screening. The incidence of rectal carcinoids in all patients undergoing sigmoidoscopy is estimated at 0.05% [15, 16]. These tumors typically appear as a solitary 1–1.5 cm mobile submucosal nodule with an intact overlying normal mucosa. Malignancy is frequently associated with carcinoids larger than 2 cm with invasion through the muscularis propria. These tumors often will appear ulcerated and present with rectal bleeding. Metastatic disease tends to occur less frequently in carcinoid tumors of the hindgut (rectum 18%) when compared with midgut carcinoids (small bowel 34%, colon 60%) and foregut tumors (stomach 23%, bronchopulmonary 21%) [6].

Carcinoid Syndrome

Systemic symptoms produced by carcinoid tumors are referred to as the carcinoid syndrome. Although classically described as the hallmark of carcinoid tumors, carcinoid syndrome occurs in only 10–18% of patients with carcinoids, and in only 50% of patients with advanced disease [3]. The symptoms include flushing of the skin, non-bloody diarrhea, and abdominal pain. The symptoms are often episodic and may be precipitated by stress or the ingestion of certain foods, caffeine, or alcohol. The flushing may involve the face or the entire body and may occur for a few minutes or last for several hours. Flushing may also be associated with excessive tearing, salivation, and bronchopulmonary spasm leading to wheezing. Flushing occurs in up to 85% of patients with the carcinoid syndrome, and it is believed that kallikrein secretion is responsible for these symptoms [17]. Abdominal symptoms such as cramping and watery diarrhea occur in 80% of patients with carcinoid syndrome, and are likely due to the secretion of serotonin. Intestinal obstruction may also develop secondary to mesenteric fibrosis, and fibrosis of the retroperitoneum may lead to ureteral obstruction. Treatment of symptoms of diarrhea includes loperamide, diphenoxylate/atropine, and other antidiarrheal medications. Antihistamines or H2 receptor antagonists may be helpful in reducing flushing symptoms.

Patients with carcinoid syndrome may also develop right-sided heart failure. Serotonin has an effect on myofibroblasts which results in fibroplasia, increased vascular tone, bronchoconstriction, and platelet aggregation. These effects may lead to pulmonary hypertension, tricuspid and pulmonary valve stenosis, and right ventricular hypertrophy and fibrosis [5]. Patients with higher levels of serotonin (higher urinary

5-HIAA levels) have been found to have increased valvular damage [3]. The left side of the heart is spared from the effects of carcinoid products as the lungs are capable of inactivating these substances. Surgical repair or replacement of the affected valves has been met with significant postoperative morbidity.

The liver is capable of metabolizing and inactivating most of the peptide hormones secreted by carcinoid tumors. It is for this reason that the carcinoid syndrome typically develops only after the tumor has developed metastases in the liver. Alternatively, primary carcinoid tumors located outside the portal venous system (bronchopulmonary) or gastrointestinal tumors that develop lymph node metastases or direct invasion into the retroperitoneum may also present with carcinoid syndrome [18].

Carcinoid syndrome occurs most frequently in patients with metastatic disease from a midgut carcinoid tumor. In fact, 90% of patients with carcinoid syndrome have midgut carcinoids, and 60% of patients with metastatic small bowel carcinoids will develop symptoms. This is likely due to the ability of midgut carcinoids to produce high levels of serotonin [19]. In contrast, foregut tumors typically lack the enzyme required to convert 5-hydroxytryptophan into serotonin, and hindgut carcinoids rarely produce serotonin. Therefore rectal carcinoids, even in the presence of metastatic disease in the liver, almost never result in the carcinoid syndrome.

Diagnostic Tests

The majority of carcinoid tumors of the colon and rectum are found during colonoscopy or are discovered during abdominal exploration for another condition. Full endoscopic evaluation of the colon and rectum should be performed to evaluate for synchronous malignancies. Endoscopic ultrasonography has been used in the evaluation of rectal carcinoids, and has been shown to have a 75% accuracy rate in determining the depth of invasion and presence of lymph node metastases [20]. This may be helpful in determining whether the carcinoid is amenable to endoscopic resection [21].

When endoscopic biopsy is not feasible, biochemical tests may help to make the diagnosis of carcinoid. Although carcinoid tumors may produce a variety of hormones, the most widely used tests are related to serotonin. The most useful biochemical test for diagnosing carcinoid in the symptomatic patient is the 24 h urine 5-HIAA assay. Normal excretion ranges from 2 to 8 mg/24 h, and a diagnosis of carcinoid syndrome in patients with excretion exceeding these levels has a sensitivity and specificity of 73% and 100%, respectively [22]. Certain medications including acetaminophen and salicylates, as well as serotonin-rich foods such as bananas, pineapples, nuts, and avocadoes may falsely elevate urinary 5-HIAA levels and should therefore be avoided during the test.

In addition to a CT scan of the chest, abdomen, and pelvis to evaluate for metastatic disease, somatostatin receptor scintigraphy (SRS) may be helpful in identifying occult metastases and to determine if the patient is likely to respond to treatment with octreotide. The majority of carcinoid tumors express receptors (SSTR 1–3) that have an affinity for somatostatin [23]. SRS therefore has a high sensitivity in detecting carcinoids; however, approximately 10% of tumors do not express the somatostatin receptor. Whole body positron emission tomography (PET) using ^{18}F-Dopa may also be useful in detecting carcinoid tumors. Hoegerle et al. compared the use of CT, SRS, and PET scans in the localization of primary and metastatic carcinoid tumors and found that PET imaging was more sensitive in localizing primary tumors and lymph node involvement, while CT was more sensitive in identifying distant disease [24]. Krausz et al. compared ^{18}F-Dopa PET/CT imaging with SRS and found that PET/CT demonstrated more true positive tumor foci and was better tolerated by patients [25]. The TNM staging of carcinoid tumors is similar to that of adenocarcinomas of the colon (Table 38-1).

Treatment

The treatment of carcinoid tumors is surgical resection. The type of surgery depends on a variety of factors, including whether the tumor is amenable to local or endoscopic resection and whether surgical debulking of tumor may help to reduce the symptoms of the carcinoid syndrome. The choice of the appropriate procedure is based on the location of the tumor, the likelihood of residual primary disease, and the presence of lymph node or metastatic disease. Guidelines for resection are summarized in Table 38-2.

Carcinoids of the small bowel are frequently multicentric and have a propensity for developing obstruction secondary to intussusception, mesenteric fibrosis, and kinking of the bowel (Figure 38-1a, b). Metastasis to regional lymph nodes approaches 50% [26], and tumors less than 1 cm in diameter are associated with a 20–30% incidence of lymph node involvement. Size of the tumor is a poor predictor of distant metastasis, as tumors less than 0.5 cm have been shown to metastasize to the liver. Surgical management should therefore include a formal small bowel resection with wide mesenteric excision of the associated lymph nodes. This should be performed even in the presence of metastatic disease to reduce the incidence of small bowel obstruction due to tumor or fibrosis of the mesentery. As one-third of carcinoids of the small bowel may be multicentric, it is important to examine the entire small intestine to evaluate for synchronous lesions [26].

Carcinoids arising in the colon are often asymptomatic until they develop into large tumors with lymph node metastases. Colonic resection similar to that performed for adenocarcinoma is therefore recommended, with the extent

TABLE 38-1. TNM staging of carcinoid tumors

Stage	Characteristics
Tumor	
T1	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades through muscularis propria into subserosa or nonperitonealized pericolic or perirectal tissues
T4	Tumor directly invades other organs or structures and/or perforates visceral peritoneum
Regional nodal metastases	
NX	Regional lymph nodes cannot be assessed
N0	No nodal metastasis
N1	Metastasis in 1–3 pericolic or perirectal nodes
N2	Metastasis in four to more pericolic or perirectal nodes
N3	Metastasis in any node along course of a named vascular trunk and/or metastasis to apical node
Distant metastasis	
MX	Presence of distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Adapted from the AJCC Cancer Staging Manuel, 7ed. (Edge, Byrd, Compton, Fritz, Green, Trotti, Eds.) Publ. Springer, NY. 2010

TABLE 38-2. Guidelines for resection

Primary tumor	Factor	Extent of resection
Small bowel	Locally limited disease	Resection of primary and metastatic tumors
	Extensive disease	Resection or bypass of primary tumor
		Debulking of metastasis
Colon		Colectomy
Rectum	<1 cm	Local excision
	1–1.9 cm	Local excision or proctectomy
	>2 cm	Proctectomy

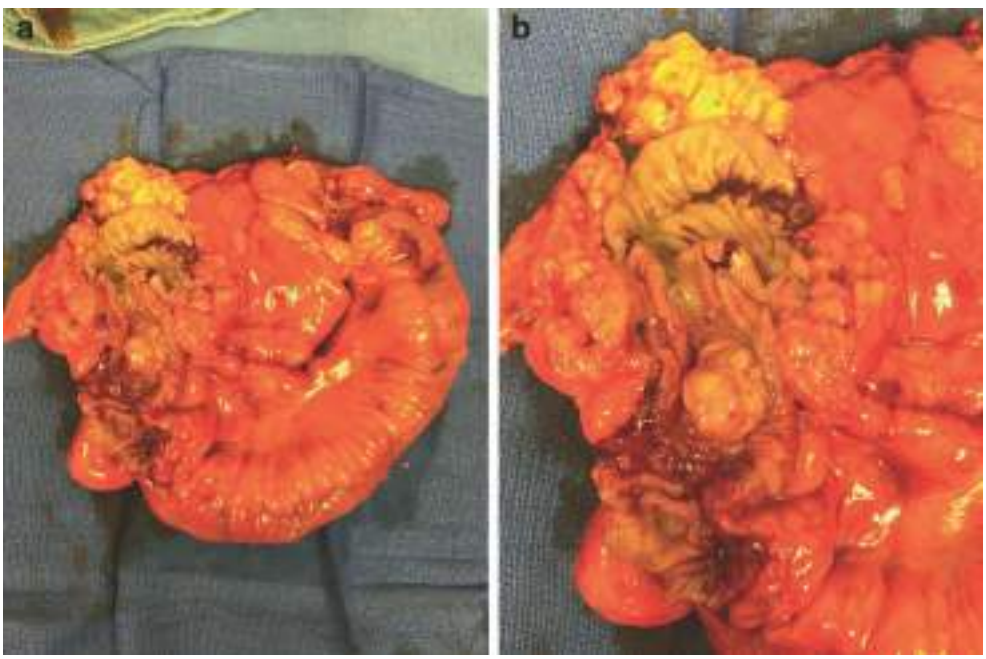

FIGURE 38-1. (**a**) Surgical specimen demonstrating a terminal ileal carcinoid. Note the desmoplastic response of the mesentery. (**b**) Close-up view of the lesion.

determined by the location of the disease [27]. Outcomes following colectomy for colonic carcinoids are varied. Welch and Donaldson [28] reported that 5-year survival was similar to that of survival in patients with carcinoma of the colon, while Berardi noted that the average survival following resection of colonic carcinoid was 26 months [29]. Location of the primary tumor may affect outcomes, as in one series cecal tumors were found to have an incidence of 71% metastases while tumors elsewhere in the colon had only a 33% incidence [30]. Spread and colleagues [31] noted that survival in patients with colonic carcinoids was significantly lower when compared with carcinoid tumors of the rectum or appendix, and was also significantly lower than survival in patients with adenocarcinoma. Al Natour and colleagues recently reviewed 929 patients with colonic carcinoids and found that those patients with intramucosal tumors less than 1 cm in diameter had only a 4% risk of lymph node metastasis [32]. They concluded that small tumors confined to the mucosa may be appropriately treated by endoscopic resection.

As carcinoid tumors of the rectum may be amenable to local excision, less invasive treatment may be an option in some patients. It is important to balance the benefits of a less morbid intervention with the risks of local recurrence and nodal involvement (and hence the risk of metastatic disease). Transanal or endoscopic excision is adequate for most tumors less than 1 cm in diameter. Formal transanal excision of the full thickness of the rectal wall allows for a precise assessment of the depth of penetration, and is more likely to result in negative margins of resection. However, this may not be necessary for many patients, as recurrence is rare even when there is an involved margin following endoscopic excision of tumors less than 1 cm in diameter. Invasion of the muscularis propria (T2) has been associated with lymph node metastases in up to 47% of patients [33]. In an analysis of 106 patients with rectal carcinoid, muscularis invasion was the only independent prognostic factor for predicting 5-year survival, and size of the tumor was significantly associated with muscular invasion [34].

In addition to muscularis propria invasion, rectal carcinoids whose size is greater than 2 cm in diameter are also at significant risk of lymph node metastases. Patients should therefore be considered for proctectomy with excision of the mesorectum to allow for assessment and clearance of the nodal basin. The treatment of rectal carcinoids measuring between 1 and 1.9 cm remains uncertain and must be individualized based on tumor features and the overall health of the patient. In a series of 62 patients, lymph node metastases were found in 69% of patients with tumors ranging 1.1–2 cm in diameter [35]. Shields and colleagues evaluated 202 patients with rectal carcinoids and found that tumor size greater than 1 cm and evidence of lymphovascular invasion were independent predictors of lymph node involvement [36]. Lymph node involvement was also associated with the development of distant metastasis and significant decrease in survival. Perineural invasion has also been demonstrated as a poor prognostic factor [37]. These findings have led some authors to conclude that rectal carcinoids larger than 1 cm should routinely be treated with radical resection in suitable patients [35, 36].

Carcinoid tumors are typically slow-growing and patients often exhibit favorable 5- and 10-year survival rates despite the presence of extensive metastatic disease. Surgical treatment of metastatic carcinoid in the liver may be of benefit in improving survival and may help to provide long-term palliation of hormone-related symptoms in patients who are unable to tolerate or do not respond to medical treatment with somatostatin analogues. Various techniques have been employed, including hepatic resection, radiofrequency ablation, cryosurgery, and chemoembolization. Wedge resection or lobectomy of hepatic metastases not only improves symptoms associated with the carcinoid syndrome but also has been shown to prolong survival [38]. As metastatic carcinoid tumors derive the majority of their blood supply from the hepatic artery (while hepatocytes receive blood supply primarily from the portal venous system), chemoembolization may play an important role in patients who are unable to tolerate hepatic resection. Patients with large tumors or those who are refractory to somatostatin frequently experience significant short-term improvement in their symptoms [39]. Liver transplantation has also been employed in patients with metastatic carcinoid, with outcome similar to those seen in patients who undergo transplantation for hepatocellular carcinoma [40].

The efficacy of systemic chemotherapy in the treatment of metastatic carcinoid is limited. Various agents have been used, including 5-FU, streptozotocin, cisplatin, doxorubicin, etoposide, and dacarbazine, either as monotherapy or in combination. The largest study reported is a comparative trial of combination therapy with 5-FU and doxorubicin versus 5-FU and streptozotocin [41]. This study demonstrated an improvement in median survival in the streptozotocin arm (24.3 months vs. 15.7 months); however, there were no differences between the two treatments with regard to response rate (16% vs. 15.9%) or progression-free survival (5.3 months vs. 4.5 months). More aggressive carcinoids may respond well to combination therapy with cisplatin and etoposide [42]. The use of continuous infusion 5-FU combined with octreotide has also shown some promise, with reports of a 24% partial response rate and disease stabilization in 69% in a small series of patients [43].

More than 80% of carcinoid tumors express surface receptors for somatostatin (especially receptor subtype 2), and therapeutic strategies have therefore focused on the development of agents that target these receptors. Activation of these receptors results in reduced hormone synthesis and secretion, thereby leading to complete or partial relief of symptoms associated with the carcinoid syndrome in up to 90% of patients [44]. Somatostatin analogues that have been used in the treatment of carcinoid include octreotide and lanreotide.

Octreotide may be given as a subcutaneous, intramuscular, or long-acting depot injection. Lanreotide has a longer half-life than octreotide; however, its use is not currently approved for use in the United States. In addition to the ability to control symptoms, somatostatin analogues may also help to limit the progression of disease. In a placebo-controlled double-blind, randomized trial of 85 patients, octreotide was associated with a significantly better median time to tumor progression (14.3 months vs. 6 months) and stable disease at 6 months of treatment (66.7% vs. 37.2%), although the trial did not comment on overall survival [45]. Interferon-alpha has also been used to treat metastatic carcinoid tumors with some success. Di Bartolomeo and colleagues reported symptomatic control in 80% of patients and reduction of 5-HIAA levels in 58% of patients treated with daily intramuscular injections of interferon-alpha [46]. When combined with octreotide in a randomized trial, interferon-alpha was found to significantly reduce the risk of progression when compared with octreotide alone, although again no survival benefit was found [47]. Significant side effects of fever, fatigue, and weight loss often limit the routine use of interferon therapy.

GISTs

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasm of the gastrointestinal tract and account for approximately 0.1–3% of all intestinal cancers. GISTs were first described by Mazur and Clark, who used electron microscopy to differentiate these tumors from other soft tissue sarcomas [48]. Most tumors arising from mesenchymal elements of the gastrointestinal tract were considered leiomyomas, leiomyosarcomas, and leiomyoblastomas; however, it was discovered that GISTs lack features associated with smooth muscle cells. Instead, it is believed that GISTs arise from the interstitial cells of Cajal or other pluripotential mesenchymal stem cells. The interstitial cells of Cajal coordinate autonomic movements of the gastrointestinal tract and are located within muscle layer of the intestinal wall.

Histology

Histologically, gastrointestinal stromal tumors typically have a spindle cell appearance and stain positive for the CD117 antigen, a marker for the KIT tyrosine kinase oncoprotein. In addition, 60–70% of GISTs will stain positive for CD34, a hematopoietic progenitor cell antigen [49]. These features help to differentiate GISTs from other sarcomas; leiomyomas stain negative for KIT and CD34 but positive for desmin, smooth muscle actin, and S100 [50].

Incidence and Distribution

GISTs typically occur in the sixth to seventh decade of life and affect men and women equally. Most tumors are sporadic; however, several hereditary syndromes are associated with GISTs. Carney's triad consists of (1) synchronous or metachronous GISTs, (2) extra-adrenal paraganglionomas, and (3) pulmonary chondromas [51]. This is usually seen in women before age 30 and is not associated with a KIT mutation. Patients with neurofibromatosis type I are also more commonly affected with GISTs. Tumors in these patients are more likely to occur at a younger age and often present with multiple small intestinal GISTs [52].

Gastrointestinal stromal tumors are most commonly found in the stomach (approximately two-thirds of cases), followed by the small intestine (about one-quarter of cases). Esophageal GISTs are rare, but tumors may also arise in extra-GI locations, principally in the mesentery, omentum, and retroperitoneum. Tumors located in the colon and rectum account for only 10–20% of GISTs, and of those, the majority arise in the rectum.

Clinical Presentation

GISTs are usually slow-growing lesions, and are often discovered incidentally during endoscopy or in the treatment of other conditions. The most common clinical symptoms are rectal bleeding and abdominal or rectal pain. Advanced lesions may present with a palpable mass, obstruction, or perforation (Figure 38-2). Kingham et al. found that symptoms were more common in patients with larger tumors; the median size of tumors was 8.9 cm in symptomatic patients, compared to 2.7 cm in asymptomatic patients [51]. Metastatic disease most frequently occurs in the liver and peritoneum; metastatic disease in the lymph nodes is uncommon [52].

Diagnostic Tests

Evaluation of a patient with a suspected GIST includes colonoscopy as well as endoscopic ultrasound, if feasible. Lesions are usually submucosal; however, biopsy may be aided with the use of endoscopic ultrasound-guided fine needle aspiration. Care must be taken as these tumors are frequently associated with neovascularization, and biopsy may result in significant hemorrhage [53]. Percutaneous biopsy with fine or core needle aspiration is an option for tumors that cannot be reached endoscopically; however, concern over tumor rupture and spread has been reported [51]. CT and MRI may aid staging and determining whether surgical resection is feasible. GISTs typically involve the muscularis propria, and radiographically have a characteristic appearance of a

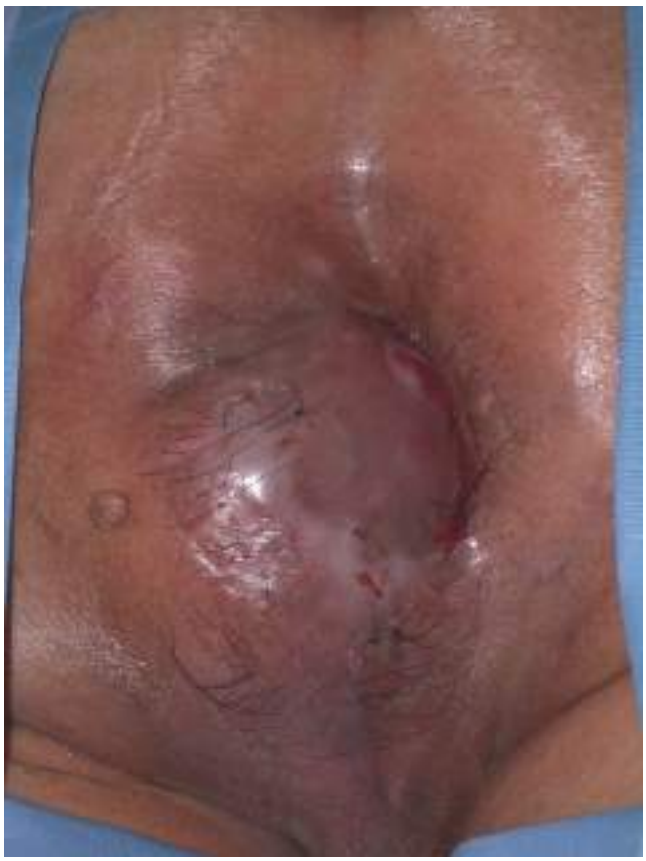

FIGURE 38-2. GIST of the rectum presenting as a perianal mass.

well-circumscribed intramural mass. Larger lesions may have evidence of central necrosis. PET scanning is not helpful in diagnosis, however may be of benefit in evaluating the response to treatment [54].

Treatment

Surgical resection of GISTs offers the best chance for cure and is therefore the treatment of choice. It is recommended that resection include the tumor en bloc with any associated contiguous tissues with margins of at least 1 cm [55]. As GISTs rarely metastasize to the lymphatic system, lymphadenectomy is not necessary [56]. Although many gastrointestinal stromal tumors may have a pseudocapsule, enucleation of the tumor without resection of the pseudocapsule should be avoided, as this has been associated with increased risk of tumor recurrence.

Resection of rectal GISTs may be accomplished by radical resection (low anterior resection or abdominoperineal resection) or local excision (transanal excision or transanal endoscopic microsurgery), provided that the tumor and pseudocapsule can be removed with adequate margins (Video 38.1). Liu et al. evaluated 21 patients with rectal GISTs and found that most patients with tumors located within 5 cm of the anal verge were successfully treated with local excision; however, positive resection margin was associated with poorer disease-free survival [57]. Changchien et al. reported outcomes of 29 patients with rectal GISTs [58]. Higher local recurrence rates were seen in those patients who underwent wide local excision vs. those who underwent radical resection (77% vs. 31%), despite smaller mean tumor size in the local excision group (4.5% vs. 7.2%).

The development of imatinib has significantly impacted the treatment of gastrointestinal stromal tumors. As mentioned previously, the majority of GISTs have abnormal activation of the KIT oncoprotein which results in unregulated cellular proliferation. Imatinib is a selective tyrosine kinase inhibitor which blocks activation of the KIT oncoprotein. When used in adjuvant therapy, imatinib has been shown to significantly decrease the risk of recurrence. The American College of Surgeons Oncology Group (ACOSOG) conducted a prospective trial of 106 patients who had undergone complete gross tumor removal but were deemed to be high risk for recurrence [59]. Patients were given 400 mg of imatinib per day for 1 year and followed radiographically. The 5-year overall survival rate of those treated was 83%, significantly better than historical 5-year survival rates of 35%. Imatinib has also been used in patients where the tumor was felt to be too large to resect. In this situation, the use of imatinib has been shown to result in tumor shrinkage in more than 50% of patients [60, 61], thereby allowing surgical resection in selected patients.

Neoadjuvant imatinib therapy for rectal gastrointestinal stromal tumors has also been reported. Wang et al. reported three patients with GISTs in the distal rectum that would require abdominoperineal resection to achieve cure [62]. Following treatment with imatinib, all three patients had both significant shrinkage of the tumor and extension of the distance to the anal verge that allowed for sphincter-preserving procedures. Tielen et al. also found that patients treated with neoadjuvant imatinib had significant reduction in the size of their rectal GISTs; however, this did not lead to less extensive surgery when compared with patients who did not undergo neoadjuvant therapy [63].

The reported incidence of local recurrence and metastatic disease following complete surgical resection of GISTs varies, but approaches 50% in some series [56]. Yeh et al. reported outcomes of 40 patients who underwent resection of rectal GISTs and found that younger age (<50 years) and a high histologic grade of tumor were the two most significant prognostic factors for recurrence [64]. In the ACOSOG trial, the recurrence-free survival rate was found to be lower with increasing tumor size, high mitotic rate, and older age [59]. Patients with metastatic GISTs are typically treated with imatinib and evaluated radiographically. Approximately 45% of patients will demonstrate partial response and 30% will have stable disease; if response to therapy is seen, lifelong treatment can be used [65]. Overall survival is

significantly better in patients with metastatic GISTs when treated with imatinib. Blanke et al. reported a median survival of 58 months, in contrast to a median of 15 months in historical controls treated with cytotoxic chemotherapy [66]. In patients whose tumors develop resistance to imatinib, sunitinib has been used as a second line treatment with some success [51]. Patients with unresectable hepatic metastases may also be candidates for radiofrequency ablation or hepatic artery embolization.

Lymphomas

The gastrointestinal tract is the most common site of extranodal lymphoma. While the majority of these lymphomas arise in the stomach (74.6%), small bowel and colonic lymphoma are less common, accounting for 8.6% and 7%, respectively [67]. In fact, in a recent review of the Surveillance, Epidemiology, and End Results (SEER) database, primary colonic lymphoma accounted for only 0.4% of all colonic malignancies, however the incidence more than doubled between 1973 and 2004 [68].

Histology

Most lymphomas of the gastrointestinal tract are non-Hodgkin's lymphoma. Diffuse large B-cell lymphoma is the most common histologic type seen in the colon [69]. Other pathologic types in the colon include MALT-associated low-grade b-cell lymphoma, mantle cell lymphoma, and T cell lymphoma [70, 71]. Correct determination of the subtype is important for optimal treatment and prognosis. It is believed that lymphomas begin in the submucosal lymphoid tissue and spread either by direct extension or through lymphatic channels. Dawson et al. established criteria for differentiating between primary gastrointestinal lymphoma and secondary involvement of the intestinal tract by systemic lymphoma [72]. The diagnosis of primary lymphoma can be made: (1) in the absence of enlarged superficial lymph nodes, (2) absence of enlarged mediastinal lymph nodes, (3) normal total and differential and white cell count, (4) at laparotomy, only regional lymph nodes have metastatic disease, and (5) the liver and spleen are unaffected.

Incidence and Distribution

Most colonic lymphomas arise in the cecum or ascending colon, likely due to the increased lymphoid tissue in this segment of the colon. In fact, 70% of lymphomas occur proximal to the hepatic flexure [73]. Patients are typically between the ages of 50 and 70; sex predominance varies among different reports. Prolonged steroid use, inflammatory bowel disease, HIV, and EBV have been postulated as possible risk factors for the development of colonic lymphoma [74]. Both a modified Ann Arbor staging system and the TNM system have been used to stage gastrointestinal lymphomas.

Clinical Presentation and Diagnostic Tests

The most common presenting symptom of lymphomas of the colon is abdominal pain. Other symptoms mimic those of adenocarcinoma and include weight loss, rectal bleeding, change in bowel habits, anemia, weakness, and possibly fever. Tender abdominal masses may be present in up to 80% of patients at the time of presentation [75]. Growth of the lesions leads to obstruction in 20–25% of cases; however, perforation is uncommon (Figure 38-3). Colonoscopy with biopsy should be performed; however, in some cases superficial biopsies may not be sufficient to confirm the diagnosis. CT scan of the chest, abdomen, and pelvis should be obtained to extraintestinal disease.

Treatment

In patients with lymphoma that is confined to the bowel, treatment is surgical excision or systemic chemotherapy. Historically, given that a sizeable fraction of patients presented with symptomatic disease that required semi-urgent operation or underwent operation to establish a diagnosis, surgical resection was most often employed as therapy. In patients with localized disease where the diagnosis can be made preoperatively, the rationale for surgical treatment is to remove tumor that has the potential to obstruct, perforate, or

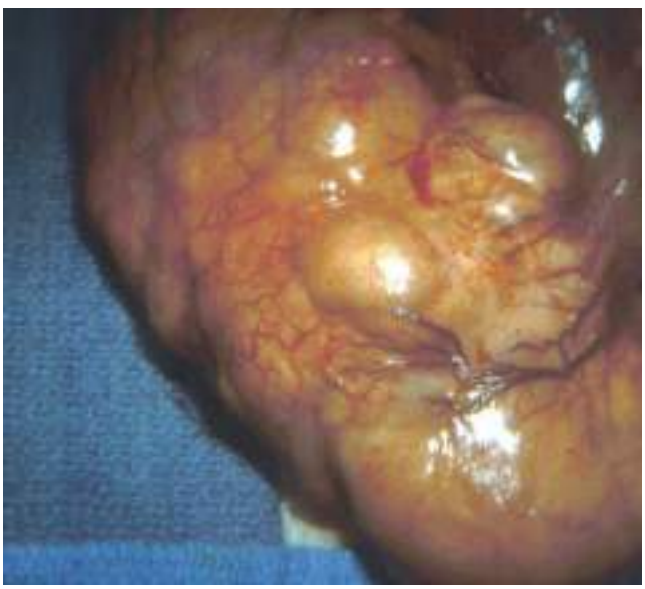

FIGURE 38-3. Lymphoma of the sigmoid colon invading the ileum (Courtesy of the ASCRS Image Library, Bruce Orkin, M.D.).

bleed, and potentially cure the patient if the tumor has not yet spread. Adjuvant chemotherapy, typically vincristine, cyclophosphamide, bleomycin, and doxorubicin, has been used to improve survival. Radiation therapy has also been advocated following resection of rectal lymphomas [76]. An alternative strategy is to treat with systemic chemotherapy and potentially avoid operation. One of the potential risks is perforation of the bowel if chemotherapy causes tumor necrosis. Given the low incidence of the disease, there are no randomized controlled trials to rely upon when making treatment decisions.

Aviles et al. treated 53 patients with B-cell lymphomas of the colon with surgery combined with chemotherapy and reported a 10-year survival of 83% [77]. Other authors, however, have reported far worse outcomes. Jinnai et al. reported results on a series of 130 patients who underwent surgical resection of colonic lymphomas [78]. Complete resection was possible in 55% of cases; however, 5-year survival was less than 40%. Prognosis was better in patients with tumors <5 cm in diameter and the absence of lymph node metastases. Lai et al. found that patients treated with surgery and chemotherapy had a 5-year survival of 62%, while 5-year survival in similar patients treated with surgery alone was only 14% [79]. Kim and colleagues compared response to treatment of 78 patients with B-cell lymphoma and 17 patients with T-cell lymphoma [80]. Those with T-cell lymphomas were younger, were more likely to present with perforation, and overall had a worse prognosis.

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Part IV
Benign Colorectal Disease

39
Diverticular Disease

Jason Hall

Key Concepts

- The optimal diagnostic test to allow for optimal assessment of severity of diverticulitis is CT imaging.
- The majority of patients with acute diverticulitis will respond to antibiotic therapy.
- CT drainage of localized abscesses in diverticulitis will often avoid the need for emergency operations, even in patients who may not initially respond to medical therapy.
- Hartmann's resection can often be avoided in most patients requiring surgery for an acute attack. Resection with primary anastomosis, with or without proximal diversion (loop ileostomy), can be performed safely in the absence of physiologic instability.
- The indications for elective resection after an acute attack of diverticulitis are evolving but should be considered in patients who remain symptomatic or develop a definite complication (stricture, fistula, etc.)

Introduction

Colonic diverticula represent saccular outpouchings of the colonic wall. Most patients with diverticulosis are asymptomatic. Symptomatic diverticular disease represents a whole range of conditions ranging from mild abdominal pain and bloating to free perforation with peritonitis and sepsis. These presentations are stratified into complicated or uncomplicated diverticulitis. Patients with left-sided abdominal pain and sometimes fever and leukocytosis are considered to have uncomplicated diverticulitis. Complicated presentations are defined as episodes of free perforation, obstruction, stricture, fistula, or hemorrhage. Diverticular hemorrhage is associated with diverticulosis and not diverticulitis. Because of the wide range of clinical presentations and potential for significant morbidity/mortality, management of diverticular disease continues to represent a major challenge to clinicians. This chapter examines the current pathophysiology, evaluation, and treatment of left-sided colonic diverticulosis and diverticulitis. The management of diverticula of the foregut and diverticular bleeding is left to other sources for discussion.

Incidence

In the twentieth century, there has been a rising prevalence of diverticular disease in industrialized nations. Diverticulosis is rare in patients younger than age 30. The incidence of this colonic finding rises with age such that over 40% of patients develop diverticula by the age of 60 years. Over 60% of patients over 80 years have diverticular disease identified [1, 2].

In almost all cases (95%), diverticula involve the sigmoid and left colon. In some series, the number of diverticula increases proportionally with age. They are also found more proximally as age increases. This may explain why in the Western societies, right-sided diverticular disease is primarily identified in older patients with pan-diverticulosis [3, 4]. In Asian countries, however, diverticulosis occurs more commonly on the right side. Some authors estimate that in Asia, 70% of the diverticula isolated to the right side [5–7].

Ten to twenty-five percent of patients who develop diverticulosis will develop diverticulitis [8–12]. Administrative data sources suggest that the incidence of diverticulitis is increasing. According to the Agency for Healthcare Research and Quality, over 295,000 patient discharges for diverticulitis were reported at the United States hospital in 2006 [13]. One modern analysis of the National Inpatient Sample demonstrated that rates of admission and elective operations rose in the United States from 1998 to 2005. Rates of admission and surgical intervention rose 82% and 73%, respectively, in patients younger than 44 years [14]. Another study examining the same data source from 1991 to 2005 period noted an increase diverticulitis discharges from 5.1 cases per 1000 inpatients in 1991 to 7.6 cases per 1000 inpatients in 2005 ($p < 0.0001$). There also appeared to be conflicting data regarding the incidence of complicated diverticular disease.

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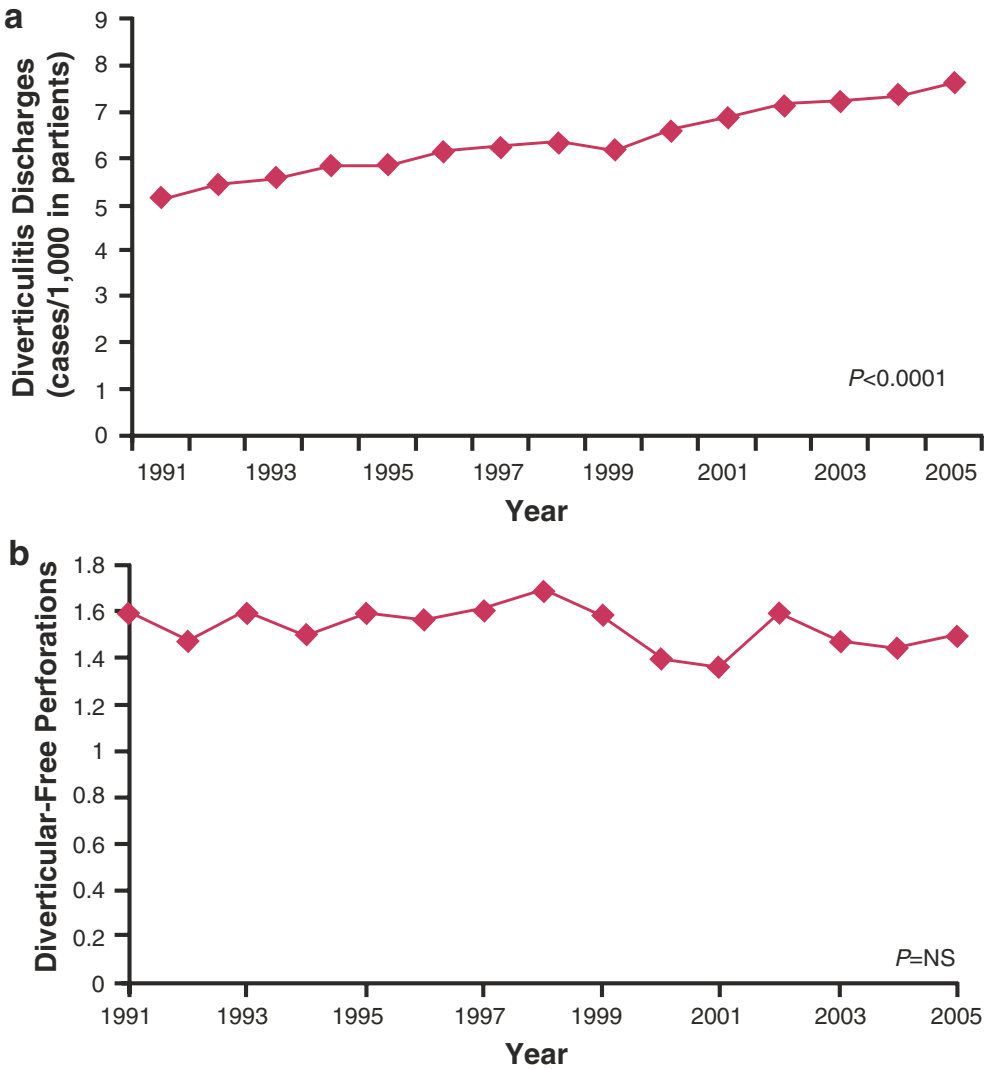

FIGURE 39-1. (**a**) Diverticulitis discharges (uncomplicated and complicated) in the Nationwide Inpatient Sample from 1991 to 2005. (**b**) Proportion of patient discharges for free diverticular perforation among all patients with diverticulitis in the Nationwide Inpatient Sample from 1991 to 2005. *With permission from Ricciardi* et al. *Dis Colon Rectum. 2009 Sep;52(9):1558–63 © Wolters Kluwer 2009* [15].

The proportion of diverticular abscess discharges increased from 5.9% in 1991 to 9.6% in 2005 ($p < 0.0001$). The proportion of free diverticular perforations, however, remained unchanged (1.5%) [15] (see Figure 39-1a, b). This increased incidence has been noted in other industrialized countries. A recent study from Norway revealed an increase in the incidence of diverticular diseases from 17.9 to 51.1 cases per 100,000 person/years over a 4-year time period [16]. More recent analysis of the National Inpatient Sample suggested that diverticulitis admissions peaked in 2008 (96/100,000). Rates of hospitalization for diverticular bleeding per 100,000 patients have declined from 32.5 to 27.1 (−5.4; 95% confidence interval (CI), −5.1 to −5.7) from 2000 to 2010 [17].

Pathophysiology, Etiology, and Epidemiology

Most colonic diverticula are pulsion or false diverticula. These types of diverticula contain only the mucosal and muscularis mucosal layers. Diverticula penetrate the colonic wall where vasa recta penetrate the circular muscle layer in order to provide blood supply for the mucous membrane (Figure 39-2) [18]. In a non-pathologic situation, diverticula are soft and compressible, allowing a free communication between the diverticulum and the colonic lumen.

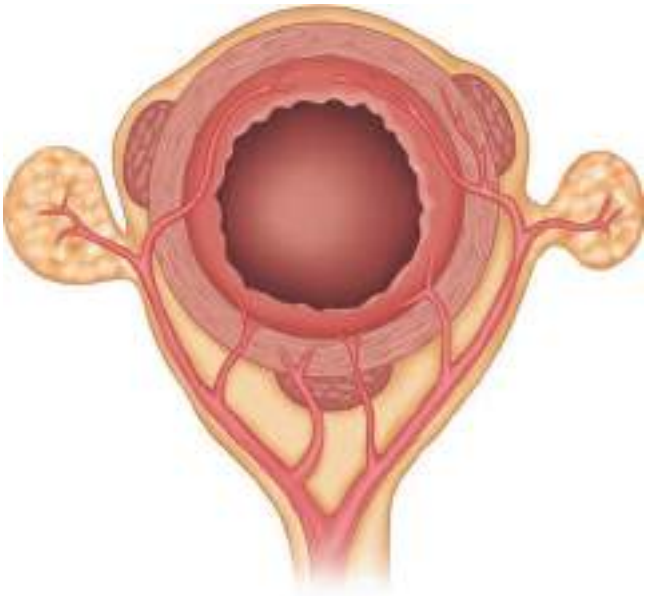

FIGURE 39-2. Vasa recta penetrate the colonic wall at taenia libera, omentalis, and mesocolica. This allows herniation of mucosa and submucosa at these sites.

The exact pathogenesis of progression from diverticulosis to diverticulitis is not clear. Classic pathophysiology mechanisms suggested that stasis or obstruction of the diverticulum orifice leads to bacterial overgrowth, increased intra-diverticular pressure, ischemia, and inflammation. This mechanism is one borrowed from the pathophysiology of appendicitis. Once the colonic mucosa is ischemic, ulceration can occur leading to a microperforation in most cases but sometimes formation of a peridiverticular abscess or free perforation with peritonitis [19].

Histology and Pathology

Many of the microscopic features of diverticulitis include thickening of the lamina propria, mucin depletion, and Paneth cell hyperplasia. Crypt abscesses and ulceration are also observed in some cases [20]. Many of the histologic features are similar to those associated with inflammatory bowel disease [21]. Hinchey developed pathologic criteria to classify the severity of diverticular disease. This classification has been used and is divided into Stages I–IV [22]. Stage I are patients with diverticulitis and a pericolic abscess. Stage II represents patients with distant abscesses such as a pelvic or retroperitoneal abscess. Stages III and IV are patients with purulent and feculent peritonitis, respectively (Table 39-1). A number of attempts have been made to extend the Hinchey criteria to a preoperative staging on CT scan [23] (Table 39-2). The utility of the system proposed by Hinchey and by others based on it is limited because purulent and feculent peritonitis can only usually be determined post hoc.

TABLE 39-1. Hinchey classification system

Stage I	Pericolic or mesenteric abscess
Stage II	Pelvic or retroperitoneal abscess
Stage III	Purulent peritonitis
Stage IV	Feculent peritonitis

TABLE 39-2. Modified Hinchey classification system

Stage 0	Mild clinical diverticulitis
Stage Ia	Confined pericolic inflammation phlegmon
Stage Ib	Confined pericolic abscess (within sigmoid mesocolon)
Stage II	Pelvic, distant intra-abdominal or intraperitoneal abscess
Stage III	Generalized purulent peritonitis
Stage IV	Fecal peritonitis

Modified from Warsavary et al. [24]

Role of Fiber

A number of authors have postulated that diverticular disease is related to fiber deficiency [25]. Painter and Burkitt studied colonic transit times and fiber contents in patients in Uganda and the United Kingdom. Patients with a higher fiber intake had more frequent bowel movements, faster colonic transit times, and larger stool volumes. Specifically, Painter and Burkitt postulated that a progressively more processed diet removed a large source of fiber from the Western diet. These data are confounded by a number of factors including differing life expectancies in industrialized and nonindustrialized countries [26]. It is interesting to not that as nonindustrialized societies have adopted a more Western diet; a number of authors have noted an increasing prevalence of diverticular disease [27].

A number of studies have examined dietary factors in large populations of patients with and without diverticular disease [28, 29]. Both studies demonstrated an inverse association between diverticular disease incidence and fiber intake. The relative risks associated with fruit and vegetable fiber intake were 0.62 [95% CI 0.45–0.86] and 0.55 [95% CI 0.37–0.84] [28]. Fiber found in fruits and vegetables conferred the most protective effect (compared with fiber from cereal), and a high intake of total fat and red meat increased the incidence of diverticular disease. Manousus et al. [29] compared individuals who ate a predominantly vegetarian diet to those who predominantly ate meat. The risk of developing diverticular disease was 50-fold greater in meat eaters. In a more recent cohort (47,228 male health professionals), popcorn, nut, and seed consumption was inversely correlated with diverticulosis or diverticular complications. This study refutes the adage that "nuts, corn, seeds, and popcorn" cause diverticulitis and should be avoided in patients who have had an attack of diverticulitis [30].

Alternative Pathophysiology Pathways and Taenia-Specific Elastosis

A number of non-dietary alternative theories regarding the evolution of diverticular disease have been proposed. Most of these theories center around the suggestion that the smooth muscle in the sigmoid colon behaves differently in other areas of the body. One particularly consistent finding in patients with diverticular disease is wall thickening often in the absence of inflammation [31]. Histologic studies have determined that colonic walls are thickened secondary to elastin deposition and not muscular hypertrophy or hyperplasia. In one study, the concentration of elastin in patients with diverticular disease was increased over 200% when compared with controls. The elastin is often laid down in a contracted form, leading to bunching of the taenia and apparent foreshortening of the bowel [32].

Despite the grossly increased muscle wall thickness, patients with diverticulosis appear to be more susceptible to mucosal herniation. In patients with diverticulitis, collagen fibrils demonstrate increased cross-linking with increased age; this process seems to increase most dramatically after 40 years of age, the age at which the incidence of diverticular disease also appears to increase. This same study demonstrated that patients with diverticulosis have an abnormally high amount of collagen cross-linkage in the colon wall. This difference persists even when patients were compared with age-matched controls. Increased cross-linkage of collagen fibers likely causes the tissues to become stiffer and less resistant to stretching. The loss of compliance of the colonic submucosa, the layer primarily responsible for tensile strength, may make the submucosa more susceptible to small tears when subjected to the higher intraluminal pressures triggered by segmentation. Any tear in this layer could potentially then lead to mucosal herniations and the formation of diverticulosis [33].

A possible genetic connective tissue defect has also been suggested because of reports of diverticular in young patients with Marfan's syndrome or Ehlers-Danlos syndrome [34–36]. It is likely that a number of processes including impaired motility, low fiber intake, inflammation, and elastin deposition contribute to the pathogenesis of diverticular disease.

Additional Risk Factors

Age

There has been considerable debate in the medical literature regarding the role of age in the pathogenesis of diverticulitis. Diverticular disease tends to affect patients during middle age as the incidence rises from 5% at age 40 to 80% by age 80 [37]. Traditionally, diverticulitis in younger patients has been described as more virulent, and young patients were thought to be more likely to have complicated disease and more likely to require resection [38, 39]. Young patients have been variably defined as under 50 years old in some series and under 40 or 45 years old in other series. Despite variability in what constitutes a "young patient," most modern series of younger patients with acute diverticulitis have noted a striking male predominance [40].

Sex

The prevalence of the disease among the sexes is difficult to ascertain. The prevalence has been estimated to be between 2:3 and 3:1 male-to-female ratio [12, 41]. More recent estimates suggest that patients with symptomatic diverticular disease under the age of 65 tend to be male. Some studies have demonstrated that male patients may present with more severe CT findings of diverticulitis than female patients [42]. Recent data suggests that men have a higher incidence of diverticular bleeding, while obstructions are more common among women [43].

Geographic Factors

Diverticulitis is much less common in Asian populations [25]. When diverticulitis does occur, it tends to involve the right-sided colon in up to 70% of cases [36]. It is unclear if this is an environmental, dietary, genetic, or geographic factor.

There is a relationship between increasing industrialization and incidence of this disease. A number of earlier studies have documented the low prevalence of the disease in African nations [44–46]. Other authors have noted increased rates of diverticulitis in Africans with increased penetration of the Western lifestyle patterns [47]. Reports from both Japan and Singapore have shown increases in prevalence approaching 20%. This is thought secondary to the increased acceptance of the Western diets [48, 49].

Physical Activity

Two studies have examined the effect of exercise on the development of diverticular disease [50, 51]. The risk of developing diverticular disease and levels of physical activity appear to be inversely related. This difference persisted even when the authors adjusted differences in dietary fiber intake. A potential drawback of the study is that the differences may have arisen from the fact that the ability to exercise might have been impaired or prohibited by symptoms of diverticular disease [50].

Smoking

The potential association between diverticular disease and smoking is contradictory. One large case-control study demonstrated that smokers had three times the risk of developing complications from diverticular disease than did nonsmokers [52]. Another large cohort study of 46,000 men in the United States failed to show a similar association [51].

Nonsteroidal Anti-inflammatory Agents

The use of nonsteroidal anti-inflammatory agents has been associated with the development of a number of gastrointestinal complications. Evidence suggests that chronic NSAID use is almost twice as common in patients with diverticular disease as healthy controls with no known colonic disease [53, 54]. While the health professionals follow-up study showed an increased incidence of uncomplicated diverticular disease in patients who used NSAIDs compared with their asymptomatic counterparts, additional studies have noted an increased risk of complicated diverticulitis with NSAID use [55]. One retrospective study showed a 23% higher risk of perforating diverticulitis in patients who took NSAIDs regularly compared with patients with diverticular disease who did not take NSAIDs [56]. An additional study of hospitalized patients demonstrated chronic NSAID use to be much higher in patients admitted with diverticular disease than the population as a whole. In addition these patients were four times more likely to develop perforated diverticulitis than patients with no history of NSAID use [57].

Caffeine Ingestion

Caffeine intake has been investigated as a possible contributing factor to the development of diverticular disease as it can affect colonic transit time [58]. No difference in caffeine consumption was identified in groups of patients with and without diverticular disease [51].

Obesity

A number of retrospective case series have noted a striking preponderance of obese patients with diverticulitis, particularly patients under the age of 40 [39, 59, 60]. In addition, two prospective cohort studies (the health professionals follow-up study and a Swedish study) have shown an association between body mass index (BMI) and diverticular disease [51, 61, 62]. The US health professionals study has shown an increased risk of diverticulitis and diverticular bleeding not only with increasing BMI but also waist circumference and waist-to-hip ratio [61]. A recent study from South Korea recently demonstrated an association between cross-sectional visceral fat area and complicated diverticulitis [63]. Obesity has been linked not only to inflammation but also to differences in the intestinal flora which may be potential mechanisms for the increased risk of diverticulitis [64–66]. Although this area of research is new, it may suggest that a large visceral fat mass may act as an immunologic or endocrine organ. This mechanism may affect incidence of diverticulitis.

Microbiome

Humans exist in a close relationship with a variety of microorganisms. Of particular interest are microorganisms which reside in the gastrointestinal tract. Microbes in the human gastrointestinal tract contain 10^{12}–10^{14} genes [67]. The aggregate, multi-organismic, genetic code of those varied microorganisms is referred to as the microbiome. There is little published clinical evidence suggesting a direct link between fecal microbiota and diverticular disease. A number of authors have extrapolated from other known relationships. For example, Daniels et al. explore findings of altered microbiota in the flora of patients with morbid obesity, colon cancer, irritable bowel syndrome, and inflammatory bowel disease. Based on these findings, they proposed that altered fecal microbiology may also have an effect on the pathogenesis of diverticular disease. While the finding of altered microbiota in various disease states is intriguing, there is still ample debate as to whether these changes are causative of disease or simply a phenotype of the disease process itself. [68].

Clinical Manifestations and Physical Findings

There are three main clinical presentations of diverticular disease (Table 39-3). The most common clinical presentation of diverticulitis is what is termed uncomplicated diverticulitis. This presentation is characterized by left-sided abdominal pain with or without an associated mass, fever, and leukocytosis. Patients generally resolve the acute episode after treatment with antibiotics. Typically most patients can be treated as outpatients.

Another manifestation is smoldering diverticulitis. This presentation only partially improves on antibiotics and medical therapy. Such patients have recurrent symptoms which can manifest with ongoing low-grade fever and left-sided abdominal pain. CT scans on such patients generally will demonstrate a persistent phlegmon, and these patients often require resection to treat ongoing symptoms. Some of these patients will present with associated obstruction, abscess, fistula, or perforation.

Table 39-3. Typical presentation patterns of diverticulitis

Acute diverticulitis
Typical, relapsing (chronic)
Subacute
Complicated diverticulitis
Obstruction
Mass/abscess
Fistula
Hemorrhage
Perforation
Chronic diverticulitis
Atypical
Atypical site (transverse, ascending)

Finally, a small group of patients may have atypical presentations. Most of these patients have chronic left lower-quadrant pain. They however lack objective evidence of diverticulitis such as leukocytosis, fever, or objective findings on CT scan. Many patients with atypical presentations of diverticulitis may have irritable bowel syndrome. Surgeons therefore must be facile with telling the difference between both conditions.

Symptoms

Patients with acute diverticulitis typically present with left-sided abdominal pain, fever, and leukocytosis. Associated with abdominal pain will be a physical finding of left lower quadrant pain and tenderness on examination. Patients with free perforation will typically present with diffuse peritonitis and signs of systemic toxicity. An abdominal mass may be palpable or mass appreciated on rectal or pelvic exam when there is a significant phlegmon involving the colon. Many patients will present with abdominal tenderness that is often associated with some degree of abdominal distension. Right-sided tenderness can be a presentation in patients that have a redundant sigmoid colon that extends to the right side of the abdomen. Free perforation is associated with diffuse abdominal pain, sometimes referred pain in the shoulder, and shortness of breath.

Many patients often describe changes in their bowel habits such as constipation, diarrhea, or an alternation in stool caliber. Rectal bleeding rarely occurs as a presentation of acute diverticulitis. If present, rectal bleeding is more suggestive of ischemic colitis or inflammatory bowel disease. In complicated presentations, an inflammatory phlegmon can be associated with a small or large bowel obstruction. Patients with an obstruction will present with abdominal distention and sometimes nausea and vomiting.

Patients with fistulas may have minimal abdominal complaints and may present initially to a urologist or gynecologist. Patients who develop complications of diverticular disease such as colovesical fistulas may present with pneumaturia, pyuria, or fecaluria, while patients with colovaginal fistulas may present with vaginal discharge, vaginal air, or stool per vagina.

A number of patients with “chronic” or atypical diverticular disease will present with pain as their predominant symptom in the absence of other physical findings. The pain is typically persistent and boring, remaining constant over long periods of time. It does not tend to be “crampy” in nature as in patients with irritable bowel syndrome but is difficult to distinguish from this entity [69].

Diagnostic Evaluation

Most laboratory tests are not terribly helpful in the evaluation of acute diverticulitis. Many patients with acute diverticulitis present with leukocytosis. Patients with a colovesical fistula may have an abnormal urinalysis and/or a culture with enteric organisms.

Although a number of different modalities have been used to evaluate patients with suspected diverticular disease, computed tomography has emerged as the study of choice. Flat and upright plain films of the abdomen are commonly obtained in the evaluation of the patient with acute abdominal pain to exclude obstruction or free intraperitoneal air. In patients with diverticular disease, the findings of plain films tend to be nonspecific [70]. Ultrasound has not gained wide acceptance in the United States. Contrast enemas are seldom currently used in the evaluation and management of diverticulitis. Water-soluble contrast studies are useful in which there is a potential need for urgent surgery and a stricture is suspected.

The most useful test for examination of patients with acute abdominal pain is the abdominal CT. CT findings associated with diverticulitis were first described over 30 years ago. These signs included the presence of diverticula, pericolic fat stranding, colonic wall thickening more than 4 mm, and abscess formation [71]. For evaluation of acute diverticulitis, CT has the ability to stage the severity of disease and adds the possibility of providing a roadmap for percutaneous drainage of an associated abscess. CT has the added advantage of detecting other intraperitoneal findings including hepatic abscesses, pylephlebitis, small bowel obstruction, colonic strictures/obstruction, and colovesical fistulas.

The first system for classifying the severity of diverticulitis on CT findings to guide clinical management was proposed by Ambrosetti. CT findings consistent with mild diverticulitis included localized wall thickening (>5 mm) and inflammation of the pericolic fat. Severe CT findings were the combination of localized wall thickening and inflammation of the pericolic fat with abscess, extraluminal air, or extraluminal contrast (Table 39-4). When the natural history of patients with diverticulitis was stratified by these CT criteria, the authors found that patients with severe CT findings underwent operative intervention more frequently than those patients with mild findings (33% vs. 15%). Patients under 50 years of age with severe findings on CT scan were also more likely to have recurrences or complications [72]. In prospectively collected dataset, patients with findings of severe diverticulitis on CT scan were more likely to have recurrent attacks of diverticulitis after an initial

TABLE 39-4. Ambrosetti CT criteria for diverticulitis severity

Mild diverticulitis	Wall thickening (>5 mm)
	Pericolic fat stranding
Severe diverticulitis	Wall thickening (>5 mm)
	Pericolic fat stranding
	with
	Abscess
	Extraluminal air
	Extraluminal contrast

Adapted from Ambrosetti et al. [72]

attack of acute diverticulitis treated with antibiotics when compared to patients with mild diverticulitis (39% vs. 14%) [73]. Poletti et al. explored CT and demographic predictors for nonoperative treatment failure in 312 patients with a first episode of left-sided diverticulitis and concluded that the presence of an abscess or extraluminal air >5 mm in diameter were significant predictors of treatment failure [74].

CT findings which are relevant to clinical management were reclassified into classification system based on the Hinchey classification system (Table 39-2). In grade 0 there is colonic wall thickening but not pericolonic fat stranding. Grade 1a consists of wall thickening and pericolonic fat stranding, while grade 1b includes a pericolonic or mesocolic abscess. Patients with grade 2 disease have distant intraabdominal or pelvic abscesses. Patients with grade 3 and grade 4 disease have purulent and fecal peritonitis, respectively. CT is somewhat limited in distinguishing between patients with grade 3 and grade 4 disease as purulent and fecal peritonitis often cannot be distinguished on imaging (Figs. 39-3, 39-4, and 39-5a–d) [75]. Kaiser et al. found that disease severity

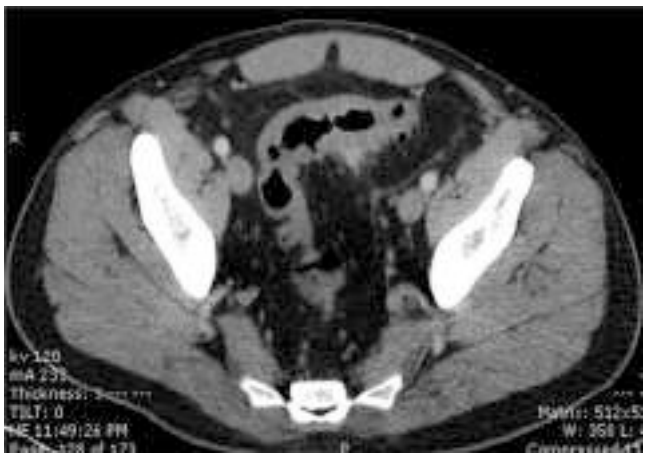

FIGURE 39-3. Modified Hinchey Stage Ia Diverticulitis—*Arrow* points to pericolic inflammation and phlegmon.

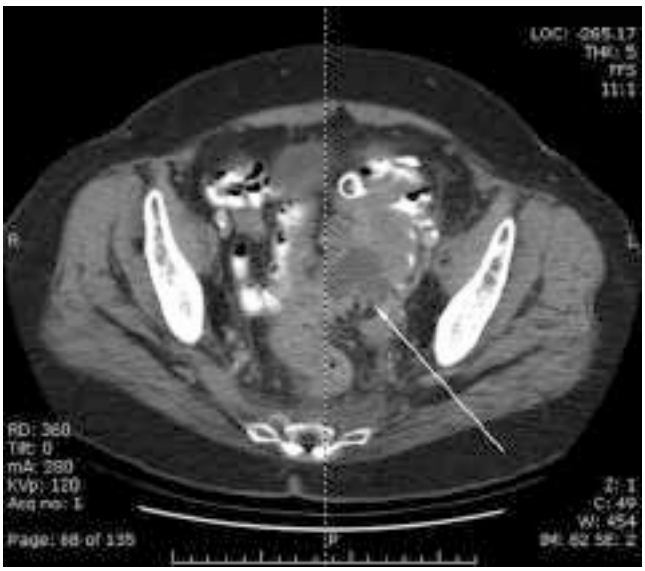

FIGURE 39-4. Modified Hinchey Stage II Diverticulitis—*Arrow* points to pelvic abscess.

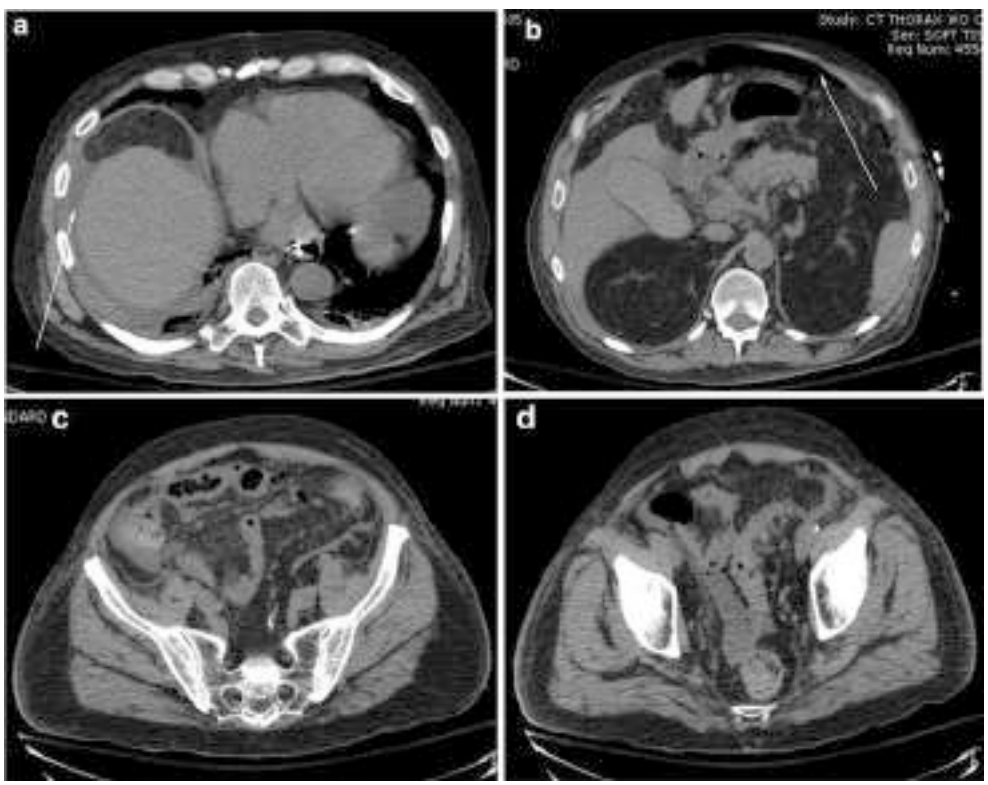

FIGURE 39-5. (**a**) Modified Hinchey Stage III Diverticulitis—*Arrow* points to free fluid. (**b**) Modified Hinchey Stage III Diverticulitis—*Arrow* points to free air. (**c**) Modified Hinchey Stage III Diverticulitis—Demonstrates intra-abdominal free fluid. (**d**) Modified Hinchey Stage III Diverticulitis—*Arrow* points to pelvic fluid.

using the modified CT Hinchey classification system correlated with postoperative morbidity and mortality. This group also found that the CT stage correlated with recurrence when patients were managed nonoperatively. The presence of a diverticulitis-associated abscess was one particular factor which was highly associated with high risk of failure of nonoperative management [76].

Endoscopic Evaluation

Endoscopic evaluation of the colon is recommended following an acute episode of diverticulitis. This approach is generally advocated to exclude the presence of a malignancy or an alternative diagnosis such as ischemic colitis or inflammatory bowel disease. In actual practice, finding a malignancy is rare. Bryan et al. evaluated 307 patients with flex sig (20%) or colonoscopy (80%) following an acute episode of diverticulitis. Interestingly, they found only 2 patients with colorectal carcinomas. A significant proportion of patients had advanced neoplastic lesions (3.4%), hyperplastic polyps (6.8%), and adenomas (8.8%) [77]. These findings were mirrored by a study by Lau et al., with 319 patients who underwent endoscopic surveillance. Overall, 26% of patients had polyps (9 polyps > 1 cm) and 2.8% were found to have colorectal cancers [78].

Endoscopic procedures (flexible sigmoidoscopy and colonoscopy) are generally not advocated during an acute episode of diverticulitis. A delay of 6 weeks following resolution of symptoms is recommended. This approach is encouraged in order to avoid potential conversion of a sealed microperforation into a free perforation [79]. This position has been questioned by other groups who have demonstrated that colonoscopy during an acute episode of diverticulitis can be safe. Even when optical examination of the colon is performed in the acute setting, a significant number of the procedures cannot be completed [79, 80].

Cystoscopy or cystography have been used to identify suspected colovesical fistulas. In CT scan era, however, the presence of air in the urinary bladder in the absence of instrumentation is considered diagnostic [81].

Differential Diagnosis

The differential diagnosis for suspected diverticular disease includes appendicitis, bowel obstruction, colorectal cancer, ischemic colitis, pyelonephritis, gynecologic disease, inflammatory bowel disease, and irritable bowel syndrome. Other diagnoses that should be entertained include endometriosis, tubo-ovarian abscess, pelvic inflammatory disease, ureteral calculi volvulus, stercoral ulcer, and ovarian torsion. Modern cross-sectional imaging is often helpful in diagnosing many of these clinical entities. The most important diagnosis to exclude on initial presentation is colorectal cancer. CT scanning confirms a diagnosis of diverticular disease, but often endoscopy is helpful to distinguish between diverticular disease and colorectal cancer and inflammatory bowel disease.

Treatment of Acute Diverticulitis

Treatment of Uncomplicated Diverticulitis

Antibiotics

Antibiotic therapy remains the most important component of the management of patients with acute uncomplicated diverticulitis. Despite the broad application of antibiotics in the operative and nonoperative therapy of diverticulitis, there have been few studies examining the optimal dosing and frequency of administration of these agents [82]. The microflora associated with diverticular microperforation include flora such as Gram-negative rods, Gram-positive rods, and anaerobic bacteria. The anaerobic bacteria are far more common and outnumber the aerobic 1000:1 [83]. There are a number of single and combination antibiotic regimens for the management of acute diverticulitis. All of the regimens have activity against the colonic flora; however, little is known about their efficacy [83]. Kellum et al. randomized 51 patients to a regimen of cefoxitin alone vs. gentamicin/clindamycin. Patients in need of an urgent operation were excluded. These authors concluded that the single-agent regimen exhibited similar efficacy to the two-agent regimen. They recommended the use of cefoxitin as this was cost-effective [84].

The American College of Gastroenterology guidelines for the treatment of diverticulitis include cefoxitin or ampicillin/sulbactam as single agents or a third-generation cephalosporin, aminoglycoside, or monobactam in combination with an anti-anaerobic agent [84]. The American Society of Colon and Rectal Surgeons published their practice parameters for the management of diverticulitis in 2006. They recommended that antibiotic therapy be selected to provide adequate coverage of the most common colonic organisms. The authors maintained that single and combination regimens were equally effective. Even with appropriate antibiotic therapy recurrences, approximately one-third of patients will have a recurrence [8].

The ASCRS guidelines were further revised in 2014 to suggest that antibiotics were “usually” used in the initial management of uncomplicated diverticulitis. These guidelines take account of new data which suggested that antibiotic therapy may be optional and uncomplicated diverticulitis [85]. de Korte et al. reported on a series of 272 patients who were studied in a case-control fashion. All patients in their study had mild diverticulitis and were admitted to one of two hospitals. In the first hospital, antibiotics were administered,

and in the second hospital, Foley IV fluids and bowel rest were prescribed. The authors found no difference in treatment failure [86]. The AVOD (Antibiotika Vid Okomplicerad Divertikulit—Swedish for 'antibiotics in uncomplicated diverticulitis') trial and a modest patient with uncomplicated diverticulitis into an antibiotic therapy and IV fluids vs. IV fluids the management of uncomplicated diverticulitis. This study treated 623 patients with CT confirmed uncomplicated diverticulitis. One group received intravenous fluids, and the other group received intravenous fluids and antibiotics. The authors found similar rates of recurrence, time to recovery, and complications in both groups [87]. A recent Cochrane Review of the subject examined three randomized trials. This study did not find a significant difference between antibiotic administration and no antibiotic administration in the management of uncomplicated diverticulitis [88].

Despite this new data, antibiotic therapy continues to be widely used in the management of all forms of diverticulitis. Patients with minimal symptoms and mild signs of peritoneal irritation can typically be treated as outpatients. Patients who present with fever, systemic symptoms, or inability to tolerate oral intake are usually hospitalized. Parenteral antibiotics are typically administered until the acute symptoms resolve. Once there is clinical improvement, the antibiotic route is changed to oral administration.

Diet

A diet that is rich in fiber may increase the bulkiness of stools, decrease colonic transit time, and therefore decreases intraluminal pressures [89]. The optimal amount of daily fiber is unknown; however, 20–30 g is a widely recommended figure. Recent evidence supports the notion that persons with diets high in fiber have decreased rates of diverticulosis and bear a lower risk of developing diverticulitis [28–30]. Based on this information, a number of dietary societies have suggested that there is little evidence to support a change of diet or elimination of specific foods following an episode of diverticulitis. The only requirement that is repeatedly emphasized across the medical literature is the need to maintain a high-fiber diet [90, 91].

Emerging Medical Therapies

Mesalamaine

As the microperforation pathophysiology of diverticular disease has come into question, there has been increased interest in the use of immunomodulatory agents in the management of diverticular disease. 5-ASA products and sulfasalazine alter DNA synthesis and cell cycle progression in lymphocytes. 5-ASA compounds are also thought to suppress leukotriene and prostaglandin synthesis, thus reducing proinflammatory states [84, 92]. Because a low-grade proinflammatory state is the proposed mechanism underlying chronic diverticular disease, a number of small trials have evaluated the effectiveness of mesalamine-like compounds. In all of these studies, the outcome of interest was symptom severity, and none reported any objective analysis of the actual inflammatory burden (i.e., imaging). In the original description of the use of mesalamine for the management of diverticulitis, Trespi et al. demonstrated that patients treated with antibiotics and mesalamine had decreased symptomatology [93].

Another study randomized patients with diverticulitis to a rifaximin-only arm vs. a rifaximin/mesalamine arm. Patients in the rifaximin/mesalamine arm demonstrated significantly improved bowel habits. They also had less recurrent episodes and demonstrated lower symptom severity [94]. In another study, mesalamine alone was compared to rifaximin alone. The authors compared several outcomes including general illness, nausea, abdominal pain/discomfort, emesis, dysuria, fever, abdominal tenderness, diarrhea, tenesmus, and bloating. Patients treated with mesalamine had significantly lower global scores than patients treated with rifaximin alone. Therefore this study concluded that mesalamine is an effective medication for preventing recurrence of diverticulitis and maintaining remission [95].

In a systematic review which included six randomized trials of 5-ASA products in the treatment of diverticulitis, patients treated with 5-ASA products had better outcomes than those not treated with 5-ASA. They also concluded, however, that larger trials which had objective confirmation of diagnosis by endoscopy are needed for confirmation of the initial data on this type of treatment [96]. Despite initial enthusiasm for the use of these products, they have not, at the time of this manuscript, found significant adoption in the United States.

Probiotics

Probiotics are marketed as preparations of naturally occurring colonic microflora which can have a beneficial effect on those that ingest them. Because patients with diverticular disease are thought to have altered colonic microflora due to constipation and stasis of fecal matter, it has been suggested that probiotics may have a role in the management of this disease [97].

Giaccari et al. examined the administration of rifaximin and *Lactobacillus* in patients with diverticular disease. They reported no complications and adequate symptom control. They concluded that the combination of rifaximin and *Lactobacillus* was an adequate regimen for prophylaxis against the complications of diverticular disease [98]. In a smaller study (15 patients), investigators compared administration of nonpathogenic *E. coli* with active coal tablets to coal tablets alone. These authors concluded that the length of remission was significantly longer when a probiotic was administered (14 months vs. 2.4 months) [99]. Although the initial results are promising, there is only a small amount of data supporting the use of probiotics.

Elective Surgical Management of Recurrent Uncomplicated Diverticulitis

For many decades, the indications for surgical management of diverticulitis were clear. Elective resection was suggested after two well-documented attacks of uncomplicated diverticulitis requiring hospitalization and/or after one episode of complicated diverticulitis. In patients under 40 years of age, elective resection was recommended after the first attack of complicated or uncomplicated diverticulitis. These guidelines were endorsed by a number of societies including the American Society of Colon and Rectal Surgeons, the Society for Surgery of the Alimentary Tract, the European Association for Endoscopic Surgery, and the American College of Gastroenterology [84, 100–102].

These recommendations have been challenged by new data. Salem et al. suggested that waiting until the fourth attack of uncomplicated diverticular disease would be associated with fewer intestinal stomas and fewer deaths [103]. Another study concluded that elective resection after the third attack would be more cost-effective. The guidelines for surgery were revised by the American Society of Colon and Rectal Surgeons in 2006 and suggested that the "number of attacks of uncomplicated diverticulitis is not necessarily an overriding factor in defining the appropriateness of surgery" [8]. These recommendations were echoed in the most current practice parameters. Recommendations should be individualized by the age and medical condition of the patient, by the severity and frequency of the attacks, and by the presence of ongoing symptoms [85].

Furthermore, most patients who present with complicated diverticulitis will have complicated disease on the first attack; resection after recovery from uncomplicated diverticulitis does not prevent the development of complicated diverticulitis [68, 104]. Interestingly, the risk of needing a colostomy following a successfully managed episode of diverticulitis is small (1/2000). Therefore, the practice of recommending elective surgery to avoid future stoma formation should be avoided [85].

Young Patients

Several authors have proposed that patients younger than 40–50 years of age present with a move virulent form of diverticulitis [104]. Historical recommendations have advocated sigmoid resection for young patients after one well-established attack of diverticulitis; however, this dictum has been called into question by recent evidence. Although younger men are proposed to have severe diverticulitis more often than older men, they require operative intervention less frequently [72]. In addition, other authors have pointed out that younger patients did not have different rates of conservative management, emergency operation, or mortality when compared to older patients [103]. Although there is some evidence that young patients present with a more virulent form of the disease, it is not clear that these patients will go on to have a recurrence. In a study by Guzzo et al., 1 patient out of 196 young patients (<50 years) had a free perforation after medical management of diverticulitis. The median follow up was 60 months. Recent analysis of a large administrative dataset suggested that young patients may indeed have a higher risk of recurrence (27%) but have low rates of emergency surgical intervention (7.5%) [105]. Given the current level of evidence, there is no clear mandate to treat young patients with diverticulitis differently than the other age groups [106].

Complicated Diverticular Disease

Complicated diverticulitis is defined as diverticulitis associated with perforation, fistula, abscess, stricture, or obstruction. Management of complicated diverticular disease is dependent on the particular presentation of the disease. Treatment of the complications of diverticulitis may range from treatment with bowel rest and parenteral antibiotics to emergent exploratory laparotomy. We will review the treatment options for each of the complications of diverticulitis separately.

Diverticular Abscess

Diverticular abscess occurs in approximately 10–25% of patients with acute diverticulitis. Abscesses include pericolic, hepatic, pelvic, and retroperitoneal abscesses. In women, a fistula from the colon to the adenexa may result in tubo-ovarian abscesses [107]. Traditionally, in patients with diverticulitis and an associated abscess, the goals of care were to treat the inflammatory process and later to operate on an elective basis when the risk of infectious complications is substantially lower. This approach was based on the observation that over 40% will develop recurrent sepsis [76]. However, reports of patients who have undergone percutaneous or operative drainage with no further septic sequelae have called this practice into question. Franklin and colleagues reported on 18 patients who underwent laparoscopic drainage of Hinchey II abscess, and at a follow-up of 4–34 months, 15 remained asymptomatic without the need to undergo resection [108].

Cross-sectional imaging of the abdomen is the most effective way of diagnosing and staging diverticular abscesses. The initial approach to patients with diverticular abscess includes bowel rest, antibiotics, and close observation. Abscesses less than 4 cm in size often resolve with intravenous antibiotics alone without the need for further procedures [8, 109–111]. For those patients with diverticular

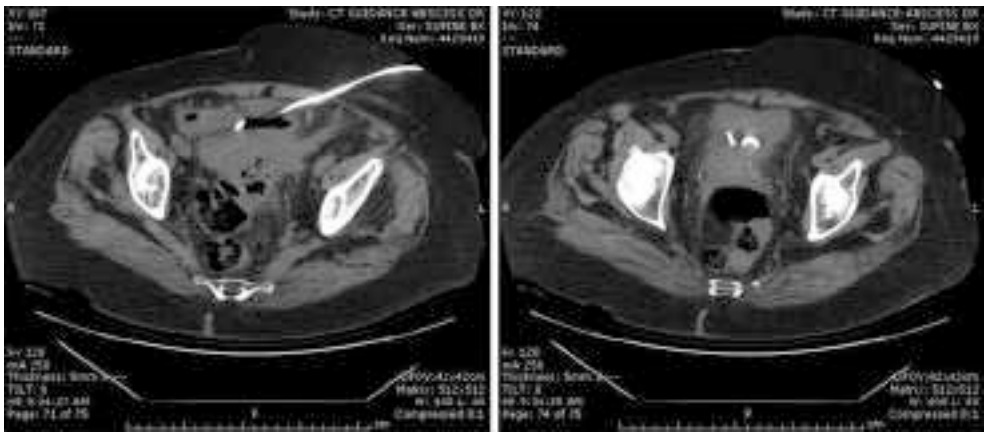

FIGURE 39-6. Pigtail catheter in a complex diverticular pelvic abscess.

abscess who do not improve on initial antibiotic therapy and continue to have signs of sepsis (fever, abdominal pain, and leukocytosis), percutaneous drainage is preferred.

A recent review suggested that 20–30% of diverticular abscesses were amenable to percutaneous drainage and the failure rate of percutaneous drainage was 20–30% [111]. The preferred approach for percutaneous drainage is usually by a transabdominal route (Figure 39-6) [112]. If the abscess is not accessible by this route, a transgluteal, transperineal, or transrectal routes may be employed. Transabdominal tends to be better tolerated in terms of patient comfort when compared to other access routes. In patients with simple unilocular abscesses, successful drainage is achieved in approximately 80%. Patients with more complex abscesses associated with loculations and fistula or whose drainage route transverses normal organs are associated with a higher failure rate [112]. The expertise and skill of the interventional radiologist is also associated with a higher success rate.

The decision for surgery following successful drainage of a diverticular abscess should be approached on a case-by-case basis. Diverticulitis associated with abscess denotes more severe diverticulitis, and a substantial number of patients require sigmoid resection. While 40–50% of patients admitted with diverticular abscesses respond to conservative treatment, sigmoid resection is recommended for selected patients particularly those with more complex or larger abscesses and those with recurrent or persistent symptoms such a colocutaneous fistula [113]. Ideally, elective surgery is performed after initial treatment with antibiotics and/or percutaneous drainage as indicated.

Perforated Diverticulitis

Approximately 1% of patients with diverticulitis develop free perforation which may include purulent or fecal peritonitis (Figure 39-1b). Free perforation almost exclusively develops on the first attack of diverticulitis and is generally not seen in patients who have had multiple attacks of diverticulitis. Similarly, there is general consensus that patients with perforated diverticulitis manifested by purulent peritonitis or feculent peritonitis require operative intervention. The mainstay of treatment for perforated diverticulitis over the last several decades has been the Hartmann procedure which resects the disease and eliminates the septic focus. A disadvantage of the procedure is the requirement for a second major surgical procedure to reverse the colostomy and the attendant morbidity and potential mortality of the procedure. Data from large administrative databases suggest that at least one-third of patients may never undergo reversal [114], and up to 70% of patients, over 77 years may not undergo reversal [115]. Women are less likely than men to undergo Hartmann reversal [114, 116].

There has been renewed interest in performing resection and primary anastomosis in selected patients with Hinchey III and Hinchey IV diverticulitis. A number of systematic reviews and meta-analyses have suggested that primary anastomosis is superior to Hartmann resection for patients with perforated diverticulitis; however there is considerable selection bias [103, 117]. In clinical practice, the decision to perform a primary anastomosis should be done on a case-by-case basis. A number of technical- and patient-related factors must be considered by the surgeon to determine if the patient is a good candidate for a primary anastomosis. Hemodynamic instability, diffuse peritonitis (either purulent or fecal), ischemia or significant edema of the bowel at an intended site of anastomosis and anemia, malnutrition, and immunocompromised state are general contraindications to a primary anastomosis [118]. Although discussed frequently in the literature, data from the Nationwide Inpatient Sample has not shown any evidence that primary anastomosis is being more commonly used as the preferred procedure for patients who undergo surgery for acute diverticulitis [14].

Recently, alternatives to resection and definitive treatment with laparoscopic lavage have been reported. Based on a small series of successful laparoscopic lavage for treatment of patients with perforated diverticulitis with purulent peritonitis, a prospective multi-institutional study of 100 patients has been reported [119]. Patients with perforated diverticulitis and generalized peritonitis underwent laparoscopic lavage

as definitive treatment. No effort was made to mobilize and resect the sigmoid colon. The median age was 62.5 years with a follow-up of 36 months. Eight patients were found to have fecal peritonitis and converted to an open procedure and underwent resection. The remaining 92 patients were successfully treated with laparoscopic lavage with a 4% morbidity and a 3% mortality. Two patients later required intervention for a pelvic abscess, and two patients presented with recurrent diverticulitis in the study period. These data challenge our conventional surgical teaching and suggest that selected patients with purulent peritonitis from diverticulitis may be successfully treated with laparoscopic lavage without resection of the affected segment of colon [119].

A subsequent review of eight studies of 213 patients with acute complicated diverticulitis managed by laparoscopic lavage has noted a 3% conversion rate. Ten percent of patients had complications, and during a mean follow-up of 38 months, 38% of patients underwent elective sigmoid resection with primary anastomosis [120]. Given these results, it appears that lavage can be appropriate in selected circumstances. However, in a substantial proportion of patients, it does not effectively eliminate the septic focus. Based on this the ASCRS clinical practice guidelines recommended against its use as alternative to colectomy until more information and longer follow-up is available [85].

Fistulas

Fistulas occur in 2% of patients with diverticular disease [121]. The localized inflammatory process develops into an abscess which then decompresses into adjacent viscera (Table 39-5). Patients who develop fistulas generally do not need emergent intervention as the abscess has decompressed; in fact many patients with fistulas may have few abdominal signs and symptoms. Colovesical fistulas are the mostly common (65%), followed by other types of fistulas including colovaginal, coloenteric, colouterine, and colocutaneous fistulas [122–125].

Table 39-5. Diverticular fistulas

Coloappendiceal
Colocolonic
Colocutaneous
Coloenteric
Colouterine
Colovenous
Cologastric
Coloperineal
Coloperianal
Coloureteral
Colovaginal
Colovesical
Colovesicovaginal

Colovesical Fistulas

Colovesical fistulas are more common in men than in women. Women affected with a colovesical fistula have usually undergone a prior hysterectomy. Patients often present with prominent urinary symptoms including polymicrobial urinary tract infections, pneumaturia, and fecaluria. CT scanning reveals air and/or contrast in the bladder in the absence of prior instrumentation (Figure 39-7a–c). If performed, cystoscopy shows inflammation generally at the dome of the bladder and, on occasion, vegetable material in the urine. Colovesical fistulas may also be associated with locally advanced bladder or primary colon cancer. Cystoscopy and colonoscopy may be an appropriate test to exclude a malignancy under the appropriate clinical circumstances.

The surgical principles for treatment of colovesical fistulas due to diverticular disease include resection of the affected segment (generally the sigmoid colon). The fistula is generally small and may be suture repaired. Ureteral stents are generally not needed. In some cases, the precise site of the fistula cannot be determined, and pinching it off is sufficient treatment; sutures are not absolutely necessary. A primary anastomosis can usually be performed safely. Omentum is used tointerpose between the anastomosis and the bladder. On occasion, nonoperative management is used for colovesical fistulas especially if the symptoms are minor and the patient has medical comorbidities conferring a significant operative risk. Suppressive antibiotics may be used to ameliorate symptoms in such cases [125].

Colovaginal Fistulas

Colovaginal fistulas occur almost exclusively in women who have undergone a prior hysterectomy (Figure 39-8). Signs and symptoms include vaginal discharge and passage of air per vagina. Often, women have seen a gynecologist initially for evaluation of vaginal discharge. A single-stage sigmoid resection can generally be performed, pinching off the site of the fistula and interposing omentum.

Colocutaneous Fistula

Colocutaneous fistulas rarely occur de novo and are generally seen in patients who have undergone prior colectomy or percutaneous drainage [125]. Risk factors for the development of colocutaneous fistula include unsuspected Crohn's disease and anastomosis to the distal sigmoid colon and not the proximal rectum.

Diverticular Stricture/Obstruction

Repeated attacks of diverticulitis may be associated with the development of a sigmoid stricture and progressive obstructive symptoms. Less commonly, complete large bowel

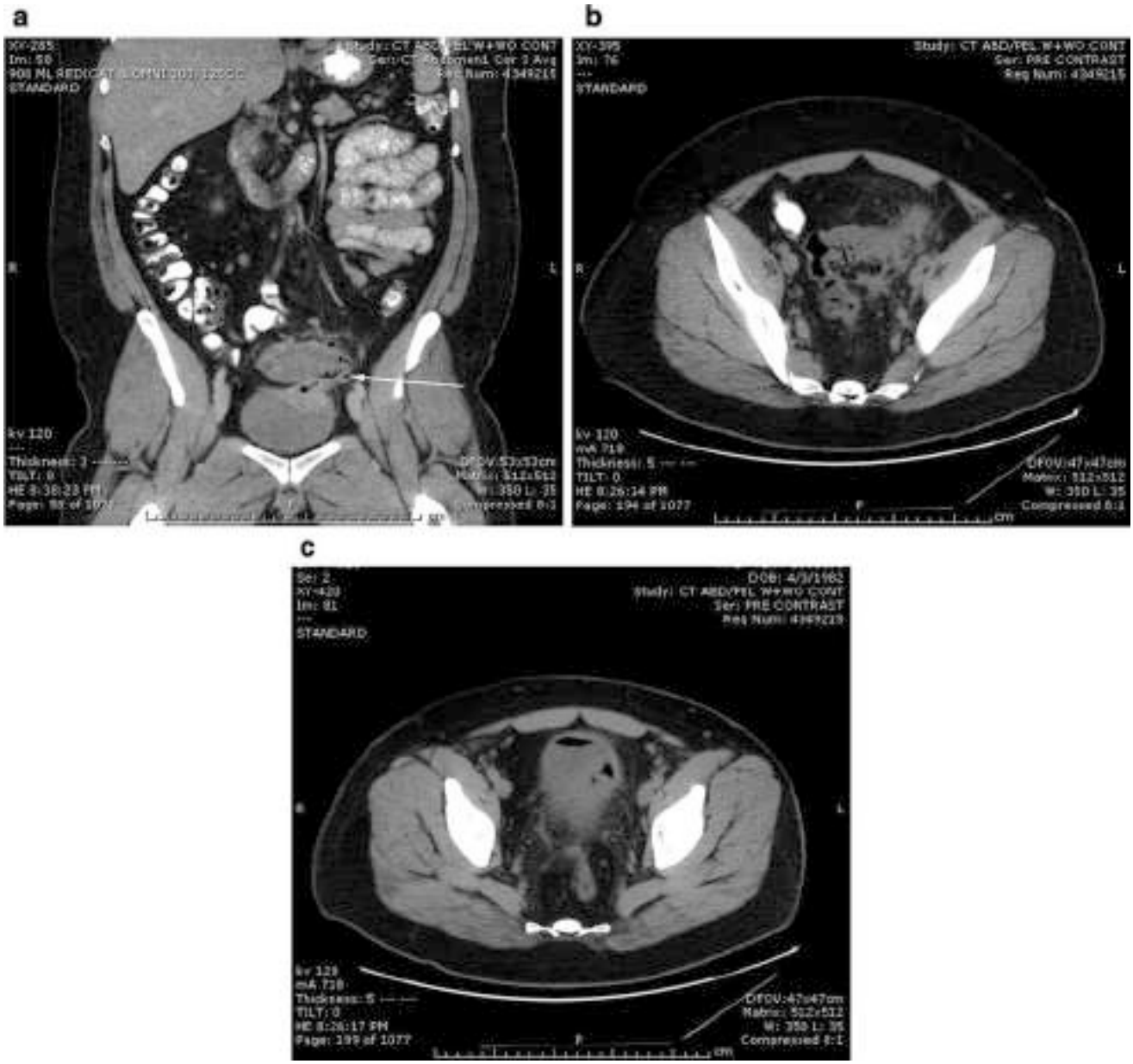

FIGURE 39-7. (**a**) *Arrow* points to colovesical fistula. (**b**) Inflamed sigmoid colon adjacent to fistula. (**c**) Air in non-catheterized bladder consistent with colovesical fistula.

obstruction associated with diverticular disease develops (Figure 39-9). The major differential diagnosis is with obstructing colon cancer. While large bowel obstruction is most commonly associated with obstructing colon cancer, approximately 10% of large bowel obstructions are attributable to diverticular disease [126]. Colonic stricturing typically develops after a number of recurrent attacks leading to fibrosis with the colonic wall. Small bowel can also become adherent to a focus of inflamed colonic tissue leading to associated small bowel obstruction.

The approach to management depends on whether the obstruction is complete or partial. Patients with a partial obstruction that resolves with bowel rest, intravenous hydration, and antibiotics may be able to undergo elective resection. In some patients, treating the acute inflammatory phlegmon allows for resolution of the obstruction. Endoscopic or radiologic evaluation can then be performed and elective resection planned. For patients with complete obstruction, there are a number of surgical options. In the past, persistence of obstruction after treatment with antibiotics typically required sigmoid resection, end colostomy, and Hartmann closure of the rectum because of the concern about the increased risk of anastomotic leakage in patients who had dilated and edematous bowel or who were not able to

undergo preoperative mechanical bowel preparation. While the Hartmann resection is still an excellent option in selected patients, other options include sigmoid resection with primary anastomosis and diverting proximal stoma (usually a loop ileostomy), on-table lavage and primary anastomosis, or colonic stenting placement followed by semi-elective sigmoid resection.

On-table lavage is a technique which allows for cleansing of the fecal laden, obstructed colon before potential anastomosis. The technique has been described by Murray et al. [127] and involves mobilization of the splenic flexure and at times the hepatic flexure. A Foley catheter attached to warm irrigation fluid is introduced through the appendix. If surgically absent, the catheter may be placed through a cecostomy or ileostomy. Corrugated anesthesia tubing is placed through the distal colon and secured with umbilical tape. The colon is lavaged until the returns are clear. The technique may be used in selected patients who are hemodynamically stable and in whom there is minimal contamination. While the need for mechanical bowel preparation has been called into question for elective colon resection, this claim has not been critically evaluated in patients with bowel obstruction [128]. Lee et al. described the use of on-table lavage and sigmoid resection with primary anastomosis in 33 patients with diverticular disease who underwent nonelective resection. There were no anastomotic leaks in this series, but there was a significant (18%) incidence of wound infection [129]. While this technique is interesting, often patients with large bowel obstruction have severely dilated colons that are not good candidates for anastomosis with or without bowel preparation.

A number of authors have demonstrated that treatment of acute colonic obstruction with self-expanding metal stents is a viable option particularly in patients with obstructing colon cancer [130, 131]. Colonic stenting for benign obstructions is associated with a high rate of stent migration as well as other delayed complications. In a series of 104 procedures from one center, eight patients had obstruction from a benign etiology [132]. After colonic stenting, many required reinterventions and only three patients achieved a benefit from stenting. From a technical standpoint, stenting a diverticular stricture which is potentially longer or more angulated may be more difficult than stenting a short segment stricture from colon cancer. Colonic stenting in benign disease remains a controversial procedure and should be embarked upon with caution [133–135].

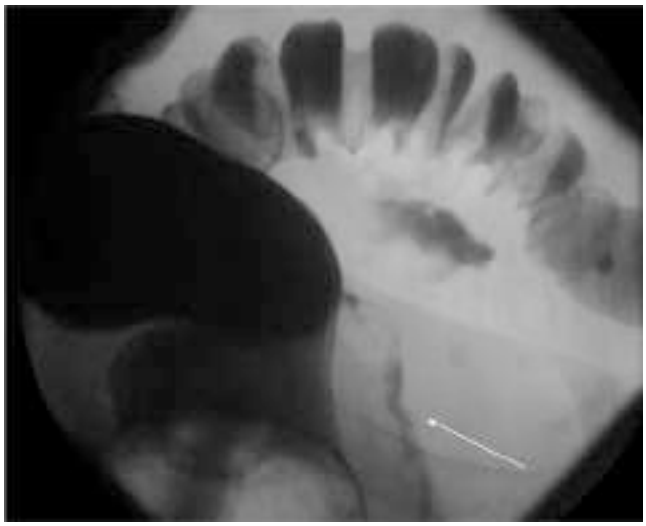

FIGURE 39-8. Colovaginal fistula. *Arrow* demonstrates vaginal filling with contrast from pericolonic abscess.

Operative Therapy

Elective Management

Open sigmoid resection is generally performed through a midline incision. Preoperative mechanical bowel preparation is not necessary but is often performed [128]. Preoperative intravenous antibiotics are administered. The sigmoid colon is mobilized, and proximal and distal points are selected for resection. The proximal resection margin should be in soft pliable bowel, and it is not necessary to resect all proximal diverticula. The distal resection margin is the proximal rec-

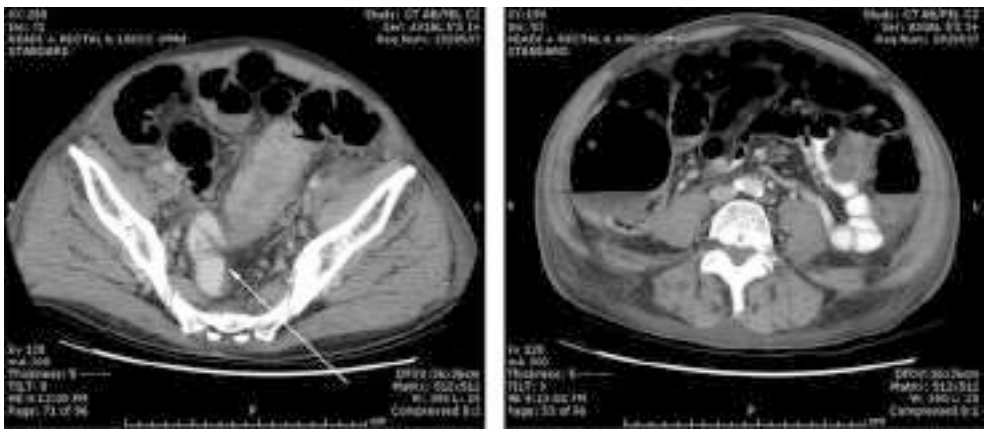

FIGURE 39-9. Large sigmoid phlegmon causing a large bowel obstruction. *Arrow* shows a retrograde injection of contrast within the rectum which is unable to pass the obstruction.

tum as anastomosis to the distal sigmoid is associated with a higher risk of recurrent diverticulitis [136, 137]. It may be necessary to mobilize the splenic flexure to perform a tension-free anastomosis; alternatively, rectal mobilization will also afford additional length. One study suggested that an inframesenteric dissection with preservation of the inferior mesenteric artery decreased the incidence of anastomotic leak [138]. A hand-sewn or stapled anastomosis is performed. The anastomosis is most often performed with an EEA stapler.

In cases of fistulas to the bladder or the vagina, the fistula may be simply "pinched off," and a resection of bladder and/or vagina is not necessary. Once a fistula is pinched off, omentum can be used to interpose between the bladder and/or vagina and the colon.

Ureteral stents are generally not necessary but may be used in selected cases. Although they do not prevent ureteral injuries, they permit easy recognition and repair of such injuries [139]. A technique that may be helpful in mobilization includes "proximal to distal" resection in which the colon is divided proximal to the phlegmon with a linear stapler, and the colon is dissected proximal to distal, rather than performing a lateral to medical dissection [140]. This technique may facilitate easier identification of the ureter and avoid injury.

Although the rectum is not primarily involved with diverticulitis, inflammation of the proximal rectum may be encountered from the diverticular phlegmon or from an associated pelvic abscess or diverticular perforation. In such cases, based on sound surgical judgment and specific intraoperative factors, primary anastomosis potentially to the mid-rectum with proximal fecal diversion may be performed.

Minimally Invasive Surgery

The advent of laparoscopic surgery is ushered in a new era in the surgical management of diverticular disease. In the last decade, increasing numbers of resections for diverticular disease have been performed laparoscopically. Conventional laparoscopic techniques allow the surgeon to perform all the major portions of the case, including the anastomosis, through small 5 or 12 mm trocars (Figure 39-9).

A commonly practiced technique involves the use of a "hand-assisted" technique. In this type of approach, the surgeon's hand is placed into the abdomen though a small vertical lower midline or Pfannenstiel incision to assist in the mobilization of the colon. The dissection can be carried out in a medial to lateral or lateral to medial approach.

In the medial to lateral approach, a plane is made below the inferior mesenteric artery (IMA). The ureter, gonadal vessels, and other retroperitoneal structures are swept away. The IMA is then divided using a stapler or energy device. The sigmoid colon can then be mobilized up to the level of the splenic flexure by sweeping down the attachments of the left colonic mesocolon to Gerota's fascia and retroperitoneum. It may be necessary to mobilize the splenic flexure to perform a tension-free anastomosis, and there is evidence that suggests that the incidence of splenic injury is lower with a laparoscopic approach [141]. Proximal and distal resection margins can then be chosen. A hand-sewn or stapled anastomosis is performed. The anastomosis can be performed in an intracorporeal fashion. Alternatively, the anastomosis can be fashioned through the specimen extraction site. The use of the extraction site in cases of fistulas or abscesses often allows the laparoscopic completion of colectomies in patients with severe disease without conversion. Nonetheless, there are a wide range of published conversion rates as demonstrated in Table 39-6.

In the "conventional or straight" laparoscopic technique, the essential elements of the operation remain the same. The colon can be mobilized from a lateral to medial or medial to lateral approach. The specimen is typically extracted through a periumbilical vertical incision and the anastomosis performed in an intracorporeal fashion.

Prospective evaluation of hand-assisted laparoscopic techniques demonstrate that although operative times are similar to conventional laparoscopic surgery, conversions are less frequent (0% vs. 13%) [24].

Minimally invasive colectomy has a number of benefits. The Norfolk surgical group demonstrated that ileus and length of stay were less in patients who had their sigmoid colectomy completed laparoscopically [142]. Other authors have demonstrated decreased postoperative pain, wound infection rates, operative blood loss, and transfusions and a faster return to preoperative activity levels [143, 144]. The outcomes of 676 patients undergoing laparoscopic colectomy for diverticulitis were compared to those undergoing laparoscopic colectomy for non-diverticular disease. No differences were noted when comparing complications, mortality, length of stay, or oral feeding [145].

TABLE 39-6. Conversion rates in selected laparoscopic colectomy series

Author	Year	Patients	Conversion rate (%)
Klarenbeek et al. [146]	2009	52	19.23
Jones et al. [147]	2008	500	2.80
Cole et al. [148]	2008	151	12.58
Hassan et al. [149]	2007	91	26.40
Belizon et al. [150]	2006	143	19.58
Chang et al. [151]	2005	85	7.28
Schwandner et al. [152]	2004	396	6.82
Buillot et al. [153]	2002	179	13.97
Trebuchet et al.	2002	170	4.12
Vargas et al. [154]	2000	69	26.09
Burgel et al. [155]	2000	56	14.29
Siriser et al. [156]	1999	65	4.62
Berthou et al. [157]	1999	110	8.18
Koeckerling et al. [158]	1999	304	7.24
Smadja et al. [159]	1999	54	9.26
Stevenson et al. [160]	1998	100	8.00

Urgent and Emergent Procedures

The Hartmann procedure resects the diseased segment of bowel, eliminates the septic focus, and allows for restoration of bowel continuity on an elective basis. The patient is approached through a midline laparotomy both to confirm the diagnosis and assess the degree of contamination and inflammation. Preoperative stoma site marking is helpful. The affected sigmoid colon is mobilized, and a proximal to distal approach is generally the easiest and safest. The bowel can be transected proximally and dissection carried down to the sacral promontory. A wide mesenteric dissection is unnecessary. The ureter should ideally be identified. All diseased and thickened bowel should be resected, and the resection margin should ideally be the proximal rectum. Alternatively, distal sigmoid, if not inflamed, can be left in place for later resection at the intended Hartmann reversal. The proximal rectum is transected with a stapler or oversewn depending on individual preference. The stoma is brought out on the left side; splenic flexure mobilization may be necessary to achieve adequate length particularly if there is significant foreshortening of the mesentery from the diverticular phlegmon. The colostomy is generally left in place for at least 3 months allowing the patient to sufficiently heal and hopefully facilitate identification of the Hartmann stump. Waiting longer can make identification of the Hartmann stump difficult secondary to fibrosis [161].

Selection of patients who may safely undergo resection and primary anastomosis in the acute setting requires considerable judgment and must take into consideration patient-related and disease-related factors. Primary anastomosis is not advisable for patients with hemodynamic instability, diffuse fecal or purulent peritonitis, immunocompromised patients, or those with severe anemia or malnutrition and those with ischemia or edema of the bowel at the proposed site of anastomosis [117]. Despite systematic reviews and a focus in the literature on performing primary anastomosis in the nonelective patient, a recent review of 267,000 patients admitted with acute diverticulitis and 335,000 patients (from 1998 to 2005) operated on electively for diverticulitis found no evidence that primary anastomosis was more commonly performed [14].

Minimally Invasive Colectomy for Complicated Disease

As laparoscopic colectomy has gained widespread use, this technique has been applied to patients with complicated diverticular disease. Martel et al. compared the outcomes of laparoscopic colectomy following treatment of complicated and uncomplicated disease in 183 patients. These authors demonstrated no difference in anastomotic leak rates and intraoperative complications. It should be noted however, that patients with complicated disease underwent conversion to open procedures more frequently (23% vs. 4%) [162]. While overall conversion rates differ among studies, higher rates of conversion in patients with complicated diverticulitis are noted in a number of series on this topic [142, 163, 164]. Some studies have noted that when complicated disease is restricted to fistula or abscess, then there is no increased risk of conversion when comparing patients with complicated and uncomplicated disease [165, 166]. A Chinese group has shown that laparoscopy is feasible in the management of complicated right-sided diverticulitis. Although patients in the laparoscopic group recovered bowel function more quickly (3.5 days vs. 5 days), the length of stay in both groups was similar [167].

Special Situations

Recurrent Diverticulitis

Recurrent diverticulitis following resection is uncommon. In the patient presenting with abdominal pain following resection for diverticulitis, a systematic evaluation should be performed to exclude other causes of pain. Etiologies such as inflammatory bowel disease, ischemic colitis, colorectal cancer, adhesive disease, gynecologic pathology, and irritable bowel syndrome should be considered. Patients with diverticular disease have significant overlap with irritable bowel syndrome. Additional pathology review of the resected segment of sigmoid colon may be helpful. Patients who present with "recurrent diverticulitis" may not have had diverticulitis (but only diverticulosis) on initial resection.

The development of recurrent diverticulitis should be distinguished from patients that develop persistent poorly characterized abdominal pain following resection. Munson et al. found that 27.2% of patients following resection for diverticular disease continued to have pain [168]. Parks and Connell noted persistence of mild symptoms in 24% of patients who underwent a three-stage resection for diverticulitis [169].

The most established risk factor for recurrent diverticulitis following resection is the level of anastomosis. Although diverticulitis may only involve a portion of the sigmoid colon, the entire sigmoid should be resected and anastomosis performed to the proximal rectum. The rectum is identified at the level at which the taenia fan out which is generally around the sacral promontory. The proximal resection margin is less well established, and the dictum has been to anastomose in "soft pliable bowel" [8]. It is unnecessary to remove all diverticula of the colon, but the anastomosis should be performed in an area that is free of diverticula. Two studies have looked at the level of anastomosis and the risk of recurrent diverticulitis. Benn et al. examined 501 patients undergoing sigmoid resection for diverticular disease. The incidence of recurrent diverticulitis was 6.7% with anastomosis to the proximal rectum compared with 12.5% in patients who underwent anastomosis to the distal sigmoid

colon. Thaler et al. also noted that the level of anastomosis was the only predictor of recurrence in regression analysis with patients with a colosigmoid anastomosis having a four times higher risk of recurrence compared to patients with a colorectal anastomosis [136].

Giant Colonic Diverticulum

The condition of giant colonic diverticulum is rare and was first reported by Bonvin and Bonte in 1946 [170]. Less than 150 cases have been reported in the literature [171]. These diverticula affect men and women equally and are most commonly found in the sigmoid colon. The average diameter is 13 cm, but diverticula as large as 40 cm have been reported. Two theories have been put forth for the development of giant diverticulum; one proposed theory is that the diverticulum becomes massive because of a ball-valve mechanism allowing air into but not out of the diverticulum [172]. Another theory suggests that air is trapped into the diverticulum because of gas-forming microorganisms without obstruction at the neck of the diverticulum.

Many patients with this entity are minimally symptomatic or present with mild episodes of pain. On abdominal palpation, a soft mobile mass may be appreciated. The differential diagnosis includes colonic duplication, pancreatic pseudocyst, Meckel's diverticulum or jejunal diverticulum, sigmoid volvulus, or emphysematous cholecystitis. More commonly, the abnormality is noted on abdominal CT scan. Treatment consists of sigmoid resection with anastomosis. Diverticulectomy, which was has been employed in earlier reports, is rarely performed today.

Diverticulitis: Other Sites

Right Colonic Diverticulitis

Right-sided diverticulitis is rare in the Western countries and more common in the Far East [173]. Cecal diverticula are of two types, both true and false. True diverticula contain all layers of the bowel wall and are usually congenital and tend to be solitary. Acquired diverticula of the cecum are false, containing mucosa and muscularis mucosa, tend to be multiple and tend to be associated with diverticula elsewhere in the colon. Patients with cecal diverticulitis present at a younger age than the average patient with sigmoid diverticulitis. The main differential diagnosis is that of acute appendicitis, and it may be difficult in the patient with right-sided abdominal pain, fever, and leukocytosis to distinguish cecal diverticulitis from acute appendicitis. Other differential diagnoses include chronic cholecystitis, mesenteric adenitis, ischemic colitis, pelvic inflammatory disease, pancreatitis, Meckel's diverticulitis, pyelonephritis, and sigmoid diverticulitis (with a redundant sigmoid loop). Laparoscopy is sometimes helpful to distinguish between cecal diverticulitis and appendicitis. A retrospective review of 49 patients at a single institution found the ratio of acute appendicitis to cecal diverticulitis to be 150:1 [174]. In the absence of peritoneal signs, patients may be treated with antibiotics. For those patients with repeated attacks or complications including perforation or abscess, resection is indicated. Fang and coworkers reviewed 85 patients treated for cecal diverticulitis [175]. Less than 40% were treated with antibiotics and bowel rest. Sixty-seven patients ultimately underwent laparotomy. In the 47 patients with a preoperative diagnosis of appendicitis, 24 underwent appendectomy, 9 underwent diverticulectomy, and 14 underwent right colectomy. In the 20 patients with a preoperative diagnosis of diverticulitis, all underwent right colectomy. Thorson and Ternent [176] have suggested a grading system to aid with the management of cecal diverticulitis (Table 39-7). These authors suggested that when diagnosis is uncertain then right colectomy is most likely the best option [176]. With refinements in technology and with the widespread use of CT scanning for evaluation of patients with abdominal pain, proceeding to laparotomy or laparoscopy without a relatively secure diagnosis is uncommon.

Table 39-7. Cecal diverticulitis classification system

Grade I	Easily recognizable projecting inflamed cecal diverticulum
Grade II	Inflamed cecal mass
Grade III	Localized abscess or fistula
Grade IV	Free perforation or ruptured abscess with diffuse peritonitis

Modified from Hinchey et al. [141]

Rectal Diverticulitis

Rectal diverticula are rare, are typically solitary, and are true diverticula including all layers of the bowel wall [37].

Transverse Colonic Diverticulitis

Diverticulitis involving the transverse colon is exceedingly rare with less than 50 cases reported and often confused with other conditions such as cholecystitis [177]. In a large series of 951 patients who all underwent CT scan on initial presentation of diverticulitis, Hall et al. found that the prevalence of transverse colon diverticulitis was 2.6% [42].

Immunocompromised Patients

Immunocompromised patients include patients on systemic steroids, patients with diabetes mellitus or renal failure, transplant patients who are immunosuppressed, patients with cirrhosis, patients with underlying malignancy, and

patients being treated with chemotherapy. Patients who are immunosuppressed are more likely to present with free perforation, presumably because of the inability to mount an inflammatory response and wall off the infection and are therefore more likely to require emergency surgery with resultant increased postoperative morbidity and mortality. In the combined series of patients who were immunocompromised who presented with diverticulitis, 40% had free perforation, 60% required emergency operation, and the overall postoperative morbidity and mortality were 65% and 40%, respectively [178–181]. Immunocompromised patients who present with acute diverticulitis and require emergent laparotomy should undergo resection, with colostomy, and should not undergo primary anastomosis because of the impaired immune system and impaired healing.

Conclusion

Colonic diverticular disease represents a wide spectrum of presentations and treatment options. While many of the current treatment methods have been used for the greater part of a century, their mode of application continues to evolve. As in all inflammatory conditions, the initial goal of therapy is to control infection. Once this is done, the surgeon is left with a variety of treatment algorithms and options which must be individualized for each patient.

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40
Large Bowel Obstruction

Karim Alavi and Charles M. Friel

Key Concepts

- Initial management of large bowel obstruction should include early correction of fluid and electrolyte abnormalities and surgical or endoscopic decompression.
- The current indications of endoluminal colonic stents include palliation in cancer and in patients who are medically unfit.
- Following correction of fluid and electrolyte abnormalities in patients with acute colonic pseudo-obstruction, intravenous neostigmine should be attempted as the next step in management.
- Following successful endoscopic decompression of a sigmoid volvulus, given the high recurrence rates, the next step in management should be a segmental resection during the same hospitalization.
- CT scan is the imaging modality of choice for the diagnosis and subsequent management of large bowel obstruction.

Introduction

Large bowel obstruction (LBO) is a common surgical emergency encountered in a colon and rectal surgical practice [1]. It is caused by the blockage of fecal flow. While most causes are mechanical, nonmechanical causes (pseudo-obstruction) have also been described. LBO is a complex problem that will challenge even the most seasoned clinicians. The surgeon must not only manage the immediate emergency (i.e., the obstruction) but also consider the treatment of the underlying etiology and consider the long-term outcomes of any particular intervention. Therefore, no one strategy will be adequate for all patients. Surgeons must be familiar with all the causes of LBO and understand the myriad of treatment options so that therapeutic plans can be tailored to a variety of clinical presentations.

Etiology

Most LBOs are due to progressive narrowing of the bowel lumen caused by intrinsic lesions of the bowel wall (Table 40-1). The most common example of an intrinsic lesion is colorectal cancer, which accounts for nearly 50% of all LBOs. In fact, approximately 10% of all colorectal cancer will present with evidence of a LBO [1]. Diverticular disease also causes intrinsic compression of the lumen and is generally considered the second most common cause of LBO (≈10–20%). Other less common examples of intrinsic narrowing include Crohn's disease, ischemia, endometriosis, and radiation, all of which cause progressive thickening of the bowel wall and obliteration of the lumen and can often be difficult to distinguish from colorectal cancer.

Extrinsic lesions can also impinge the bowel lumen. Most commonly extrinsic compression is caused by non-colorectal malignancy, such as ovarian cancer. Other less common causes of extrinsic compression are hernias and adhesions, the most likely causes of small bowel obstructions but rare for LBO.

Because both intrinsic and extrinsic compressions are slowly progressive, the clinical presentation of LBO is often insidious. Even when patients seemingly present with an acute LBO, the astute physician can elicit a history of progressive constipation and narrowed stools for left-sided obstruction or crampy abdominal pain for right-sided disease. Depending on when patients seek care, the clinical presentation can be quite varied and management strategies will have to be adjusted accordingly. Mild obstruction, or bowel stenosis, may cause symptoms such as pain, cramps, and constipation. During colonoscopy, the endoscope may not pass through the stricture, and on barium enema the patient may have a classic "apple-core" lesion (Figure 40-1). Since these patients have no proximal bowel dilation and no stool and fluid accumulating upstream of the obstruction, they will not present with signs of systemic toxicity. Management of

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TABLE 40-1. Etiology of large bowel obstruction (LBO)

1. Intrinsic lesions
Colon cancer[a]
Diverticular disease[b]
Crohn's disease[c]
Endometriosis[c]
Radiation[c]
Ischemic[c]
2. Extrinsic lesions[c]
Non-colorectal malignancy (e.g., ovarian cancer)
Hernia
Adhesions
3. Volvulus[b]
4. Other[c]
Foreign body
Impaction
Acute colonic pseudo-obstruction (ACPO)

[a]Most common cause of LBO
[b]Common causes of LBO
[c]Uncommon causes of LBO

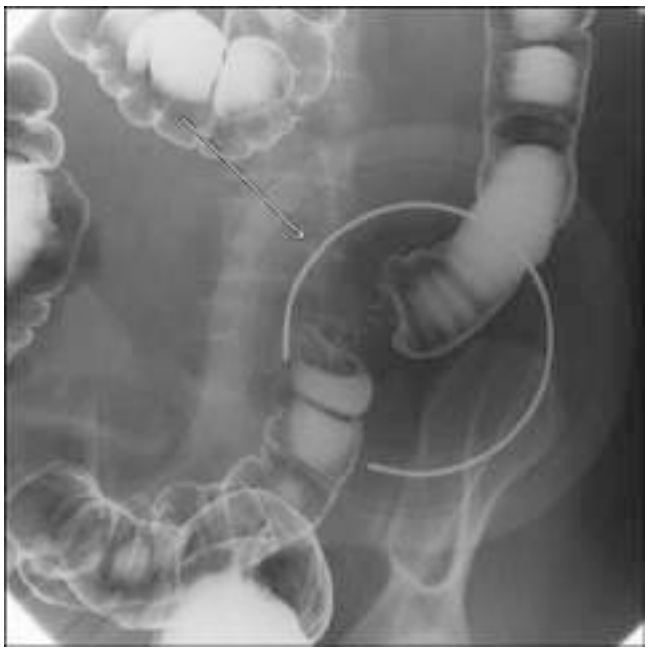

FIGURE 40-1. Air-contrast enema demonstrating apple-core lesion of the sigmoid colon.

these patients is generally simpler since there is no immediate danger and surgery can be planned on a semi-elective basis. Moderate obstruction will present with proximal bowel dilation and accumulation of feces and fluid upstream. Bacterial overgrowth is also common. These patients will be very distended on exam but may only have mild tenderness (Figure 40-2). Signs of systemic toxicity, including an elevated heart rate and increased leukocytosis, are usually absent. Nevertheless, depending on the degree of colonic dilation, these patients can be on the precipice of grave illness and need prompt management. Severe obstruction will present similarly except signs of systemic toxicity will be present. These patients need immediate resuscitation and often require emergent surgery.

The last major category of LBO is volvulus, a twisting of the redundant colon about the colonic mesentery (Figure 40-3). Colonic volvulus accounts for approximately 10–15% of all LBOs reported in the United States and other Western countries. Worldwide, however, colonic volvulus accounts for a significantly higher proportion of LBO [2–5]. It can occur anywhere in the colon, but sigmoid and cecal are by far the most common [2, 3]. In most series, the sigmoid colon accounts for the 50–75% of all colonic volvuli with the majority of the remaining being located in the cecum [2, 3]. In a review of the Mayo experience, Ballantyne noted that 56% of the patients had a sigmoid volvulus compared with 41% of patients who were referred from the local county [2], and this distribution seems typical of other studies. Cecal volvulus tends to be in younger patients and has a slight female predilection. In a review from Rabinovici of 561 cases over a 30-year period, the average age at presentation was 53 years and the ratio of female to men was 1.4:1 [6]. Similarly, Friedman reported that patients with cecal volvulus were 10 years younger than patients with sigmoid volvulus (61 years vs. 71 years of age) [3]. Lack of

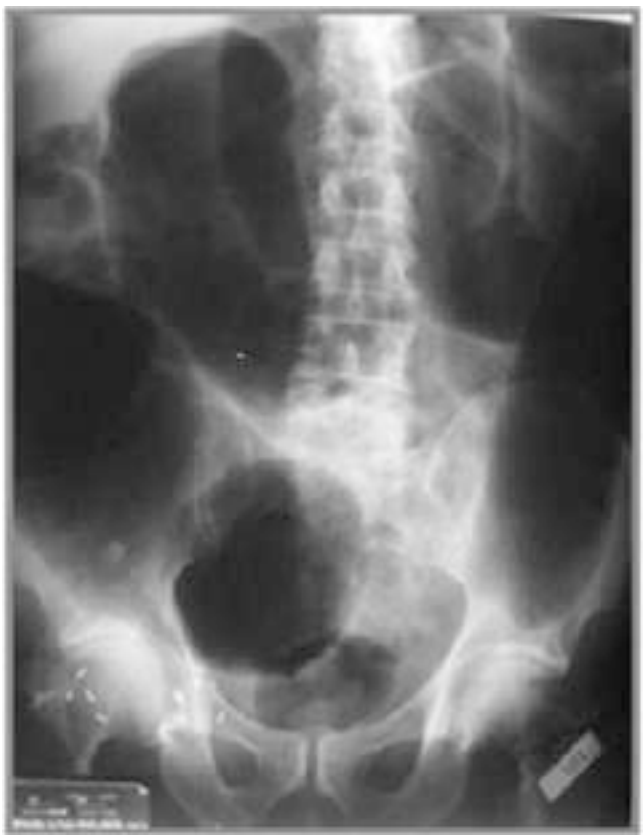

FIGURE 40-2. Plain radiograph demonstrating a diffusely dilated colon.

FIGURE 40-3. Surgical findings of sigmoid volvulus.

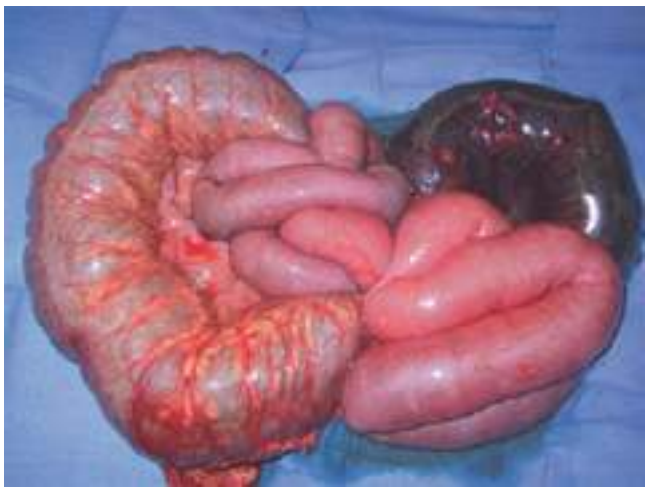

FIGURE 40-4. Necrotic sigmoid colon in the setting of sigmoid volvulus and distended proximal colon.

fixation of the cecum and ascending colon to the retroperitoneum seems to be a predisposing factor, and oftentimes patients have had a previous surgical history, suggesting adhesions may also play a role [2, 3]. In contrast, sigmoid volvulus seems associated with chronic constipation and elongation of the colon, indicative of an acquired pathology. In the United States, patients are often elderly and frequently institutionalized [3, 4] with significant medical comorbidities, including psychiatric diseases. Worldwide, however, patients tend to be younger and live in rural environments [4, 5]. Unlike other causes of LBO, a volvulus often presents acutely with rapid onset of distension and pain. Since the mesentery is involved in this process, the risk of strangulation and ischemia is significantly higher when compared with the more common causes of LBO [3] (Figure 40-4). Therefore, rapid identification is critical to ensure prompt intervention to prevent bowel necrosis.

Pathophysiology

Competency of the ileocecal valve is critical in determining the urgency by which decompression is required. LBO, in the setting of a competent ileocecal valve and a distal obstruction or colonic volvulus, results in a closed-loop obstruction. The ileum continues to pour contents into the colon without reflux leading to an increase in intraluminal pressure colonic distension. These effects are often compounded by bacterial overgrowth. As intraluminal pressure rises, intramucosal and intramural hypoperfusion lead to venous occlusion, followed by arterial occlusion, thrombosis, and eventual necrosis. The evolution and extent of these changes depends on the degree and duration distension [7, 8]. The risk of progression to ischemia and subsequent necrosis is lessened to some degree by the presence of an incompetent ileocecal valve and reflux of colonic contents into the small bowel. Finally, in the setting of colonic volvulus, necrosis may manifest rapidly due to a sudden, tight compression of the mesenteric vessels caused by ongoing distension of the colon and twisting of the mesentery along the mesocolic axis.

The consequences of increased intraluminal pressure in various segments of the colon depend on the amount of tension to which the walls are subjected and vary based on the law of Laplace. For example, the cecum, which has the largest diameter, is exposed to the greatest tension [9]. According to Laplace's law (Pressure = Tension/Radius), the tensile force on the wall of the colon is equal to the intraluminal pressure multiplied by the diameter of the segment in question [7–10]. Given the large diameter of the cecum, the tensile forces on the wall are the greatest, thus posing the greatest risk for perforation. The cutoff for cecal diameter on plain abdominal film has long been cited to be 12 cm above which the risk of ischemia and perforation increase [11–14]. An arbitrary cutoff, however, should be used within the context of the overall patient condition. The characteristics and risk for ischemia are dependent on several factors, including (1) the degree of distension, (2) the duration of

distension, (3) the amount of tension on the colonic wall, and (4) the baseline characteristics of the system vasculature [8].

Presentation

Patients with LBO present with abdominal distension, crampy abdominal pain, and obstipation. As previously stated, the degree of stenosis often determines the acuity of the presentation. They may have associated emesis which is directly related to the competency of the ileocecal valve, location, and the duration of the obstruction. Patients with a competent ileocecal valve do not experience emesis and instead exhibit increasing distension and pain. These patients are at increased risk of necrosis and subsequent perforation [10]. An incompetent valve vents the colonic contents into the proximal bowel allowing for a more measured approach. Often, the acuity of the presentation helps clarify the underlying etiology. Obstruction may present acutely in the setting of volvulus but may be more chronic, with a history of preceding constipation, in the setting of cancer, diverticulitis, or inflammatory bowel disease (IBD).

On physical examination, patients present with a distended and tympanic abdomen. In the setting of ischemia, localized peritonitis along with signs of systemic sepsis may be present demanding urgent surgical exploration. In addition, there may be signs of intravascular volume depletion as the obstructed colonic segment becomes distended with fluid and gas due to bacterial overgrowth. A digital rectal examination should be performed in all patients to evaluate for a distal rectal or anal canal mass and to exclude other etiologies, such as fecal impaction or a foreign body.

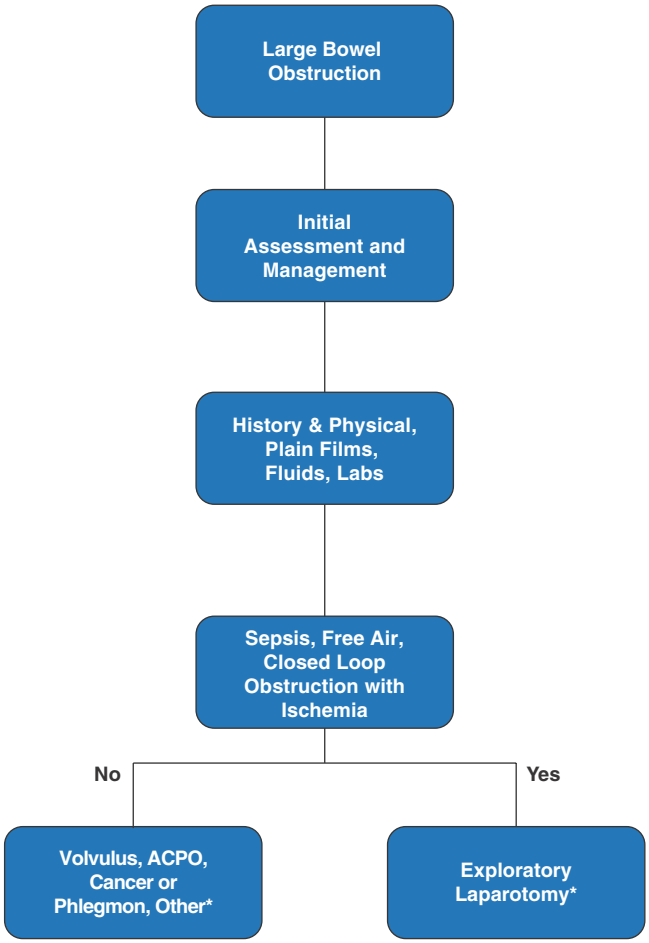

FIGURE 40-5. Proposed algorithm for initial presentation and management of LBO. ACPO = acute colonic pseudo-obstruction; *See Figures 40-9, 40-10, 40-18, and 40-21.

Initial Resuscitation (Fig. 40.5)

Initial assessment and management of patients with LBO, regardless of the diagnosis, should include a focused history and physical examination, complete blood work,including a complete blood count and serum chemistries, and flat and upright abdominal films. These initial tests can rapidly establish the diagnosis and exclude ischemia and/or associated perforation. Given the significant derangement in fluid and electrolytes, these patients are in need of aggressive fluid resuscitation and correction of electrolyte abnormalities. The adequacy of resuscitation should be closely monitored with insertion of a urinary catheter. In the setting of small bowel distension and associated emesis, decompression with a nasogastric tube may be helpful in averting an urgent exploration allowing time for ongoing resuscitation efforts. Stable patients, without signs of localized or systemic sepsis, can be studied further with radiologic imaging if necessary [14]. Diffuse peritonitis, however, mandates emergent surgical exploration.

Diagnostic Imaging

Abdominal Plain Film

Plain abdominal films are usually the first diagnostic imaging performed as they are quick and inexpensive and provide immediate feedback of underlying pathology. They also allow confirmation of abdominal catastrophe, such as free perforation or pneumatosis coli. Plain films help provide an estimation of colonic diameter, with a cecal diameter of 9–12 cm concerning for impending perforation. As discussed previously, an absolute cecal diameter associated with

impending perforation is debatable. Other variables, such as the duration of distension, appear to be as important as predictor [15]. In some cases, such as foreign body or volvulus, a plain film may be all that is necessary [1, 16, 17].

Plain films confirm the diagnosis of sigmoid volvulus by the classic presence of a "bent inner tube" or an "omega loop" pointing to the right upper quadrant (Figure 40-6). However, these findings are present in only 50–70% of cases [18–20]. Conversely, cecal volvulus presents with a "coffee-bean" deformity pointing to the left upper quadrant (Figure 40-7). Radiographs, however, demonstrate this condition in less than 20% of patients [19]. In a retrospective review of the presentation and management of colonic volvulus in Minnesota [21], plain films were insufficient in establishing the definitive diagnosis in 85% of cecal and 49% of sigmoid cases. In the setting of less common causes of volvulus, such as ileosigmoid knotting, or transverse or splenic flexure volvulus, abdominal plain films are even less reliable. Characteristic radiographic features of ileosigmoid knotting have been described and consist of double obstruction with a distended, obstructed sigmoid loop pulled toward the right and a proximal small bowel obstruction on the left [22, 23]. In practice, however, plain films are atypical and difficult to interpret leading to diagnostic delays [24]. In the absence of characteristic radiographic findings, the etiology of LBO can present a diagnostic challenge which can be compounded by the presence of coexisting megacolon or small bowel distension. If the patient's condition permits, additional studies may be necessary to establish the diagnosis.

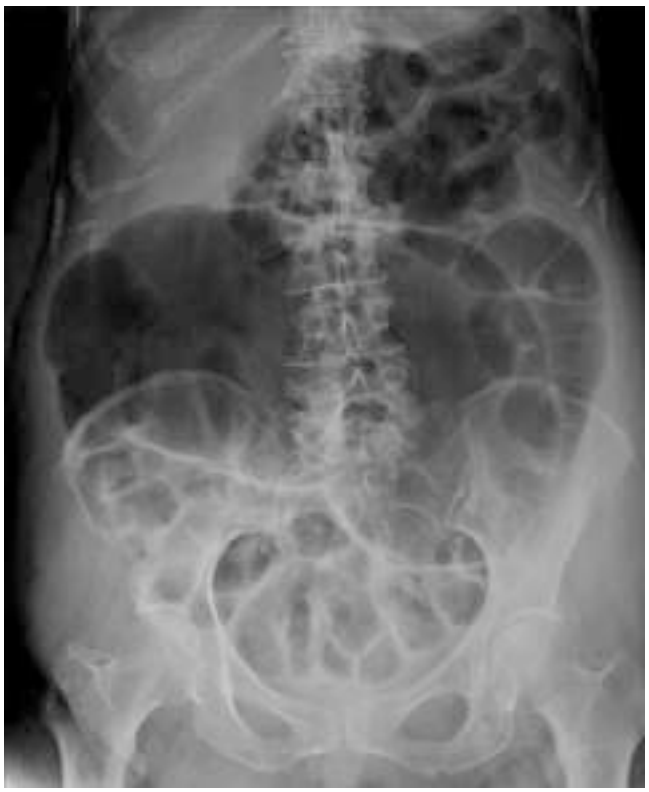

FIGURE 40-7. Plain radiograph demonstrating "coffee-bean "sign of cecal volvulus with apex pointing to the left.

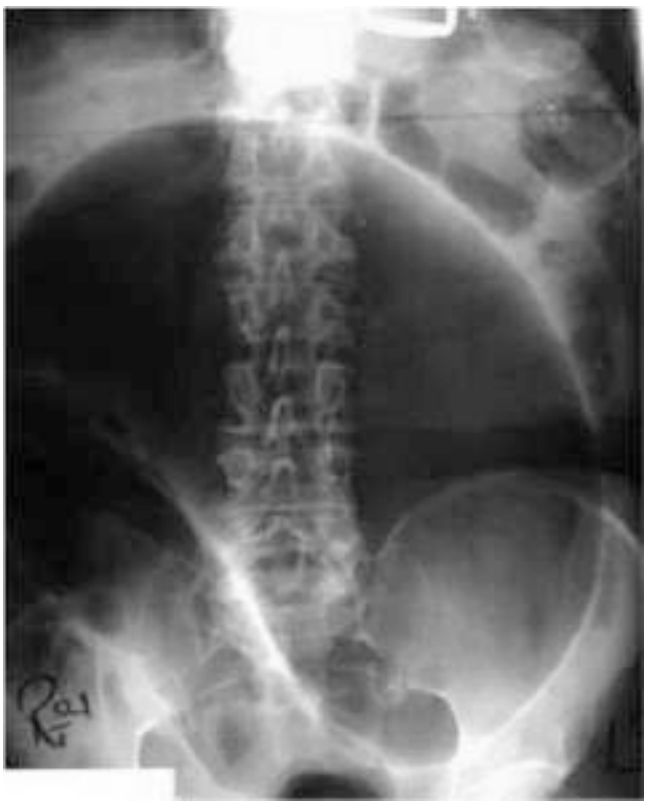

FIGURE 40-6. Plain radiograph demonstrating "bent inner tube" sign of sigmoid volvulus with apex pointing to the right.

Contrast Enema

When the etiology of LBO is in doubt, contrast enema (CE) may establish the diagnosis and localize the site of obstruction [25, 26]. Water-soluble contrast is preferred as the mortality of peritonitis secondary to barium is high if perforation is encountered. Furthermore, barium instilled proximal to a known stricture can exacerbate the LBO. In a study of 140 cases of LBO over a 4-year period examining the accuracy of contrast enema to plain abdominal film, CE had a sensitivity and specificity of 96% and 98%, respectively, in diagnosing LBO compared to a sensitivity and specificity of 84% and 72%, respectively, for plain films [27]. A CE classically shows a "bird's beak" deformity at the end of the column of contrast at the site of the torsion or obstruction. In the case of volvulus, the "bird's beak" deformity will classically be on the left side for sigmoid volvulus and on the right side for cecal volvulus. CE in colonic pseudo-obstruction will show free flow of contrast proximally and no obstruction or transition point. In some instances, such as fecal impaction, administration of the contrast may even be therapeutic [28]. Conversely, CE performed in LBO due to either an intrinsic or an extrinsic process may demonstrate a wisp of contrast

through the smooth narrowed channel. The presence of a channel and its anatomic properties, such as length, width, tortuosity, and smooth versus jagged, provides insight into the role of endoluminal stenting for relief of LBO. However, contrast enemas are not readily available, are associated with increased patient discomfort, and increase the risk of perforation. Finally, the sensitivity of CE is dependent on the experience of the radiologist and the patient body habitus [29].

Computed Tomography

Computed tomography (CT) is the imaging modality of choice [30, 31] providing valuable diagnostic information, such as the presence of proximal lesions, extrinsic disease, a closed-loop obstruction, or distant metastasis, helping guide management [32] (Figure 40-8). There are few studies comparing the CE and CT in the setting of LBO. Beattie et al. [31] studied the efficacy of CT scan in the diagnosis of LBO. They demonstrated a sensitivity, specificity, and positive predictive value of 91% for CT, which compares favorably to CE. Frager et al. [33] reported the results of CT, endoscopy, and CE in 75 patients with LBO. On subgroup analysis, CT compared favorably with a sensitivity of 96% compared to 80% for CE. Furthermore, CT correctly localized the point of obstruction in 94% of patients. Generally, CT is more readily, easier to obtain, and has supplanted CE as the diagnostic modality of choice for the diagnosis of LBO [32].

Management

Management of LBO is complex and can challenge even the most experienced surgeon. The rapidity with which decompression is achieved depends on the severity of the stenosis, acuity of the presentation, baseline clinical status of the patient, and the presence of overt sepsis. Frequently, efforts at decompression must occur despite unclear etiology providing a significant challenge for all providers. In actuality, the treatment algorithm for LBO is complex and is often guided by provider expertise, availability of resources, and resectability and location of the obstructing lesion.

Emergent Setting (Fig. 40.5)

Regardless of the etiology, patients presenting with LBO and signs of peritonitis, perforation, or closed-loop obstruction with evidence of ischemia or gangrene require emergent surgery following initial resuscitative efforts. If the patient's condition permits, the stoma site should be marked preoperatively. Appropriate broad-spectrum antibiotics should be administered with good aerobic and anaerobic coverage. As part of the informed consent, the indications, risks, and benefits of the different surgical options should be discussed. Patients should be placed in lithotomy position to allow ease of access to the rectum if necessary. Entry of the abdomen is best achieved through a midline incision as the distended colon usually precludes laparoscopic exploration. The proximal dilated colon can be decompressed by passage of a 12-gauge needle obliquely through the taenia coli of the transverse colon and attaching it to suction. This allows for immediate decompression and enhances handling. If the small bowel is dilated, the contents can be milked back into the stomach and removed through the nasogastric tube [34].

Unresectable Lesion (Fig. 40.9)

As previously mentioned, surgical options in the emergent setting are multifactorial. A proximal diversion without

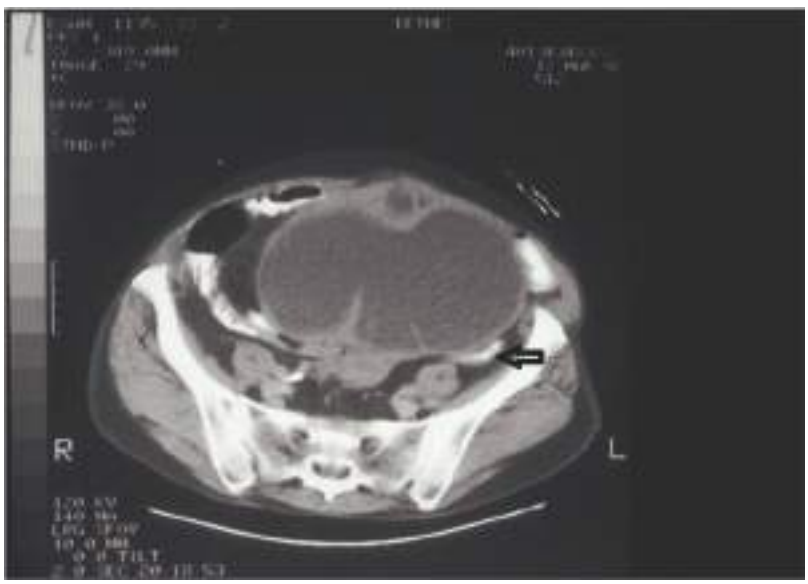

FIGURE 40-8. Pelvic extracolonic lesion causing LBO due to extrinsic compression. *Arrow* points to compressed descending colon.

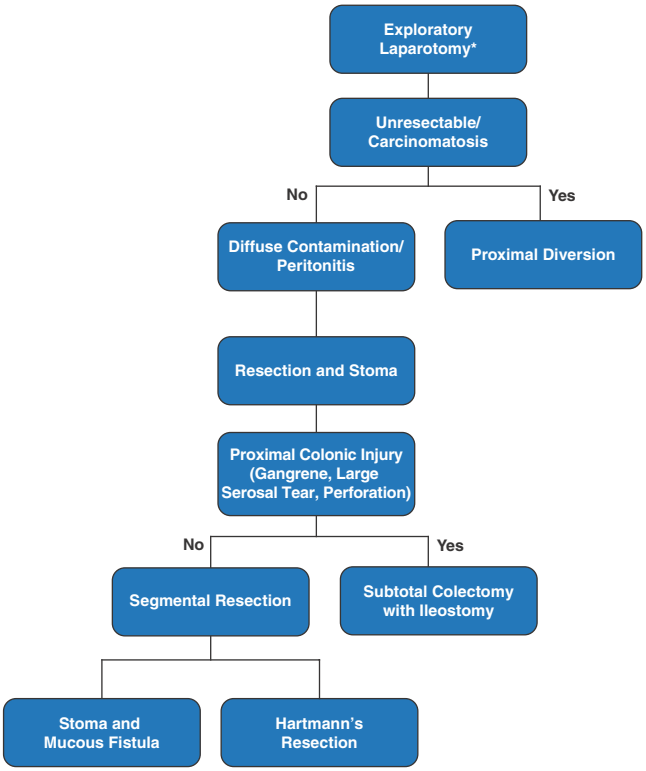

FIGURE 40-9. Proposed algorithm for patients presenting with LBO and associated closed-loop obstruction with ischemia, free air, or sepsis.

resection of the primary obstructing lesion is rarely required but may be necessary in the setting of diffuse carcinomatosis, hemodynamic instability, an unresectable inflammatory phlegmon, due to cancer, diverticulitis, or Crohn's disease, or inexperience of the surgical team. In this setting, a proximal diversion may be the only realistic option and does not always guarantee a permanent stoma. Gutman et al. [35] reported their experience on 71 patients with LBO secondary to cancer who underwent proximal loop colostomy without resection. Forty-nine patients (75.4%) eventually underwent resection of the tumor and closure of the colostomy within 3 months. The remainder of the cohort did not undergo further surgery due to either diffuse metastatic disease or severe comorbidities. Kronborg [36] performed a randomized trial of staged resection versus acute resection in 121 patients presenting with acute left-sided LBO secondary to cancer. They reported similar recurrence and survival rates between groups. While a staged procedure appears to have comparable outcomes to a single-stage surgery, the morbidity associated with repeat surgery is significant. A staged approach should be reserved for circumstances where the clinical condition of the patient, existing comorbidities, and intraoperative findings preclude resection of the obstructing process. Finally, a proximal diversion, such as with a loop colostomy, in the setting of an obstructing rectal cancer allows time for treatment with neoadjuvant chemoradiation, improving respectability of the primary lesion.

Resectable Lesion (Fig. 40.10)

During exploration and following resection of the obstructing lesion, the decision to restore intestinal continuity is dependent of the intraoperative findings and the general condition of the patient. If generalized peritonitis, hemodynamic instability, or gross fecal contamination is present, a primary anastomosis would be contraindicated. While laparoscopic approaches have been described, an open approach is more appropriate in the emergent setting. When feasible, the distal colon conduit should be exteriorized as a mucous fistula or buried in the subcutaneous tissue, in the inferior pole of the midline incision or at the stoma site. This allows for ease of access and early identification during reversal surgery. All attempts should be made to inspect the proximal colon for evidence of gross injury or synchronous pathology. In the presence of ischemia, perforation, coexisting lesion, or large serosal injury of the cecum, a subtotal colectomy may be indicated (Figure 40-11). Given the difficulty in identifying the underlying etiology in an emergent setting, every effort should be made to perform an en bloc resection following oncologic principles [34].

Non-emergent Setting (Fig. 40.10)

In the non-emergent setting, the management algorithm is based on the skill of the surgeon, the condition of the patient and proximal colon, the resources of the institution, and the etiology of LBO [1]. In a hemodynamically stable patient with no overt signs of sepsis, free air, or generalized peritonitis, the etiology of the obstruction, such as foreign body, pseudo-obstruction, or volvulus, can easily be identified on plain abdominal films. In the absence of these findings, more advanced imaging, such as a CT scan, is essential in defining the etiology and extent of LBO as well as other associated findings, such as diffuse carcinomatosis, metastasis, anatomy of the obstruction, and involvement of surrounding structures [30–32]. In the non-emergent setting, LBO secondary to right and transverse colon pathology proximal to the splenic flexure should be managed by primary resection and anastomosis when feasible. In fact, several authors have shown that primary anastomosis in the setting of right-sided LBO is safe with acceptably low anastomotic leak rates in the range of 2.5–5.2% [37, 38].

The management of LBO secondary to lesions distal to the splenic flexure is complex, challenging, and controversial. Specifically, the controversy has its roots in the uncertainty of the diagnosis, i.e., benign versus malignant, and the oncologic safety and efficacy of endoluminal decompression,

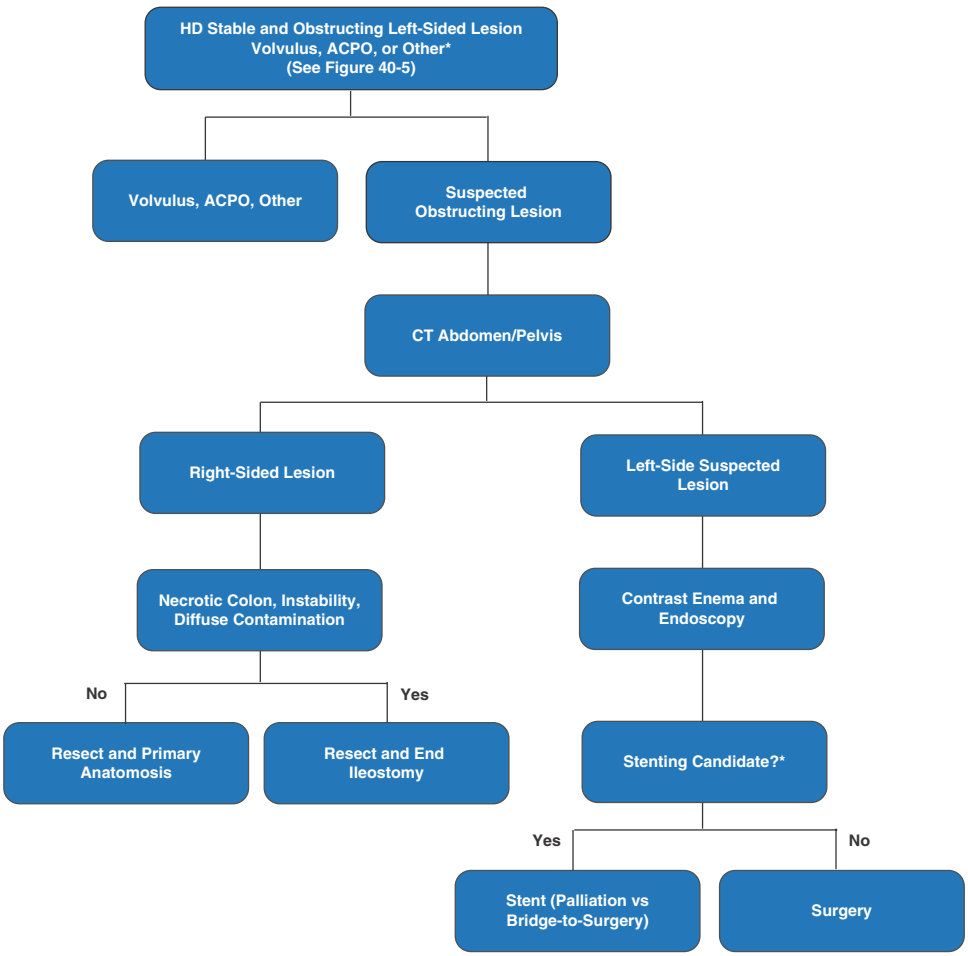

FIGURE 40-10. Proposed algorithm for LBO in a stable patient secondary to a left-sided lesion (diverticular or Crohn's phlegmon, cancer, or unclear etiology).

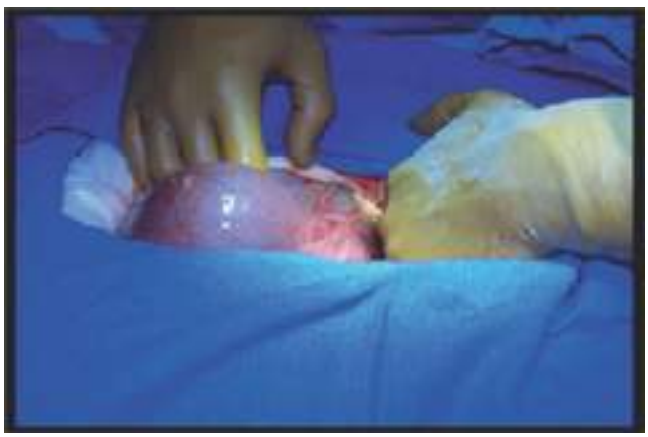

FIGURE 40-11. Distended and tense cecum with large serosal tear along the antimesenteric wall.

used as palliation or as a bridge to surgery. Furthermore, opinion on the timing and role of endoscopy, primary anastomosis with or without proximal fecal diversion versus staged resection with end stoma, on-table colonic lavage, and segmental resection versus subtotal colectomy remains divided and is often driven by the skill of the surgeon, intraoperative findings, and the clinical condition of the patient.

Endoscopy and CE

Endoscopy and CE are important tools in the initial management of LBO and should be considered *early* both as part of its diagnosis and management [1]. In the setting of LBO secondary to a luminal mass, endoscopy aids in the initial diagnosis. The risk of perforation and worsening obstruction can be obviated by the use of CO_2 insufflation. Studies on the use of CO_2 colonoscopy in ambulatory settings have demonstrated that CO_2 insufflation attenuates post-procedure abdominal bloating and pain compared to conventional air colonoscopy [39, 40]. Yasumasa et al. [41] studied parietal blood flow in rodent colon distended with air or CO_2. They reported that CO_2-distended colons resolved their distension sooner than conventional air-insufflated colons. Furthermore, they showed that prolonged colonic distension is associated with disturbances in parietal blood flow, resulting in

increased pain. In general, CO_2 colonoscopy is well suited and thus recommended in the setting of LBO as it is absorbed 250 times faster than air and is less likely to lead to proximal colonic distension and subsequent perforation. The order in which the tests should be performed is not established. If a colonic stent is contemplated, a CE is often obtained first to define the presence and anatomy of the channel and its suitability for stent deployment.

Self-Expanding Metallic Stents

Over the last several decades, enteral stenting has emerged as an alternative to surgery for many obstructions of the GI tract. Most of the early experience with stenting has been in the biliary tree and the esophagus. However, in 1991, Dohmoto described the use of a palliative colonic stent for a malignant obstruction [42]. Shortly thereafter, Tejero et al. reported his first experience with a self-expandable metal stent (SEMS) to relieve colonic obstruction prior to curative resection [43] and followed this with his report on a series of patients in 1997 [44]. In that series, Tejero et al. treated 38 patients presenting with colonic obstruction. There was 100% technical and 92% clinical success, and the era of the colonic stent was born. As GI interventionist has become more experienced, colonic stenting has emerged as an alternative to relieve a colonic obstruction, potentially obviating the need for emergency surgery and the associated morbidity of this approach [45].

Conceptually, SEMS are used either for palliation or as a "bridge to surgery." Patients who present with incurable disease and who have limited life expectancy may be able to avoid major surgery and the need for a colostomy with the successful placement of a colonic stent [46]. In contrast, patients with curable disease who present with a colonic obstruction may be stented to relieve the immediate indication for surgery. Patients can then be prepared for an elective procedure, allowing the opportunity to medically optimize patients with significant comorbidities, to complete a full colonoscopy, and to decompress a distended colon, all of which should produce a better overall outcome [47]. In addition, patients, who may have needed a large incision and a colostomy if emergency surgery was done, may now be candidates for a minimally invasive approach and a primary anastomosis [48].

Clearly, there are many potential benefits to colonic stenting for LBOs as outlined above. Complications of stents include technical failure, stent migration, re-obstruction, and perforation. Of these complications, perforation is the most concerning as it can lead to an immediate worsening of the clinical situation. In a systematic review of the literature, Watt et al. reported a wide range of perforations reported in the literature (0–83%) with a median of 4.5% [49]. Perforations can either be immediate, often from the guidewire, or delayed. While perforation is most likely at the site of the obstruction, overdistension of an already dilated colon can cause perforation in the more proximal colon [50]. Therefore, judicious use of air insufflation is important while inserting the stent. Perforation is also more likely with the use of balloon dilation, which causes a rapid expansion of the strictured area, and should be avoided. Instead, the strictured area should slowly dilate through the forces of the self-expanding stent [51, 52]. Delayed perforations are more common with stents that are placed for palliation as these stents are in for a prolonged period [53]. This is particularly true of stents across acute angles that can erode over time. More recently, several studies suggest a high rate of stent perforations in patients who are receiving bevacizumab for treatment of metastatic disease [53, 54]. Therefore, when bevacizumab is being considered as part of the treatment plan, stents should be used cautiously, and surgery to relieve the obstruction should be considered [52].

While full-thickness perforation can result in immediate septic decompensation and is usually clinically evident, several studies have noted silent perforations at the time of surgery as well. In the setting of potentially curable cancer, these perforations could negatively impact cancer control [55, 56] and remain a major concern with the use of colonic stents [52].

Technique

The majority of the literature on colonic stenting focuses on obstruction secondary to left-sided colon cancer. These lesions tend to be very focal and often quite short. Classically, they will resemble an "apple core" or a "napkin ring" on a barium enema. Conceptually, these tumors seem the most amenable to colonic stenting and probably have the highest rate of technical success. Pre-procedural imaging, such as a water-soluble CE or a CT scan with rectal contrast, can be helpful in delineating the anatomy and assessing the degree of obstruction. In the setting of complete obstruction, when no contrast passes, the probability of success diminishes and the potential for complications may increase [53]. When even a small amount of contrast passes through the lesion, the likelihood of passing a wire should also increase, which is the first important step in successful deployment of a stent (Figure 40-12).

SEMS have been placed using fluoroscopic guidance alone or with a combination of endoscopy and fluoroscopy [57]. It is prudent to administer some distal enemas to evacuate distal feces to facilitate placement [52]. Pre-procedural antibiotics are not routinely indicated. The colonoscope can then be passed to the lesion and the area inspected. Contrast can then be injected to outline the extent of the lesion and to estimate its length and contour. A guidewire is then passed through the strictured area and the location confirmed using fluoroscopy (Figure 40-13). Once the guidewire is in place, two colonic stent systems have been described.

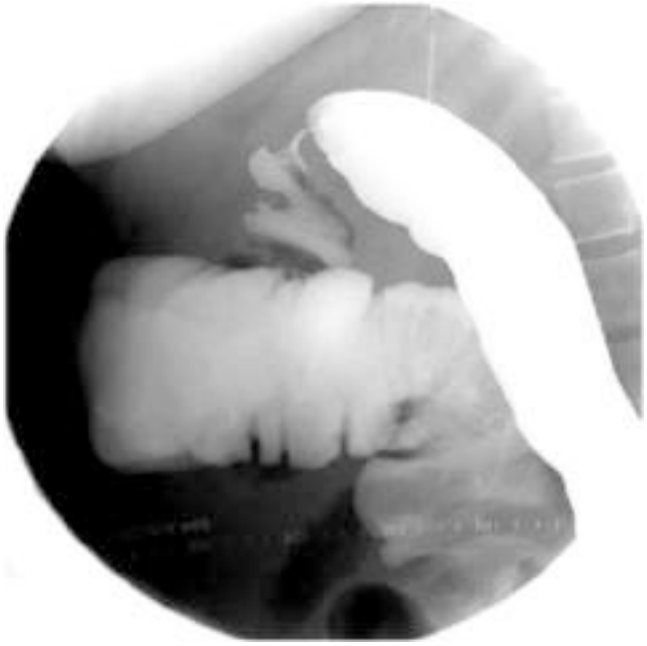

FIGURE 40-12. Water-soluble contrast enema in a patient with LBO demonstrating narrow channel and apple-core lesion with proximal colon dilatation.

FIGURE 40-13. Fluoroscopy demonstrating .successful passage of guidewire across stricture.

The "through-the-scope" (TTS) system will allow the stent to be placed through the therapeutic channel of the colonoscope and then over the wire. Alternatively, if the stent will not fit through the channel, the stent can be placed entirely over the wire using the "over-the-wire" (OTW) technique. Ideally, the stent should be deployed with at least 2 cm of overlap above and below the stricture [52] (Figure 40-14).

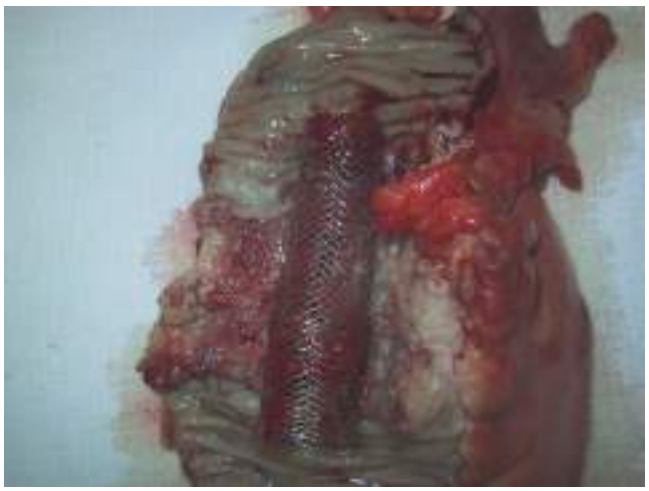

FIGURE 40-14. Gross picture of stent across tumor with appropriate overlap above and below tumor.

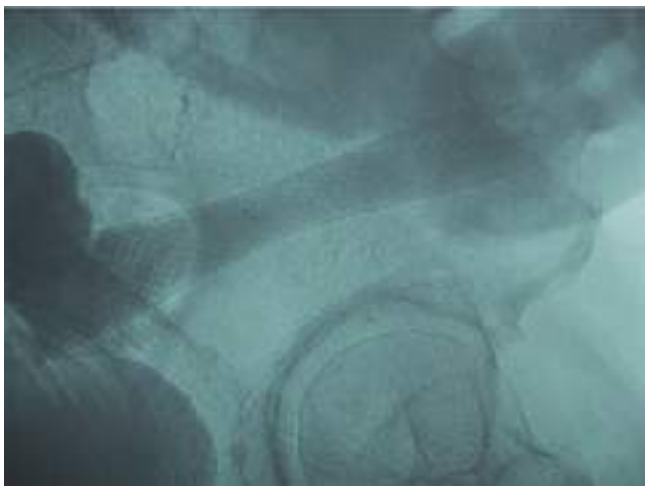

FIGURE 40-15. Radiograph demonstrating excellent positioning of the stent across stricture with the characteristic waisting at mid-stent.

To prevent re-obstruction, the diameter should be 24 mm at the mid-stent position [52]. Balloon dilation is associated with higher complications and should be avoided [52]. Upon completion, plain films can be obtained to confirm stent location, demonstrating appropriate waisting at mid-stent, and to ensure colonic decompression (Figure 40-15).

Once successfully deployed, the obstruction should resolve over the next few days allowing patient evaluation to be completed. Plain films can be obtained to confirm stent location and to ensure colonic decompression. For patients with resectable tumors, definitive surgery is best done within 7–14 day of stent placement [52].

Results

"Bridge to Surgery"

Most of the literature report technical success rates of approximately 90% for SEMS. In a pooled analysis of 1198 patients, which included 54 studies, Sebastian et al. reported an overall technical success rate of 93%. Interestingly, the clinical success for palliative stents was 91% but was only 71% for when used as a "bridge to surgery," since nearly 30% of these patients still required a stoma at the time of surgery [58]. Small et al. reported on the 10-year experience at the Mayo clinic, which included 168 patients when stents were placed for palliation and 65 as a bridge to surgery. In the preoperative group, the technical success was a very high 95%. Immediate clinical success was also quite high at 98%. However, 23% of the patients did experience a stent-related complication, including stent occlusion/migration (17%) and perforation (5%). Of the 65 preoperative patients, 4 (6%) required emergency surgery. A primary anastomosis was done in 39 (60%) of the patients, but 26 patients (40%) still required a stoma despite preoperative stenting to alleviate this need. Five risk factors were identified associated with stent complications, including male gender, complete colonic occlusion, mid-stent diameter less than 22 mm, balloon dilation prior to stent placement, and placement of the stent by an interventionalist not familiar with pancreaticobiliary procedures [53].

Unfortunately, most studies on colonic stents are single-institution retrospective reviews and are therefore subject to the usual biases associated with these reports. Most importantly, the exact "definition" of a LBO is often lacking. Are these patients completed obstructed, presenting with massive colonic distension and perhaps signs of toxicity? Or are many of the patients having mild symptoms from a tumor that a colonoscope could not traverse? Patients in the latter category are more likely to have technical success and fewer complications compared with patients in the former group, as shown in the Mayo clinic experience [53]. Direct comparisons between studies and, more importantly, comparisons with surgery, which is likely to have patients that are completely obstructed with signs of toxicity, can therefore be challenging.

The first randomized, prospective study comparing an endolaparoscopic approach (SEMS followed by a laparoscopic resection) vs. conventional open surgery for patients with left-sided colonic obstruction was reported in 2009 by Cheung and colleagues [48]. In this study, technical and clinical success was 83%. Importantly, no stent-related complications were reported, which is unusual. The primary endpoint was a successful one-stage operation. In this series, 67% of the patients in the endolaparoscopic arm had a successful one-stage procedure, compared with only 38% in the conventional arm. Furthermore, all the stomas in the endolaparoscopic group were reversed, whereas six patients in the conventional group had a permanent stoma. They concluded that preoperative stenting allowed for a minimally invasive approach and was more likely to leave patients' stoma free both in the short and long term. Key to the success was the lack of stent-related perforation or other complications.

More recently, there have been two multicentered, prospective, randomized trials looking at immediate emergency surgery compared with stenting followed by surgery for curable, obstructing colon cancer (one from France and one from the Netherlands) [55, 56]. The technical successes in these studies were both relatively low, at 53% and 70%, respectively. Furthermore, in both studies, the final stoma rates did not differ between the surgery and stenting arms. Of particular concern were the rates of perforation, reported at 19% in the Netherlands study. In both studies, there were a number of "silent" perforations that were not clinically identified but were discovered at the time of surgery and pathological evaluation. While the significance of these perforations is unclear, there is certainly concern about the long-term oncologic outcomes in these patients with potentially curable cancer [52]. Because of these issues, both of these studies were prematurely closed due to safety concerns with colonic stents. The major criticism of these studies is the low success rate of stent placement and the complications associated with these stents, which could be related to the experience of the operator or, more likely, to the patients having a complete LBO in these prospective series.

Finally, in a recent meta-analysis of three randomized trials, stents were less effective than surgery in relieving the bowel obstruction (53% vs. 99%) without improvement in overall morbidity, mortality, and permanent stoma rates (47% vs. 52%). While stents did offer some initial advantages, such as lower initial stoma placement, overall stents did not seem to offer the benefit that was once hoped. Appropriately, the authors did caution that these studies are underpowered and thus more studies are necessary to properly answer these questions [59]. Because of these concerns, current European guidelines published in 2014, which have been endorsed by the American Society of Gastrointestinal Endoscopy (ASGE), only recommend SEMS for patients with a nonmetastatic large malignant bowel obstruction who are poor surgical candidates and need medical optimization. According to ASGE, routine use of SEMS for this clinical scenario is no longer advocated [52].

Palliation

Colonic stenting may be appropriate for patients presenting with inoperable cancer, either from colorectal cancer or another malignancy, causing a LBO. This is particularly true of patients with short life expectancy due to the advanced disease [52]. Many of these patients can be successfully palliated without the need for a stoma or a major

abdominal procedure. Stents are more likely to re-obstruct over time compared with surgery but can often be treated with additional procedures, including a second stent [52, 53]. Choi et al. recently reported on 83 patients treated with colonic stents for palliative purposes. Initial technical and clinical success was reported to be 100 and 94%. However, short-term and long-term complications were noted in 11% and 31% of the patients, respectively. These complications included re-obstruction (22%), stent migration (11%), and perforation (6%). Not surprisingly, they demonstrated that stent complications accumulate over time and that at 6 months nearly 40% of the patients have had some complication related to the stent. Furthermore, as in previous studies, Choi and colleagues also concluded that complications were greater in patients with complete obstruction. Despite these problems, however, only 11 of the 83 patients ultimately required a colostomy for palliation [60]. Small et al. [53] reported similar results in the Mayo experience when stents were placed for palliation in 168 patients. In this series, initial clinical success was very high. At 6 months, however, 25% of the patients had additional obstructive problems requiring intervention. Ultimately, 35 patients (21%) did require surgery, but the majority of patients remained stoma-free until death. Success seems to be greater in patients with primary colorectal cancer, in comparison to extracolonic tumors causing extrinsic compression, where stents have been less effective [52, 61]. In conclusion, palliative stents provide an alternative for patients with advanced disease and a short life expectancy. For patients with longer life expectancy, palliative stents are likely to cause long-term complications. Under these circumstances, therefore, surgical palliation may be more appropriate.

Benign Disease and Right-Sided Lesions

While malignancy is the most likely cause of colonic obstruction, there are benign diseases, such as diverticular disease and Crohn's disease, which can also cause a LBO. The role of stenting under these circumstances remains unclear. These strictures tend to be long and tortuous, making for a challenging stenting procedure. While still possible, complications seem to be higher and results less promising [62, 63]. Long-term uses of stents under these conditions are often associated with perforations, fistula, and pain and should be avoided. Therefore, stenting for benign disease is currently not recommended [52].

Most of the literature on stenting is with left-sided lesions. While there are reports on stenting right-sided obstructions, the rationale for this approach is less clear. Since many obstructions proximal to the splenic flexure can be managed with a primary anastomosis, stents are not likely to improve the clinical picture and therefore are not routinely advocated. However, under situations when surgery is not an option, right-sided stents have been successfully deployed [64].

Resection

Emergent surgery and resection for a left-sided colonic obstruction was first introduced by Wangensteen [65]. As mentioned previously, in the setting of overwhelming sepsis, diffuse peritonitis, free perforation, or a closed-loop obstruction with ischemia, emergent exploration and resection, when feasible, are indicated and often necessary. A traditional three-stage operation is rarely performed but may be necessary in the setting of diffuse carcinomatosis, non-resectable inflammatory phlegmon or cancer with dense adherence to critical pelvic or retroperitoneal structures, or inexperience of the surgical team. Chereau et al. [66] presented their results on the surgical management of 83 patients presenting with LBO secondary to colorectal cancer. Sixty-one patients had an initial colostomy with an intention of performing a resection after recovery. Subsequent elective resection and primary anastomosis were performed in 45 (74%) patients with minimal morbidity and mortality. Despite these encouraging findings, a two-stage operation, with either resection of the obstructed segment and primary anastomosis with or without a proximal diversion or resection and Hartmann's procedure, is more commonly performed [1]. In the non-emergent setting, the choice of the operation is closely associated with the condition of the patient, viability of the bowel, site of the obstruction, and skill of the operating surgeon.

The advantages of Hartmann's procedure are clear and include avoidance of an anastomosis and shorter operative times. The procedure is completed by resection of the diseased segment, end colostomy, and closure of the distal segment which is left either buried in the subcutaneous tissue, intraperitoneal, or opened at the skin level as a mucous fistula. Management of the distal stump depends on large part on the length of the stump, health of the tissues, and thickness of the abdominal wall. Previous studies have shown that 35–55% of colostomies are not reversed, either due to patient wishes or existing comorbidities precluding reversal [67–69]. Technical difficulties can complicate reversal surgery and include identification of the rectal stump, dense adhesions, anastomosis to a short rectal stump, and the need for a proximal diversion. Thus, reversal of Hartmann's procedure is associated with substantial morbidity, including anastomotic leak rates ranging from 4 to 16%, and mortality [70–75]. Minimally invasive approaches, while feasible, can be technically challenging. A systematic review of thirty-five included studies comparing conventional to laparoscopic reversal of the Hartmann procedure showed that the laparoscopic approach has a shorter hospital stay (6.9 days vs. 10.7 days), longer operative times, and decreased morbidity when

compared to the conventional surgery. Regardless of the approach, the mean time interval between reversal and Hartmann's was 7.5 months [76]. Currently, however, high-level evidence demonstrating superiority of the laparoscopic approach to conventional surgery for Hartmann's reversal is lacking. Finally, Hartmann's procedure and its subsequent reversal surgery represent a substantial cost burden. Schilling et al. [77] studied 55 patients undergoing segmental resection for perforated sigmoid diverticulitis, 13 with Hartmann's procedure, and 42 with a segmental resection and primary anastomosis. As expected, the overall expenses and reimbursement for restoration of intestinal continuity were significantly higher for those patients undergoing Hartmann's procedure.

Primary anastomosis, when feasible, should be the procedure of choice for LBO due to left-sided LBO secondary to a cancer or benign process. Variables influencing the decision to perform a primary anastomosis are multifactorial and include the degree of proximal colon dilatation, clinical condition of the patient, and operative findings, such as diffuse fecal contamination, peritonitis, cecal perforation, and synchronous proximal lesions. Lee et al. [38] performed a retrospective review of 243 patients undergoing emergent resection and primary anastomosis for obstructing colorectal cancers. Both the operative mortality and anastomotic leak rates following primary resection and anastomosis were acceptable, 8.1% and 6.1%, respectively. Other studies have shown similar results [37, 78, 79]. In a survey of 500 US-based gastrointestinal surgeons, 53% of the respondents would perform a single-stage operation for LBO in "good-risk" patients [80]. Despite a relatively poor response rate, the findings of this survey and others are consistent and suggest that, if feasible, the majority of surgeons favor a single-stage resection for LBO [81, 82]. In summary, in carefully selected and hemodynamically stable patients, a single-stage operation is well tolerated and should be considered when technically feasible. Finally, the decision to perform a proximal diversion at the time of resection is up to the discretion of the surgeon and is multifactorial. Important considerations are the clinical condition of the patient, status of the bowel, and degree of contamination of the surrounding tissues. This decision is not without consequences, and the benefits must be balanced against the emotional and financial burden of a stoma and the associated morbidity of its reversal.

A subtotal colectomy with a primary anastomosis is a viable option in select patients presenting with a left-sided LBO. Accepted indications for subtotal colectomy include cecal perforation, synchronous proximal lesion, ischemia of the proximal colon, or serosal injury of the cecum. The SCOTIA study group [83] conducted a randomized trial comparing segmental resection with intraoperative lavage to subtotal colectomy in patients with a malignant left-sided LBO. They reported comparable morbidity and mortality, but at 4 months the number of bowel movements was significantly higher in the subtotal group. Furthermore, following an ileosigmoid or ileorectal anastomosis, there appears to be a clear impact on the postoperative quality of life compared to those undergoing a segmental resection [84]. In general, the decision to perform a subtotal colectomy depends on the overall condition of the patient, operative findings, continence status, and comorbidities.

On-Table Colonic Lavage

On-table colonic lavage is another alternative that may allow a single-staged primary surgery for patients presenting with colonic obstruction. While there have been many reports questioning the need for routine bowel preparations prior to colon surgery, it is important to note that these studies were all done for elective colon resections when the bowel is decompressed [85]. The obstructed colon, with the associated distension and fecal loading [86], represents a different clinical situation with an increased rate of complications if a primary anastomosis is performed. In situations, therefore, when patients are clinically stable, an on-table colonic lavage may successfully relieve the colonic distension and fecal loading, allowing for a primary anastomosis.

Technique

On-table colonic lavage is best accomplished once the obstructing lesion has been resected. At this point, the surgeon should assess the surgical environment and as long as the patient remains clinically stable may proceed with the lavage. Mobilizations of both flexures are done to facilitate the procedure. The left colon needs to be fully mobilized so that the colon can easily extend beyond the abdominal cavity. An appendectomy is performed and a large-bore catheter inserted into the cecum and secured with a purse string. Alternatively, if the cecum is distended and thin walled, the catheter can be inserted in the terminal ileum with a purse string. Sterile-corrugated tubing is then secured to the descending colon using an umbilical tape. The tubing is draped over the bed into a waste container (Figure 40-16). Saline can then be used to irrigate the colon until it is clear which usually requires approximately 3–6 L. Initially, flow can be slow due to the solid stool and the surgeon may need to milk some of these contents through the tubing. However, once the stool becomes more liquid, the cleansing process flows smoothly. Upon completion of this procedure, the colon is often significantly decompressed and an anastomosis can be performed. Prior to the anastomosis, the colon should be carefully inspected for any injuries that may have occurred due to the colonic distension or from the procedure itself. An end-to-end anastomosis can be done, but, if there is

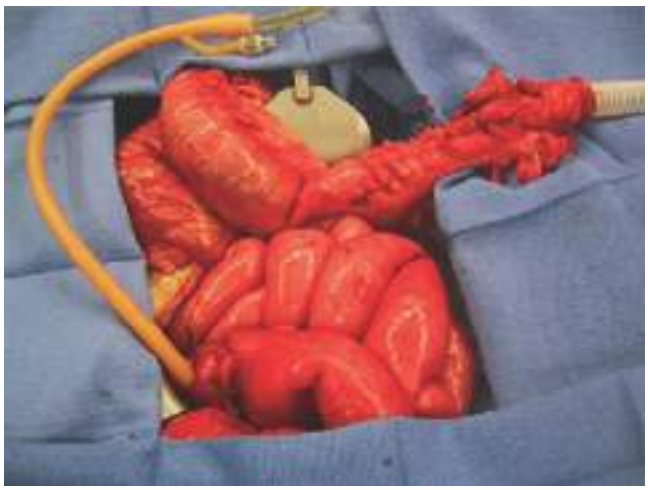

FIGURE 40-16. Technique for on-table lavage prior to creation of the anastomosis following a left colectomy for LBO. Sterile-corrugated tubing is secured to the descending colon using umbilical tape. Both the hepatic and splenic flexures have been mobilized to aid in the evacuation.

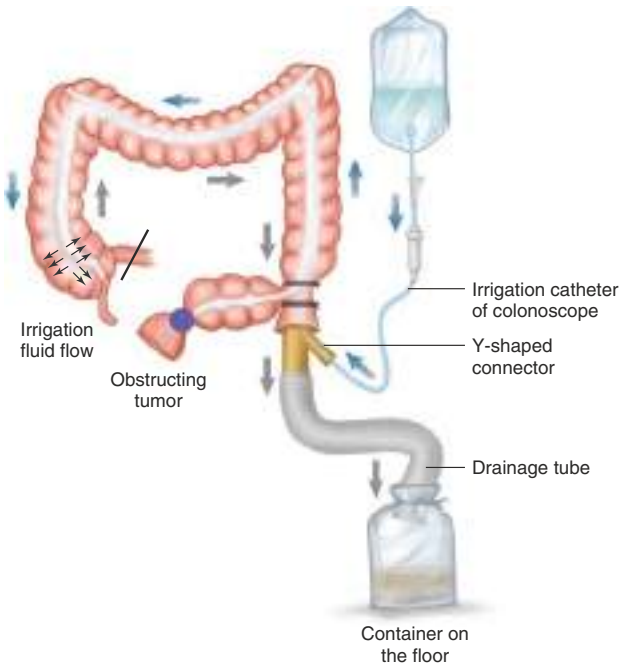

FIGURE 40-17. The new device for intraoperative colonic lavage, with an irrigation catheter or colonoscope entering the proximal colon through the Y-shaped connector up to the cecum. Flow of prewarmed saline solution irrigation (*clear arrow*). Flow back of feces (*black arrow*).

a significant caliber mismatch between the colon and the Hartmann pouch, an end-to-side procedure is preferred.

More recently, an alternative technique has been described using a Y-connector and a long colonic tube [87, 88]. The tube is placed through the descending colon just proximal to the obstructing lesion and passed into the cecum. The warmed saline can then be administered through the tubing, and fluid is evacuated out the other side of the Y-connector (Figure 40-17). By doing this, the surgeons can avoid an appendectomy and perhaps some infectious complications. Reportedly, this technique is faster and less likely to have associated contamination, although this has not been formally studied.

Results

Several studies have reported successful primary resections with acceptable rates of anastomotic leak. Murray et al. reported the early experience at Lahey Clinic. In this series, 21 patients had an on-table colonic lavage with no anastomotic leaks and only three wound infections [89]. Forloni et al. reviewed his experience with intraoperative colonic lavage in the setting of a left-sided bowel obstruction and also reported no leaks in 61 patients. He reviewed the literature at that time and reported leak rates that ranged from 0 to 13% in selected studies [90]. More recently, Jung and colleagues reported on 171 patients treated with intraoperative colonic lavage and a primary anastomosis over a 12-year period. The rate of anastomotic leakage was 5%, which was nearly exactly the rate for non-obstructed patients having the same procedure during that time period. Similarly, the wound infection rate of 3.5% was not different than the elective cases. These results are particularly good given that the patients in the obstructed arm were more ill and more likely to have an emergent operation [88] compared with the non-obstructed patients.

In 1995 a multicentered, prospective trial comparing subtotal colectomy with intraoperative colonic lavage with a segmental colectomy reported on 91 total patients. The anastomotic leak rate was 9% for the subtotal colectomy group compared with 5% for the colonic lavage group, but this was not statistically significant [83]. However, functional outcomes were significantly better for patients having a segmental resection, with regard to bowel frequency and the ultimate need for a permanent stoma. The authors concluded that intraoperative colonic lavage with a segmental resection was safe and the preferred technique when compared with subtotal colectomy [83]. In a similar nonrandomized retrospective review, Torralba et al. compared their experience with intraoperative lavage and subtotal colectomy. More complications were associated with the colonic lavage (41% vs. 14%), the majority of which were infectious in nature. Functional outcomes, however, appeared to be similar. He concluded that subtotal colectomy is preferred when part of the sigmoid colon can be preserved. However, in the setting of distal sigmoid or rectosigmoid obstruction or when patients have anal incontinence, intraoperative colonic lavage may be preferred [91].

While many surgeons believe the lavage is critical to the procedure, there are several reports of one-stage resections

of obstructing left-sided lesions with limited colonic decompression without colonic lavage [92–94]. In these series, the stricture is resected and the left colon decompressed of most of the solid stool. The rest of the colon, however, is not fully irrigated as described above. In these series, the leak rates ranged from 1.7 to 4.1%. These studies suggest the possibility that decompression and not cleansing are the major contributors to success. However, without randomized trials, it is very difficult to come to firm conclusions.

More recently, a randomized, prospective trial comparing colonic stents with intraoperative colonic lavage was reported [95]. The authors hypothesized that complications between the two groups would be similar, but, given the concerns of perforation with colonic stents, intraoperative colonic lavage would be the preferred technique. However, after just 28 patients, the trail was stopped due to the high rate of anastomotic leakage in the lavage cohort (30%) compared with the stent group (0%). In addition, the long-term cancer survival between these two small groups was similar.

In summary, intraoperative colonic lavage is an acceptable alternative to managing a LBO. The major disadvantages include the additional time to perform, which can be as much as 60 min, and the additional dissection it often requires [91]. Anastomotic leak rates seem acceptable but, given the results of the most recent randomized trial [95], may need further prospective studies. The major advantage is the ability to do an anastomosis while preserving colon and colonic function. Until we fully understand the potential disadvantages of colonic stents on oncologic outcomes, intraoperative colonic lavage remains a viable option for surgeons.

Special Circumstances

Volvulus

Sigmoid Volvulus

Presentation and Diagnosis

Patients with sigmoid volvulus present with abdominal pain, distension, and a paucity of bowel movements. Emesis is rare and usually represents a chronic process with associated small bowel distension. A history is often difficult to obtain as most patients presenting with sigmoid volvulus are infirm and residents of long-term care facilities. Physical exam findings include a distended and tympanitic abdomen. If peritonitis is present, then ischemia and/or gangrene of the colon must be assumed and further diagnostic testing is unnecessary. Emergent exploration and resection, with or without a stoma, are recommended. In the non-emergent setting, an abdominal radiograph is usually the first diagnostic test obtained. Plain radiographs are diagnostic for a sigmoid volvulus in 57–90% of patients [18, 21, 96, 97]. However, the classic "coffee-bean" or "bent inner tube" sign is present in <60% of cases [18, 98] (Figure 40-6). Given the ease with which it can be obtained and the wealth of additional information provided, CT scan may be supplanting plain film as the diagnostic study of choice in suspected volvulus. Furthermore, in the presence of coexisting proximal colon and/or small bowel distension creating a diagnostic dilemma, CT scan provides valuable diagnostic information. A primary finding on CT scan is the presence of a whirl sign in the mesentery. However, its presence is not pathognomonic for sigmoid volvulus. The sensitivity of the whirl sign in the setting of sigmoid volvulus is variable ranging from 57 to 100% [99, 100]. While its absence does not exclude the presence of a volvulus, the location of the whirl sign, right versus mid-left, may differentiate a sigmoid from a cecal volvulus [100]. If the diagnosis remains in doubt, a CE may confirm the presence of a sigmoid volvulus by a bird's beak deformity on the left side compared to a right upper quadrant location for a cecal volvulus [25–27].

Treatment

Immediate reduction and prevention of recurrences are the tenets of management of sigmoid volvulus. Endoscopic reduction and decompression is the initial treatment of choice in uncomplicated sigmoid volvulus [18]. While a rigid proctoscope is effective in reducing sigmoid volvulus and may be more readily available in emergent and rural settings, flexible endoscopy is preferred due to its overall safety and ability to inspect the mucosa of the involved segment for ischemia [101]. The characteristic finding on endoscopy includes a "pinwheel" configuration of the mucosa (Figure 40-18). Detorsion and decompression is successful in 60–80% of cases [24]. A long flexible tube, such as a small-caliber chest tube or nasogastric tube, may be left in place to allow for continued decompression and to prevent retorsion. However, evidence demonstrating safety and efficacy of this maneuver is lacking.

Elective resection, preferably during the same hospital setting, following successful reduction is strongly recommended as endoscopic decompression alone has recurrence rates ranging from 20 to 90% [18]. Turan et al. [101] reported on 81 patients that presented with sigmoid volvulus and underwent endoscopic detorsion. Twenty of the 39 patients nonoperatively decompressed did not agree to an elective resection. The majority were lost to follow-up but 3 out of the 20 patients presented with a recurrence requiring surgery. A retrospective study of a 7 hospital system in Metropolitan Minnesota reported on the presentation and management of colonic volvulus in 103 cases of volvulus in 92 patients [21]. Of the 21 patients with sigmoid volvulus treated nonoperatively, 47.6% were readmitted with a recurrence. Of those

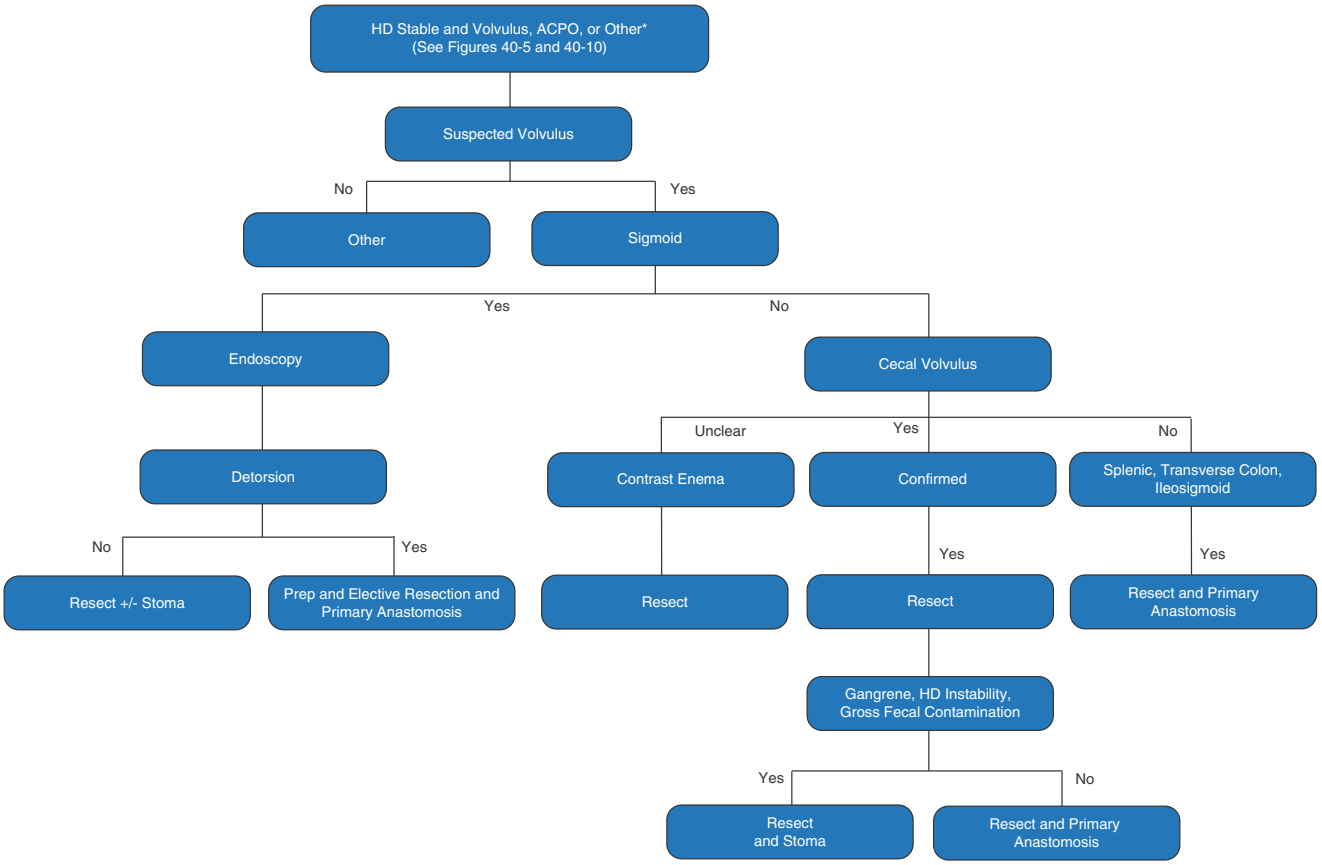

FIGURE 40-18. Proposed algorithm for LBO secondary to a volvulus in a stable patient.

admitted with a recurrence, 64% ended up undergoing surgery. Bruzzi et al. [102] reported on their experience of 65 patients treated for sigmoid volvulus over a 10-year period. Nonsurgical reduction was successful in 95% of patients. Recurrence after initial decompression was 67% at a median follow-up of 5 years. Hougaard et al. [103] reviewed their experience with 41 patients presenting with sigmoid volvulus. Fourteen patients were treated with decompression alone with a recurrence rate of 82% and a 1-year mortality of 50%. The high recurrence rate after detorsion alone coupled with the high 30-day mortality of emergent resection, 43% vs. 6% [24, 96, 97, 103], favor elective resection during the same hospitalization for most eligible patients. In preparation for elective resection, a colonoscopy should be performed to evaluate for proximal pathology.

The standard procedure includes a sigmoid resection and primary anastomosis accomplished using either open or minimally invasive techniques [104, 105]. Due to the redundancy of the colon and elongated and narrowed mesentery of the sigmoid colon, an open approach, utilizing a minilaparotomy incision, is usually all that is necessary [106, 107]. Recurrences are rare when sigmoidectomy is performed in an elective setting with a primary anastomosis [102, 108, 109]. Recurrence rates increase in the presence of coexisting megacolon and diffuse colonic dysmotility. Chung et al. [110] reported on 35 patients treated for sigmoid volvulus. Six patients had a recurrence following sigmoid colectomy with coexisting megacolon and megarectum. Morrissey and colleagues [111] reviewed their single-institution experience with recurrence rates following sigmoidectomy in 29 patients with sigmoid volvulus. Their review included all procedures, including Hartmann's and laparotomy with non-resection. They reported a recurrence rate of 36% for sigmoidectomy and primary anastomosis. The most consistent variable associated with recurrence was the degree of colonic involvement. Patients with disease limited to the sigmoid colon had a 6% recurrence rate compared to 82% for those associated with megacolon [18]. Enthusiasm for performing a subtotal colectomy in the setting of megacolon and presumed dysmotility must be tempered against the morbidity of a radical surgery in a frail and often institutionalized patient population.

A number of non-resectional techniques have been proposed for the treatment of sigmoid volvulus. A common

element among all these procedures is fixation of the colon to the abdominal wall for prevention of recurrence. These techniques include extraperitoneal sigmoidopexy [112], endoscopic sigmoidopexy with or without tube fixation [113], mesenteric fixation techniques [114, 115], parallel colopexy [116], tube sigmoidostomy [117], and percutaneous endoscopic colostomy [118–120]. The majority of reports in the literature are small single-institution case series with no randomized trials demonstrating direct head-to-head comparisons. Lack of strong supporting evidence for nonresectional techniques and improved perioperative management techniques favors resection and primary anastomosis as the procedure of choice.

If endoscopic decompression is unsuccessful or if there is concern for gangrene of the colon, emergent exploratory laparotomy and sigmoid resection are indicated. Exploration is typically through a midline incision with open reduction of the volvulized sigmoid. In the presence of gangrene, care must be taken to control the vascular pedicle prior to reduction in order to avoid severe hemodynamic instability. If resection is considered, the decision to perform a primary anastomosis is based on common surgical principles: hemodynamic stability, nutrition status, adequacy of blood supply, presence of tension, or degree and characteristics of contamination. If any of these factors are present, then Hartmann's procedure should be contemplated. In the emergent setting, timely assessment of the patient for proper location of the stoma is not feasible. This problem is compounded by a dilated colon mandating creation of a larger than usual trephine. Consequently, these patients are at increased risk of parastomal hernias [24].

Emergent surgery for sigmoid volvulus is associated with significant morbidity and mortality and should be avoided if possible. Kuzu et al. [121] reported on 106 patients that underwent emergent resection for sigmoid volvulus over an 8-year period. Fifty-seven cases had a primary anastomosis. The overall mortality rate was 6.6%, and this rate increased to 11% if the colon was ischemic or gangrenous. In a Veterans Affairs study [122] designed to review the outcomes of emergent treatment for sigmoid volvulus, the mortality rate was 24% for those undergoing emergent surgery versus 6% for elective resection following endoscopic decompression. Atamanalp et al. [109] reported on their single-center experience for the treatment of 686 patients with sigmoid volvulus over a 46-year period. Emergent surgery was performed in 447 patients with a morbidity and mortality rate of 35% and 16%, respectively, compared to 12.5% and 0%, respectively, for elective surgery. Despite a trend toward increased complication and mortality rates, the majority of studies support sigmoid resection and primary anastomosis, even in the emergent setting. Nevertheless, the surgeon must balance the risks of an anastomosis against the increased morbidity and decreased quality of life of a stoma as well as the risks of a second surgery.

Sigmoid volvulus is the most common cause of intestinal obstruction in pregnancy worldwide occurring at rates of 3.1–12.5% [123]. Despite its association with intestinal obstruction during pregnancy, its incidence is rare presenting a diagnostic and treatment challenge [18]. The diagnostic delay is often compounded by reluctance of physicians in obtaining radiographic imaging out of concern for harm to the developing fetus. The delay in diagnosis can increase the risk for gangrene and septic complications [124]. As with nonpregnant patient, flexible sigmoidoscopy is the diagnostic and treatment modality of choice. Endoscopic detorsion should be undertaken in the first trimester with elective resection delayed until the second trimester, when the risk to the fetus is diminished. During the third trimester, endoscopic detorsion should be followed by close observation allowing for completion of fetal maturity, followed by delivery, and then elective resection [24]. At any time during the initial presentation or during the observation period, if signs of gangrene and peritonitis are present, then exploratory laparotomy and Hartmann's procedure are indicated.

Cecal Volvulus

Presentation and Diagnosis

The clinical presentation of cecal volvulus is directly linked to the acuity of the presentation and the type of volvulus. Cecal volvulus involves the axial clockwise rotation of the colon around its mesentery. Findings such as abdominal distension, pain, nausea, vomiting, and obstipation can mimic signs and symptoms of small bowel obstruction. If the volvulus is allowed to progress to strangulation, then peritonitis and systemic sepsis will ensue. Diagnosis is first suspected by the classic appearance of a dilated colon in the shape of a "coffee bean" with the apex pointing to the left upper quadrant (Figure 40-7). This classic radiographic finding, however, is present in less than 20% of cases [19]. If the diagnosis is in question, a CE can provide clarity by demonstrating the characteristic column of contrast ending in a "bird beak," the sight of the torsion, in the right upper quadrant. If CE is unavailable or the diagnosis remains in question, a CT scan may be helpful in establishing the diagnosis. CT may reveal the coffee-bean or bird beak signs, as well as the presence and location of the whirl sign [100]. Due to its ready availability, CT is the first imaging test ordered, on initial presentation, often obviating the need for further imaging. Conversely, in cecal bascule there is no axial twist but an anterior-superior folding of the cecum over the proximal ascending colon, without rotation (Figure 40-19). The cecum is often located in the right upper quadrant on imaging [125]. There is no axial twist of the mesentery and thus these patients often present in subacute fashion. Patients present with intermittent nausea, vomiting, and abdominal pain with

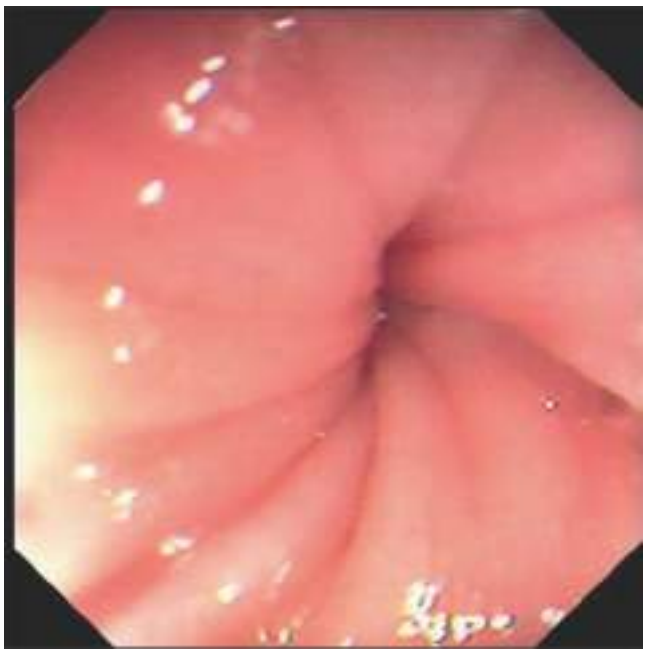

FIGURE 40-19. Classic endoscopic "pinwheel" appearance of a sigmoid volvulus.

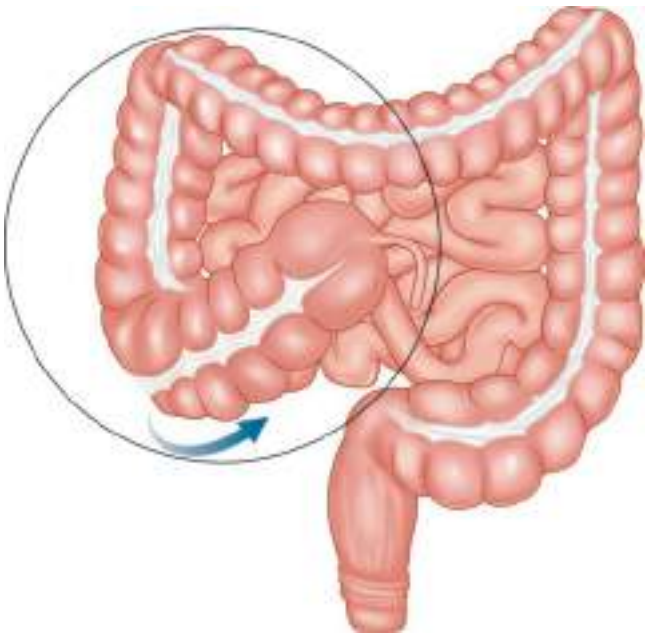

FIGURE 40-20. Illustration of cecal bascule demonstrating the anterior-superior folding of the mobile cecum over the proximal ascending colon.

symptoms improving with passage of flatus. Typically, the symptoms are vague and chronic in nature leading to diagnostic delays.

Treatment

Endoscopic attempts at decompression of a cecal volvulus are typically unsuccessful and should not be attempted [126]. Exploratory laparotomy is the treatment of choice with the findings at exploration helping dictate the course of the operation. In the setting of a gangrenous colon, attempts should not be made to untwist the colon prior to resection due to the risk of the release of toxins and ensuing septic shock [19, 127]. Vascular control should be obtained and the nonviable segment of colon resected. In reality, anatomy of the volvulized segment precludes resection without untwisting of the segment first. It is, therefore, critical that the surgical and anesthesia team work closely together during this critical moment of the operation. The extent of hemodynamic instability, contamination, malnutrition, and comorbidities will determine the safety of a primary anastomosis following resection.

Non-resection techniques have also been described. These include untwisting only, cecopexy, and insertion of a cecostomy tube. A cecopexy is performed by developing a flap of peritoneum and affixing it to the anterior border of the right colon. A cecostomy entails insertion of a tube into the cecum for venting of air as well as to allow for a point of fixation. Detorsion of the bowel alone is associated with recurrence rates as high as 70% and should be abandoned [128]. In a study comparing different techniques for management of cecal volvulus, the morbidity, mortality, and recurrence rates of cecopexy were 15%, 10%, and 13%, respectively. The same study reported that cecostomy morbidity, mortality, and recurrence rates were even worse at 52%, 22%, and 14%, respectively [6]. Given the improved perioperative and anesthetic techniques of the modern era and the low morbidity of segmental resection, these techniques should be abandoned except in rare instances where the patients' condition and operative findings preclude a resection.

Uncommon Types

Ileosigmoid Knotting

Ileosigmoid knotting is the wrapping of the ileum around the sigmoid colon leading to obstruction (Figure 40-20) [22]. Patients with ileosigmoid knotting present with nausea, vomiting, abdominal distension, and pain. Their clinical presentation is often more dire, with associated sepsis, dehydration, acidosis, hypotension, and tachycardia. Due to its rarity, there is often a diagnostic delay leading to potentially catastrophic consequences. Imaging may suggest the diagnosis by a distended sigmoid colon on the right and distended small bowel loops on the left [23, 129]. However, these findings are not consistently present, and 70% of patients will have gangrenous bowel at surgery [19]. In general, if ileosigmoid knotting is suspected, these patients should be resuscitated and emergently explored. Four variants of the

ileosigmoid knot have been previously described and include (1) type I (most common), the ileum (active component) revolves around the sigmoid colon; (2) type II, the sigmoid colon (active component) revolves around the ileum; (3) type III, the ileocecal portion revolves around the sigmoid colon; and (4) undetermined, difficult to decipher which is the active or the passive component. Types I and II can be further classified into subtypes A and B depending on whether the torsion is clockwise or counterclockwise, respectively [130]. The intraoperative options are largely dependent on the overall condition of the patient, the anatomy of the ileosigmoid knot, the state of the bowel segments involved, and the surgeon experience. It is not uncommon that several segmental resections are required with creation of one or several anastomosis.

Splenic and Transverse Colon Volvulus

Splenic and transverse colon volvulus has rarely been reported with incidence rates ranging from 2 to 3% [19]. Risk factors include an elongated and redundant colon, narrowing of the mesenteric attachments, malfixation of the mesenteries, and constipation [131]. Chilaiditi syndrome or transposition of a loop of transverse colon between the diaphragm and the liver with an associated elongated mesentery and a hypermobile colon has also been implicated as a potential cause [132, 133]. Patients with either a transverse or splenic flexure volvulus will present with symptoms of acute or chronic LBO. Due to the rarity of its presentation, diagnosis is often delayed risking necrosis of the involved segment and increased mortality [24]. Radiographic features previously attributed to splenic and transverse colon volvulus include (1) a markedly dilated, air-filled colon with an abrupt end at the splenic flexure; (2) two widely separated fluid-filled loops, one in the cecum and the second in the transverse colon; (3) an empty descending and sigmoid colon; and (4) a characteristic beak at the splenic flexure on CE [19, 134]. A transverse colon volvulus may also present with an "inverted coffee-bean" sign in the upper abdomen [135]. Absence of these radiographic features does not exclude the diagnosis; thus, a high index of suspicion is required to avoid diagnostic delays. The treatment of splenic and transverse colon volvulus typically involves surgical exploration and resection with or without a primary anastomosis. Similar to other types of volvulus, the decision to create a stoma depends on several factors, including the overall condition of the patient and the bowel, the degree of contamination, and the feasibility of the anastomosis.

Acute Colonic Pseudo-Obstruction

Acute colonic pseudo-obstruction (ACPO) can have a varying clinical presentation depending on the duration of onset and the overall condition of the patient. Common signs and symptoms include a paucity of bowel movements and gas, severe abdominal distension, and pain [12]. Unless an incompetent ileocecal valve is present, nausea and vomiting are typically absent in the acute setting. Signs of systemic toxicity are typically absent unless gangrene and/or perforation have occurred. While in rare cases, a plain radiograph may be diagnostic; more commonly, the distinction between functional and mechanical causes of LBO requires advanced imaging. A CE and CT scan are most commonly used to distinguish between these possibilities. As discussed previously, a water-soluble CE has high sensitivity and specificity in the diagnosis of a LBO [27]. However, due to its variable availability and risk of perforation in an already compromised setting, CE has been largely replaced by CT scan as the diagnostic modality of choice in ACPO [136]. Common CT findings of ACPO include proximal colonic dilatation and a transition at or near the splenic flexure [136]. Finally, CT also allows for evaluation of mechanical causes of LBO.

The majority of patients with ACPO can be managed conservatively with bowel rest, aggressive fluid and electrolyte replacement, and elimination of offending agents, if possible (Fig. 40.21). Variable success rates have been reported using hourly position changes, including prone, left, and right lateral decubitus. However, broad implementation and overall success of these measures in the standard clinical setting is limited. In general, supportive measures alone are successful in about 70% of patients with morbidity and mortality rates of 6% and 10%, respectively [137].

When supportive measures fail, more advanced treatment options become necessary. Historically, colonoscopic decompression was the treatment of choice, usually after 3–4 days of failed supportive therapy. However, multiple prospective studies have reported on the efficacy and validated the use of neostigmine as first-line treatment in ACPO [138–141]. Valle et al. [142] performed a meta-analysis of four randomized trials reporting on the use of neostigmine in ACPO. One hundred and twenty-seven patients were included. Neostigmine effectiveness to resolve ACPO with only one dose was 89.2% versus 14.65% ($P < 0.001$, NNT = 1 [95% CI 1–2]). They concluded that neostigmine is a safe and effective option for patients failing supportive measures. Neostigmine is a reversible acetylcholinesterase inhibitor thus increasing acetylcholine and promoting intestinal activity. Optimal dose and route of administration of neostigmine are debatable. The standard dose is a 2–2.5 mg bolus administered over a 3–5-min period. The onset of action is usually 20–30 min. A repeat dose may be necessary in refractory cases [15]. Several authors have also reported on the effectiveness of continuous infusion technique in ACPO [139, 143]. Oral administration is generally not recommended due to its erratic absorption in the gastrointestinal tract. The parasympathetic overactivity attributed to

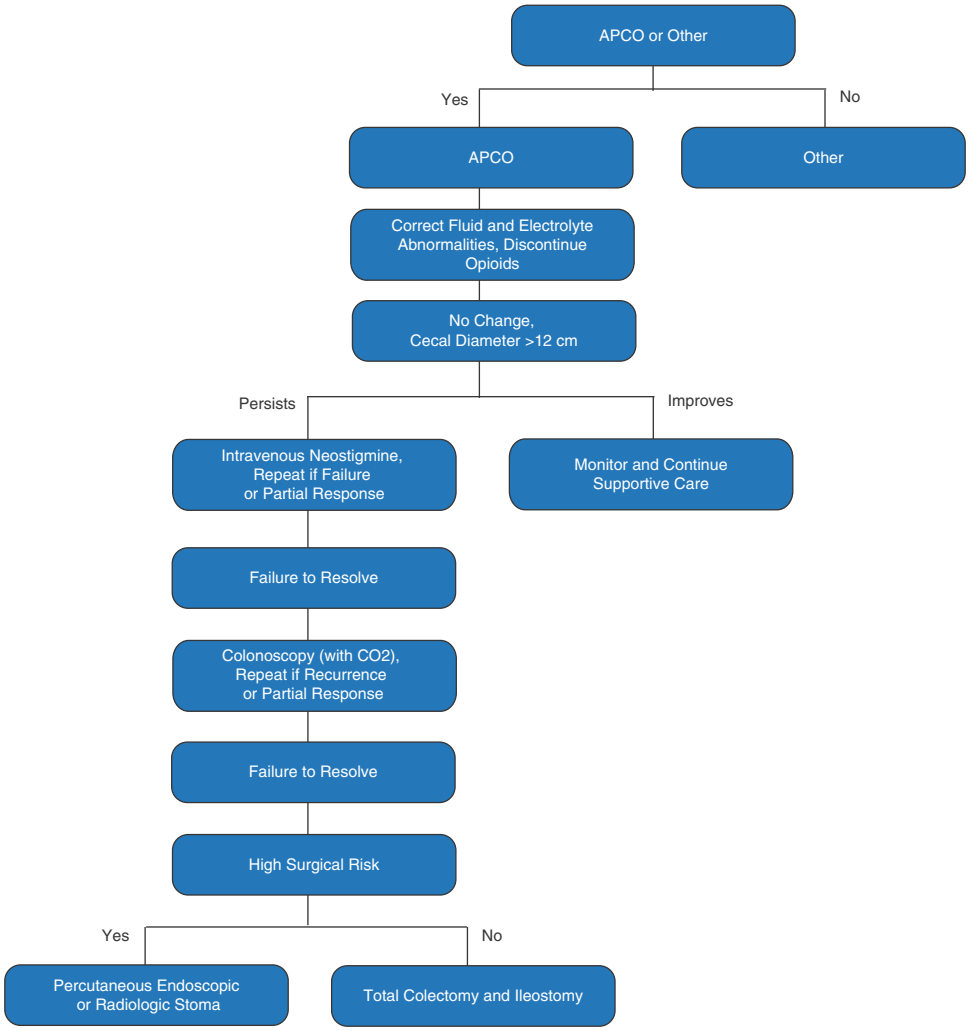

FIGURE 40-21. Proposed algorithm for LBO secondary to ACPO.

neostigmine can lead to predictable adverse events, including bradycardia, hypotension, asystole, seizures, restlessness, nausea, emesis, and abdominal cramps. Patients should be closely monitored in a telemetry unit for cardiac arrhythmia. Relative contraindications to its use include recent myocardial infarction, acidosis, asthma, chronic obstructive pulmonary edema, bradycardia, renal insufficiency, and therapy with β-blockers [12]. Recurrence rates after neostigmine administration vary from 17 to 38% [15]. Recurrences may be prevented by administration of polyethylene glycol (PEG) following decompression. Sgouros et al. [28] reported on 25 patients initially treated with neostigmine with resolution of ACPO in 88%. ACPO recurred in 33% of patients in the placebo group compared to 0% in the group receiving PEG. Recently, alternatives to neostigmine have been studied. These include pyridostigmine, a long-acting acetylcholinesterase inhibitor with less severe side effects than neostigmine, a μ-opioid receptor antagonist such as methylnaltrexone, and 5-hydroxytryptamine receptor 4 (5-HT4) agonists such as prucalopride [144–146]. While initial data appears promising for the use of these agents as alternatives to neostigmine, further studies are needed to establish efficacy and safety of these agents.

When all supportive and pharmacologic measures fail, endoscopic decompression is recommended. The efficacy of colonoscopic decompression has not been established in randomized clinical trials. The Standards of Practice Committee of the American Society for Gastrointestinal Endoscopy (ASGE) has issued guidelines for colonoscopy in ACPO [147]. In general, it is a safe procedure; however, there are important issues to consider when performing a colonoscopy in a patient with ACPO. Colonoscopy for ACPO should be

performed without administration of oral laxatives or bowel preparation and with minimal air insufflations. If available, carbon dioxide (CO_2) should be substituted for room air as it is absorbed faster with less residual distension and pain and minimal changes in pCO_2 [148, 149]. In patients undergoing colonoscopy for decompression of ACPO, sedation with benzodiazepines alone is preferred because narcotics further inhibit colonic motility. Cecal intubation is generally not necessary. Decompression at the level of the hepatic flexure is usually sufficient to achieve decompression. Some authors report on placement of a decompression tube over guidewire to allow for continued decompression [147]. Controlled trials demonstrating success of this technique are lacking; thus, its routine use cannot be advocated. Success rates of colonoscopic decompression alone vary ranging from 61 to 95% after an initial procedure and 73–88% after one or more procedures. Recurrences, however, continue to be problematic and have been reported to occur in up to 40% of patients [12, 150]. It is, therefore, not uncommon to require a second decompression after the initial successful colonoscopy. Complications, specifically perforations, while rare remain a major concern [15]. In general, the risks of colonoscopy and its high recurrence rates outweigh its benefits as a first-line treatment in the setting of ACPO. In summary, colonoscopy should be considered rescue therapy in those patients that have failed all supportive and pharmacologic measures.

Alternative endoscopic measures have also been described for the treatment of refractory ACPO. Percutaneous endoscopic colostomy (PEC) of the cecum, performed either with combined fluoroscopy and endoscopy or endoscopy alone, allows for venting of the colon and administration of antegrade enemas with PEG solution, if necessary. An introducer method using T-fasteners that secure the cecum to the abdominal wall has also been described. There are no reports establishing superiority of any single method. Reported complication rates are as high as 42% and include wound infection, bleeding, hematoma formation, perforation, granuloma, retraction, and buried bumper, making removal difficult [151]. The major advantages of PEC are avoidance of general anesthesia and the morbidity of a colectomy and an ileostomy. Conversely, the PEC is at risk of occlusion with thickened residual stool, dislodgement and diffuse peritonitis, leakage, and skin erosion. Further studies are required to define its efficacy, safety, and overall role in the management of ACPO. For now, it may be a useful option in patients with refractory ACPO who are otherwise poor surgical candidates.

Exploratory surgery with either a cecostomy or total abdominal colectomy is rarely necessary and should be reserved for patients with diffuse peritonitis or refractory ACPO. Cecostomy, via a minilaparotomy or laparoscopy, can provide effective decompression of the colon while minimizing the morbidity of a laparotomy and colectomy. While laparoscopic approaches have been described, they can be challenging in the setting of a diffusely dilated colon. Regardless of the approach, a cecostomy is often confronted with similar challenges facing PEC, including skin erosion, appliance fit and management, and catheter displacement [15]. More commonly, exploratory laparotomy is indicated with the extent of colon resection dictated by the degree of colon involvement. If feasible, enough colon remnants should be left behind to act as either a mucous fistula or a long Hartmann's pouch, left buried in the subcutaneous tissue or free intraperitoneal. Morbidity and mortality rates for surgery are significant ranging from 6 to 30%, respectively, reflecting significant underlying disease [152]. In summary, surgery should be reserved for patients who fail all conservative and endoscopic measures.

Other

Notwithstanding the etiology, the overall management of LBO is similar. Fluid and electrolyte replacement, bowel rest, radiographic imaging, and relief of the obstruction, either by surgery or endoluminal measures, remain the pillars of management of any patient presenting with a LBO. The following section discusses some of the more rare causes of LBO.

Endometriosis

Bowel obstruction is a rare outcome of ectopic endometrial glands. The rectum and sigmoid are the most common sites for implantation of ectopic endometrial implants in the gastrointestinal tract [153]. Once implanted, endometrial implants become intrinsic to the bowel wall leading to progressive luminal narrowing [154] (Figure 40-22). Typical symptoms include dyschezia, rectal bleeding, and constipation. Bowel obstruction occurs in less than 1% of patients with endometrial bowel implants [155]. On endoscopy, a submucosal mass may be seen with eccentric wall thickening and narrowed lumen (Figure 40-23). CT scan and water-soluble CE are invaluable in preoperative evaluation and allow for detailed characterization of the obstruction and surrounding organ involvement. Lesions causing LBO are typically large (>2 cm) and are unlikely to respond to medical therapy. Surgery is often necessary for definitive treatment and symptom relief. Excision of the implant only is rarely successful in the setting of large implants causing a LBO. These patients will require a segmental resection and a low or ultra-low colorectal anastomosis performed as a single- or two-stage surgery. Long-term follow-up data demonstrate improvements in dyschezia, no anastomotic recurrences, and thus no rectal bleeding [154, 156].

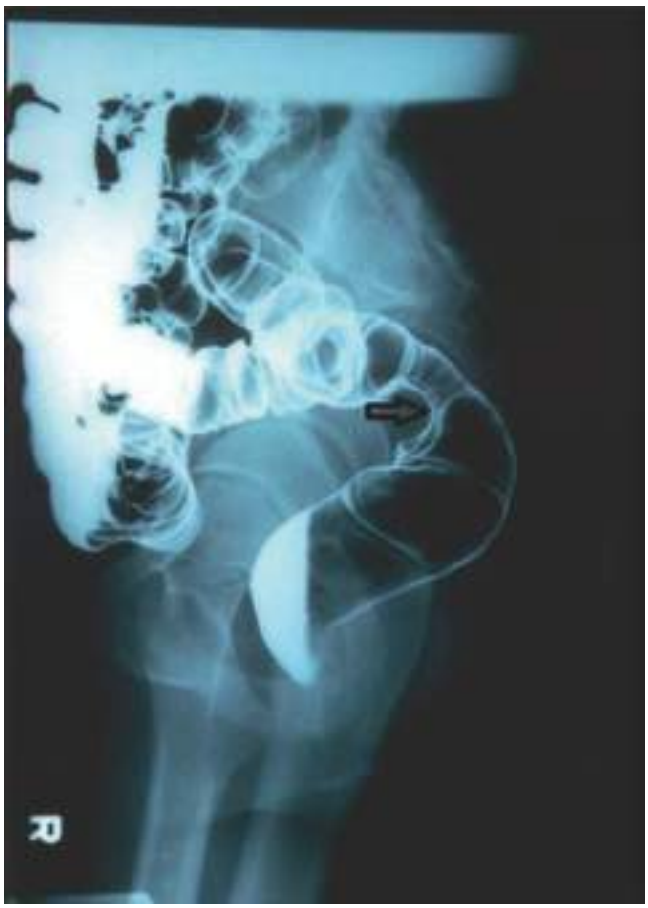

FIGURE 40-22. Water-soluble CE demonstrating smooth narrowing at rectosigmoid due to endometrioma. *Arrow* points to sight of obstruction at rectosigmoid junction.

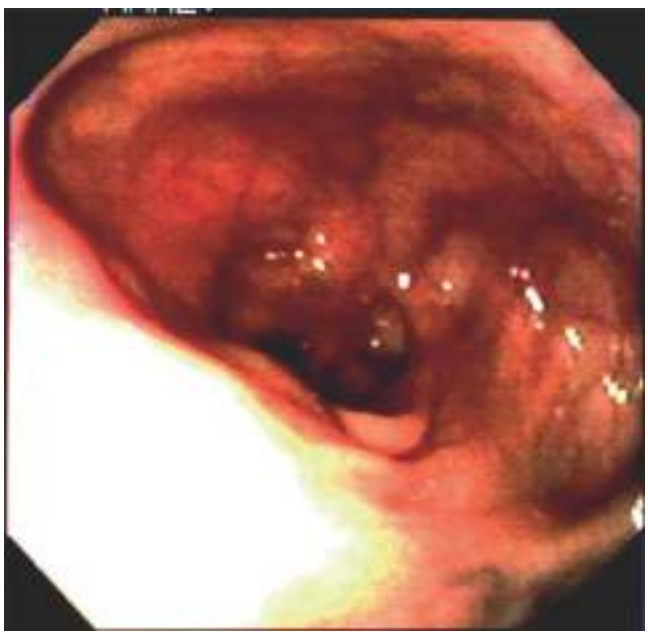

FIGURE 40-23. Endoscopic appearance of submucosal causing luminal narrowing.

Fecal Impaction

Patients with LBO due to fecal impaction, especially the infirm and mentally impaired, present with nonspecific symptoms presenting a diagnostic challenge [157]. A history of chronic constipation along with new-onset abdominal pain, pelvic pressure, and diarrhea are not uncommon findings. The diagnosis is often confirmed by performing a digital rectal examination with the hallmark findings of copious hard or clay-like stool in the rectal vault. Plain abdominal radiographs or more advanced imaging, such as CT scan, may be required if the impaction is more proximal. The traditional treatment of fecal impaction involves digital manipulation, enema instillation, or disimpaction under anesthesia. For more proximal impaction, the hydrostatic effects of a water-soluble contrast enema may be diagnostic and therapeutic. Starting a bowel maintenance program, following successful disimpaction, is critical. Laparotomy is rarely necessary and required only in the presence of complications such as stercoral ulcer perforation.

Gallstone

Gallstone ileus, a rare complication of cholelithiasis, is an infrequent cause of mechanical bowel obstruction. The gallstone usually passes through a biliary-enteric fistula and lodges most commonly in the terminal ileum and ileocecal valve. LBO due to a migrating gallstone is even a rarer event, occurring in 4% of all patients presenting with gallstone ileus [158]. Typical signs and symptoms of LBO are present in addition to pneumobilia on imaging. CT scan remains the gold standard for diagnosis. Surgical exploration and stone extraction via colotomy are often necessary. A simultaneous cholecystectomy is not recommended as these patients are typically infirm with multiple comorbidities and are at risk of significant perioperative morbidity and mortality.

Intussusception

Intussusception is a rare cause of bowel obstruction in adults with the majority occurring in the small bowel or ileocecal valve. Colocolonic intussusceptions account for 17% of confirmed cases of intussusception [159]. The majority of colonic intussusceptions are due to malignant lesions, primarily adenocarcinoma and lymphoma (Figure 40-24). Benign causes, such as lipoma, adenomas, and Peutz-Jegher polyps, have also been described. Adult intussusception presents with acute, subacute, or chronic nonspecific symptoms leading to diagnostic delays. Due to the concern over malignancy, hydrostatic reduction is usually not recommended [160]. Given the concern of underlying malignant etiology, segmental resection is often required following oncologic principles.

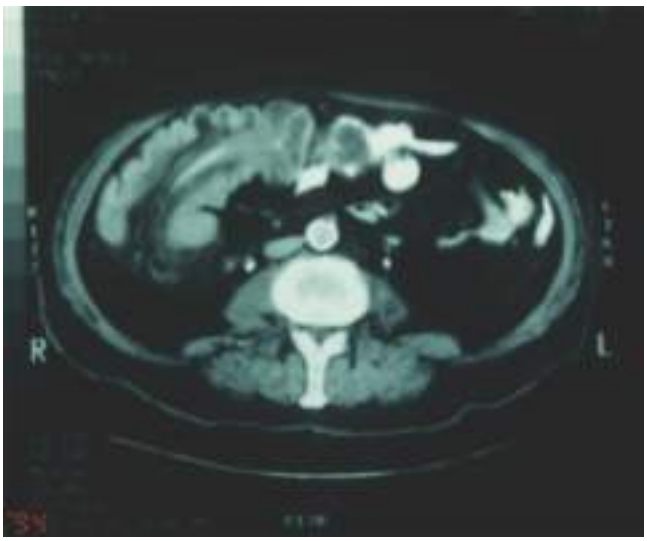

FIGURE 40-24. CT scan demonstrating colocolonic intussusceptions due to a lipoma.

Conclusions

LBO is a complicated clinical scenario that presents significant challenges to surgeons. Management will depend on many factors, including the location of the obstruction, the etiology of the obstruction, and the medical condition of the patient. There are multiple options available to treat these complicated patients, including surgery and, more recently, endoscopic procedures. Ideally, emergent situations can be converted to elective or semi-elective procedures with improved surgical morbidity and mortality. However, despite our best efforts, there will still be patients who require emergency surgery and the creation of a colostomy, which should never be considered a failure. Ultimately, the surgeon who is willing to explore different options depending on the clinical presentation is likely to achieve the best outcomes.

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41
Lower Gastrointestinal Hemorrhage

Brian R. Kann and H. David Vargas

Key Concepts

- Common etiologies of lower gastrointestinal hemorrhage include diverticular disease, angioectasia, ischemic colitis, and neoplasm.
- The primary consideration in managing the patient with acute lower gastrointestinal hemorrhage is ensuring adequate volume resuscitation.
- Patients presenting with massive lower gastrointestinal bleeding should be evaluated for upper gastrointestinal and anorectal sources via gastric lavage and anoscopy/proctoscopy.
- Screening for active bleeding via CT angiography or ^{99m}Tc-RBC scan increases the likelihood of identifying active bleeding on mesenteric angiography.
- An active bleeding source seen on mesenteric angiography can often be managed with superselective transcatheter embolization.
- The patient with a self-limited major lower gastrointestinal hemorrhage that has stopped should undergo colonoscopy for further evaluation after a mechanical bowel prep.
- In certain circumstances, colonoscopy for the evaluation of active lower gastrointestinal bleeding may be considered; if active bleeding is encountered, therapeutic options include clipping, injection, and argon plasma coagulation.
- The unstable patient with uncontrolled, unlocalized lower gastrointestinal hemorrhage should undergo a total abdominal colectomy, in most cases with an ileostomy.
- The patient with ongoing or recurrent hemorrhage from a localized lower gastrointestinal source may be managed with a targeted, segmental resection.
- Clinical pathways and predictive models may help better guide the management of patients with acute lower gastrointestinal hemorrhage, limiting unnecessary admissions and optimizing the use of resources.

Introduction

Lower gastrointestinal bleeding (LGIB) refers to the passage of visible blood from the rectum and classically originates from a source distal to the ligament of Treitz. This distressing condition challenges both the clinician and patient, as LGIB may potentially arise from anywhere along a large anatomic distribution, may result from an array of pathologic conditions, can vary widely in severity, and frequently stops spontaneously prior to definitive diagnosis. In fact, no definitive source is found in approximately 10% of all cases of LGIB [1–3].

Descriptions reported by patients and witnesses can offer a spectrum of qualifiers in regard to the volume, color, associated symptoms, and hemodynamic consequences. The patient and family often experience significant stress and emotion by the sight of any significant quantity of blood passing from the rectum and likely experience an understandable sense of urgency to seek rapid medical evaluation and treatment. Thus, it is not uncommon for patients to present to emergency departments with less serious degrees of rectal bleeding. In fact, a report from an urban medical center reviewed over 1100 patients admitted for LGIB and found that over 20% of their hospitalized patients ultimately were identified to have a diagnosis of hemorrhoids [4]. The financial burden of LGIB per hospitalization ranges from $9700 to $11,800 [5, 6]. Clinicians bear the burden of determining which cases represent potentially life-threatening bleeding that mandates hospitalization and utilization of critical and costly resources.

The purpose of this chapter is to review the scope of the problem of LGIB, to identify underlying causes and their clinical presentation, and to help surgeons and other clinicians develop a rational approach to the diagnosis and treatment of patients experiencing LGIB.

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Epidemiology

LGIB represents a broad clinical entity of varied severity and etiologies, and obtaining accurate epidemiologic data represents a formidable endeavor. Outpatient office visits provide one measure of the prevalence of LGIB, with over 1.7 million office visits in the United States for rectal bleeding occurring in 2009 [7]. Hospitalization data presumably reflects more serious LGIB, and in a review of a large hospital administrative database, admissions for all gastrointestinal bleeding [upper gastrointestinal bleeding (UGIB) and LGIB] were found to occur in approximately 97 cases per 100,000 persons, with 60.6 cases/100,000 persons due to UGIB and 35.7 cases/100,000 persons for LGIB [8]. This report assessed trends from 2001 to 2009 and revealed that the incidence of UGIB dramatically decreased (78.4–60.6 cases/100,000 persons), while cases for LGIB decreased as well but to a lesser extent (41.8–35.7 cases/100,000 persons). A study sponsored by the Agency for Healthcare Research and Quality queried the Nationwide Inpatient Sample Database and also noted a decreasing trend in the incidence of UGI bleeding (decreased by 14%), while during the time period of 1998–2006, the incidence of LGIB actually increased by 8% [9]. In this study, LGIB attributable to diverticulosis decreased by 7%, while anorectal hemorrhage increased by 41%. In Spain, a study involving ten academic hospitals between 1996 and 2005 found a similar decrease in UGIB (87/100,000–47/100,000), while LGIB increased from 20/100,000 to 33/100,000 [10]. Lastly, a recent prospective and population-based study from Iceland reported the highest incidence of LGIB at 87/100,000 persons, which equaled the incidence of UGIB [2].

While LGIB affects both the young and the old, the incidence of LGIB increases dramatically with age. Laine et al. reported that the incidence of LGIB for patients age <65 was 9.8/100,000, while individuals age >65 were found to have an incidence of 127.7/100,000 [8]. This phenomenon is likely explained by the simple fact that many of the conditions responsible for LGIB, such as diverticulosis coli and angioectasia, increase in incidence with age. Gender differences have not been consistently found in studies with regard to LGIB, and a recent survey of the Nationwide Inpatient Sample Database did not identify any difference in diverticular bleeding among men and women [11]. However, in this study, race was examined and found to be a significant factor with African Americans experiencing a higher prevalence of diverticular bleeding (34.4/100,000 persons) than Caucasians (20.3/100,000). Racial demographic data have not been consistently reported among most of the large database epidemiologic studies [7, 8, 12].

Etiologies of LGIB

Benign Anorectal Causes: Hemorrhoidal Bleeding and Fissures

Hemorrhoids and anal fissures commonly are associated with the appearance of bright red blood with bowel movements. The latter is commonly differentiated by the presence of pain during and after evacuation. Blood may be reported on the toilet paper with wiping, on the stool, or in the toilet bowel itself. In some cases, patients with bleeding internal hemorrhoids describe dripping of blood, or even streaming of blood, into the toilet bowl. Hemorrhoidal bleeding accounts for a substantial number of hospitalizations, representing 5–20% of all admissions for LGIB [1, 2, 4, 12]. Chronic bleeding from hemorrhoids over time also may result in iron deficiency anemia [13]. Hemorrhoids and anal fissures are generally not a likely cause of massive lower GI hemorrhage, although persistent bleeding hemorrhoids may require urgent operative intervention on occasion [4].

Diverticulosis Coli

Diverticulosis coli represents an acquired outpouching of the mucosa through the muscular layers of the colonic wall adjacent to penetrating vessels, the vasa recta. Diverticulosis increases with age; roughly 60% of individuals will develop diverticula by the age of 80, although it is estimated that perhaps only 15% will develop actual bleeding as a complication [14, 15].

Though the majority of patients with diverticulosis are not likely to experience clinically significant bleeding, diverticulosis is generally felt to represent the most common cause of LGIB not of anorectal etiology, accounting for 30–65% of cases [2, 4, 14–17]. In terms of severe hemorrhage, diverticular bleeding is certainly recognized as the most likely etiology [18, 19]. The theory behind diverticular bleeding describes the erosion of vasa recta through the mucosa at the neck or at the dome of the diverticulum [20]. Risk factors that predispose to diverticular bleeding include the use of nonsteroidal anti-inflammatory drugs (NSAIDs), hypertension, and anticoagulant use [1, 19, 21].

The diagnosis of a diverticular bleed is often considered presumptive, noting the presence of diverticulosis on colonoscopy without any other definitive bleeding site. Colonoscopy will provide definitive confirmation in the minority of cases (22%); criteria for diagnosis include colonoscopic identification of active bleeding or stigmata of bleeding such as an adherent clot or visible vessel [1]. Most diverticular bleeds present with painless hematochezia, which is often significant in volume. The natural history of

these episodes generally indicates spontaneous cessation in up to 80% of cases [1, 18]. The incidence of recurrent bleeding varies and has been noted to be as high as 40% in one series, though more recent series indicate rates on the order of 10–15% [22–24].

Angioectasia

Angioectasias [also known as angiodysplasia, arteriovenous malformations (AVMs), and vascular ectasias] are dilated, tortuous vascular abnormalities of the submucosa (Figure 41-1). The most widely accepted theory proposes that, with aging, low-grade obstruction of the submucosal veins traversing the colonic muscular layers results in incompetency of the precapillary sphincters, producing a small arteriovenous communication and subsequent dilation [25]. Colonic lesions more commonly occur in the cecum and right side of the colon, tend to be multiple, and are estimated to be the underlying etiology of bleeding in 3–15% of LGIB episodes [26–28].

The clinical presentation of LGIB due to angioectasia varies, and the color of blood has been reported to range from occult blood to melena to painless hematochezia [29]. Historically, angiodysplasia has been characterized by chronic or recurrent LGIB [30–32]. Factors that predispose to bleeding include increased age, comorbid conditions, multiple lesions, and the use of antiplatelet and anticoagulant therapy [33]. Recurrent bleeding is associated with multiple lesions, anticoagulation and antiplatelet therapy, the number of prior bleeding episodes, and rate of bleeding (events/year) [25].

In regards to recurrent bleeding, one must consider that angioectasias tend to be multiple and often involve proximal regions of the intestinal tract that require investigations in addition to colonoscopy. A recent report (which included diagnostic studies of the small bowel such as capsule endoscopy and double balloon enteroscopy) identified angioectasias most commonly in the jejunum (80%), followed by the duodenum (51%), stomach (22.8%), right colon (11.4%), and ileum (5.4%); nearly two-thirds of patients had lesions in multiple locations [2].

Ischemic Colitis

Ischemic injury of the colon occurs as a result of compromised blood flow and may be responsible for up to 16% of cases of LGIB, although most series indicate the incidence to be in the range of 10% [1, 3, 34, 35]. Bleeding typically occurs as a result of reperfusion of an ischemic segment of bowel, with sloughing of the mucosa and varying degrees of ulceration and necrosis (Figure 41-2). Bleeding generally is less severe when compared to diverticular bleeding or that related to angioectasias and, in some cases, may not be part of the clinical presentation at all. There is a spectrum of scenarios that may fall under the category of ischemic injury. Clinically, ischemic injury of the colon may be broadly considered as two distinct entities: (1) the traditional concept of "ischemic colitis" which affects primarily the left colon and is notable for transient and rapidly reversible ischemia and (2) other variants of "colonic ischemia" (CI) which may be due to arterial occlusion, thromboembolic disease, venous occlusion due to mesenteric venous thrombosis, or severe hypotension with a resultant low-flow state, also called non-occlusive mesenteric ischemia (NOMI). The mechanism of interrupted blood supply, the anatomic distribution at risk, and the prognosis vary between the two entities. The latter forms are more typically associated with severe, irreversible ischemic injury, greater risk of necrosis, increased risk of surgical resection, and mortality [36].

"Ischemic colitis" generally refers to a less severe ischemic intestinal injury that tends to be transient and revers-

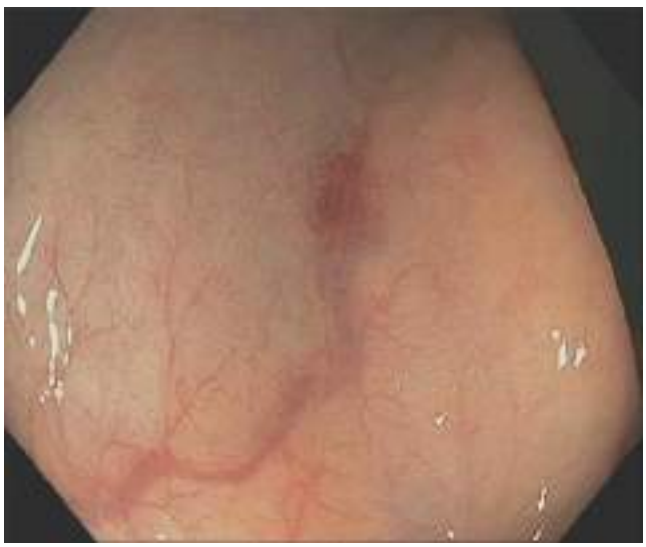

FIGURE 41-1. Angioectasia, seen on colonoscopy.

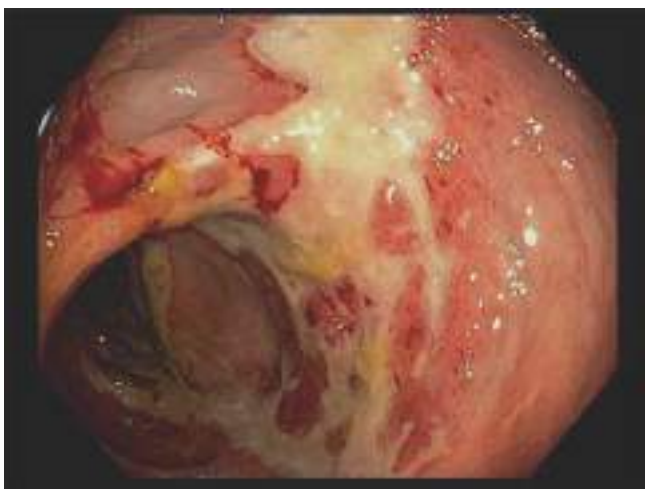

FIGURE 41-2. Ischemic colitis, seen on colonoscopy.

ible. Certain segments of the hindgut appear more vulnerable to this transient interruption of blood flow. These segments classically are referred to as the "watershed" regions: (1) the splenic flexure (Griffith's point), where vessels originating from midgut (superior mesenteric artery distribution) and hindgut (inferior mesenteric artery distribution) communicate via the marginal artery of Drummond, and (2) the rectosigmoid colon (Sudeck's point), where the marginal artery generally is not present and the arterial blood supply is provided by end sigmoidal vessels with less collateral redundancy [37].

Patients with ischemic colitis often present with cramping, abdominal pain, and associated tenderness localized to the left side of the abdomen; they may also experience associated nausea, vomiting, and an urgency to defecate. Typically, patients describe diarrheal stools that become bloody within 24 h of onset and can be either bright red or maroon-colored. Generally, bleeding from ischemic colitis is less severe and blood transfusion is necessary in fewer than 5% of patients. Symptoms generally resolve quickly (within 2–3 days) due to rapid restoration of blood flow, and acute complications requiring surgical intervention occur rarely.

Conversely, patients experiencing acute mesenteric vascular occlusion due to thromboembolism or mesenteric venous thrombosis, or those suffering from profound hypotension requiring vasopressor therapy (NOMI), are at greater risk for severe and irreversible ischemia, bowel necrosis, and need for urgent surgical intervention. Patterns of ischemia tend to be either pancolonic or isolated right colonic ischemia (IRCI) and are more likely to be associated with small bowel ischemia and infarction. Outcomes following surgical resection are remarkable for high mortality rates, ranging from 37 to 47% [38, 39].

Neoplasms of the Large Intestine

As with diverticulosis and vascular ectasias, the incidence of colorectal cancer increases with age [40]. Bleeding from neoplastic lesions of the large intestine generally presents according to anatomic location, with cecal and right-sided lesions more likely to cause occult blood loss, whereas left-sided and rectal lesions tend to present with visible blood per rectum. Acute massive hematochezia due to ulceration of the tumor is rare in the setting of colorectal cancer, and colorectal cancer represents less than 10% of all cases of LGIB requiring hospitalization [2, 4].

Additional Causes of LGIB

The definition of LGIB describes a large anatomic region with multiple additional conditions that may potentially give rise to bleeding, and these are briefly discussed in this section.

Post-polypectomy hemorrhage occurs after less than 1% of colonoscopic polypectomies [41]. However, given the vast numbers of colonoscopies and polypectomies performed annually (1.7 million colon cancer screening colonoscopies in the United States), this may account for up to 8% of all episodes of LGIB [42].

Inflammatory bowel disease (IBD) commonly presents with LGIB. However, severe, massive hemorrhage as the primary symptom prompting hospitalization occurs infrequently and accounts for less than 6% of all patients with a diagnosis of either Crohn's disease or ulcerative colitis [43–45]. Crohn's disease involving the colon and rectum is more likely to be a cause of LGIB as compared with isolated small bowel disease. While IBD more commonly affects the young patient, one must keep in mind the bimodal age distribution of IBD, which should be considered as a potential etiology of LGIB in the older patient as well.

Nonsteroidal anti-inflammatory drugs (NSAIDs) increase the risk of LGIB, especially in patients with diverticular disease. Remarkably, the prevalence of NSAID use among patients experiencing LGIB remains high, reported to be 86% in one series [46]. The association of NSAID use and LGIB may be the result of a specific effect of the medication on the mucosa or alternatively may exacerbate an underlying condition such as diverticulosis. In regard to the former, NSAIDs can cause a type of colitis that can be confused with IBD, characterized by ulcerations and weblike strictures, afflicting primarily the terminal ileum and right colon. Clinically, this can present with massive LGIB and even perforation [47].

Infectious hemorrhagic colitides due to bacterial infection must be considered in the individual experiencing LGIB. Inflammatory diarrhea is characterized by bloody and mucopurulent stool that is often associated with fever, tenesmus, and severe abdominal pain [48]. Common pathogenic bacteria causing inflammatory diarrhea include *Campylobacter*, *Salmonella*, *Shigella*, enteroinvasive and enterohemorrhagic *Escherichia coli*, and *Yersinia* species [49]. In North America, the most common clinically significant strain is *E. coli* O157:H7 [50]. These bacteria naturally occur in the intestines of healthy cattle. Transmission to humans occurs by eating undercooked ground beef or by drinking unpasteurized milk or juice. Consuming food or water contaminated with cow manure or raw ground beef can also lead to infection. The disease can be transmitted from person to person, notably from a child's diapers to their caregivers; additionally, low levels of chlorine in wading/swimming pools can predispose to infection [51, 52]. The infection causes mucosal injury with resulting bloody diarrhea, which is generally self-limited, requiring only supportive care. The most severe consequence of infection is hemolytic-uremic syndrome, characterized by thrombocytopenic thrombotic purpura and renal failure.

HIV-positive patients may experience LGIB from a variety of potential causes. Viral infections may be due to herpes simplex virus, cytomegalovirus, and HIV-related idiopathic proctocolitis. Additionally, one must also consider Kaposi's sarcoma. Sexually transmitted pathogens causing bloody diarrhea include *Chlamydial* species, with *C. trachomatis* infection being the most prevalent among homosexual males. *Neisseria gonorrhoeae* also can produce hemorrhagic proctitis, presenting with bloody mucoid diarrhea [49].

Radiation injury to the large intestine can be either acute (<3 months) or chronic. The incidence of chronic proctitis after pelvic irradiation is approximately 5–20% [53]. Chronic injury results in endarteritis obliterans that leads to neovascularization and telangiectasias, most commonly in the rectum. The incidence of radiation proctitis appears more likely if acute toxicity was observed during the course of treatment [54, 55]. The most common symptom of chronic radiation-induced proctitis remains rectal bleeding, while other associated symptoms include fecal urgency, incontinence, rectal pain, and mucoid discharge. More severe consequences include stricture and necrosis, resulting in potential fistulization to the urethra [56]. Endoscopy represents the diagnostic test of choice for evaluating radiation-induced proctocolitis and should be performed to exclude the possibility of an associated neoplasm of the large intestine, which can be seen in up to 12% of cases [57]. Typical endoscopic findings include telangiectasias, edema, ulceration, necrosis, and stenosis. Biopsy should be performed judiciously due to the known risk of non-healing ulcers and development of fistulae to the urethra and/or bladder [58].

Ulceration of the rectum has been described as a source of LGIB that can be severe and unrelenting, often requiring urgent colonoscopy and intervention. These ulcerations can result from stercoral injury or de novo in acutely ill patients.

Dieulafoy's lesions, most commonly found in the stomach, may be located elsewhere in the gastrointestinal tract 30% of the time, including the colon, the rectum, and the small intestine. These lesions represent a rare cause of GI bleeding (1–2%), though it has been suggested that this may underrepresent the true incidence due to a lack of recognition of the entity [59], as they have been identified via endoscopy and colonoscopy with increasing incidence in recent decades. Characteristic endoscopic findings describe a solitary vessel, histologically normal but large in diameter, protruding through the mucosa without surrounding ulceration [60]. Bleeding can be violent and voluminous and lead to life-threatening hemorrhage. The cause of Dieulafoy's lesions remains uncertain, and the range of clinical presentation includes reports occurring in acutely ill hospitalized patients as well as in newborn infants [59]. Approximately 5% of Dieulafoy's lesions are estimated to occur in the colon and rectum, with the right colon being the most common location [60].

Ectopic varices represent another rare but sinister cause of LGIB. Ectopic (non-esophageal) varices may occur in up to 70% of patients with portal hypertension and cirrhosis. Colorectal varices are well described but fortunately not a common cause of hemorrhage. Rectal varices result from portosystemic shunting and decompression of the inferior mesenteric vein and superior rectal veins via the middle and inferior rectal veins. Rectal varices do not prolapse, tend to be blue-gray in color, and may extend from the rectum superiorly to the squamous epithelium of the anus distally, in distinction to internal hemorrhoids, which may prolapse, tend to be purple in color, and generally do not extend proximally into the rectum [61]. The vessels tend to be serpentine in morphology, submucosal, and extend from the squamous epithelium cranially [62]. Bleeding from varices results from wall tension that is proportional to transmural pressure and the radius of the vessel. Similar to esophageal varices, the major determining factors are vessel size and portal venous pressure [63]. Fortunately, bleeding from rectal varices is rare, occurring in 0.5–3.6% of all cases [64–67]. However, when bleeding occurs, hemorrhage can be massive and life-threatening, requiring urgent intervention. Optimization of medical management remains paramount, including consideration of decompression procedures such as transjugular intrahepatic portosystemic shunt (TIPSS) [68]. Endoscopic techniques, such as injection sclerotherapy, as well as interventional radiology techniques, such as embolization, have been reported to be effective. While band ligation has been described as a treatment modality for esophageal varices, rectal varices less commonly are amenable to ligation technique, with variceal size (>9 mm) being an important predictor of poorer outcome [69].

Obscure bleeding from a small intestinal source has been estimated to account for 5% of LGIB episodes. Previously an anatomic territory that proved difficult to image endoscopically, the small bowel can now be directly visualized using techniques such as device-assisted enteroscopy (balloon and double balloon enteroscopes) and video capsule endoscopy. Such technologies prove far more sensitive than contrast studies or computed tomography and can identify many of the varied diagnoses causing bleeding, such as angioectasias, ulcerations, small bowel tumors, and IBD. In younger patients with LGIB, one must always consider Meckel's diverticulum, especially when bleeding is acute and massive [70]. Radionuclide imaging identifying ectopic gastric mucosa assists in confirming this diagnosis.

Table 41-1 summarizes the distribution of causes of LGIB, as reported in a number of large epidemiologic studies.

TABLE 41-1. Lower gastrointestinal bleeding—distribution of etiologies

Author (Year)	Diverticulosis (%)	Hemorrhoids (%)	Neoplasm (%)	Angioectasia (%)	Ischemic colitis (%)	IBD (%)	Colitides (%)	Ulcers (%)	Post-polypectomy (%)	Small bowel (%)	Radiation (%)	Other (%)	Unknown (%)
Longstreth 1997 [1]	41.6	4.6	9.1	2.7	8.7	2.3	5.0					10	11.9
Strate 2003 [3]	30	12	6	3	10	4	8		7		3	7	9
Velayos 2004 [72]	30	12	6	4		4		4	2	6			11
Strate (NIS) 2008 [12]	33.1	20	21.3	6.0	6.6	4.4							11
Gayer 2009 [4]	37.3	21	11.8	2.3		5.4	10.7 (includes ischemic)			8		6.58	3.45
Hreinsson 2012 [2]	23.3	10.4	10.5	3.1	16	11.7				3.1		11	9.2

Models Predicting Severity of LGIB

Patients presenting with LGIB represent a considerable challenge to healthcare teams and hospital systems, given the heterogeneous nature of causes, spectrum of severity, and often elusive nature with spontaneous cessation of bleeding prior to definitive diagnosis. While occasionally dramatic in presentation, the vast majority of patients with LGIB do not require surgical intervention and experience exceedingly low mortality. Ideally, healthcare teams could better serve patients by employing a model to predict which episodes require hospitalization and help direct rational use of diagnostic testing and intervention. Validated models predicting severity and guiding management for UGIB exist and are widely employed [71]. However, models for predicting LGIB behavior have been much more difficult to develop and validate, given the heterogeneity of the clinical syndrome and the complexity of its clinical presentation.

Velayos et al. prospectively evaluated parameters identified within the first hour of presentation with LGIB to an emergency department and attempted to identify risk factors for adverse outcomes. A total of 448 patients were prospectively followed, and multivariate regression analysis identified three independent risk factors for severe LGIB: initial hematocrit less than 35%, presence of abnormal vital signs 1 h after initial medical evaluation, and gross blood on initial rectal examination. Severe LGIB occurred in 79% of patients with three risk factors, 57% of patients with two risk factors, 17% of patients with one risk factor, and zero patients with no risk factors [72].

Strate et al. also sought also to identify risk factors for severity of LGIB and predict which patients would most benefit from aggressive care and intervention. Multivariable logistic regression analysis of a cohort of 252 patients identified seven independent risk factors for severe LGIB: initial heart rate greater than 100/min, initial systolic blood pressure less than 115 mmHg, syncope, non-tender abdomen, bleeding per rectum during the first 4 h of evaluation, aspirin use, and Charlson Comorbidity Index score of more than 2. Severe LGIB was seen in 84% of patients with more than three risk factors, 43% of patients with one to three risk factors, and 9% of patients with no risk factors [3].

As a follow-up, Strate et al. then prospectively validated their predictive model in a cohort of 275 patients, noting that the number of positive risk factors, calculated within 4 h of presentation, significantly correlated with major clinical outcomes, including surgery, death, blood transfusions, and length of hospital stay. They concluded that the triage of high-risk patients (three or more risk factors) to urgent interventions could be used to improve utilization of resources and quality of care [34]. It should be noted that this model made the assumption that hemorrhage due to ischemic colitis and IBD is generally mild to moderate, so LGIB due to these etiologies was not included in the study group.

Patel et al. prospectively applied an algorithm to the evaluation of patients presenting with uncomplicated rectal bleeding. If the patient's hemoglobin was >13 g/dl, SBP> 115 mmHg, and the patient was not anticoagulated, the patient was discharged with plans for an outpatient flexible sigmoidoscopy within 6 weeks. This algorithm was applied to a series of 57 patients, and potential inpatient admissions were avoided in 35%. Only one discharged patient was readmitted with severe colitis, and avoidable admissions were reduced from 50 to 1.8% [73].

Although predictive models such as these have been developed and validated, it is unclear as to what extent their implementation will impact clinical practice and improve patient outcomes. Certainly, the application of practical and predictive clinical models for the evaluation and management of LGIB will become more relevant to physicians in the future, given the economic and administrative pressures on healthcare systems to demonstrate appropriate resource utilization and cost reduction efforts.

Presentation, Evaluation, and Management

Due to the diversity in underlying etiologies, the presentation of LGIB can range from occult bleeding to life-threatening hemorrhage. Of paramount importance is rapid assessment of the patient's hemodynamic stability. Patients presenting with massive gastrointestinal bleeding and signs of hemodynamic instability, chest pain, shortness of breath, or orthostatic hypotension should immediately have two large-bore intravenous lines placed and undergo rapid volume resuscitation with crystalloid while awaiting labs and availability of cross-matched blood; in extreme circumstances, one may consider transfusion with non cross-matched type O negative blood. Continuous monitoring of vital signs is essential, and a Foley catheter should be placed to monitor urine output.

Placement of a nasogastric tube and gastric lavage is essential. Aspiration of frank blood, clot, or coffee grounds should prompt further investigation for UGIB via upper endoscopy. A bilious aspirate all but excludes an upper gastrointestinal source, while a clear aspirate is indeterminate, as there could be source of bleeding distal to a contacted pylorus.

A thorough history and physical examination should be performed, including an intake of the patient's medications, paying particular attention to NSAIDs, anticoagulants, and antiplatelet agents that may exacerbate bleeding, as well as beta-blockers that may mask the physiologic response to hypovolemia. Pertinent points in the history should include onset and duration of bleeding, volume and frequency of bleeding, color of blood (bright red, maroon, or tarry), and presence or absence of clots. A history of abdominal pain and weight loss may suggest IBD, ischemia, or malignancy, though colorectal cancer rarely presents with massive

hematochezia. The presence of significant pain represents a branch point in the evaluation of the patient with LGIB and should prompt earlier cross-sectional imaging if the patient is hemodynamically stable. Other salient questioning should focus on comorbidities such as cardiovascular, pulmonary, or hepatic disease, the presence or absence of chest pain, shortness of breath, lightheadedness, anorectal pain, and the date and findings of the patient's most recent colonoscopy and/or upper endoscopy. Particular attention should be paid to those who have undergone prior intestinal surgery due to the possibility of an anastomotic ulcer and those who have been previously treated with abdominopelvic radiation, implicating radiation proctitis/colitis/enteritis.

Physical examination should begin with assessment for signs/symptoms of hypovolemic shock. Once the patient's volume status has been assessed and appropriate resuscitation has been initiated, a more focused physical exam should ensue. Abdominal examination should focus on the presence of pain, palpable masses, distention, scars from prior surgeries, and hepatosplenomegaly. Stigmata of chronic liver disease, such as jaundice, caput medusa, or palmar erythema, may suggest variceal bleeding. Visual inspection of the perineum should be performed to evaluate for thrombosed or prolapsing hemorrhoids, anal fissure, or anal masses. Digital rectal examination should be done to assess for the presence of a rectal mass, and anoscopy and/or rigid proctosigmoidoscopy should be performed to evaluate for a distal source of bleeding, such as internal hemorrhoids, proctitis, ulcers, or varices.

Laboratory studies should include a basic chemistry panel, complete blood count, coagulation parameters, and type and cross. Coagulopathies should be corrected via transfusion of blood products and/or factors as appropriate. Patients with cardiovascular disease or those with chest pain or shortness of breath should undergo an electrocardiogram, and if abnormal, cardiac enzymes should be assessed.

Initial volume resuscitation of the hypovolemic patient should include bolus infusion of isotonic crystalloid, such as normal saline or lactated Ringer's solution, aiming to restore normotension. Continued hypotension despite aggressive crystalloid infusion should prompt transfusion of packed red blood cells. Further transfusion should be guided by the patient's hemodynamic response and change in hemoglobin. A hemoglobin transfusion threshold of 9–10 g/dL has traditionally been employed, especially in patients with significant cardiovascular disease. While data regarding a more restrictive pattern of transfusion specifically in patients with LGIB is lacking, a number of studies in patients with UGIB have demonstrated improved outcomes using a more restrictive threshold, as low as 7 g/dL, in low-risk patients [74–76]. For patients requiring transfusion of multiple units of PRBC, concurrent administration of platelets and fresh frozen plasma may prevent dilutional coagulopathy.

Colonoscopy

When patients present with a self-limited LGIB, colonoscopy is the diagnostic modality of choice, identifying either a definitive or presumed source of bleeding in 74–100% of cases [77–83]. The major advantage of colonoscopy is the potential for concurrent diagnosis and therapeutic intervention, even in the absence of active bleeding. Because most bleeding stops spontaneously, colonoscopy is typically performed semi-electively, usually following a mechanical bowel preparation. However, the optimal means of bowel preparation and timing of colonoscopy is often a topic of debate. While the use of a mechanical bowel purge allows for more complete visualization of the colonic mucosa, it also necessitates a delay in performing the procedure. If bleeding has stopped by the time colonoscopy is performed, it is often difficult to know which, if any, of identified abnormalities was responsible, especially when multiple sources, such as diverticula or AVMs, are identified.

A pooled analysis of studies looking at colonoscopy after mechanical bowel preparation for the evaluation of LGIB found a diagnostic yield of 91% [25]. Early colonoscopy has been found to correlate with a shorter length of admission, primarily due to increased yield. Strate and Syngal reported that time to colonoscopy was an independent predictor of length of hospital stay in patients presenting with hematochezia. The absence of visible blood or active bleeding at the time of colonoscopy was also related to a shorted length of stay [84]. A number of other studies have suggested that urgent colonoscopy within 12–24 h of presentation can improve the diagnostic yield [79, 80, 85, 86].

In contrast to "early" colonoscopy is the concept of "urgent" colonoscopy, usually performed within a few hours of the patient's arrival. Jensen et al. studied the role of urgent colonoscopy (within 6–12 h of hospitalization) in patients with hematochezia and known diverticulosis after a 3–4 h mechanical colon purge in two sequential prospective trials. In the first trial, 23% of patients were found to have definitive signs of diverticular bleeding during colonoscopy and were managed medically, not endoscopically. Nearly half of these patients experienced rebleeding, and two-thirds of those that rebled required emergency hemicolectomy. In the second trial, 21% of patients had signs of diverticular hemorrhage at the time of colonoscopy, half of which were found to have active visible bleeding. All patients with signs of diverticular hemorrhage were treated endoscopically, and none had recurrent bleeding or required surgery [79].

Others have reported conflicting data regarding improved outcomes with urgent colonoscopy. Green et al. randomized patients with lower GI bleeding to urgent colonoscopy after a raid purge or a standard care algorithm based on angiographic intervention and expectant colonoscopy. They reported no differences in main outcome measures, including mortality, hospital stay, ICU stay, transfusion requirements, early and late rebleeding, and need for surgery [80]. Laine et al. performed

a prospective randomized trial comparing urgent colonoscopy (within 12 h of presentation) to elective colonoscopy (36–60 h after presentation). Though the trial closed prematurely due to inadequate enrollment and statistical power, the urgent group showed no decrease in diagnostic or therapeutic interventions, number of transfusions, length of stay, or hospital charges [87]. A number of other studies have also reported data indicating that urgent colonoscopy for acute LGIB may not be advantageous [78, 88].

In an effort to minimize the delay needed for mechanical bowel preparation, some have proposed the use of enemas to clear the left colon, though oral bowel preparation has been shown to clearly increase the diagnostic rate for colonoscopy compared with enemas alone [89]. In some instances, rapid enemas can be used prior to immediate colonoscopy after the onset of massive hematochezia to simply help distinguish a right-sided from a left-sided source; if blood is only seen in the left colon, further diagnostics should focus there [90]. Often, an acute bleed will clear the colon distal to the bleed of any solid stool, though there may be significant clot to clear during the procedure. Repaka et al. published a prospective feasibility study looking at urgent colonoscopy without oral bowel preparation aided by water jet pumps and mechanical suction devices (hydroflush colonoscopy). In a series of 13 procedures, a presumed or definitive source of bleeding was seen in all patients, a defined source was identified in 5/13 (38.5%), and endoscopic hemostasis was achieved in four of these. Complete colonoscopy to the cecum was performed in 9/13 (69.2%), and no patients required a repeat colonoscopy due to inadequate preparation [91].

In addition to the increased diagnostic yield, another advantage of early or urgent colonoscopy is the potential for therapeutic intervention if a source is identified. Colonoscopic interventions for cessation of active bleeding include clipping, band ligation, injection of epinephrine or saline, monopolar or bipolar electrocautery, laser coagulation, or argon plasma coagulation (APC). Bleeding diverticula can be treated by submucosal injection of epinephrine (diluted 1:20,000 in saline) in 1-mL aliquots into four quadrants around the base of the diverticulum. This can be done either with or without application of a heater probe applied at a low power setting for 1–2 s, though this does increase the risk of perforation. Early rebleeding rates for injection range from 0 to 35%, with minimal procedure-related complication [79, 80, 92].

Endoscopic clips can also be applied, either alone or as an adjunct to injection. A number of case series and retrospective studies have described successful endoscopic clipping for the management of LGIB of diverticular origin with rebleeding rates ranging from 0 to 21% [93]. Endoscopic clipping of the base of the diverticulum has been reported to have comparable success rates and complication profiles when compared with epinephrine injection [94–96]. Clipping of diverticula located in the right colon, as opposed to the left colon, has been reported to be a predictor of refractory hemorrhage [97].

Alternatively, endoscopic band ligation has been described in the management of diverticular hemorrhage with excellent success rates and low rebleeding rates [98, 99]. Setoyama et al. compared patients treated with endoclips and those treated with EBL and found initial success rates of 100% in both groups; however, rebleeding was seen in only 6% of patients treated with EBL, compared with 33% of those treated with clips [100].

AVMs can be treated either with electrocautery, APC, or laser coagulation. Multiple sessions may be required, and long-term rebleeding rates range from 10 to 39% [32, 101]. A combination of APC and endoscopic clipping has also been reported [102]. The risk of complications, including perforation, ranges from 2 to 7%. One must keep in mind that AVMs in particular are more often located in the thinner-walled right colon, increasing the risk of perforation with any intervention.

A novel means of obtaining endoscopic hemostasis for diffuse bleeding diatheses in the colon, such as radiation- or NSAID-induced colitis, has been described by Kratt et al. who reported the use of Hemospray (Cook Medical, Bloomington, IN), a mineral-based granular powder that absorbs water and induces the clotting cascade. They reported introducing it via a colonoscope throughout the cecum and ascending colon in an elderly patient with NSAID-induced colonopathy, successfully ceasing hemorrhage and avoiding the need for an urgent colectomy [103].

Radionucleotide Scintigraphy

Nuclear scintigraphy has long been utilized as a means of detecting active GI bleeding. Two techniques can be employed for the detection of active GI bleeding—^{99m}Tc-sulfur colloid and ^{99m}Tc-labeled RBCs, the latter of which has been shown to be superior for the detection of GI bleeding [104, 105]. ^{99m}Tc-RBC scanning requires labeling a small sample of the patient's blood with technetium and then injecting it back into the patient's bloodstream, followed by scintigraphic scanning. Active hemorrhage is indicated by extravasation and pooling of the radionucleotide tracer (Figure 41-3).

The procedure is not invasive, carries little risk, and does not require mechanical bowel preparation. Other benefits include its high sensitivity and the slow washout of the tracer, which allows repeat scanning over periods of up to 24 h in instances of intermittent bleeding. This is important to take into consideration, given that rebleeding can be seen in up to 27% of patients after an initial negative ^{99m}Tc-RBC scan [106]. The main drawbacks are that this technique requires some prep time to extract and tag the RBCs (approximately 30 min), and there is no possibility for therapeutic intervention.

Detection of bleeding as slow as 0.04–0.05 cm^3/min has been reported with ^{99m}Tc-RBC scans [107, 108]. The sensitivity

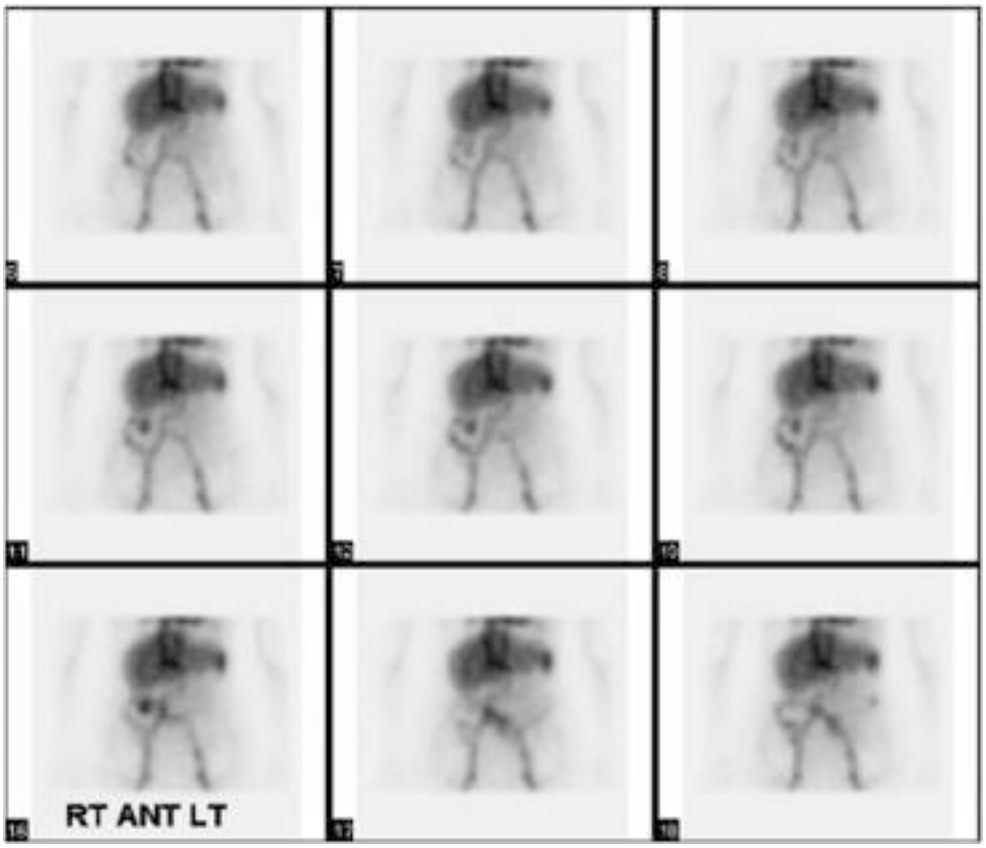

FIGURE 41-3. ^{99m}Tc-RBC scan showing active extravasation in the right lower quadrant. RBC = red blood cell.

is linked to the volume of extravasated RBC at the site of bleeding. While detection of low rates of bleeding is possible, hyperperistalsis may distribute the labeled RBCs over a substantial length of bowel, reducing the sensitivity. Feingold et al. found that patients who were hemodynamically unstable at presentation were more likely to have a positive ^{99m}Tc-RBC scan than those who were hemodynamically stable (62% vs. 21%) [109]. Reported accuracy in detection of the anatomic site of bleeding varies widely (41–94%) [110, 111], mainly because of rapid movement of tracer within the lumen of the bowel due to peristalsis and gravity, as well as difficulty discriminating colon from overlying small bowel. Because of the variability in accurate localization of the anatomic site of bleeding, most algorithms that include ^{99m}Tc-RBC scanning in the evaluation of patients with LGIB use it as a screening study prior to proceeding with mesenteric angiogram rather than as a localizing study. In a retrospective review of 271 angiograms published by Gunderman et al., the use of screening ^{99m}Tc-RBC scans prior to mesenteric angiography improved the diagnostic yield from 22 to 53% [112].

Because of the lack of reliability in determining the actual anatomic site of bleeding, segmental resection based on ^{99m}Tc-RBC scan localization alone is generally not advocated. However, a number of studies have attempted to refute this dogmatic approach. Suzman et al. retrospectively evaluated patients with LGIB who underwent a preoperative ^{99m}Tc-RBC scan and ultimately required surgery; 97.3% had correct localization based on surgical pathology, and only one of 50 patients over the 5-year period of the study required subtotal colectomy because of nonlocalized bleeding [113]. In a similar study, Gutierrez et al. reported an 88% accuracy of ^{99m}Tc-RBC scans in determining the site of bleeding [114]. Despite these reports, the decision to perform a segmental resection based on ^{99m}Tc-RBC scan localization alone should be made only after careful consideration.

Computed Tomography Angiography

Recent advances in computed tomography have led to the development and validation of CT angiography (CTA) techniques. Sixty-four-row CTA allows thinner collimation, faster scanning times, greater anatomic coverage, and better multiplanar reformatted images, greatly expanding its diagnostic role for the evaluation of LGIB [115]. With its widespread availability, CTA has largely supplanted ^{99m}Tc-RBC scanning as the initial means of evaluating most patients presenting with acute LGIB who do not have a contraindication such as renal insufficiency or allergy to contrast dye. Besides the detection of active bleeding, CTA has the added

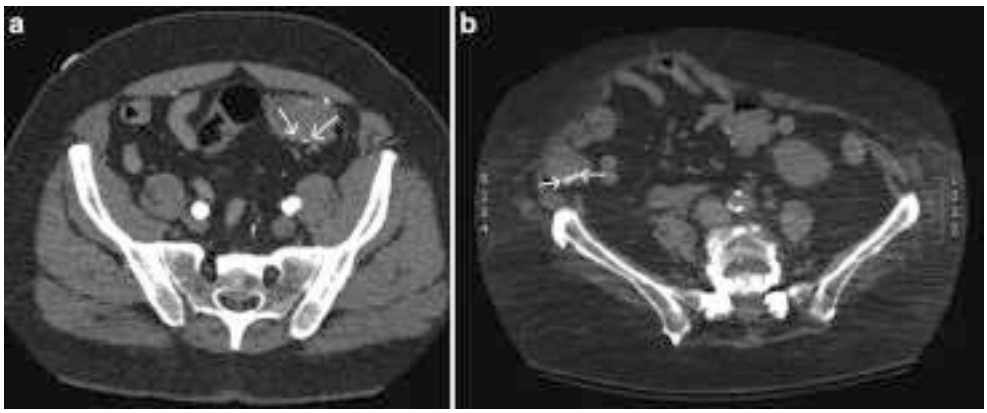

FIGURE 41-4. (**a**) CT angiogram showing active extravasation in the sigmoid colon. (**b**) CT angiogram showing active extravasation in the cecum.

advantages of being able to localize the site of bleeding and identify any coexisting pathology. A positive CTA (Figure 41-4) should prompt further therapeutic efforts, such as angiographic embolization, or if the patient is showing signs of massive hemorrhage, targeted surgical resection of the culprit segment of intestine.

The rate of bleeding able to be detected by CTA has been reported to be as low as 0.3 mL/min [116]. The sensitivity of CTA for localization of a LGIB source is 91–92% when active bleeding is present, though it drops to as low as 45–47% when bleeding is intermittent [117]. In a prospective trial, Ren et al. found that CTA had an accuracy of 90.5% in the detection of active GI bleeding, and treatment planning was correctly established on the basis of CTA findings with an accuracy of 98.4%. Another prospective study comparing the diagnostic performance of CTA with angiography, colonoscopy, and surgical findings reported a sensitivity of 100%, specificity of 96%, positive predictive value (PPV) of 95%, negative predictive value (NPV) of 100%, and accuracy of 93% [118].

A prospective trial published by Obana et al. found that the detection rate of colonic diverticular bleeding by CTA alone was only 15.4%, but jumped to 46.2% when combined with colonoscopy [119]. Nagata and colleagues evaluated rates of detection of a LGIB source comparing early colonoscopy following urgent CTA with early colonoscopy alone and found that the detection rate was higher with colonoscopy following CTA than with colonoscopy alone for vascular lesions (35.7% vs. 20.6%, $p=0.01$), leading to more endoscopic therapies (34.9% vs. 13.4%, $p<0.01$) [120].

A major advantage of CTA in the evaluation of the patient with LGIB is its ready availability and ease with which the study can be performed and rapidly interpreted, leading to earlier and more targeted therapeutic intervention. It is a noninvasive study that does not require mechanical bowel preparation and carries very little risk. The main disadvantage is the small risk of contrast nephropathy, which may limit its use in patients with renal insufficiency.

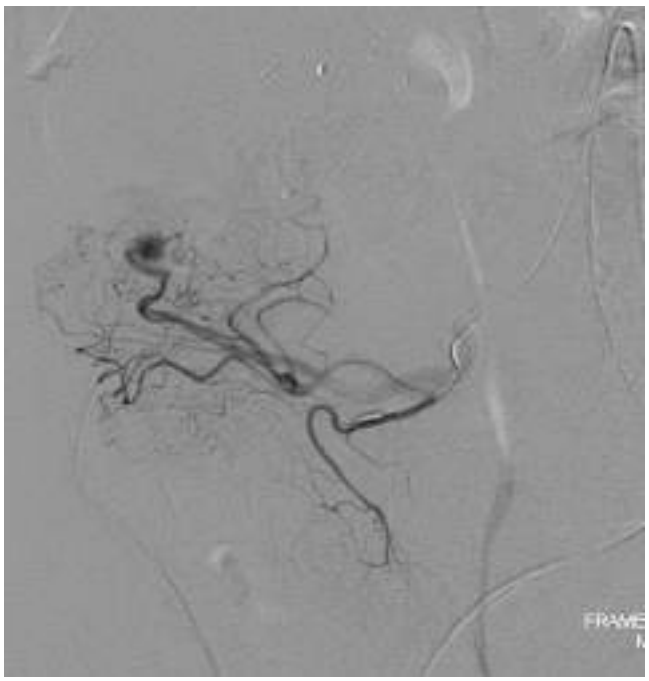

FIGURE 41-5. Mesenteric angiogram showing active extravasation from a branch of the ileocolic artery.

Angiography

Diagnostic Angiography

Diagnostic mesenteric angiography was first reported in the evaluation of hematochezia in 1963 [121]. Despite being an invasive procedure with a number of potential complications, its major advantage is the ability to perform a therapeutic intervention if active bleeding is identified (Figure 41-5). Angiography requires a more rapid rate of bleeding (0.5–1.5 cm^3/min) than nuclear scintigraphy to detect active extravasation. Identification of active bleeding following a positive "screening" ^{99m}Tc-RBC scan or CTA may be hampered by the intermittent nature of most LGIBs and the time

delay between the positive scan and the performance of angiography.

Ng et al. studied the timing of extravasation in a ^{99m}Tc-RBC scan and its role in predicting a positive mesenteric angiogram. They found that an immediate blush had a 75% PPV for active extravasation found on angiography, whereas a delayed (>2 min) blush had an NPV of 93%, suggesting that patients with a delayed blush may not require diagnostic angiography and may instead be observed and evaluated with colonoscopy after a bowel prep [122].

The diagnostic yield of mesenteric angiography depends on patient selection, the timing of the procedure, and the skill of the angiographer [123, 124]. A review by of the literature by Vernava et al. [77] reported diagnostic yields ranging from 40 to 86%. Abbas et al. found that angiography successfully localized bleeding sites in 51% of LGIB episodes; positive localization correlated with hemodynamic instability on arrival, a drop in hemoglobin level ≥50% from previous admission, and a transfusion requirement of ≥5 U of PRBC within 24 h [125].

Tan et al. reviewed patients with LGIB who had a positive CTA followed by mesenteric angiography and found that factors associated with a positive mesenteric angiography included nondiverticular etiology and hemoglobin <10 g/dL; when mesenteric angiography was performed within <150 min of the CTA, it was 2.89 times more likely to identify an active bleeding source [126]. A similar study by Koh et al. also found that mesenteric angiography after a positive CTA was 8.56 times more likely to be positive when performed within 90 min of the CTA [127]. Rasuli et al. reported that older age, ICU admission, and having received 4 U of PRBC over 12 h or 5 U over 24 h were indicators of a positive mesenteric angiogram [128].

For patients with recurrent intermittent LGIB that continue to escape localization despite multiple diagnostic studies, one technique that is often discussed but rarely utilized is provocative angiography, which incorporates the use of heparin, thrombolytics, vasodilators, or some combination of these to induce a bleed that has ceased. Before considering provocative angiography, one must balance the risk of uncontrolled hemorrhage or intracranial hemorrhage against the potential diagnostic and therapeutic benefit. Small series have been reported with low complication rates and diagnostic yields ranging from 29 to 38% [129–131].

The risks associated with diagnostic mesenteric angiography include bleeding, access complications such as vascular injury and pseudoaneurysm, thromboembolic events, and contrast-induced nephropathy. Contraindications include contrast dye allergy and renal insufficiency that might limit the ability to administer intravenous contrast.

Therapeutic Angiography

If a blush or area of obvious extravasation is seen during diagnostic angiography, therapeutic intervention should be attempted. In the 1970s, the technique of vasopressin infusion via a selectively placed mesenteric arterial catheter to induce vasospasm was introduced, and fairly recently, this was the preferred means of intervention. Transcatheter infusion generally begins at 0.2 U/min and may be increased to 0.4 U/min if bleeding persists. Cessation of active bleeding is seen in up to 90% of patients, though the rate of rebleeding upon discontinuation of the infusion approaches 50% [132]. Because of the antidiuretic effect of vasopressin, there is a tendency toward fluid retention and congestive heart failure, so its use in patients with significant cardiac disease becomes somewhat limited, especially considering the significant volume resuscitation many patients with LGIB require.

Vasopressin infusion was previously favored over intravascular embolization due to the high rates of intestinal ischemia and perforation (in as many as 20% of cases) reported with the use of larger catheters, which only allowed for embolization of larger vessels. However, the availability of "microcatheters" now allows for transcatheter superselective embolization of much smaller target vessels with a negligible risk of intestinal ischemia. Success rates with cessation of active arterial bleeding range from 50 to 100% with rebleeding rates of 22–24% [133–136]. Complications such as transmural ischemia and stricture formation, which were more common in the past following embolization of larger segmental vessels, now occur rarely with the use of superselective embolization angiography and are usually asymptomatic. Due to its efficacy and low risk of complications, superselective embolization is now considered by most to be the first-line angiographic therapy for LGIB. Materials used for embolization include microcoils, polyvinyl alcohol particles, and gelfoam.

Tan et al. published a retrospective review of 265 patients undergoing mesenteric angiography for LGIB, of which 32 (12%) underwent superselective embolization. Immediate cessation of bleeding was seen in 31 (97%), though only 20 (63%) were subsequently discharged with no further interventions. Seven patients rebled, and a total of nine required surgery; postembolization ischemia was seen in only one patient (3%). Rebleeding was more likely to occur if the bleeding source was the small bowel or if the presenting hematocrit was <20.0% or platelet count was <140; surgical resection was more likely if the underlying etiology of bleeding was diverticular disease or if the presenting hematocrit was <20.0% [134].

Compared with nuclear scintigraphy as a "screening" test for LGIB, pre-angiography localization of hemorrhage site by CTA has been shown to be more precise and consistent with angiographic findings. Pre-angiography CTA followed by therapeutic angiography typically results in administration of similar cumulative volumes of intravenous contrast when compared to angiography preceded by ^{99m}Tc-RBC, presumably due to pre-angiographic localization of the anatomic site of bleeding. The use of CTA prior to mesenteric angiography has been shown to have no effect on the incidence of contrast-induced nephropathy, given the similar volumes of contrast administration [137].

Localization of Small Bowel Bleeding

When a patient shows signs of ongoing GI bleeding in the face of negative evaluations of both the upper and lower GI tracts, one should consider evaluation for a small bowel source of bleeding. Options include video capsule endoscopy (VCE), double balloon enteroscopy (DBE), radionucleotide Meckel's scan, and, as a last resort, intraoperative push enteroscopy.

VCE and DBE have both been shown to have diagnostic yields in range of 55–65% in patients with hematochezia [117]. One disadvantage of VCE is failure to pass the capsule in instances in which structuring or obstructive disease is present, necessitating further intervention for retrieval. A dissolvable test capsule can be ingested prior to performing the study in an attempt to avoid this. Another disadvantage is that of missed lesions. As VCE generally records 2 frames/s, there have been reports of missed lesions subsequently seen on DBE [138]. Leung et al. randomized patients presenting with GI bleeding and nondiagnostic upper/lower endoscopy to undergo further evaluation via either VCE or angiography and found a higher diagnostic yield with VCE (53.3% vs. 20.0%, $p=0.016$) with no differences in long-term outcomes, including further transfusion, rebleeding, and mortality [139]. Newer devices are able to capture as many as 35 frames/s, which should greatly enhance the diagnostic accuracy. VCE takes significant time to perform and is most commonly utilized to evaluate for an occult source of chronic bleeding, not in the presence of massive LGIB.

DBE is a technically challenging and time-consuming procedure that should only be attempted by a skilled endoscopist who has training and significant experience with the technique. Despite these limitations, DBE compared to VCE has the added benefit of both localization and potential therapeutic intervention if bleeding source is identified. If a site of bleeding is identified but endoscopic intervention is not possible, the endoscopist can mark the site of bleeding with endoclips or tattooing for later identification at the time of possible radiologic or surgical intervention. Similar to VCE, the role of DBE in the setting of acute, massive LGIB is somewhat limited. However, Mönkemüller et al. have reported a series of 17 emergency DBEs for overt obscure GIB in which they successfully identified a source of bleeding in 59% [140].

A Meckel's scan relies on uptake of ^{99m}Tc-pertechnetate in ectopic gastric mucosa within a Meckel's diverticulum that has the potential for GI hemorrhage (but not active GI hemorrhage, for which ^{99m}Tc-RBC scanning would be more appropriate). The procedure is noninvasive, has minimal morbidity, and has both specificity and PPV approaching 100%, though its sensitivity is much lower at 62% [141–143]. Concurrent administration of H-2 blockers has been shown to increase the diagnostic yield.

Surgery

Despite the frequency with which patients present for evaluation of LGIB, the number of patients who require emergency surgery without a preoperatively localized site of bleeding is less than 5% [4]. However, in hemodynamically unstable patients with ongoing LGIB unresponsive to initial resuscitative efforts, emergent surgical intervention is indicated. Also, patients in whom a source of bleeding has been localized but therapeutic efforts are either unsuccessful or not feasible should be considered surgical candidates, as should those with massive transfusion requirements. Six units of PRBC in a 24-h period has traditionally been considered the threshold trigger prompting surgical intervention, though this varies depending on institution and the clinical state of the patient. Bender et al. reported a 45% mortality rate for patients undergoing emergency surgery for LGIB when a total of ten or more units of PRBCs were transfused preoperatively, compared with 7% when less than ten units were transfused [144].

When ongoing LGIB hemorrhage is present and a source cannot be localized despite multiple diagnostic studies or if the patient is too unstable for additional diagnostic studies, the patient should undergo exploratory laparotomy. The small bowel should be thoroughly examined to exclude a Meckel's diverticulum or a palpable mass that could be a source of bleeding. Transillumination of the small bowel may reveal small tumors or angiodysplasia. If the patient is stable, an intraoperative colonoscopy can be performed with luminal lavage and irrigation of sequential segments with proximal compression of the colon. Intraoperative push enteroscopy can also be considered if a colonic source is not identified and there is bright red blood and/or clots in the terminal ileum, though this can be technically challenging and time-consuming.

If a clear source cannot be identified and there is no obvious source in the stomach or small bowel (and an anorectal source has been excluded), the bleeding source is presumed to be colonic. In this scenario, and in the face of ongoing hemodynamic instability or ongoing frank hemorrhage, a total abdominal colectomy should be performed with either an end ileostomy or, in select circumstances, an ileoproctostomy. Generally speaking, most would advocate avoiding an anastomosis, given the indication for emergent laparotomy. If the patient is unstable or on vasopressors, has required multiple transfusions, or is markedly hypoalbuminemic, an end ileostomy is usually the safer option, as it eliminates the risk of anastomotic leak. Furthermore, ongoing bleeding from a source proximal to the colon can be identified quickly and more easily identified endoscopically via an ileoscopy. An ileoproctostomy, while an acceptable choice in properly selected patients, carries with it the risk of anastomotic leak, which can have devastating consequences, especially given that most patients who require emergency surgery for LGIB have numerous preexisting comorbidities; many of these patients may require ongoing use of vasopressors in the immediate post-op period, further compromising the anastomosis. Plummer et al. found a mortality rate of 17% in patients undergoing emergency surgery for unlocalized

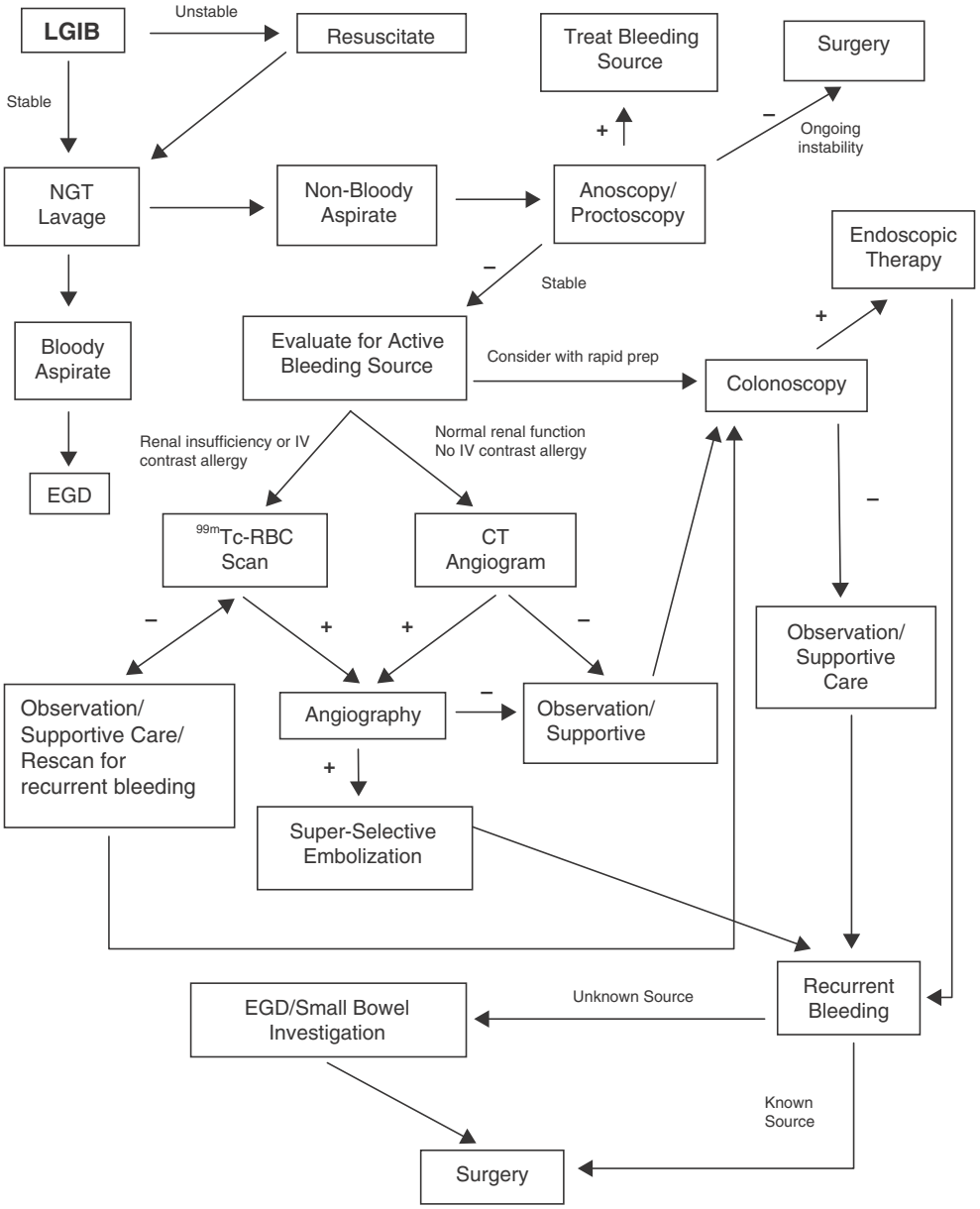

FIGURE 41-6. Algorithm for the evaluation and management of the patient with LGIB (lower gastrointestinal bleeding).

LGIB, with the main contributor being sepsis from an anastomotic leak [145]. Rebleeding rates after total abdominal colectomy generally are less than 5%, and modern advances in postoperative ICU care have reduced postoperative mortality to 2–6% [146–151].

When the bleeding site has been localized but endoscopic or angiographic attempts to control it have failed, a targeted segmental resection is indicated, either with primary anastomosis or a stoma dictated by the patient's clinical condition at the time of surgery. In this scenario, rebleeding rates and mortality are 4–10% and 0–40%, respectively [77, 147–149]. Compared with subtotal colectomy and ileorectal anastomosis, segmental colectomy provides measurable improvements in postoperative morbidity, BM frequency, social restrictions, and overall quality of life [152].

A "blind" segmental resection without preoperative localization should not be performed. The previously held tenet that the majority of GI bleeds are left-sided is no longer felt to be accurate. Blind segmental resections have been shown to have mortality rates ranging from 30 to 57% with rebleeding rates of 33–75% [148, 151, 153, 154].

Summary

LGIB is a commonly encountered condition, with a number of possible etiologies and several options for evaluation. Key points in the management include restoring hemodynamic stability, identifying and localizing ongoing bleeding, and cessation of hemorrhage, either by radiographic or

surgical means. There are a number of options in the evaluation of patients with LGIB, which should be individualized to the experience of the evaluating physician and available resources.

New technologies such as CTA and earlier use of colonoscopy now allow for more rapid and accurate detection of active bleeding; the number of nondiagnostic invasive angiograms has diminished, and pre-angiographic localization of an active bleeding site via CTA helps to facilitate treatment via therapeutic angiography. Advances in interventional techniques and use of microcatheters have improved the efficacy of therapeutic angiography and reduced the risk of postembolic ischemia. Fewer patients are undergoing emergency surgery for nonlocalized bleeding, even fewer are requiring subtotal colectomy for nonlocalized LGIB, and those who do require surgery fare much better than in the past due to improvement in postoperative ICU care.

However, despite the advances and new technologies, LGIB can still present significant diagnostic and therapeutic challenges to the treating physician. Employing a well-defined strategy in the evaluation and management of the patient can help to minimize unnecessary hospital admissions and make the best use of healthcare resources. An algorithm summarizing the evaluation and management of the patient presenting with LGIB is presented in Figure 41-6.

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42 Endometriosis

Michael J. Snyder

Key Concepts

- Endometriosis is a common cause of young women having major surgery.
- Endometriosis causes infertility, pelvic pain, and dyschezia.
- Laparoscopy has revolutionized the diagnosis of endometriosis.
- Symptomatic endometriosis usually requires surgery.
- Excision of deep pelvic endometriosis is often a combined procedure with gynecologists and urologists.

Introduction

Endometriosis is a disease characterized by the presence of endometrial glands and stroma outside the uterine cavity. It is one of the most common conditions requiring surgery for women during their reproductive years. Endometriosis, while not fatal, may be associated with disabling pain and intractable infertility. The degree of symptoms varies widely and does not always correspond to the extent of pathology encountered at surgery. Small lesions may cause severe pain and infertility, while larger lesions may be asymptomatic and be found only incidentally during surgery for other diagnoses. Diagnosis is typically made or confirmed at laparoscopy or during laparotomy. Colon and rectal surgeons often become involved in the management of patients with intestinal endometriosis. This involvement may occur as a result of a combined procedure with a gynecologist or in management of an endometrioma masquerading as a neoplastic or inflammatory lesion. Treatment for endometriosis is usually multimodal and may require surgery in those patients with infertility, pelvic pain, obstruction, or a poor response to hormonal suppression. While advances in diagnostic tests and therapy have been made, endometriosis remains a frustrating and incompletely understood disease for both the patient and her physicians.

Epidemiology

The true prevalence of endometriosis is unknown. There is no noninvasive screening test for endometriosis, and its diagnosis depends on the visual or pathologic identification of implants during laparoscopy or laparotomy. Various authors have estimated that up to 15% of all women of reproductive age and one-third of infertile women have endometriosis [1, 2]. A study by Houston et al. is the only population-based study of endometriosis [3]. After reviewing the medical records for Caucasian women in Rochester, Minnesota, during the 1970s, they estimated that 6.2% of premenopausal women have endometriosis. The potential economic and societal cost of endometriosis was illustrated by the US Health Interview Survey. It found that 50% of women with endometriosis were unable to work at some time during the prior 12 months, losing an average of 17.8 days [4].

While endometriosis is primarily a disease of the reproductive years, the widespread use of exogenous estrogens and increasing obesity in our society have made it more prevalent in postmenopausal women. Conversely, there is a decrease in the incidence of the disease when women use oral contraceptives or experience multiple pregnancies [5]. These observations, coupled with the fact that the incidence of endometriosis increases over time after a woman's last childbirth, suggest that uninterrupted menstrual cycles predispose susceptible individuals to the development of endometrial implants [6]. An inverse relation with smoking and exercise is most likely due to diminished estrogen levels. There is no racial predilection for endometriosis other than in Japanese women who have double the incidence of the disease than do Caucasian women [7].

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Etiology

The precise etiology that completely explains the cause and pathogenesis of endometriosis is unknown. The two most popular theories as to its etiology are coelomic metaplasia and the implantation of viable endometrial cells from retrograde menstruation through the fallopian tubes. Coelomic metaplasia, postulated by Meyers, suggests that under the correct hormonal milieu, the coelomic epithelium will undergo metaplastic changes and transform into endometrial tissue [8]. He bases his theory on studies demonstrating that the peritoneum and uterine endometrium both originate from embryonic coelomic epithelium. While this theory offers a good explanation for endometriosis in men and non-menstruating women, it does not adequately address the anatomical distribution and clinical pattern of endometriosis. The vast majority of endometriosis occurs in the pelvis, but the peritoneum at risk with this theory is evenly distributed throughout the abdominal cavity. In addition, metaplasia should worsen with age, and endometriosis clearly does not.

Retrograde menstruation, first proposed by Sampson in 1921, remains the most plausible explanation for the distribution of endometrial implants [9]. This theory postulates that endometriosis arises from retrograde menstruation through the fallopian tubes and into the peritoneal cavity. Viable endometrial tissue has been demonstrated in menstrual effluent, and endometriosis has been induced both in primates, with artificially produced retrograde menstruation [10], and in women volunteers who permitted injection of menstrual tissue into their peritoneum [11]. This theory, however, is probably only part of the answer.

While retrograde menstruation is very common, occurring in virtually all women, endometriosis affects only a small minority. Clearly other factors must be involved to permit the implantation and growth of endometrial tissue. Several studies indicate a possible genetic aspect to endometriosis. Simpson et al. demonstrated that the disease appears to occur more commonly within families. He found a 7% relative risk for blood relatives of affected individuals as opposed to a 1% relative risk for non-blood controls [12]. Additionally, the clinical manifestations of the disease were more severe among the related group. It appears that the inheritance pattern is polygenic or a combination of genetic and environmental factors. This conclusion is consistent with the clinical associations with delayed childbearing and uninterrupted cyclic menstruation.

Dmowski et al. have theorized that the genetic factor may involve the immune system [13]. They demonstrated depressed cellular immunity in monkeys with spontaneous endometriosis. Other investigators have confirmed alterations in both cellular and humoral immunity in humans [14, 15]. The most striking change observed in cellular immunity is the high concentration of activated macrophages and decreased functional capacity of natural killer cells. The most significant abnormality in humoral immunity is the presence of autoantibodies against different cellular components. These changes have been observed in both the peritoneal cavity and the systemic circulation, suggesting that endometriosis may be a systemic disease. It is still unclear whether these changes represent manifestations of the disease or a subsequent reaction to it. This research, however, suggests that mild subclinical immunosuppression may subsequently lead to endometriosis many years later.

Table 42-1. Sites and incidence of endometriosis

Common	Less common
Ovaries 60–75%	Appendix 2%
Uterosacral ligaments 30–65%	Ureter 1–2%
Cul-de-sac 20–30%	Terminal ileum 1%
Uterus 4–20%	Bladder < 1%
Rectosigmoid colon 3–10%	Abdominal scars < 1%

Rare, the diaphragm, inguinal canal, liver, spleen, kidney

Clinical Manifestations

The most common sites where endometriosis occurs are summarized in Table 42-1. The most frequent of these are in the pelvis. Potential sites of implantation in the abdomen include the appendix, small bowel, and diaphragm. Rarely, implantation may occur in the inguinal canal (in patients with hernias), surgical incisions, the vulva, vagina, cervix, or systemically in the lungs, bronchi, or kidneys.

As the majority of women have disease confined to the pelvis, the most common presenting complaints relate to menstrual irregularities, pelvic pain, and infertility. Many women with endometriosis may be completely asymptomatic, and the natural history of the disease in these patients has never been well defined. In studies with placebo arms, a few interesting observations have been made. A trial involving infertile women with otherwise asymptomatic endometriosis revealed that laparoscopic scoring of the severity of the disease increased over the length of the study in almost 50% of the placebo group [16]. Another study compared pain scores in women receiving placebo versus gonadotropin-releasing hormone (GnRH) analogs [17]. The cumulative dysmenorrhea rate and severity of pain were significantly lower in the treatment group suggesting a progressive course of the disease. Other studies on infertile women revealed that mild endometriosis can spontaneously resolve and that medical therapy may only suppress the disease until hormonal stimulation resumes [18].

Pelvic Pain and Dysmenorrhea

Pain is the most common symptom of endometriosis, affecting up to 80% of patients subsequently diagnosed with the disease. Endometriosis has been discovered in 30–50% of women undergoing laparoscopy for pelvic pain [19].

Pelvic pain associated with endometriosis presents as dysmenorrhea, dyspareunia, or chronic noncyclic pelvic pain. There are women, however, with extensive endometriosis and little or no pain. Total lesion volume does appear to correlate directly to the degree of pain [20]. Symptoms are related to the depth of penetration of the lesion, the type of lesion, and its location. Implants involving the uterosacral ligaments and rectovaginal septum are most often implicated. The pain is typically most intense just prior to menstruation and lasts for the duration of menstruation. The pain is often associated with back pain, dyschezia, and levator muscle spasm and is more severe with advanced stages of endometriosis.

Dysmenorrhea occurs in most women with endometriosis. The association is not well understood, and some have hypothesized that high uterine pressures cause dysmenorrhea with retrograde menstruation a consequence of these elevated pressures [21]. Other investigators, however, have failed to show an increase in the prevalence of dysmenorrhea with early stage endometriosis [22].

Dyspareunia, deep pelvic pain with vaginal penetration, is usually a symptom of advanced endometriosis. Dyspareunia is most pronounced just prior to menstruation and is associated with specific coital positions. The presence of dyspareunia is often indicative of the degree of fixation of the pelvic organs, especially in the cul-de-sac of Douglas and the rectovaginal septum.

Chronic noncyclic pelvic pain is pain present for longer than 6 months and may be intermittent or continuous. The pain is often associated with both perineural inflammation and uterosacral ligament involvement with endometriosis [23]. Gastrointestinal and urinary complaints may accompany the pain.

Pain in the shoulder during or just preceding menstruation may be due to endometrial implants involving the diaphragm. The diaphragm should always be viewed during laparoscopy, so these diaphragmatic deposits can possibly be treated with laser vaporization. Differentiation from adhesions associated with pelvic inflammatory disease (Fitz-Hugh-Curtis syndrome) is usually not difficult unless the two pathologies coexist.

The pathophysiology of pain arising from endometriosis is not completely clear. Pain may occur from the cyclic growth and subsequent increase in pressure within the capsule surrounding the implant. Alternatively, extravasation of menstrual debris into the surrounding tissue may occur with subsequent edema and release of inflammatory mediators. As the implant matures with surrounding unyielding scar tissue, the stretching of this scar by the products of the endometrial glands may produce pain. This scenario is probably particularly true for deeper implants. A study by Cornille discovered that all women with implants deeper than 1 cm experienced severe pelvic pain [23].

Adhesions, very common in endometriosis, may be associated with pain. Adherence of the colon and small bowel along with retroflexion of the uterus from extensive posterior adhesions may occur. Such retroflexion and fixation of the rectosigmoid can result in pressure on the sacrum with consequent back and rectal pain.

Since the 1960s, multiple investigators have attempted to define the role of prostaglandins in the pathogenesis of pelvic pain [24, 25]. Macrophages are responsible for the removal of foreign material such as the endometrial implants. They are present around the endometrial implants and are potent producers of inflammatory mediators such as the prostaglandins. Both prostacyclin (PGI-2) and prostaglandin E-2 are able to sensitize pain receptors to chemical mediators. Leukotriene B-4, another macrophage product, is a potent chemotactic agent and leukocyte activator. These factors are thought to explain some of the pelvic pain, but not all the studies agree [25]. The relative transient nature of prostaglandin action and the inherent difficulty in measuring pain complicate attempts to quantify the impact of chemical mediators.

Infertility

The relationship between endometriosis and infertility is also unclear. Some studies have demonstrated a high percentage of infertile patients with endometriosis [26]. Certainly, those reports comparing rates of endometriosis for women undergoing elective laparoscopic sterilization versus laparoscopy for infertility have demonstrated a fourfold or greater increase in the infertile group. In women with known endometriosis, the infertility rate is 30–50%. Whether endometriosis causes infertility or is the product of uninterrupted menstruation is still hotly debated.

There is little disagreement that moderate to severe disease with mechanical distortion of the fallopian tubes, ovaries, and peritoneum can potentiate infertility. Pelvic endometriosis and the resulting inflammatory response can produce dense, fibrotic adhesions that may significantly interfere with both the oocyte release from the ovary and the ability of the fallopian tube to pick up and transmit the oocyte to the uterus. Blockage of the tube may produce a hydrosalpinx, and in one recent study, endometriosis was the etiology in 14% of patients undergoing tubal reconstruction for occlusion [27]. In moderate or severe endometriosis, the pregnancy rates following surgery are 50% and 40%, respectively, compared to only 7% when expectant management is practiced [28, 29]. Surgical treatment of these patients is clearly beneficial.

Treatment of infertile patients with mild endometriosis is more problematic. A study by Inoue on 2000 infertile women with mild endometriosis did not reveal any improvement in fertility with either medical or surgical therapy when compared to expectant management [30]. Other studies have demonstrated a lower pregnancy per cycle rate in patients with endometriosis compared to those free of the disease [31].

Intestinal Symptoms

Although some women with intestinal endometriosis may be asymptomatic, some degree of intestinal complaints is found in those women with moderate to severe disease.

Bowel involvement occurs in 12–37% of cases of endometriosis. Depending on the site of involvement, the symptoms of endometriosis may vary somewhat. In patients with intestinal endometriosis, the rectosigmoid is involved in over 70%, followed by the small bowel and appendix. Rectosigmoid disease often results in alterations in bowel habits such as constipation, diarrhea, a decreased caliber of the stool, tenesmus, or, rarely, rectal bleeding. Such symptoms appear more often around the time of menses and are most likely due to the inflammatory nidus of the endometrial implant. Anal physiology performed between menses does not reveal any evidence of motility or neural disorders except an increase in the resting pressure of the internal anal sphincter [32]. Colonic endometriosis can present with obstruction and may be difficult to differentiate from other causes of large bowel obstruction, such as Crohn's disease or neoplasm. This difficulty is of particular concern in the postmenopausal woman on hormone replacement therapy.

Intestinal perforation may occur with endometriosis. Colonic perforation has been reported during pregnancy from endometriosis [33]. Perforation also occurs with transmural appendiceal endometriosis. For those patients with asymptomatic intestinal endometriosis, the natural history appears to be benign. Prystowsky and Stryker, who followed 44 patients with known intestinal endometriosis for a period of 1–12 years, found that only one patient developed clinically significant gastrointestinal symptoms [34]. Consequently, intestinal resection in these asymptomatic patients is probably unwarranted.

Confusion between small bowel endometriosis and Crohn's disease is common, as both can produce similar laparoscopic, endoscopic, and even histologic findings (Figure 42-1). Small bowel implants involving the terminal ileum are often noted incidentally at the time of laparoscopy and may often be asymptomatic. When symptoms occur, they are usually nonspecific such as recurrent abdominal pain and bloating. Occasionally, acute or chronic small bowel obstruction develops from extensive fibrotic adhesions which are due to endometriosis.

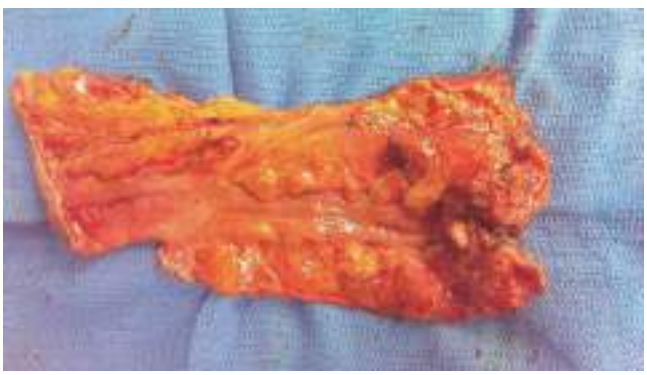


FIGURE 42-1. Gross pathologic specimen of endometriosis involving the small intestine. The specimen cut open with the typical appearance of an endometrioma after hormonal therapy inducing diminished vascularity.

The next most frequent site of intestinal endometriosis is the appendix. Endometrial implants are not infrequently found when the appendix is removed incidentally. The clinical significance of appendiceal endometriosis is less than that involving the small bowel and colon. Although endometrial implants may produce acute appendicitis with right lower quadrant abdominal pain, nausea, fever, and leukocytosis, historically most abdominal explorations for presumed acute appendicitis with a subsequent diagnosis of endometriosis have been due to ruptured endometrial cystic implants involving the ovary. Endometriosis of the appendix may also produce a chronic obstruction of the intestinal lumen with formation of a mucocele or peri-appendiceal inflammatory mass that is difficult to distinguish from a neoplasm. Finally, endometrial implants of the appendix and cecum may serve as lead points for an intussusception.

Malignant Transformation

Malignant transformation of endometriosis was previously considered an uncommon complication of the disease. Almost 80% of the tumors are ovarian, and two-thirds are endometrial carcinomas. An increase in the incidence of ovarian cancer in women with endometriosis has been reported in multiple studies [35, 36]. The histiotypes involved are endometrioid and clear cell tumors. Endometriosis and ovarian cancer are both seen in hyperestrogenic states, and patients with ovarian neoplasms arising from endometriosis are younger than the typical ovarian cancer patient with most tumors occurring in the fourth decade of life [37]. Symptoms of pelvic pain and an enlarging pelvic mass are the most common symptoms. In women with known endometriosis, a cyst larger than 10 cm, cyst rupture, or a change in the nature of the chronic pelvic pain are potential signs of malignancy. Interestingly, while oral contraceptive use decreases the risk of ovarian cancer in general, the effect is exaggerated in those tumors associated with endometriosis [38]. As endometrioid and clear cell ovarian cancers carry a poor prognosis, the long-term use of oral contraceptives is recommended by some to decrease the risk of malignant degeneration [38].

The rectosigmoid colon is the most common site for extragonadal tumors arising from endometriosis. Prolonged unopposed estrogen exposure is a significant risk factor, and rectal bleeding is the most common symptom. Recurrent symptoms of pelvic endometriosis following hysterectomy and bilateral salpingo-oophorectomy can be possible signs of malignant degeneration. Endometrial carcinoma is the most common tumor type. Histologically, the tumor must be shown to arise from the colon rather than invading it from another source. The diagnosis also requires that endometriosis or premalignant changes in endometrial glands be found contiguous with the invasive neoplasm [39].

Treatment of both ovarian and extragonadal tumors is based on the particular stage of the tumor. The prognosis is generally good with tumors confined to the ovary or an extragonadal site having 5-year survivals greater than 60%. Even if a locally extensive tumor is encountered, there may be a benefit from aggressive local resection.

Diagnosis

Physical Examination

Patients with mild cases of endometriosis may have a normal physical examination, and the diagnosis may not even be suspected unless the patient undergoes laparoscopy. For patients with pelvic pain, careful bimanual and rectal examination may reveal nodularity or induration especially in the uterosacral ligaments or cul-de-sac of Douglas. Fixed tender retroversion of the uterus in a patient without previous pelvic surgery may raise suspicion for endometriosis. Palpation of the ovaries may reveal an ovarian mass. As these ovarian masses are generally soft and cystic, those less than 5 cm in diameter may be difficult to palpate. Cyclical pain or bleeding from any location, especially coinciding with menses, should be adequately investigated for endometriosis. The inguinal canal, previous incisions, umbilicus, and lungs can all be potentially involved with endometrial implants.

Laboratory Evaluation

CA-125, an antigen expressed on tissues derived from human coelomic epithelium, is elevated in women with moderate to severe endometriosis. However, the sensitivity and specificity of this test are poor as the antigen may be mildly elevated in other diseases and within the normal range in women with mild endometriosis. The concentration of CA-125 does correlate with the severity of the disease and is probably most useful in gauging response to medical therapy. It may also be of value in following women postresection who had elevated levels preoperatively and are again exhibiting symptoms of endometriosis. No other serum markers are commercially available, but assays of antiendometrial antibodies and endometrial secretory protein PP14 are currently being evaluated for clinical relevance [40].

Endoscopy

As the lesions begin on the outside of the intestine, endoscopic evaluation of the large bowel is often normal except in severe disease or infiltrating nodular endometrial implants. Occasionally, serosal involvement with adhesions can lead to obstruction. Endoscopically, the mucosa is generally intact, occasionally associated with significant luminal narrowing. Infiltration of the submucosa, while uncommon, may produce

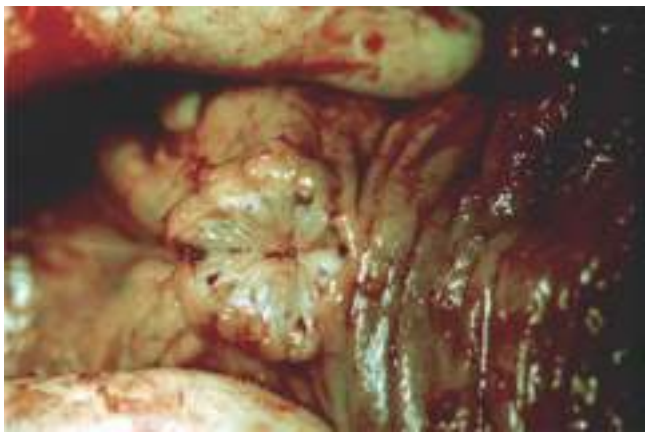


FIGURE 42-2. Polypoid endometrial implant of the colon causing mucosal abnormalities.

nodularity and distortion of the overlying mucosa (Figure 42-2). These findings may be difficult to visually differentiate from Crohn's disease, ischemia, or malignancy. Pressure against these areas of distorted bowel may produce pain that suggests the diagnosis of endometriosis. In addition, biopsies of the mucosa, taken in areas of endometriosis, can resemble solitary rectal ulcer or prolapse syndromes. Rarely is the diagnosis of endometriosis definitively confirmed by endoscopy or from endoscopic biopsies. Colonoscopy is, however, useful in excluding colon cancer from the differential diagnosis, especially in older patients presenting with a rectosigmoid mass while on hormone replacement.

Rigid proctoscopy is very helpful in predicting the depth of rectosigmoid involvement in patients with severe endometriosis of the cul-de-sac of Douglas. After two enemas are given to remove any fecal debris, the rigid proctoscope is deployed above the rectosigmoid and slowly withdrawn with care to maintain adequate insufflation. The mucosa is often fixed over an area of submucosal or deep muscular involvement with tethering or puckering and loss of the normal mucosal mobility. In our experience, these mucosal findings have correlated with significant intestinal wall invasion by the endometrial implant and often a need for intestinal resection.

Imaging Techniques

Imaging techniques used to facilitate the diagnosis of endometriosis include ultrasonography, barium enema, computerized tomography (CT), magnetic resonance imaging (MRI), and immunoscintigraphy. Many of these tests are obtained for the evaluation of chronic pelvic pain and/or bleeding from the reproductive tract or colon. They are primarily utilized to rule out more common conditions, but there are some findings that may strongly suggest the diagnosis of endometriosis before visual or pathologic confirmation by laparoscopy or laparotomy.

Transvaginal ultrasound has been used for several years to evaluate ovarian endometriomas. It is a sensitive test and in experienced hands provides specificity greater than 90% for ovarian endometriosis. Ultrasound of the pelvis, however, is not very sensitive in detecting focal non-ovarian endometrial implants. Endometriosis has been termed "the great mimicker" because the appearance on ultrasound is highly variable with some lesions being nearly sonolucent and others quite echogenic.

Endorectal ultrasound is a potentially valuable tool to determine rectal wall invasion by endometrial implants in the cul-de-sac. Chapron and colleagues studied the reliability of endorectal ultrasound in assessing the depth of bowel invasion with rectovaginal endometriosis [41]. In seventeen patients with proven deep pelvic endometriosis, the ultrasound revealed infiltration of the bowel wall and suggested the need for intestinal resection. The ultrasound findings were subsequently confirmed at laparoscopy and evaluation of the pathologic specimen in sixteen patients. Twenty-one other patients with endometriosis of the cul-de-sac of Douglas whose ultrasounds did not show infiltration of the rectal wall did not require intestinal resection and were able to have complete removal of the endometriosis with laparoscopic techniques without complications. The accuracy of ultrasound was confirmed by Doniec and colleagues who determined both the sensitivity and specificity of preoperative staging of rectal wall involvement by endometriosis to be 97% [42]. The only real concern in evaluating patients having cul-de-sac endometriosis by endorectal ultrasound is the significant discomfort experienced by the patient when rectal distention from the balloon probe compresses the endometrial implant.

Barium enema examination is another imaging technique often obtained by gynecologists for the intestinal complaints associated with deep pelvic endometriosis. The lateral and prone cross table views of the rectum offer excellent evaluation of the cul-de-sac of Douglas as long as care is taken in ensuring that the balloon is kept in the distal rectum (Figure 42-3). Studies in patients without bowel wall involvement are either normal or reveal smooth extrinsic compression with normal mucosa. Deep invasion of the bowel wall by endometriosis produces a variety of appearances on barium enema. Irregularities of the rectal wall such as tethering or even polypoid lesions may be difficult to distinguish from inflammatory bowel disease or neoplasm. Strictures of the rectosigmoid may also be identified on barium enema.

Computerized tomography is the imaging technique probably used most frequently for the evaluation of abdominal and pelvic pain. Unfortunately, there is no standard CT appearance for a mass cause by endometriosis to clearly differentiate it from pelvic masses due to other causes. Cystic lesions are more commonly seen on the ovaries, while deeper pelvic disease usually consists of either solid lesions or mixed cystic/solid lesions. CT evaluation of the pelvic sidewall for endometrial implants is better than ultrasound, but there is still significant overlap between infectious and malignant pathology. CT scanning is probably most useful for patients with pelvic pain and a negative ultrasound to assess the musculoskeletal boundaries of the pelvis and the rectosigmoid colon.

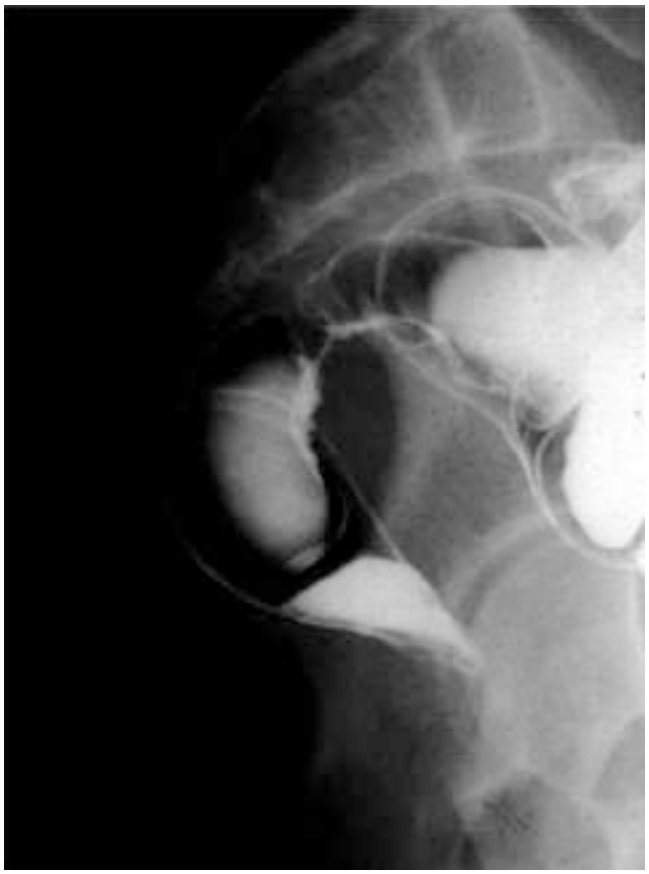


FIGURE 42-3. Barium enema demonstrating a rectosigmoid stricture from endometriosis.

When pelvic endometriosis is strongly suspected, magnetic resonance imaging (MRI) is more useful than CT scanning because of the benefit of imaging in multiple planes and the lack of ionizing radiation. MRI may be the best noninvasive modality for imaging suspected endometriosis. Colorectal involvement on MRI is strongly suggested when there is disappearance of the fat plane between the rectum and the vagina, loss of the hypointense signal of the anterior bowel wall on T2-weighted images, and a contrast-enhanced mass on T1-weighted images involving the bowel wall [43]. Sagittal images are particularly valuable in imaging the cul-de-sac of Douglas. MRI is superior to CT scanning for extraperitoneal lesions and the evaluation of pelvic masses [44]. Identification of endometrial implants is dependent on the hemorrhage that occurs in these lesions. The time between imaging and the most recent hemorrhage may determine in which weighted images the masses are most intensely seen. The sensitivity and specificity of MRI for detecting and adequately evaluating colorectal endometriosis are approximately 78% and 98%, respectively [44].

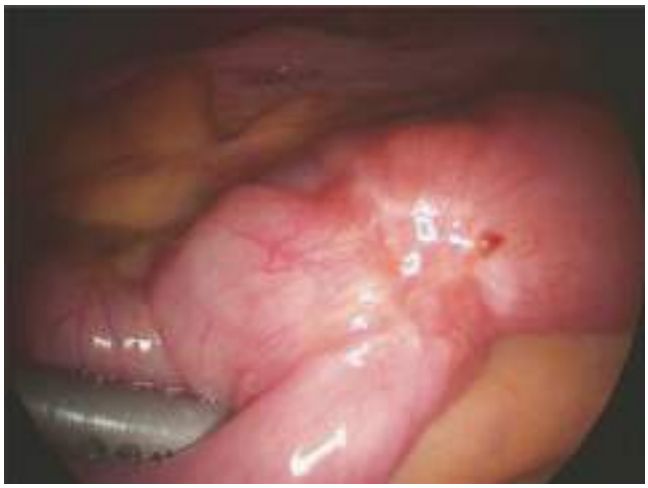


FIGURE 42-4. Laparoscopic view of an endometrial implant on the small intestine.

Immunoscintigraphy with radioactive iodine-labeled CA-125 monoclonal antibodies has been studied to clarify the extent of pelvic endometriosis, particularly in the face of severe pelvic adhesive disease [45]. In such a study of 28 women, 22 had a positive test with 16 confirmed to have endometriosis. Two of five women had a negative test despite having histologically confirmed endometriosis. As such, immunoscintigraphy is not currently recommended for screening and remains primarily a research tool.

Laparoscopy

The diagnosis of endometriosis usually requires direct visual and/or tactile assessment of the abdomen and pelvis. Laparoscopy is currently the initial approach to many patients suspected of having endometriosis and has revolutionized both its diagnosis and treatment (Figure 42-4). In experienced hands, laparoscopic evaluation is 97% sensitive and 77% specific diagnosing endometriosis [46]. Obtaining a biopsy to confirm the visual diagnosis is strongly recommended for at least one lesion and is especially critical for deep disease and endometriomas greater than 3 cm in diameter to exclude malignancy [47]. Most patients with severe pelvic pain and many patients with refractory infertility undergo laparoscopy. The timing of laparoscopy in relation to the menstrual cycle is unimportant except in patients being evaluated for infertility. In these patients, the procedure is performed in the luteal phase to provide additional valuable information concerning ovarian function.

The technique of diagnostic laparoscopy has become widespread in both the surgical and gynecologic literature. A camera, often attached to a video monitoring system with photographic and recording capabilities, is introduced at the level of the umbilicus or upper abdomen, while a second instrument is placed in a suprapubic location to allow manipulation of the pelvic and abdominal viscera. A thorough examination of the entire abdomen and especially the pelvis is critical to enable complete assessment of the disease. Both ovaries should be mobilized to evaluate the pelvic peritoneum, and the uterus should be manipulated to allow complete visualization of the cul-de-sac of Douglas, uterosacral ligaments, sigmoid colon, and ureters. It is important to view the base of the appendix as well as the distal small bowel.

Obtaining a complete assessment of the abdominal and pelvic viscera can be technically demanding. The accuracy of laparoscopy is completely dependent on the surgeon's visual evaluation of the abdomen and pelvis. The findings of endometriosis can be very subtle, and several studies have demonstrated that visually normal peritoneum may have microscopic evidence of endometriosis [48]. The extent of endometriosis should be carefully documented and staged. The current staging system has been formulated primarily for infertility and was revised by the American Society for Reproductive Medicine in 1998 (Figure 42-5) [49]. This revision is certainly an improvement over previous staging systems that were more concerned with adhesions than with implants. Virtually all patients with intestinal lesions requiring resection are stage 4 especially if they have cul-de-sac involvement.

The current classification system, however, is often not useful for the gastrointestinal surgeon. The more critical information for the surgeon is the identification and location of intestinal lesions. There is no uniform type of endometrial lesion. The classic implant is nodular with a variable degree of fibrosis and pigmentation. The color may be black, white, brown, blue, or even red. The appearance of the lesion may be vesicular, papular, or hemorrhagic (Figure 42.5). Glandular tissue is found in the great majority of these lesions. Lesions may change color or consistency over time, with red lesions noted early in the course of the disease and blue/black ones typical of older implants. Healed implants appear as fibrotic nodules. There are also a wide variety of atypical lesions occasionally associated with positive biopsies. The inability to definitively identify endometriosis through purely visual means necessitates pathologic confirmation of the disease before a definitive diagnosis can be made, especially in mild disease.

Implants in the cul-de-sac of Douglas, which occur in nearly 20% of women with endometriosis, were initially described by Cullen in 1920. Ninety percent of these represent an important variant that is especially relevant for the intestinal surgeon. Histologically, these lesions are characterized by desmoplastic tissue composed of fibrous and smooth muscle cells with strands of endometrial glands and stroma. The major component of the lesion is the fibromuscular tissue and not the endometrial tissue typical of other locations. These implants are both proliferative and infiltrating, and more than 25% extend at least five millimeters in

Patient's Name _____ Date _____

Stage I (Minimal) - 1–5
Stage II (Mild) - 6–15
Stage III (Moderate) - 16–40
Stage IV (Severe) - > 40
Total _____

Laparoscopy _____ Laparotomy _____ Photography _____
Recommended Treatment _____
_____
Prognosis _____

PERITONEUM	ENDOMETRIOSIS	< 1cm	1–3cm	> 3cm
	Superficial	1	2	4
	Deep	2	4	6
OVARY	R Superficial	1	2	4
	Deep	6	16	20
	L Superficial	1	2	4
	Deep	4	16	20

POSTERIOR CUL-DE-SAC OBLITERATION	Partial	Complete
	4	40

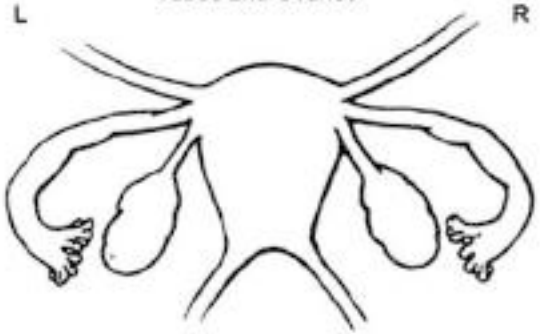
OVARY	ADHESIONS	< 1/3 Enclosure	1/3–2/3 Enclosure	<2/3 Enclosure
	R Filmy	1	2	4
	Dense	4	8	16
	L Filmy	1	2	4
	Dense	4	8	16
TUBE	R Filmy	1	2	4
	Dense	4•	8•	16
	L Filmy	1	2	4
	Dense	4•	8•	16

•If the fimbriated end of the fallopian tube is completely enclosed, change the point assignment to 16.
Denote appearance of superficial implant types as red [(R), red, red-pink, flamelike, vesicular blobs, clear vesicles], white [(W) opacifications, peritoneal defects, yellow-brown], or black [(B) black, hemosiderin deposits, blue]. Denote percent of total described as R___ %,W___ % and B___ %. Total should equal 100%.

Additional Endometriosis: _____
_____
_____
_____

Associated Pathology: _____
_____
_____
_____

To Be Used with Normal Tubes and Ovaries



To Be Used with Abnormal Tubes and/or Ovaries

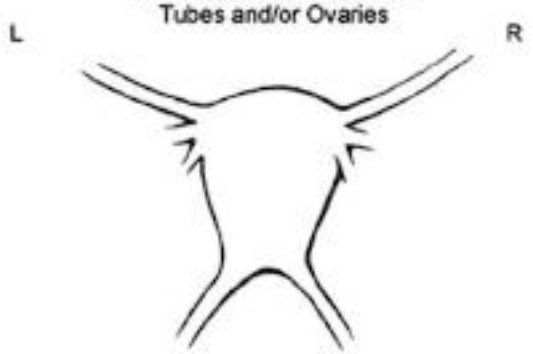


FIGURE 42-5. Revised American Society for Reproductive Medicine 1996 classification of endometriosis.

depth [50]. The depth of invasion may be difficult to assess laparoscopically, and the full extent of the implant may not be appreciated until laparotomy. The progressive fibrosis leads to narrowing of the intestinal lumen and occasionally to bowel obstruction.

These rectovaginal implants also behave differently during the menstrual cycle. There is poor to absent secretory changes during the luteal phase. Vasodilatation and not necrosis and bleeding occur at menstruation. Resistance to medical therapy is common with several studies demonstrating no significant decrease in mitotic activity in rectovaginal endometriosis after GnRH agonist treatment [51]. This resistance is felt to be due to estrogen receptor inactivity, inadequate drug access, or genetic programming that is only secondarily affected by estrogen.

Treatment

Treatment options for women with endometriosis are currently based upon the severity and type of symptoms. Currently, prevention of endometriosis is not yet possible, and therefore treatment is primarily begun to ameliorate symptoms. Some women with endometriosis are completely asymptomatic, and the implants are found incidentally at the time of surgery for other reasons. A study by Martin in 1989 revealed that 25% of women undergoing elective tubal ligation had asymptomatic endometrial implants [52]. This finding strongly suggests that not all women with endometriosis require treatment. Other authors have analyzed the prevalence of endometriosis in these asymptomatic women with regard to the time from their last pregnancy. They discovered that the odds of having endometrial implants increased significantly at 10 years following the last pregnancy [6, 53]. Consequently, as the natural history appears unclear, long-term follow-up of these patient cohorts may demonstrate late development of symptoms and the need for more aggressive medical or surgical management.

Before the introduction of diagnostic laparoscopy in the 1960s, exploratory laparotomy was the only modality available for the diagnosis and treatment of endometriosis. Laparoscopy revolutionized the diagnostic evaluation of these women and allowed patients with limited disease to undergo medical therapy. With improvements in laparoscopic techniques and equipment in the past decade, notably the development of laparoscopic laser techniques, many if not most early endometrial lesions can now be ablated or excised at the time of diagnosis. Even complex excisional surgery involving the bowel and ureter can be performed safely via a laparoscopic approach in many patients especially with mild and moderate disease. As advanced laparoscopic techniques have become more widespread, the indications and use of medical therapy are also evolving.

Medical Management

Medical therapy is designed to treat the symptoms of endometriosis, notably pelvic pain. As pelvic pain may have causes other than the endometriosis seen during laparoscopy, a trial of ovarian suppression is often used to help determine the contribution of the pain from the endometrial implants. In those patients with infertility, with or without pelvic pain, the primary goal is an intrauterine pregnancy. After other causes of infertility have been excluded, ovarian suppression may allow for laparoscopic removal of smaller endometrial lesions with optimal preservation of ovarian tissue.

Despite the many advances in the surgical treatment of endometriosis, there are still some significant advantages to medical therapy. Surgery can remove only lesions that are both visible and accessible. Microscopic disease or disease on vital structures is often left behind. Subsequent recurrence is not surprising. Additionally, there are complications associated with ablative surgery in the pelvis, especially if the woman requires multiple attempts at control of her disease. For infertile women, the adhesions that can form following any pelvic surgery may further impair the ability to conceive. In addition, laser destruction of ovarian implants may destroy germinal tissue and conceivably limit the reproductive potential from the involved ovary. In limited disease, medical therapy is comparable with surgery in terms of relief of symptoms, recurrence of disease, and subsequent pregnancy rates. Finally, medical therapy does not require specialized training or equipment and is much less costly than surgery.

Medical therapy alone also has significant potential disadvantages. All the hormonal therapies subsequently discussed have side effects and often require prolonged treatment. For example, medical therapies manipulate the hormonal environment to suppress the cyclic secretion of ovarian estrogen and progesterone, and this suppression induces atrophy of the ectopic endometrium so that over several months the implants regress. Advanced lesions, especially those with a nodular, proliferative histology, will often only partially regress. No current hormonal regimen can completely eradicate these lesions, and upon cessation of therapy, the lesions may again become symptomatic.

Oral Contraceptives

The first effective medical therapy for endometriosis was introduced by Kistner. He proposed the administration of high-dose, continuous estrogen/progestogens in 1958. These agents result in the induction of pseudopregnancy with hyperhormonal amenorrhea. Pituitary and ovarian function is thereby suppressed, and in the later stages of the treatment regimen, endometrial implants resorb and resolve. The usual treatment regimen consists of daily administration of a tablet for 6–9 months. When Vercellini and colleagues compared

oral contraceptives with GnRH agonists, they found that deep dyspareunia and pelvic pain were reduced in both groups with fewer side effects experienced by the oral contraceptive women. Pain relief appeared similar in the two groups at 1 year [54]. Side effects rarely cause cessation of treatment, but exacerbation of endometriotic symptoms may occur early in the course of treatment.

Another drug regimen used for the treatment of endometriosis involves administration of synthetic progestogens alone. This may induce a pseudopregnancy by acting in concert with endogenous estrogens. Ovarian suppression is often inconsistent. Both oral and depot preparations are available. In patients who do not desire pregnancy and in whom surgery is contraindicated, depot progestogens have been effective in ameliorating pelvic pain with equivalent efficacy to danazol [55]. Side effects include breakthrough vaginal bleeding, weight gain, and fluid retention.

Danazol

Danazol was first used extensively for endometriosis in the mid-1970s and, until the introduction of GnRH agonists (GnRH-a), was the most widely used drug for suppression of the ectopic endometrium. Danazol lowers peripheral estrogen and progesterone levels by a direct effect on ovarian steroidogenesis and pituitary production of FSH and LH. Danazol also binds directly to endometrial cellular receptors leading to atrophy and suppression of proliferation. In addition, danazol is a potent immunomodulator with beneficial effects on both humoral and cellular immunity [56].

The side effects of danazol necessitate discontinuation in less than 5% of patients for short courses [57] but are poorly tolerated for long-term suppression. Predictable manifestations of menopause are most common. Danazol also raises free testosterone levels and produces a hyperandrogenic state, especially at lower doses. Hirsutism, acne weight gain, and deepening voice changes may occur. In addition, since danazol alters lipid metabolism and liver function, it should not be used in women with elevated liver enzymes, liver disease, or complications of atherosclerosis.

Gonadotropin-Releasing Hormone Agonists

The introduction of GnRH-a as a new treatment modality for endometriosis has improved results primarily by a reduction in side effects. GnRH-a is a synthetic molecule derived from the ten-peptide-long GnRH. Continuous administration of GnRH-a completely suppresses pituitary release of FSH and LH. Administered either by injection or intranasally beginning in the mid-luteal phase of the menstrual cycle, the current recommended length of therapy is 6 months. Pain relief is complete in over 50% of women and significantly decreased in over 90%. Laparoscopic evaluation after 6 months of treatment indicates resolution or a significant decrease in size of the lesions in the majority of patients. Studies comparing danazol and GnRH-a indicate similar clinical efficacy [58].

Side effects of GnRH-a are predictably due to the sometimes profound hypoestrogenic state many of these women experience. Cessation of therapy for side effects is uncommon. The degree of bone mineral density loss that can occur with the typical 6-month treatment regimen is 5–6%. This limits the use of GnRH-a to 6 months. The bone mineral loss usually recovers 6–12 months after discontinuation and can be significantly prevented by the daily administration of tibolone [59]. Obviously, GnRH-a is not recommended for women with preexisting osteoporosis. Interestingly, a potentially serious complication can result when GnRH-a is inadvertently administered at the wrong point in the menstrual cycle, and a brief period of hypersecretion of FSH and LH occurs. Rarely, this upsurge in gonadotropin activity may precipitate an acute exacerbation in endometriotic symptoms, occasionally necessitating emergency surgical intervention [54].

A frequent use of GnRH-a is as a neo-adjuvant or adjuvant therapy for surgery. Benefits to include a reduction in postoperative adhesion formation and recurrence in the pelvis from lesions not visualized or removed at the time of surgery have been theorized [55]. Studies evaluating postoperative GnRH-a administration have failed to establish efficacy although ongoing investigation may still show a benefit [60]. Using the GnRH-a for a preoperative course clearly shrinks many of the nodules of endometriosis especially on the pelvic sidewalls, ovaries, and small intestine. It is important to document the location of these lesions as they may significantly change morphology. After a 3-month course of GnRH-a, the lesions have often lost much of their mass and may appear white. They can be difficult to see and may extend much deeper than appear initially. Unfortunately, the deep infiltrating lesions of the cul-de-sac and rectovaginal septum do not shrink as much, although the patient often has relief of her severe pelvic pain during the course of treatment. Most importantly, the dissection of the pelvic sidewalls is technically less challenging, facilitating removal of the peritoneal implants and better pelvic hemostasis and allowing careful preservation of the gonadal vessels in patients desiring children.

Future Drugs

Aromatase is an enzyme that catalyzes the conversion of androgens to estrogens. It is the rate-limiting step in the production of estrogen and endometriotic implants that express high levels of aromatase. There are currently two kinds of inhibitors, steroidal and nonsteroidal. Both classes of inhibitors reduce circulating estrogen to less than 10% of pretreatment levels in postmenopausal women or premenopausal women with nonfunctioning ovaries [61]. Consequently, as they do not block estrogen production completely, they are primarily indicated for postmenopausal women or in

conjunction with other agents to reduce the toxicity of the therapy. In a randomized trial, patients with severe endometriosis received either a combination of GnRH-a and an aromatase inhibitor or a GnRh-a alone. The combination therapy was effective in alleviating pelvic pain without concomitant bone mineral density changes and may become an alternative to extirpative surgery in some patients [61].

Another avenue of investigation has been with immunomodulators and anti-inflammatory drugs. As mentioned earlier, defects in the immune system may play a role in the development of endometriosis. Peritoneal macrophages are increased in both number and activity. Whether the elevated cytokines and other inflammatory agents are causing the disease or are the result of the lesions, the cascade of agents amplifies the response and appears to assist the progression of the disease [62]. Cyclooxygenase inhibitors have been studied in a prospective randomized trial compared to a placebo. Pelvic pain and dyspareunia were reduced in patients with stage 4 endometriosis [62]. While tumor necrosis factor (TNF) is elevated in the peritoneal fluid of patients with endometriosis, none of the TNF inhibitors have shown any efficacy although studies are ongoing [62].

Surgical Management

Surgical treatment of endometriosis has evolved significantly over time. Before the advent of laparoscopy and suppressive medical therapy, most operations were performed for advanced disease and consisted of radical removal of the uterus and ovaries. While the most effective treatment of pelvic pain still consists of surgical castration along with resection of the endometrial implants, many of these young patients strongly desire to maintain their options for pregnancy. Currently, surgery is considered conservative only when reproductive potential is preserved. Therefore, the major goal of surgical therapy for endometriosis is to completely excise or ablate the endometrial implants. Secondary goals include preservation of ovarian function and minimizing postoperative adhesion formation. Currently, we approach these patients in concert with gynecologists experienced with treating ovarian endometriosis to completely remove all gross disease, restore normal anatomy, and optimize fertility.

General Principles

Endometriosis is an invasive disease that can extend deeply into the retroperitoneum and is often surrounded by a rim of fibrosis that may make it difficult to completely assess the true extent of the implant. Removal of the lesions requires sharp excision or vaporization with electrocautery and/or the CO_2 laser. Both techniques have the potential for iatrogenic injury to the intestinal or urinary tracts. Recognizing when a lesion is completely ablated is highly dependent on surgical technique and the expertise of the surgeon. Utilizing techniques that minimize injury to the surrounding tissue, such as a cutting current to outline lesions to be removed by electrocautery and high-power density settings with the CO_2 laser, is desirable. Laparoscopic hydrodissection is also very useful in identifying normal surrounding tissue.

Meticulous hemostasis and frequent irrigation are critical to maintaining good visualization of the operative field in both open and laparoscopic surgery. Tissue planes are often distorted, especially in the cul-de-sac of Douglas, and intraoperative instrumentation of the vagina or proctoscopic evaluation of the rectum may help avoid iatrogenic injury to these structures. Finally, minimizing tissue trauma with gentle handling will decrease adhesions and maximize potential fertility.

All patients undergoing surgery for advanced endometriosis, either by an open or laparoscopic approach, should have a full mechanical and antibiotic bowel preparation. Prophylactic antibiotics and other appropriate practices for patients undergoing major abdominal or pelvic surgery are standard. Patients are positioned in the low lithotomy position with access to both the vagina and rectum for instrumentation. Ureteral stents are liberally used and are especially useful in women with severe obliterative disease in the cul-de-sac and in reoperative pelvic surgical procedures.

Provided that complete removal of the endometriosis is performed, no specific technique or approach has been proven to be superior. With endometriosis, the surgeon's experience and skill are paramount. In experienced hands, laparoscopic removal of extensive endometriosis can be accomplished. However, removal of deep lesions in the rectovaginal septum necessitating bowel resection still often requires open laparotomy to safely and completely excise the endometrial implant with restoration of intestinal continuity.

The management and techniques concerning the surgical treatment of ovarian and ureteral endometriosis are extensively discussed in the appropriate gynecologic and urologic literature. This discussion on surgical therapy will concentrate on management of intestinal lesions (Figure 42-6).

Rectovaginal Endometriosis

Endometriosis of the cul-de-sac of Douglas that extends into the rectovaginal septum is the most common site of intestinal involvement and may require intestinal resection. These lesions are often deep fibrotic nodules that extend from the posterior vagina and anterior rectum to the uterosacral ligaments (Figure 42-7a–d). Small superficial lesions involving the intraperitoneal rectum may be vaporized with the CO_2 laser or electrocautery. When using either technique, it is critical to initially outline the lesion to be removed to ensure complete extirpation as distortion of the planes, and tissue can otherwise make it difficult to assess the completeness of excision. Cutting current as opposed to coagulating current is preferred. The former technique minimizes carbonization

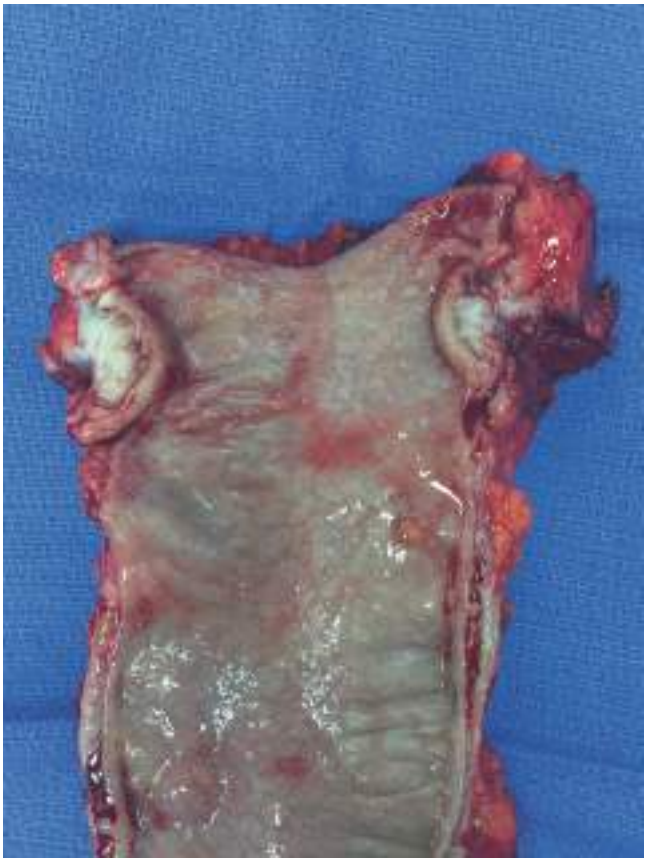


FIGURE 42-6. Opened specimen demonstrating the endometrial implant into the bowel wall.

that can make it challenging to recognize when an adequate depth has been achieved by the appearance of normal tissue. After the lesion is removed, the bowel wall is carefully assessed. Since most of these superficial lesions can be removed without entering the mucosa, the defects can be closed with interrupted transversely placed Lembert stitches.

The technique of removing superficial lesions is modified somewhat when it is performed laparoscopically. It is termed "shaving" and consists of meticulous removal of the lesion without entering the rectal mucosa. The endometriotic nodule is carefully dissected from the bowel wall, and any exposed mucosa is carefully sutured close. A series by Donnez and Squifflet of 500 patients undergoing "shaving" reported a 1.4% rate of rectal perforation and a recurrence rate of 7%. They felt that this superficial resection resulted in better postoperative intestinal function as opposed to segmental resection [63].

Surgical treatment of the deeper lesions is more controversial. Removal of the rectosigmoid with reanastomosis is technically demanding and should be performed by skilled intestinal surgeons to minimize complications in these young patients. As experience has grown, there has been a shift to more aggressive therapy, usually in conjunction with gynecologists who remove endometrial deposits on the ovaries and fallopian tubes. Medical treatment has not proven adequate for these infiltrating lesions, so it is no surprise that castration alone has also proven ineffective [64]. Many of these women suffer from chronic pain or partial colonic obstructive symptoms following bilateral salpingo-oophorectomy when the endometrial implant is not resected. As a result, excision of the implant either with a disk of rectal wall (Figure 42-8) or a formal anterior resection is recommended for women with symptoms related to the endometriosis. Both procedures can occasionally be performed laparoscopically if the endometriosis is completely removed. Unfortunately, laparoscopy often misses lesions that are not visually apparent and discernible only by palpation. It should be noted, however, that for severe disease, laparoscopic ablation, when possible, had similar crude pregnancy rates in comparison to laparotomy, and both techniques were clearly superior to medical management alone [65].

Indeed, the most appropriate surgical therapy for infertility complicating severe endometriosis is unknown. There are no randomized controlled trials demonstrating an improvement in fertility after segmental bowel resection. However, an observational study by Stepniewska and colleagues comparing a group of patients undergoing segmental bowel resection, with a group of patients having resection of endometriosis without a bowel resection, revealed an improved pregnancy rate when patients underwent resection [66]. Proponents of bowel resection also note the decrease in recurrence with bowel resection for severe endometriosis compared to more conservative options. Recurrent endometriosis has a significant negative impact in the pregnancy rate for women undergoing repeat surgery for endometriosis [67]. Achieving pregnancy was reduced almost 50% with recurrent endometriosis, and in vitro fertilization may be considered instead of another surgery for recurrent disease.

The infiltrating nodular endometrial implants involving the rectovaginal portion of the cul-de-sac often invade both the vagina and rectum (Figure 42-7a–d). Since removal of the implant will require resection of a portion of the rectal wall, dissection of the lesion from the vagina allows for en bloc removal of the lesion with the rectal wall. There is often no discernible plane between these lesions and the walls of the rectum or vagina. Care must be taken to avoid penetration of the vaginal wall with possible injury to the cervix, especially in women desiring eventual pregnancy. Often it is advantageous to mobilize the rectum in the posterior and lateral tissue planes to adequately define the lesion before attempting the anterior dissection. Blunt dissection of the rectovaginal plane below the area of involvement may help clarify the distorted anatomy and avoid inadvertent entry into the bowel lumen. After careful dissection of the lesion from the vagina, the normal rectovaginal plane is reached, and the fixed, hard mass may suddenly become mobile and amenable to resection.

Disk excision of the anterior rectal wall, by either laparoscopic or open technique, is performed for single lesions

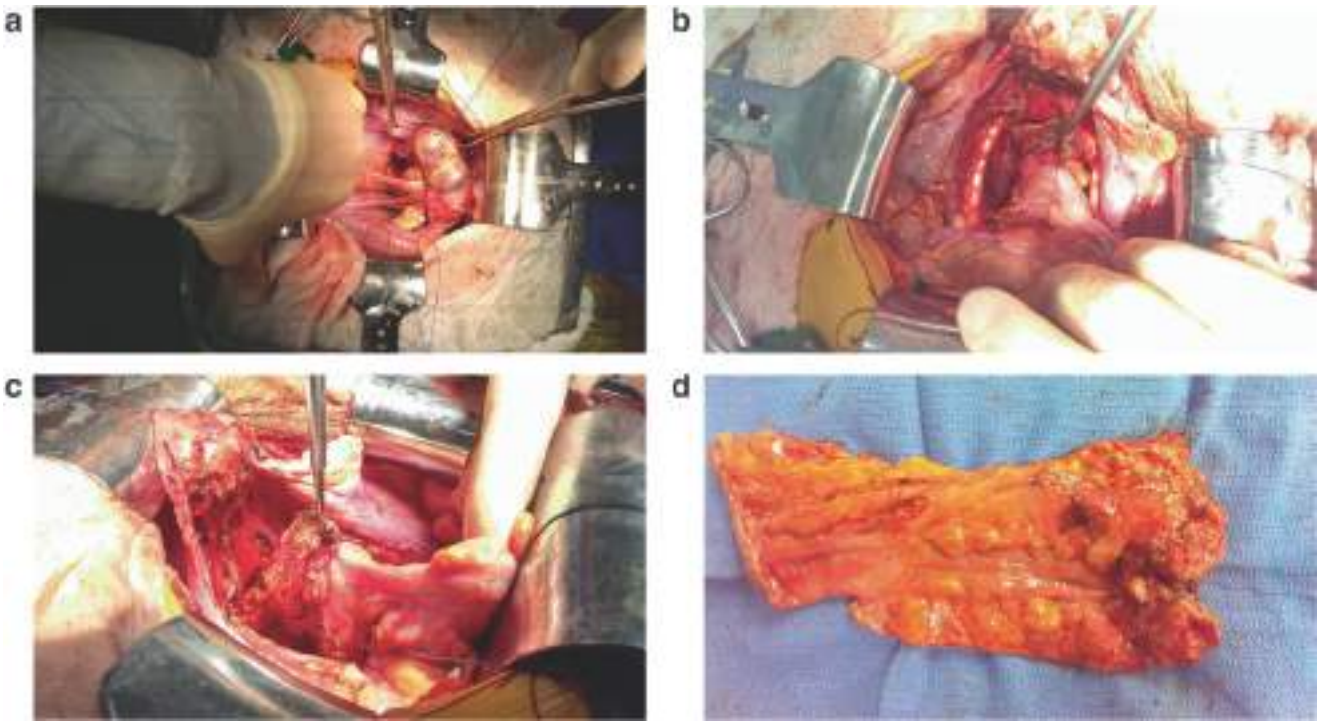
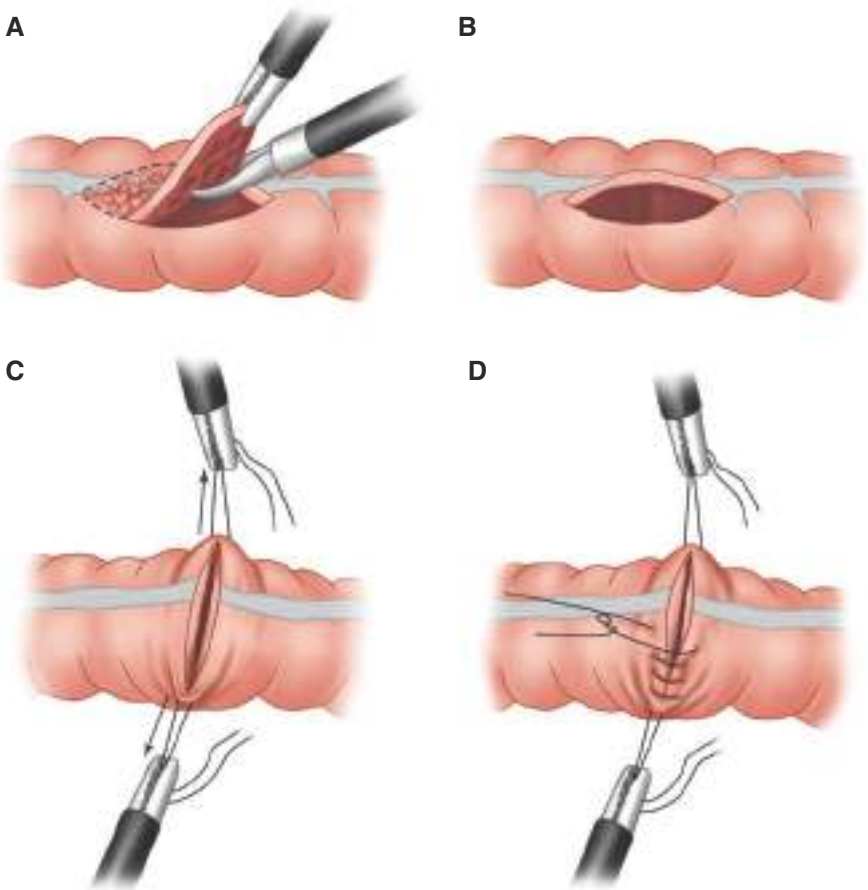


FIGURE 42-7. (**a**) Demonstrates the view of the endometrial implants obliterating the pouch of Douglas and an associated large endometrioma on the left ovary at the start of the procedure; (**b**) the large nodule of endometriosis has been dissected from the ureters and posterior vagina (note the lighted ureteral catheters that facilitate the dissection); (**c**) demonstrates visualization of the normal fat within the rectovaginal plane after fully dissecting cul-de-sac of Douglas and mobilizing the lesion rostrally out of the pelvis to allow resection; (**d**) demonstrates sectioning of the specimen to show the typical appearance of an endometrioma after hormonal therapy which induces diminished vascularity of the lesion.

FIGURE 42-8. (**a**)–(**d**) Disk excision of an endometrial implant.



usually less than 3 cm in diameter. Contraindications to disk excision performed laparoscopically include sigmoid involvement; bowel stenosis, more than 50% circumference involvement; and multicentric disease [68]. After marking the lesions circumferentially with electrocautery, stay sutures are placed on either side of the endometrial implant. Full-thickness bowel wall excision is then performed with the cutting current electrocautery. Interrupted transverse absorbable sutures are subsequently placed to close the resulting defect. When performing the disk excision laparoscopically, the technique can be very similar to open surgery or may be done using a transanal stapler. An initial "shaving" may be performed to debulk the lesion. After placing a guide suture at the level of the lesion, a circular stapler is deployed, and the bowel lesion is sandwiched in the groove anteriorly between the stapler and the anvil by pulling gently on the guide suture. A full-thickness, partial circumference of the bowel wall is excised with the firing of the stapler [69]. The major complication of this laparoscopic technique is bleeding with significant bleeding requiring blood transfusion in about 10% of patients in two series [70, 71].

Segmental resection of the rectosigmoid is performed for larger lesions or when neoplasia is a concern. Margins are to grossly normal colon, and unless there are multiple lesions, a large colonic resection is not required. High ligation of the sigmoid vessels is also unnecessary, and the anastomosis may be either hand-sewn or stapled. When resection is performed laparoscopically, the involved segment may be removed by extending one of the port sites. Nezhat and Pennington have described a technique of prolapsing the lesion outside the anus for resection [72]. Redwine has described a transvaginal approach for specimen removal [73]. Open or laparoscopic excision of these deeply infiltrating rectovaginal lesions is very technically demanding. The lack of discernible tissue planes, the intimate association of the rectum and vagina, and the frequent occurrence of distal infiltration of endometriosis down to the mid- to lower rectum make laparoscopic resection possible only by surgeons very experienced in complex intestinal laparoscopy. A series by Senagore had eighteen patients with stage 4 endometriosis treated by laparoscopic intestinal resection. While they concluded that laparoscopic resection was technically possible, complications included a ureteral injury and an anastomotic leak requiring an ileostomy for diversion [74]. Even in the hands of experienced laparoscopists, rectovaginal fistula requiring ileostomy has been reported to occur following these resections [75]. Proctoscopic insufflation to assess for leak is practiced routinely by the authors with all rectal anastomoses, whether performed open or laparoscopically.

Small Bowel and Appendiceal Endometriosis

While endometriosis involving the small bowel or appendix is much less common than rectosigmoid disease, careful inspection of these organs is critical in patients with advanced endometriosis to ensure complete removal of all gross disease and to minimize recurrence. Superficial small bowel implants may be treated with sharp excision, electrocautery, or the laser, as described above. Deeper implants may require small bowel resection and, if within 5 cm of the ileocecal valve, may need an ileocecectomy. Appendiceal endometriosis is treated with appendectomy. Occasionally, a surgeon will encounter a patient with an endometrial implant while operating for another condition. While the lesion may exhibit a classic visual appearance consistent with endometriosis, a biopsy to confirm the diagnosis and exclude malignancy is important. Several studies have suggested that few patients with small asymptomatic endometrial implants of the appendix will become symptomatic, but no study has yet defined the natural history of these lesions. As a result, for those patients with asymptomatic endometriosis, observation is probably sufficient, but hormone replacement therapy should be avoided.

Results After Surgical Therapy

Recurrence of endometriosis after surgical excision is difficult to assess because of a wide variability in the operative approach to endometriosis by various authors and the obvious need for postoperative laparoscopy to document asymptomatic recurrence. While there are no long-term prospective studies to date, the larger studies suggest a histologically confirmed rate of recurrent endometriosis of approximately 19% [76]. Gauging the response to surgery by the resolution of preoperative pelvic pain or infertility is easier to measure. The largest series of intestinal resections for advanced intestinal endometriosis by Bailey et al. found that 86% of patients had complete or near complete relief of their preoperative pelvic pain. In addition, a 50% crude pregnancy rate was achieved which was comparable with rates found when treating much lower stages of disease [77]. These results in over 130 cases with a median follow-up of 5 years were achieved with minimal morbidity, no anastomotic leaks, and no documented instance of recurrent colorectal endometriosis. Laparoscopic series of intestinal resections performed for extensive endometriosis have reported similar pregnancy rates albeit with smaller number of cases, higher complication rates, and shorter long-term follow-up.

Combined Medical and Surgical Therapy

Both medical and surgical therapies for endometriosis have potential reasons why each treatment alone may not be successful in eradicating the disease and minimizing recurrence. Medical therapy affects endometrial implants variably, and there is a high instance of recurrence following cessation of therapy. Surgery may not remove microscopic disease, and postsurgical adhesions may contribute to postoperative

pelvic pain and infertility. For these reasons, combination therapy either pre- or postoperatively has been used for several years, although with a paucity of prospective randomized data to conclusively prove long-term improvement in recurrence and symptoms.

The rationale for preoperative medical therapy conducted over a period of 3–6 months is principally to decrease the inflammation and possibly the size of the endometrial implants. Presumably, this therapy will allow easier excision with diminished adhesion formation. Medical therapy may also reduce the vascularity of endometrial implants. A prospective study by Buttram in 1985 revealed an improvement in pregnancy rates with 6 months of danazol given preoperatively with all stages of endometriosis [78]. The optimal length of therapy and long-term (and not just delayed) recurrence rates must still be elucidated. Postoperative treatment with danazol and oral contraceptive pills has not been shown to have durability, and the initial excitement over improved recurrence rates at 12 months has not been duplicated after longer follow-ups. Our current use of combined therapy is a 3–6-month course of a GnRH-a prior to definitive surgery.

Conclusion

The diagnosis and management of intestinal endometriosis have evolved tremendously over the last 20 years with the widespread availability of laparoscopy and a clear understanding of the necessity to remove all endometrial implants in symptomatic patients. With the advent of stapling devices that facilitate low pelvic anastomoses, the intestinal surgeon should be able to resect the endometrial implants and restore bowel continuity in virtually all patients with minimal morbidity and preserved fertility, when desired. Further improvements in outcomes will probably not occur until a better understanding of the precise etiology and growth of the endometrial implant is discovered.

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43
Trauma of the Colon, Rectum, and Anus

W. Brian Perry

Key Concepts

- Primary repair is the treatment of choice for all nondestructive colonic injuries.
- Resection and anastomosis is the treatment of choice for most destructive colonic injuries.
- Diversion should be considered in patients undergoing damage-control laparotomy or who have significant pre-injury comorbidities or significant hemodynamic derangement.
- Primary repair is appropriate for accessible rectal injuries.
- Diversion alone without direct repair is sufficient to treat isolated extraperitoneal rectal injuries.
- Presacral drainage and distal washout are no longer recommended for rectal injuries.
- Anal injuries are often amenable to delayed reconstruction.

Introduction

The management of the injured colon has evolved considerably over the past century and a half. Accumulated wartime experience demonstrates that mortality fell from >90% during the American Civil War to <10% in Iraq and Afghanistan (Figure 43-1). Many factors have led to this improvement, including better transport time (Figure 43-2), resuscitation, transfusion, antibiotics, and improved surgical techniques. Civilian experience paralleled this and further refined current treatment algorithms. Multiple well-done studies confirm the safety of primary repair for most injuries although care must still be used in damage-control situations. Extraperitoneal rectal trauma is typically managed by proximal diversion; the utility of routine distal washout and presacral drainage has recently been shown to be of no benefit. Anal trauma lends itself to delayed reconstruction in many cases.

Colonic Trauma

Epidemiology

Most colonic injuries are due to penetrating abdominal trauma. Gunshot wounds are the most common cause (Figure 43-3), followed by stabbing and impalement. The colon is the second most commonly injured organ in penetrating abdominal trauma, behind only the small bowel [1].

Blunt colonic injuries are rare, accounting for <10% of lesions found at laparotomy for blunt trauma, primarily from motor vehicle crashes. Lap belt use, especially without concomitant shoulder harness, increases the risk of visceral injury (Figure 43-4). Most blunt injuries are minor—small hematomas or serosal tears; more serious injuries typically involve devascularization due to avulsion from the adjacent mesentery (Figure 43-5). "Blowout" injuries due to a blast overpressure wave are occasionally seen in victims of explosions, sometimes without external signs of abdominal trauma [2].

The American Association for the Surgery of Trauma has published a grading scale for colonic injuries (Table 43-1) [3].

Diagnosis

Prompt abdominal exploration accurately finds the majority of colonic injuries in penetrating anterior abdominal trauma. It is important to remember that the diaphragm may rise as high as the nipple line or the bottom of the scapula at full exhalation. Wounds to the flank or back can cause colonic trauma in the absence of initial peritoneal irritation or hemodynamic instability; computed tomography (CT) with triple contrast is useful for delineating such injuries, with 90% sensitivity and 96% specificity [4].

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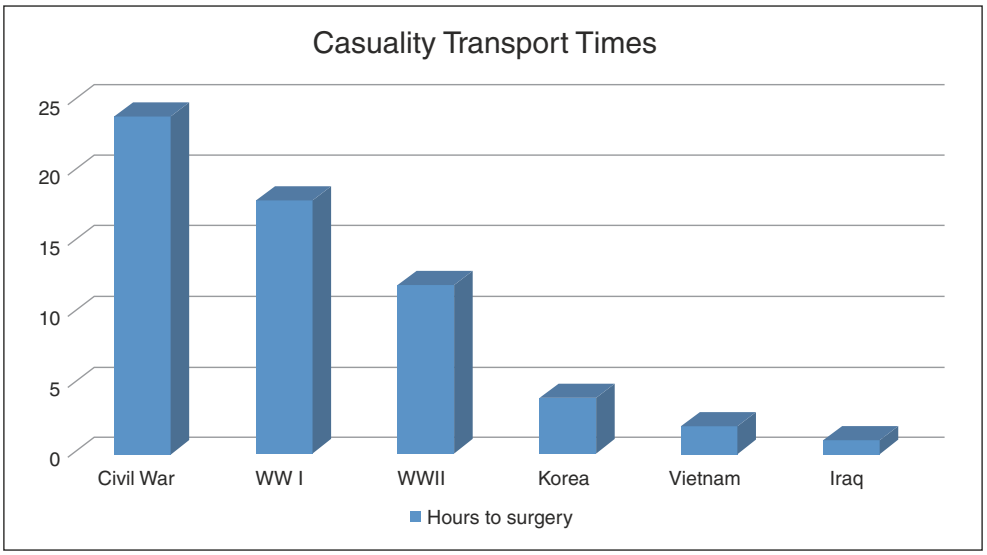

FIGURE 43-1. Time from injury to surgical management in American wars.

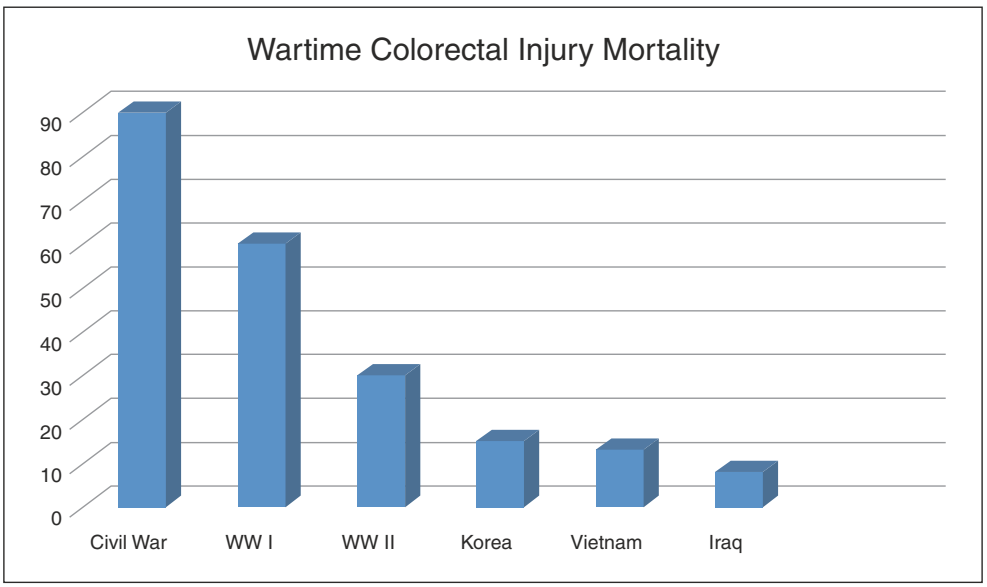

FIGURE 43-2. Mortality rate of penetrating colorectal trauma in American wars.

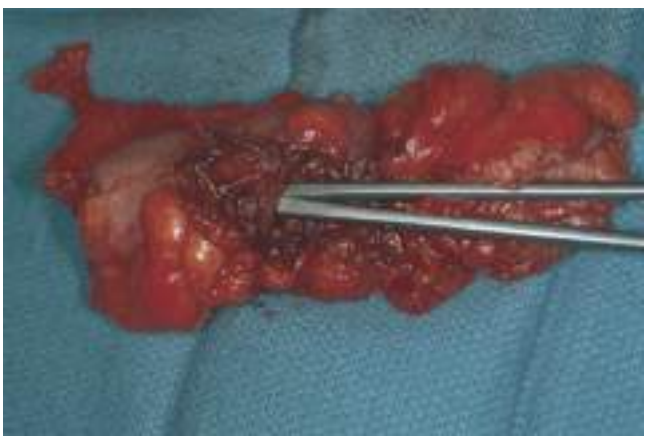

FIGURE 43-3. Destructive gunshot wound to the colon.

Accurate diagnosis of colonic injury is more difficult for a bluntly injured patient, whose examination is often compromised by concomitant brain or spinal cord trauma. Triple-contrast CT is the examination of choice in such instances. Organ-specific diagnosis is not always possible (or necessary). The presence of free intraperitoneal air mandates exploration for perforated hollow viscus. Free intraperitoneal fluid in the absence of solid organ injury should significantly raise the index of suspicion for bowel injury (Figure 43-6).

Diagnostic peritoneal lavage is rarely used in the contemporary evaluation of patients with suspected colonic injury. It may be useful in the austere environment where CT is unavailable or in the patient who cannot be safely transported due to profound instability or who is in the operating

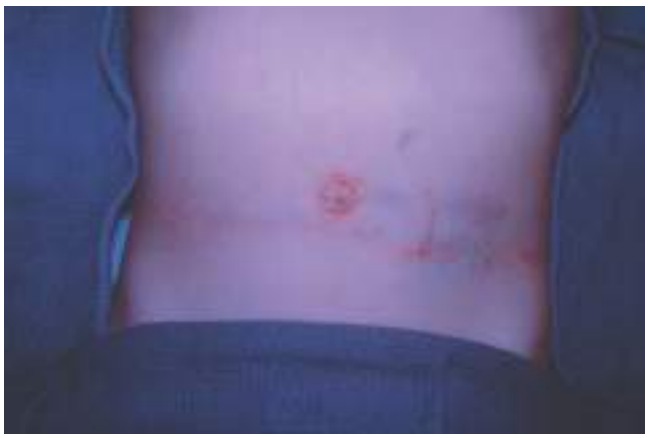

FIGURE 43-4. "Seat belt sign" from improperly worn lap belt.

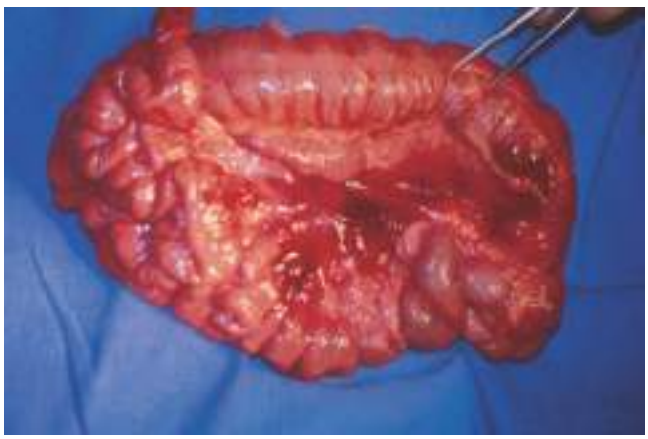

FIGURE 43-5. Blunt colonic mesenteric avulsion.

TABLE 43-1. American Association for the Surgery of Trauma Colonic Injury Scale

Grade	Injury description
I	(a) Contusion or hematoma without devascularization
	(b) Partial-thickness laceration
II	Laceration ≤50% of circumference
III	Laceration >50% of circumference
IV	Transection of the colon
V	Transection of the colon with segmental tissue loss

theater for a prolonged period for other injuries. The presence of gross blood or fecal matter on aspiration or >500 white cells/>100,000 red cells on lavage analysis is highly suggestive of significant intra-abdominal injury and should prompt exploration [5].

Laparoscopy has little role in evaluating the most penetrating anterior abdominal trauma, but may be useful in stable patients with back, flank, or pelvic wounds.

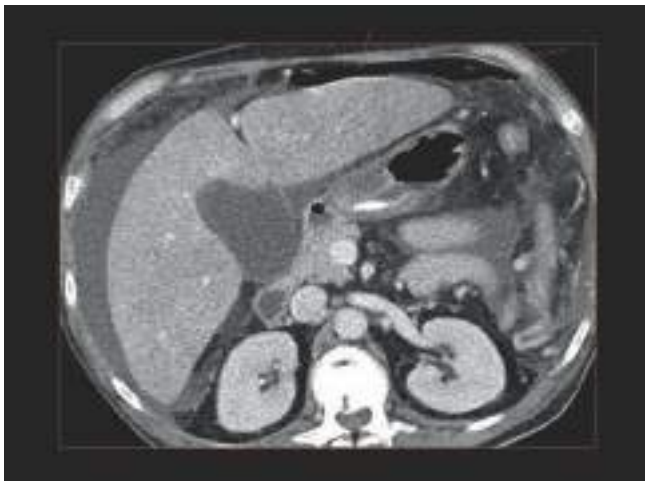

FIGURE 43-6. Computed tomography scan of a blunt trauma patient showing free air and free fluid in the absence of solid organ injury. Exploration revealed a cecal injury.

History of Military Colonic Injury Management

The accumulated experience of military surgeons has been critical to the evolution of current civilian colonic injury management [6].

With only a few exceptions, laparotomy was considered futile in the management of penetrating abdominal injury until the early stages of World War I. Wallace, in defiance of accepted doctrine, insisted that hemorrhage was killing soldiers and advocated for prompt laparotomy [7]. This approach was accepted by June 1915 and was augmented by more expeditious evacuation of the wounded (Figure 43-7); mortality decreased from 87 to 40% by Armistice Day [8].

Ogilvie reported his experience in the North African Campaign in World War II, recommending colostomy, although his data did not clearly support it. Mortality ranged from 44% for simple suture repair to 100% for resection and anastomosis [9]. Multiple authors have failed to find the "colostomy or court-martial" edict, but the US Army Surgeon General Circular clearly mandated colostomy for penetrating injuries [10]. Regardless of the true impact of this specifically, mortality declined further to around 30%.

Mortality continued to improve through the Korean War, but primary repair remained rare. During the Vietnam War, there were multiple series showing the feasibility of resection and anastomosis for right-sided injuries; left colon and rectal injuries were still treated with colostomy. Mortality fell to just over 13% [6]. Recent experiences in Iraq and Afghanistan with primary repair or resection and anastomosis showed some success in selected cases. However, intra-abdominal repair failure was >15% in one review, typically in patients with other injuries; such failure complicated subsequent continuity restoration in 75% of patients. This experience reinforces the concern for primary repair in patients who experience significant hemodynamic derangement pre- or intraoperatively. Despite the challenges of devastating injuries, mortality fell again to 8% [11, 12].

Current Operative Management

Civilian experience has paralleled the military experience. While surgeons returning from World War II adopted mandatory colostomy, this was questioned as early as the 1950s. Woodhall and Ochsner's case series showed success in highly selected cases of primary repair, with a mortality rate of 9% [13]. Stone and Fabian's landmark 1979 study randomized patients with penetrating colonic trauma to primary repair vs. mandatory colostomy, with significant exclusion criteria for devastating injuries, treatment delay, or extensive blood loss. With the selected cohort, repair proved to be superior to colostomy [14]. Subsequent studies have expanded on this seminal work.

Accumulated high-quality data have conclusively shown the safety and efficacy of primary repair in patients with grade II injuries, even in the presence of risk factors such as hypotension, multiple transfusions, and gross spillage. Studies by Chappuis [15], Sasaki [16], and Gonzalez [17] together randomized more than 300 patients to primary repair or colostomy, finding fewer complications in the repair group (Table 43-2).

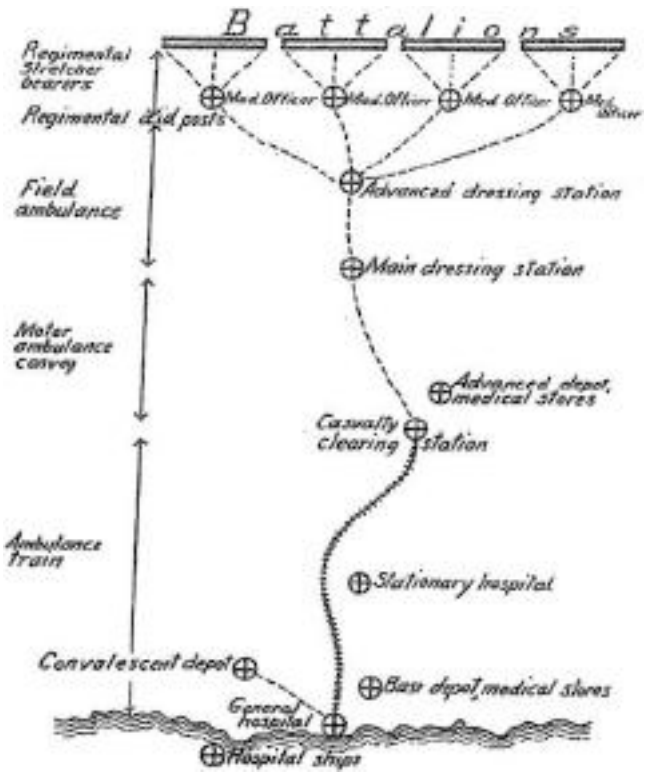

FIGURE 43-7. British Army system of casualty evacuation in World War I [7].

Grade III, IV, and V injuries require resection. Initially, primary anastomosis was reported to be successful in small retrospective series, with a leak rate of <3%. However, subsequent nonrandomized prospective single-institution reports called into question the universal applicability of this approach. Cornwell found two fatal anastomotic leaks in 25 patients [18]. Stewart et al. reported an overall leak rate of 14% but on subgroup analysis of patients needing >6 units of blood found the leak rate increased to 33% [19]. Murray found similar abdominal sepsis rates whether anastomosis or diversion was used, but also found higher leak rates in the more severely injured [20]. It is interesting that based upon this data, there is little advocacy for colonic repair/resection with protective diversion by loop ileostomy in select cases to minimize the impact of stoma reversal surgery.

To address these concerns, the American Association for the Surgery of Trauma (AAST) conducted a multicenter randomized prospective trial of diversion vs. resection and anastomosis for destructive colonic injuries. Colon-related mortality was 1.3%, all in the diversion group. Anastomotic leak rate was 6.6% with no deaths. Severe fecal contamination, transfusion of more than three units of blood, and inappropriate antibiotic selection were identified as risk factors for abdominal complications, up to 60% if all three were present. Shock on admission, delay of surgery, penetrating abdominal trauma index >25, and method of colon management (diversion vs. anastomosis) were not independent predictors of complications. The authors concluded that resection and anastomosis are the treatment of choice in all destructive colonic injuries regardless of severity of injury [21].

Sharpe et al. reported that adherence to a simplified management algorithm for penetrating colonic injuries reduces morbidity and mortality. In short, nondestructive injuries underwent primary repair without regard to underlying illness or patient condition. Destructive injuries had resection and anastomosis unless they had >6 unit transfusion requirement or significant pre-injury comorbidities. Protocol compliance was 90%; three-fourths of all the patients with destructive injuries avoided diversion. When compared to similar colonic injuries before the protocol was introduced,

TABLE 43-2. Randomized prospective trials of primary repair vs. diversion without exclusion criteria

	Primary repair		Colonic diversion	
Study	Number of patients	Rate of abdominal septic complications (%)	Number of patients	Rate of abdominal septic complications (%)
Chappuis [15]	28	14.3	28	17.9
Sasaki [16]	43	2.3	28	28.6
Gonzalez [17]	89	18	87	21
Total	160	13.1	143	21.7

those patients thus managed had fewer abscesses (18% vs. 27%) and colon-related mortality (1% vs. 5%). Suture line failure rates remained low (5% vs. 7%). They concluded that, with reasonable exclusions, destructive colonic injuries can be safely managed with resection and anastomosis [22].

Over the past two decades, the damage-control laparotomy (DCL) approach to devastating abdominal trauma significantly reduced morbidity and mortality. Abbreviated laparotomy and intensive ongoing resuscitation aim to avoid the lethal triad of coagulopathy, acidosis, and hypothermia [23]. The management of colonic injuries in these situations is evolving. Early in the DCL era, colostomy was considered mandatory. This eliminated the morbidity of intra-abdominal leak, but created other issues, especially during the reconstructive phase of patient care, as the presence of a stoma can make abdominal wall reconstruction problematic. Several authors reported their initial positive experience with selected repair or resection and delayed anastomosis after DCL, citing the potential ability to inspect the suture or staple line at subsequent operations [24–26]. Other series voice more caution in this patient population, especially when resection and anastomosis are required [27] or there is a persistent need for vasopressors to maintain stability (Table 43-3) [28]. Interestingly, the leak rate in studies where the authors touted the safety of delayed anastomosis was nearly identical to those who urged caution.

Sharpe and colleagues again analyzed their results using the previously described management algorithm in patients undergoing delayed anastomosis following DCL. Protocol adherence was only 55%. Adherence to the algorithm resulted in significantly lower rates of suture line failure (4% vs. 32%) and colon-related morbidity (22% vs. 58%). They were unable to identify other risk factors that would predict suture line failure [29]. Clearly additional multicenter trials are needed in this critically injured patient population.

Ciesla and Burch have developed an algorithm for the management of colonic injuries, utilizing the metabolic status of the patient, the location of the injury, the need for segmental resection, and the condition of the bowel wall at the time of repair. Taking into consideration the data presented, such an approach should lead to safe initial restoration of colonic continuity in 70–90% of injured patients (Figure 43-8) [30].

Technical Considerations

During the initial exploration for penetrating trauma, control of gross spillage with quick suturing or stapling should occur rapidly, as soon as exsanguinating hemorrhage is stopped. This needs not be definitive resection or repair. The colon needs to be fully mobilized above and below suspected injuries, with particular care paid to the flexures and rectosigmoid junction. In penetrating trauma, paracolic hematomas must be fully explored; this is less important for blunt injuries unless there are other signs of perforation such as soiling or retroperitoneal emphysema. In nearly all cases of penetrating colonic injury, the skin is left open, with planned delayed primary closure or secondary closure with a vacuum-assisted closure device.

Primary repair can be safely accomplished in a number of methods. There is little difference between single- and double-layered suture techniques [31]. Isolated injuries to the more capacious right colon may be amenable to elevation and application of a linear stapler (Figure 43-9). Perforations that are within a few centimeters of each other are best treated by removing the intervening bridge of tissue and performing a single repair (Figure 43-10).

Similarly, there is little difference between stapled and sutured anastomoses [32]. Adherence to the standard principles of no tension, good tissue approximation, and adequate blood supply is critical (Figure 43-11). There is typically no need for colonic lavage, even when a left-sided anastomosis is constructed. Ileocolostomy is associated with fewer leaks

TABLE 43-3. Delayed colonic anastomosis following damage-control laparotomy

Study	Number of patients with DCL and colonic injury (early deaths prior to re-exploration excluded)	Number of patients receiving primary repair or delayed anastomosis without proximal diversion (%)	Number of colonic leaks (%)	Notes
Miller [24]	19	11 (58%)	0 (0%)	
Georgoff [25]	61	28 (46%)	4 (14%)	Two additional leaks in patients with proximal diversion
Kashuk [26]	29	21 (72%)	6 (28%)	Four leaks confirmed, two suspected
Weinberg [27]	56	49 (88%)	6 (12%)	
Fischer [28]	68	41 (60%)	7 (17%)	Leak rate 50% in patients with persistent vasopressor requirements
Sharpe [29]	149	74 (50%)	9 (12%)	Leak rate 32% when established protocol not followed

DCL damage-control laparotomy

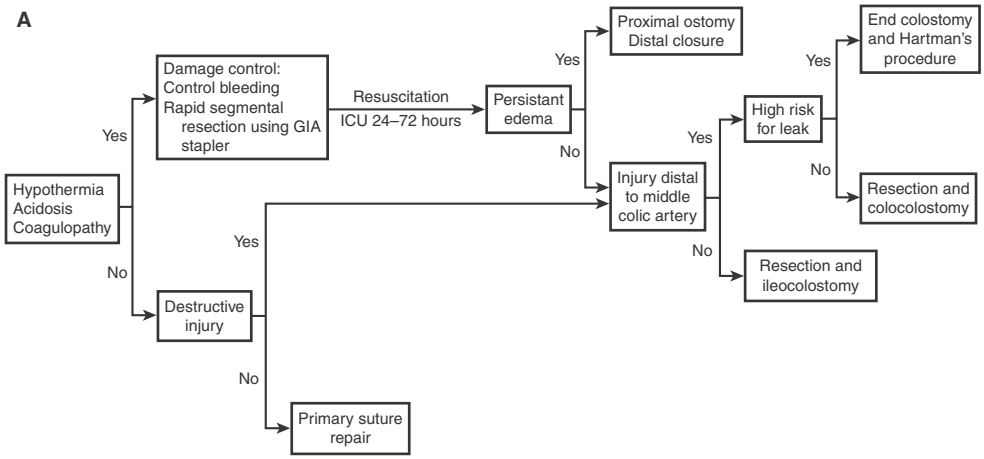

FIGURE 43-8. Algorithm for colonic injury management [30].

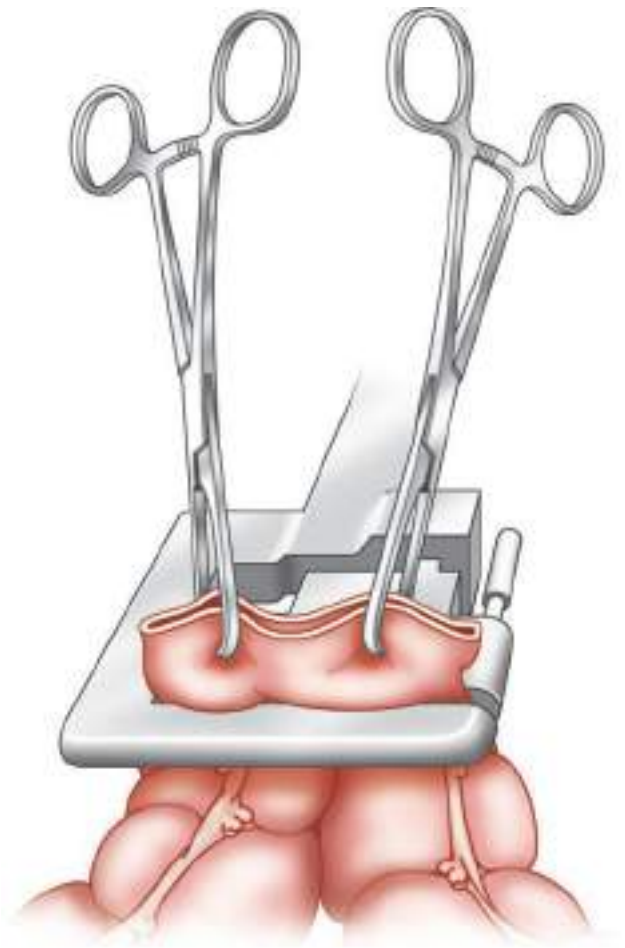

FIGURE 43-9. Grade II colonic injuries can be elevated and closed with a linear stapler, with care taken not to cause luminal narrowing.

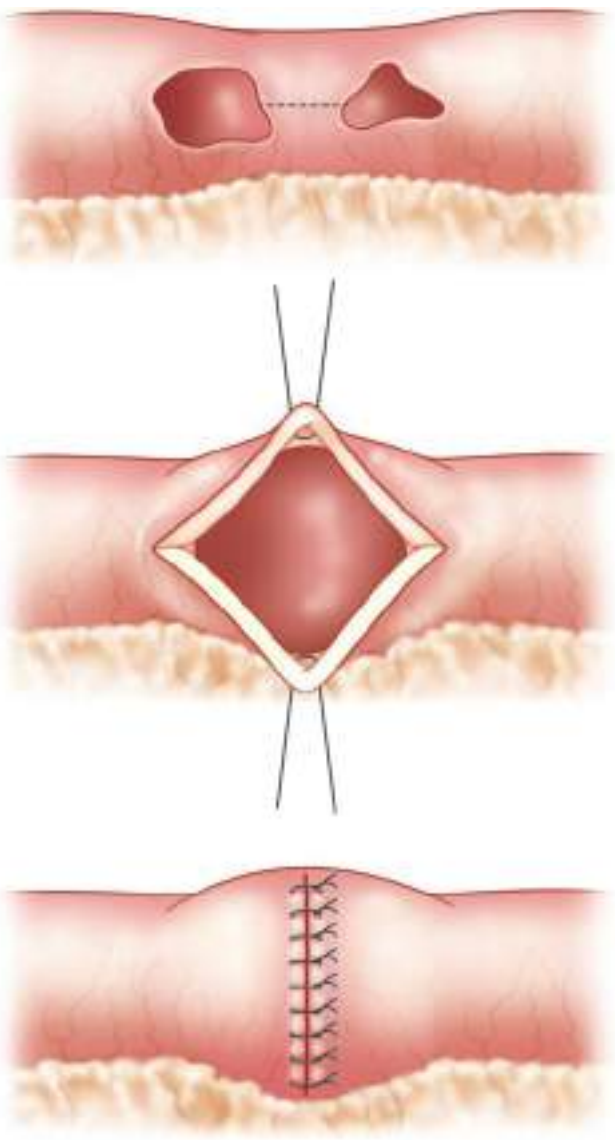

FIGURE 43-10. The intervening bridge of tissue between two close perforations can be removed and the resulting single defect can be closed transversely.

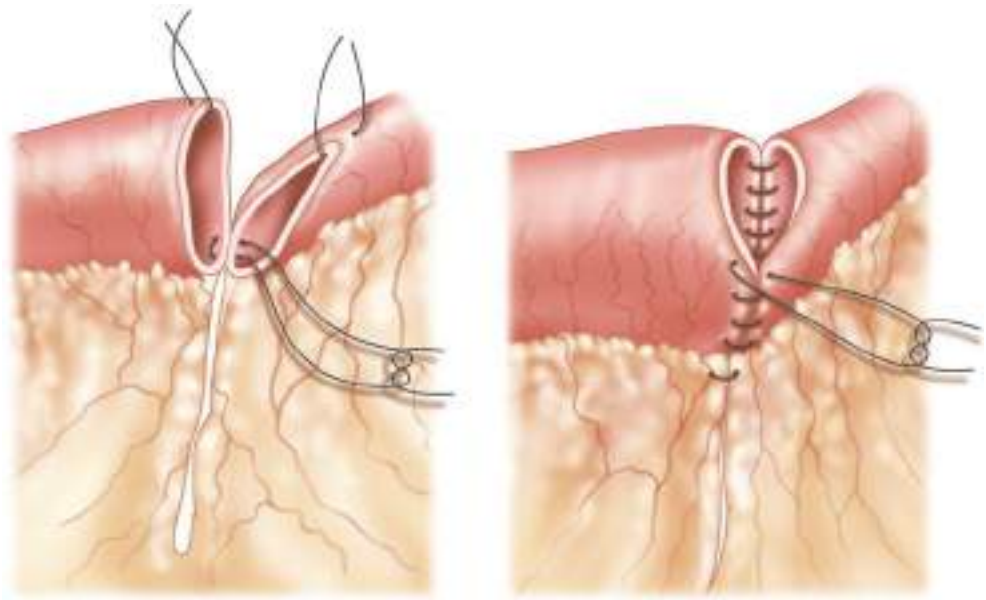

FIGURE 43-11. Single-layer hand-sewn colocolostomy.

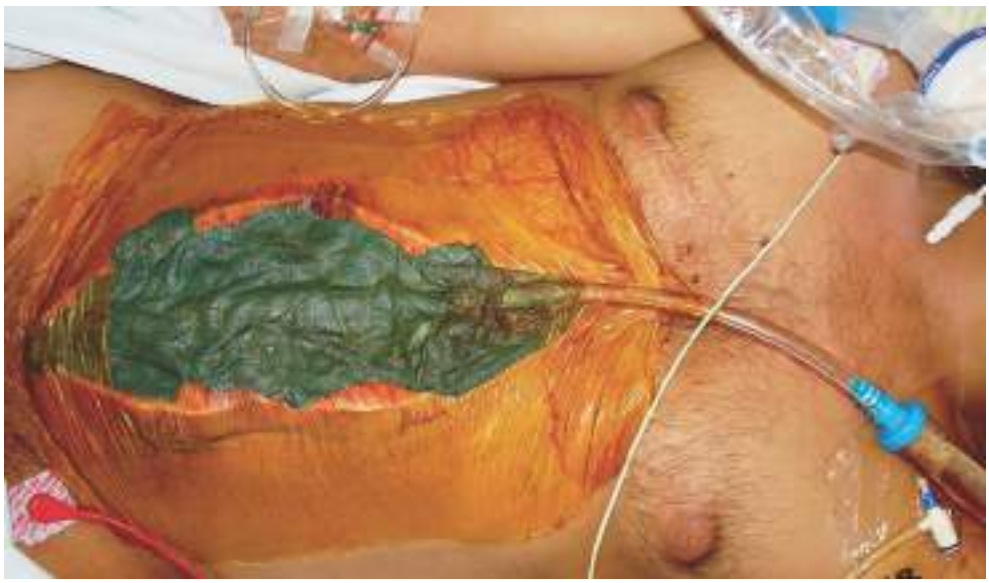

FIGURE 43-12. Temporary abdominal closure can be accomplished with towels, a chest tube, and adhesive drapes if vacuum-assisted wound closure materials are not available.

than colocolostomy, making right hemicolectomy the procedure of choice for ascending colon and cecal injuries; there is little another difference between right- and left-sided colonic injuries.

Primary anastomosis with proximal fecal diversion with a loop colostomy or ileostomy has proven efficacious in elective resections for rectal cancer or in urgent resections for diverticulitis. The data are less clear in the setting of trauma. If chosen, loop ileostomy is easier to construct and take down. Loop transverse colostomies should be avoided when possible as they tend to be difficult to adequately pouch and tend to prolapse.

Should DCL be necessary, the colon can be left in discontinuity at the initial exploration; creation of a colostomy is not necessary. The abdomen is temporarily closed over nonstick plastic drapes, and a suction method of collecting fluid is fashioned (Figure 43-12). Once restoration of normothermia and correction of acidosis and coagulopathy are accomplished, the patient is returned to the operating room for further treatment based on the factors discussed above. When possible, the fascial edges should not be allowed to retract causing loss of domain (Figure 43-13). Temporary bridging mesh, either prosthetic or biologic, can be serially tightened at subsequent surgeries, facilitating eventual primary fascial closure (Figure 43-14).

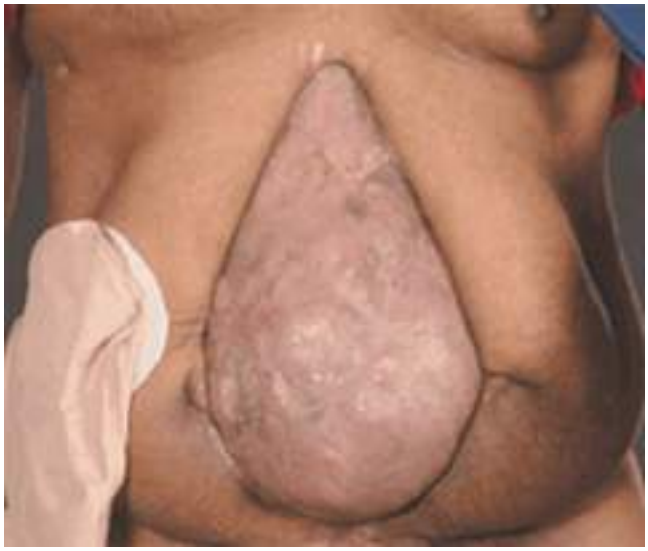

FIGURE 43-13. Loss of domain with subsequent skin grafting becomes necessary if the fascial edges are allowed to retract.

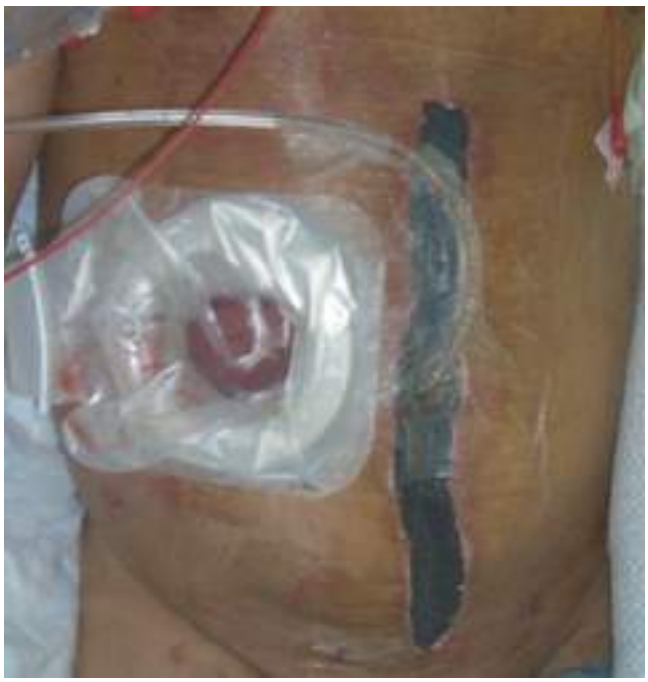

FIGURE 43-14. Serial tightening of temporary bridging mesh allows for fascial closure after damage-control laparotomy.

Rectal and Anal Trauma

Epidemiology

The majority of rectal injuries are from penetrating pelvic trauma, more than 80% from gunshot wounds in most series. Accidental or intentional impalement, iatrogenic injuries, and rectal foreign bodies account for the rest. The rectum may be perforated in blunt force trauma, typically by the intrusion of sharp bony edges from severe pelvic fractures (Figure 43-15); direct blunt rectal injury in the absence of pelvic fracture is very rare [33, 34]. The anus may be injured in a similar manner. This chapter does not cover obstetrical anal injury.

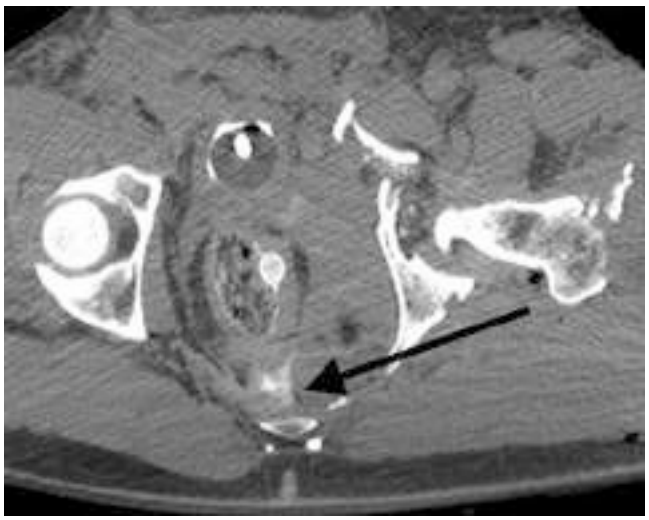

FIGURE 43-15. Computed tomography showing rectal injury with contrast extravasation from a severe pelvic fracture.

TABLE 43-4. American Association for the Surgery of Trauma Rectal Injury Scale

Grade	Injury description
I	(a) Contusion or hematoma without devascularization
	(b) Partial-thickness laceration
II	Laceration ≤50% of circumference
III	Laceration >50% of circumference
IV	Full-thickness laceration with extension into the perineum
V	Devascularized segment

The American Association for the Surgery of Trauma has published a grading scale for rectal injuries (Table 43-4) [3].

Diagnosis

The presence of gross blood on digital rectal examination is highly suggestive of rectal injury and mandates further evaluation. Sigmoidoscopy, either rigid or flexible, should be quickly performed, with an expected diagnostic accuracy of 80–95% [35]. Genitourinary injuries accompany up to one-third of rectal injuries; CT scan with bladder and rectal contrast is indicated for preoperative planning in stable patients [36]. Certain injury patterns, particularly transpelvic or buttock gunshot wounds, need thorough investigation even in the absence of rectal blood. Most anal injuries are obvious on external inspection, although occult sphincter disruption may occasionally occur.

History of Military Anorectal Injury Management

Mortality from penetrating battlefield rectal trauma was greater than 90% in World War I and still exceeded 60% early in World War II. With the edict mandating colostomy and the introduction of presacral drainage, mortality fell to <30% by the end of the war. The addition of distal rectal washout and improvements in casualty evacuation, resuscitation, and antibiotics were credited with mortality rates falling to <15% in Korea and Vietnam [6]. This leads to the classic "three Ds" of rectal injury management—diversion, drainage, and distal washout [37]. Recent reports from Iraq and Afghanistan showed overall mortality to be less than 8%. Soldiers with rectal injuries were more likely to have head, neck, or extremity injuries as compared to those with colonic injuries, largely due to the efficacy of modern body armor, which covers most of the abdomen and thorax [12].

Anal injuries in earlier conflicts were usually reported in series with rectal injuries, stressing prompt diagnosis, adequate debridement, and mandatory colostomy [38]. McCune noted in 11 of 41 patients that some function could be regained with a series of guided gluteal and sphincter exercises [39]. One of the signature injuries in the Iraq and Afghanistan conflicts is complex pelviperineal trauma caused by ground-level improvised explosive devices [40]. Glasgow analyzed 46 combatants with anal canal or sphincter injuries, the largest such series to date. Nearly 80% underwent fecal diversion; acute sphincter reconstruction was attempted in about 25%, but this did not influence eventual restoration of intestinal continuity. Of the patients available for long-term follow-up, 30% had a permanent colostomy, which was strongly predicted by the presence of concurrent intra-abdominal injury, hypogastric artery ligation, or pelvic fracture [41].

Current Management and Technical Considerations

While not specifically addressed in separate studies, there is consensus that intraperitoneal rectal injuries can be treated as colonic injuries.

Each of the "three Ds" has been challenged in the modern civilian management of rectal trauma. Several studies have shown that small perforations can be safely closed without proximal diversion, either transanally if low enough or from an abdominal approach if minimal rectal mobilization is required. Inaccessible injuries are still best managed by proximal diversion; extensive rectal mobilization is not recommended. If perforations cannot be safely closed, proximal diversion is still required [34, 42]. A recent study from South Africa demonstrated that laparoscopy is useful for evaluating stable patients without peritoneal signs who are suspected of having an isolated extraperitoneal rectal injury. If there is no evidence of intraperitoneal injury, then a loop sigmoid colostomy may be easily constructed [43]. Resection with stapling of the rectum distally and end colostomy is required for destructive injuries. Abdominoperineal resection is occasionally necessary in devastating open pelvic fracture [44]. These patients typically need damage-control surgery with pelvic packing; ligation or angioembolization of the hypogastric arteries may be necessary (Figure 43-16a, b).

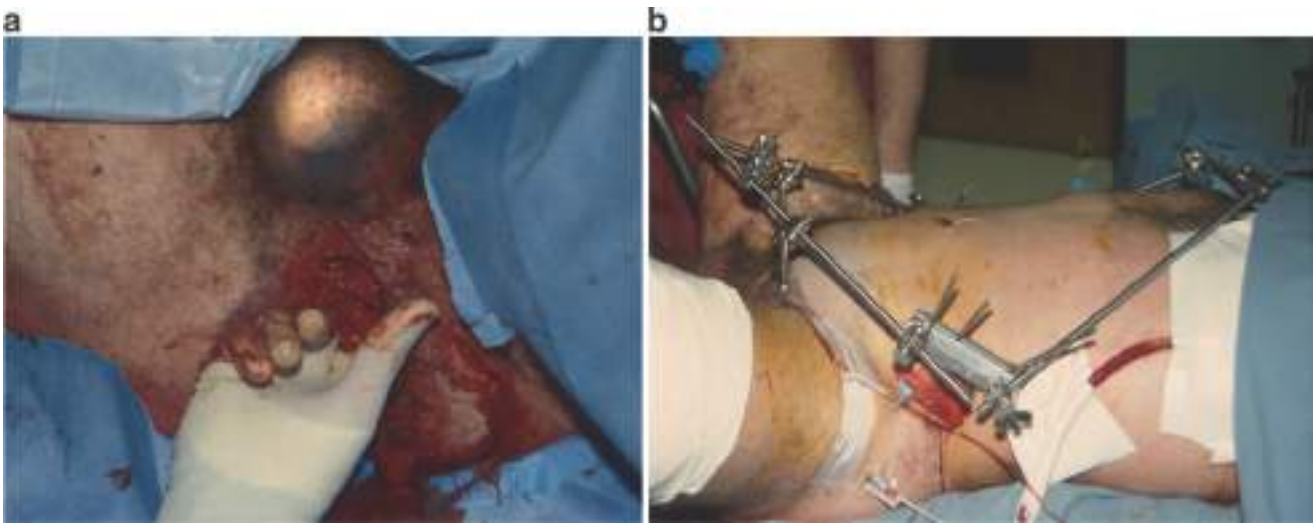

FIGURE 43-16. Severe open pelvic fracture with rectal injury. (**a**) Open perineal wound with exsanguinating hemorrhage which required expedient packing and angioembolization. (**b**) Note positioning of external pelvic fixation to allow laparotomy. Attention to colostomy siting is important to decrease the risk of pin tract infections.

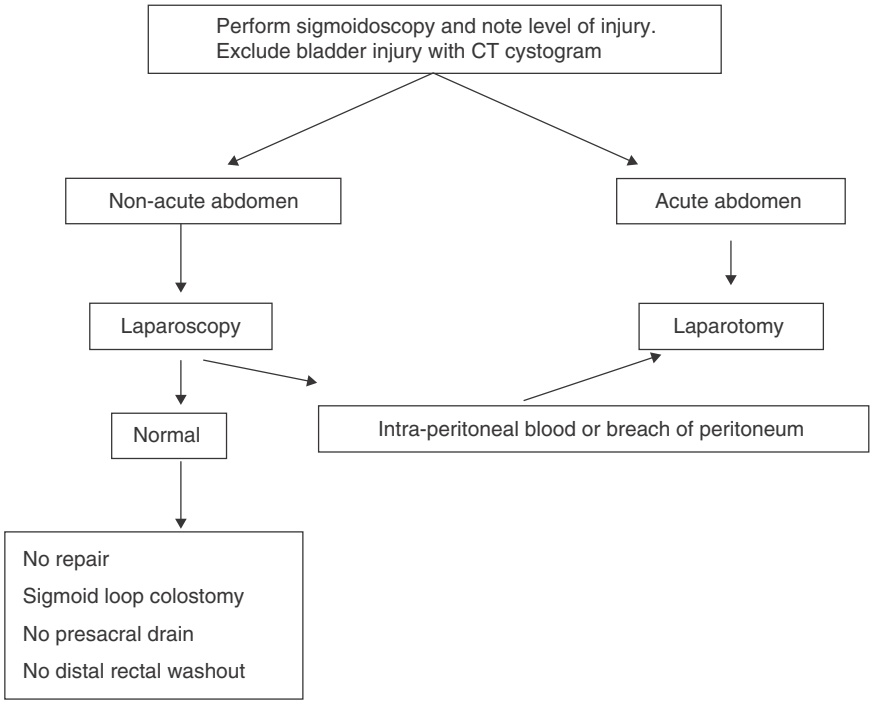

FIGURE 43-17. Algorithm for rectal injury management [43].

Routine presacral drainage has been examined in several studies, including one randomized prospective trial. The extensive disruption of normal tissue planes required showed no benefit. Presacral drainage is no longer recommended [34, 43, 45]. Closed suction drains placed in the pelvis after mobilization and repair of mid-rectal injuries at laparotomy may still be useful, as clean tissue planes are not violated.

Similarly, distal washout of the rectum has not been shown to have any benefit in the routine management of penetrating civilian rectal trauma. Liquefaction of the stool column with subsequent spread into the pelvic spaces has been touted as a potential negative result of vigorous rectal irrigation in traumatic injuries [34].

Nichol and Navsaria have developed an algorithm for the management of penetrating civilian rectal injuries, taking into account recent accumulated experience (Figure 43-17). At laparotomy, small visualized wounds can be primarily repaired, while destructive injuries will require resection and end colostomy.

Anal injuries can be repaired primarily in relatively clean wounds in stable patients; routine proximal fecal diversion is not required. For destructive perineal wounds, appropriate debridement and proximal diversion are paramount. A vacuum-assisted wound closure device can be used on the perineum for short periods while serial debridement is ongoing. Marking of the ends of the sphincters with nonabsorbable suture can aid later reconstruction. It is imperative to investigate the genitourinary tract, as many patients will have combined injuries (Figure 43-18a–e).

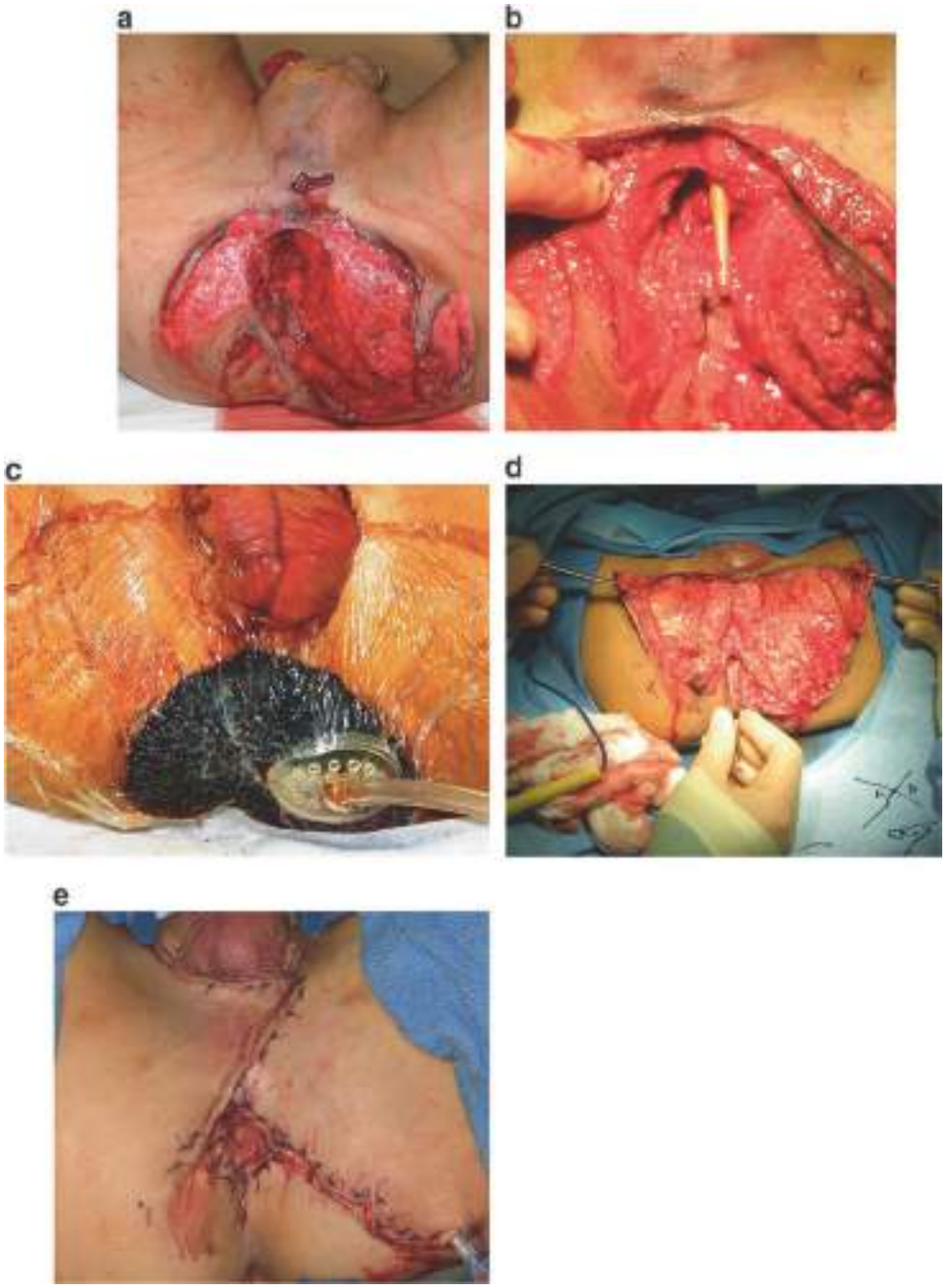

FIGURE 43-18. Destructive perineal and anal injury. (**a**) Mortar fragment entered the right hemiscrotum and exited the perineum, causing a massive injury. (**b**) Urethral transection was repaired through the perineum. (**c**) Serial debridements and vacuum-assisted wound closure changes created a healthy wound bed. (**d**) Flaps were constructed to facilitate closure. (**e**) After sphincteroplasty, the final wound closure. Colostomy was closed 6 weeks later and patient had excellent continence.

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44
Inflammatory Bowel Disease: Pathobiology

Tara M. Connelly and Walter A. Koltun

Key Concepts

- The current theory on the etiology of inflammatory bowel disease is an exposure to an environmental factor of host or foreign origin in the individual with a genetic predisposition to dysregulated immunity.
- Over 150 genes and several hundred polymorphisms have been associated with the disease through genome-wide association studies (GWAS). Some are associated with CD, others with UC, and some with both diseases suggesting distinct but overlapping pathobiologies.
- The NOD2 gene, which is involved in bacterial recognition and response, was the first gene to be associated with the disease and is the most commonly associated gene.
- Defects in both innate and adaptive immunity have been demonstrated in murine models and human tissue from patients with the disease.
- Innate immunological processes involved in disease pathobiology include epithelial barrier function including tight junction integrity, autophagy, and pathogen recognition.
- Adaptive immunological processes involved in disease pathobiology include T cell activation, differentiation, and function.
- All major innate and adaptive immunological processes involved in both UC and CD have at least one associated gene known to be correlated with IBD through GWAS.

Introduction

Ulcerative colitis (UC) and Crohn's disease (CD) are the two broad subcategories of idiopathic, inflammatory bowel disease (IBD) first officially described in 1859 and 1932, respectively [1, 2]. They are relapsing, inflammatory conditions of the gastrointestinal tract with distinct yet overlapping clinical and pathological features due to the shared and yet disparate pathobiologies of each (Table 44-1). Their common characteristics are so pronounced particularly in Crohn's colitis and UC that prior to the hallmark paper formally differentiating the diseases written by Charles Wells in 1952, the two diagnoses were frequently but incorrectly thought to be a single illness [1].

Although the precise etiology of these two inflammatory bowel diseases is unknown, the current research model suggests that an environmental trigger causes disease in a host predisposed due to intrinsically impaired immunity [3–5]. Environmental factors suggested to play a role in either the cause or course of IBD include external agents (e.g., cigarette smoking, nonsteroidal anti-inflammatory drugs) or agents that are present within the host itself, namely, the commensal and pathogenic organisms comprising the intestinal microbiome. Some environmental factors such as prior appendectomy play a greater or lesser role in disease pathogenesis while others, such as smoking, have an opposite effect in the two diseases. Recently, using genetic techniques developed over the course of the Human Genome Project, significant genetic (allele) associations have been identified in both CD and UC. Although the majority of such IBD alleles are associated with both CD and UC, others are exclusive to one or the other disease. The combination of these host genetic factors with some environmental stimulus ultimately leads to an imbalance in the host immune system causing unregulated inflammation and compromise in the gut's mucosal integrity (Figure 44-1). The numerous and widely variable combinations of these host and environmental factors likely result in the many different features (or phenotypes) among individuals with either UC or CD.

Besides host immunologic predisposition, environmental factors, and the native microbiome, other theories of pathogenesis include exposure to noxious agents including pathogenic bacteria or viruses. Such theories both suggest a "triggering event" that precipitates IBD but also might "downregulate" the nascent immature immune system, as is suggested by the hygiene hypothesis (see below). Finally, IBD, besides being a dysregulated inflammatory condition,

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TABLE 44-1. Biological characteristics of Crohn's disease and ulcerative colitis

	Crohn's disease	Ulcerative colitis
Environmental factors		
Smoking	Risk	Protective
Appendectomy	Risk	Protective
NSAIDs	+++	++
Pathogens	++	+++
Microbiome	++	+++
Genetic predisposition	+++	++
Familial association	+++	++
Number of genes associated with disease	++++	++
Innate immunity		
Mucosal integrity	++	+++
Autophagy	++++	++
Paneth cells	++++	–
Adaptive immunity		
Th1 cells	++++	++
Th2 cells	++	++++
Treg cells	++++	++
Th17 cells	++++	++
Cancer/dysplasia risk	++ (Colitis)	++++

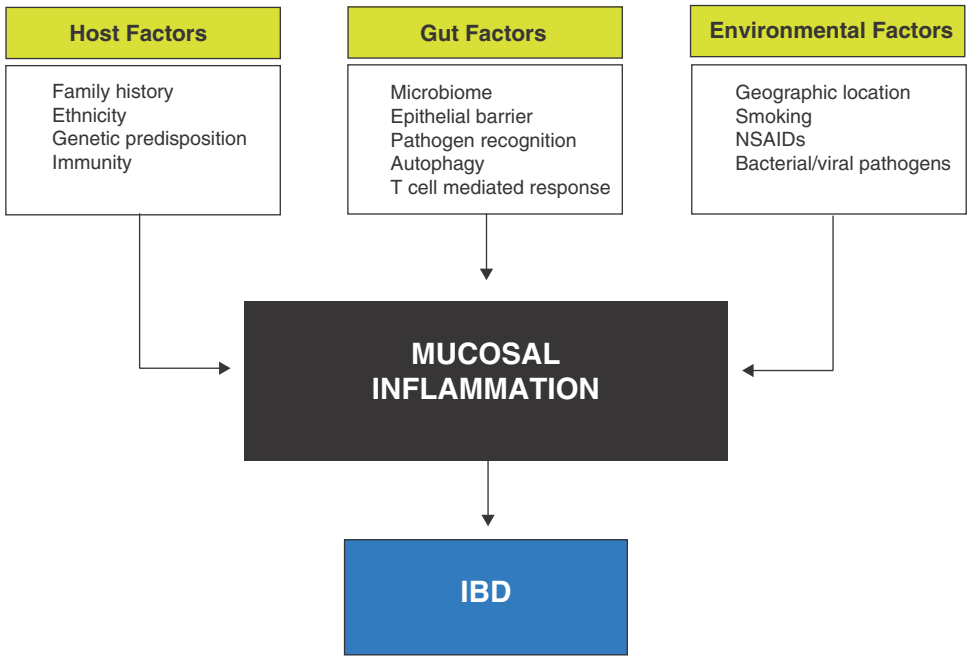

FIGURE 44.1. Host, gut, and environmental factors in the pathogenesis of IBD.

may also reflect defects in epithelial cell health and compromised reconstitution or healing after injury, caused by again either an intrinsic genetic defect or environmental factors.

The Host Environment in UC and CD

IBD is more prevalent in more industrialized countries, among higher socioeconomic populations, in urban areas, and in geographic regions further from the equator [6–13]. Risk is increased in specific ethnic groups, such as the Ashkenazi Jewish population, the ethnic group with the highest disease incidence regardless of geographic location [8, 14]. These epidemiological phenomena suggest a genetic basis for disease but also a potential role for infectious causes, through an exposure to indigenous microbes or pathogens.

Possible Infectious Causes of IBD

Early observations of families with multiple affected members led to theories of an infectious etiology for IBD, specifically *Mycobacterium avium* subspecies *paratuberculosis* (MAP).

MAP causes Johne's disease, a CD-like illness in livestock. Despite intense early interest, no role for MAP in IBD has been proven to date, and these "familial" cases were likely due to a shared genetic predisposition [15]. However, at least three viruses (including the common Epstein-Barr virus and *Cytomegalovirus*), 6 yeasts, and over 20 bacteria have been associated with IBD through medical record reviews and serum antibody testing (Table 44-2) [16]. Although the majority of these organisms have been correlated with increased risk of disease development, some such as *F. prausnitzii* and *B. fragilis* may actually be protective [17–19].

The most robust evidence for pathogens in the etiology of IBD is the raised titers of antibacterial and antifungal antibodies including anti-CBir, anti-OmpC, anti-*Saccharomyces cerevisiae* antibodies (ASCA), and perinuclear antineutrophil cytoplasmic antibodies (pANCA) that are well documented in IBD patients (see Chap. 45 on IBD diagnosis) [20, 21]. It is not known if infection by these organisms is causative of disease (unlikely) or if their presence is due to an increased susceptibility secondary to impaired immunity or facilitated invasion of these pathogens through the ulcerated mucosa inherent to both UC and CD. This is a common problem in clinical studies of IBD patients, namely, what is causative vs. what is epiphenomenon, or simply related to the consequences of intestinal inflammation.

Smoking

Of all environmental factors studied, tobacco smoking has the most replicated association with IBD. There is increased risk of disease development and a more aggressive disease course with higher rates of both surgery and clinical recurrence documented in Crohn's patients who are current or former smokers. These associations appear to be "dose dependent" with the strongest association found in current smokers followed by former smokers [22–25]. In contrast, smoking appears to have a protective effect in UC patients. Smokers with UC have lower medication requirements and require surgery less frequently than UC patients who have never smoked [26]. The mechanism for these associations has not yet been elucidated. Studies on nicotine and nicotine replacement in the form of patches and chewing gum and the disease course of CD and UC have been inconclusive [27–29].

Nonsteroidal Anti-inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAID) use has been commonly found to be associated with an increased risk of IBD development [30, 31]. The inhibition of COX-2 is the most studied mechanism in both human UC and CD tissue samples as well as animal models of colitis [32]. An alteration of gut microbiota, including an increase in the number of *Enterococcus* species, has been seen in IBD patients treated with NSAIDs. However, how such translates into disease is not known [33]. Studies on the role of NSAIDs in relapse/flares have produced conflicting results with the exception of aspirin which has not been shown to adversely affect disease activity [34–36]. Despite this lack of clarity, avoidance of NSAIDs is currently recommended in most IBD patients.

The Microbiome

Early exposure to a variety of pathogens is required for the development of a healthy immune system. A lack of varied pathogenic exposure, particularly in infancy and early childhood, may lead to an exaggerated immune response when the individual is exposed to these pathogens later in life [11]. This theory forms the basis of the "hygiene hypothesis" [37]. In IBD, this hypothesis is supported by the geographical clustering of patients in more "westernized" countries and in urban areas where more sanitary conditions, and thus less pathogenic exposure, can be found. This observation has led to trials administering Helminthes that are not commonly found in high-risk areas. Such early trials utilizing larvae from the porcine whipworm *Trichuris suis* suggested promising results in the amelioration of both CD and UC symptoms, but further, larger randomized control trials are needed [38, 39].

The inability to induce colitis in murine models with predisposing genetic mutations when raised in germ-free environments is further evidence of the concept of a role for the microbiome in disease. Such animals, when transferred to a

TABLE 44-2. Pathogens most commonly associated with IBD

Viruses	Bacteria	Fungi
Epstein-Barr [16, 205]	*Bacteroides* [206]	Basidiomycota [207]
Cytomegalovirus [16]	Firmicutes [206]	*Candida albicans* [208, 209]
Norovirus [210]	Adherent-invasive *Escherichia coli* [206, 211, 212]	*Aspergillus clavatus* [208]
	Faecalibacterium prausnitzii [206, 211]	*C. neoformans* [208]
	Ruminococcus [211]	*Saccharomyces* [209]
	Clostridium histolyticum [212]	
	Klebsiella [212]	
	Bifidobacterium [213]	

non-sterile environment and populate their intestinal tract with bacteria, then rapidly develop colitis [39]. Critics of the hygiene hypothesis note that as individuals migrate from a high childhood pathogenic exposure area (i.e., a "low-risk IBD" area) to a more westernized geographic location (i.e., a "high-risk IBD" area), their risk of developing IBD increases to nearly that of the new population suggesting early exposure is less critical than thought [40–42].

The observations of reduced intestinal microbiota diversity in IBD patients vs. non-IBD controls and the improvement of symptoms after stomal diversion of the fecal stream [17] have led to studies focused on further elucidating the role of gut bacterial imbalance or "dysbiosis" in IBD [43–49]. Thus, the promotion of gut microbe diversity by probiotic consumption has been investigated but thus far has been disappointing in CD. However, a role for the treatment and/or prevention of pouchitis in UC patients with ileal pouch-anal anastomosis (IPAA) has been seen, especially in decreasing pouchitis recurrence [50]. Similarly, fecal transplantation after initial treatment with antibiotics is suggested to promote microbial diversity. Results, again, have been conflicting and limited by small numbers, but possible benefits appear to be short-lived. Meta-analysis of 18 of these fecal transplant studies including 79 UC and 39 CD patients demonstrated a clinical remission of approximately 20 % for UC but as high as 60 % for CD, suggesting a possible though not definitive role in IBD pathogenesis and/or treatment [51].

Gut microbiomes vary by geographic location, and thus results from microbiome studies may not be relevant to all IBD populations. In a recent comparison of the gut microbiomes of Western European vs. Indian IBD populations, the majority of microbes detected differed. However, the presence of common overlapping microbes (e.g., *Faecalibacteria* and *Papillibacter*) was also demonstrated [52]. In addition to geographic location, earlier microbiome research may have been affected by the frequent antibiotic and steroid use seen in IBD patients. Controlling for treatment, Morgan et al. studied the gastrointestinal microbiome of 121 CD, 75 UC, and 27 healthy patients using fecal and biopsy samples. The majority of microbes showed a concordance in all IBD patients vs. controls. However, high Enterobacteriaceae counts were specific to CD, and Leuconostocaceae were decreased in UC. Interestingly, disease activity did not affect microbiome composition; however, age, smoking status, and IBD treatment did. Disease location was shown to affect the microbiome in CD patients with reduced Ruminococcaceae and *Faecalibacterium* seen in patients with ileal involvement [33].

An effort to more carefully characterize this microbiome as a "second genome" within the individual patient and to study the interaction between host genetics and microbial susceptibility has begun [53]. Controlling for antibiotic and immunosuppressant use, Knights et al. studied the microbiome and a panel of over 10,000 immunity-related genetic polymorphisms in over 450 IBD patients and found significant associations between 48 genetic variants and the increased presence of specific bacteria (e.g., NOD2 mutations and Enterobacteriaceae) [53]. This field is in its infancy with research rapidly expanding, which will probably be facilitated by the "big data" analytic techniques being used in genome analysis.

Appendectomy

Similar to smoking, an appendectomy paradox has been suggested in IBD. An increased likelihood of being diagnosed with CD is found in the first year following appendectomy by meta-analysis. However, this rate falls to that of the general population within 5 years [54]. Appendicitis may in fact be a misdiagnosed first manifestation of CD, contributing to this statistical association [55]. Separate meta-analysis has demonstrated a potential protective role of appendectomy in UC [56]. Mesenteric adenitis has also been suggested to have a protective effect in UC [57] but has not been studied in CD. The lymphoid appendix is involved in the adaptive immune response. Thus, it has been suggested that removal of the appendix impairs immunity and confers additional risk of developing IBD. Others suggest that the appendix sequesters antigens and so its removal with attendant antigens may prevent IBD.

The Role for Genetics in IBD

Early observations suggesting an infectious agent in the pathobiology of familial cases of IBD more likely reflected a genetic predisposition to both UC and CD that has now been well established. Genetic predisposition to both CD and UC was confirmed in early twin and familial studies using carefully maintained Scandinavian national registries and has since been replicated in multiple worldwide cohorts. In fact, the presence of a family member with IBD is the number one risk factor for developing the disease [58]. Up to 40 % of IBD patients have at least one affected family member [58]. Affected family members from "IBD families" are generally concordant for age of onset, location, and disease behavior [59–62]. As many as 75 % of families with multiple affected members manifest only a single type of colitis (either CD or UC). In the remaining 25 %, different family members can be affected by both CD and UC [40, 63]. Although genetic associations are well documented in both diseases, genetics plays a stronger role in CD than UC. This is particularly evident in twin studies. Monozygotic twin concordance rates for CD range from 20 to 50 % but only 14–19 % for UC. In UC, a familial concordance for extraintestinal manifestations has been demonstrated [64].

Early research was tedious and focused on genetic investigation of sibling pairs, searching for high rates of shared alleles in affected vs. non-affected individuals [65], candidate gene studies investigating the few known IBD-associated

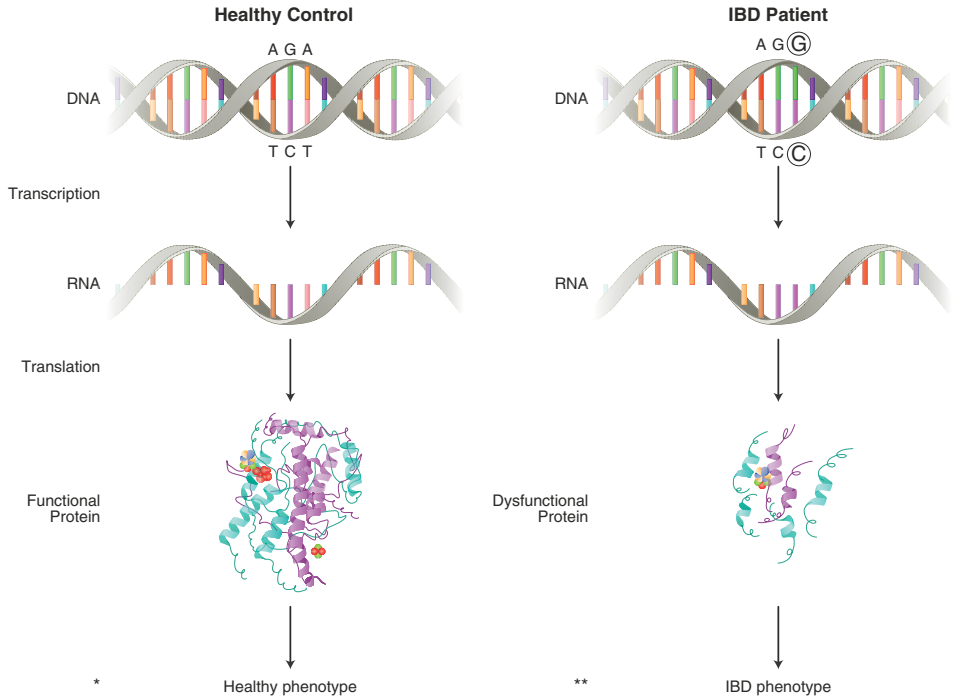

FIGURE 44.2. The possible downstream consequences of a single nucleotide polymorphism (SNP).

genes at the time and linkage studies where portions of the human genome or portions of specific chromosomes were shown to "travel" through generations with the disease process [66, 67]. The Human Genome Project (completed in 2003) [68] and the HapMap Project (completed in 2005) [69] have provided publically available databases of the most common genetic variants. These databases were used to interpret results obtained from genome-wide association studies (GWAS) where the genetic results from a large number of non-diseased control individuals were compared to those with IBD searching for significant genetic differences between the two groups (Figure 44-2) [70–72]. Typically 500,000–1 million single nucleotide polymorphisms (SNPs) were studied in thousands of diseased vs. healthy controls. SNPs, differentially expressed and identified using complex statistical analysis, were then "mapped" to relevant genes (usually through proximity) thereby identifying potential mechanistic pathways of disease pathogenesis.

Since the sequencing of the first human genome, genotyping coverage has increased while the cost has decreased. This trend is predicted to continue such that a complete human DNA sequence will soon be completed for less than $100 per patient [73, 74].

To date over 300 SNPs implicating over 150 genetic loci/genes have been associated with IBD (Figure 44-3) [70, 75, 76]. No single gene appears to be causative of either CD or UC, and thus inheritance is not the simple, Mendelian pattern seen in some diseases. Interestingly, several gene associations are shared between IBD and other immune-related diseases such as rheumatoid arthritis, multiple sclerosis, and even leprosy [76] suggesting overlapping pathobiology. The majority of the genes associated with IBD that have been discovered to date have roles in immune function, including innate and acquired immunity, and are discussed in more detail in the section below, Genetic Correlates Suggesting Mechanisms of Disease in IBD. A second group of genes appear to be involved in the health of the intestinal epithelium such as cation transporters and tight junction proteins suggesting IBD can also be the consequence of imperfect epithelial integrity or difficulty with reconstitution after injury [4, 70, 76].

Innate Immunity in Crohn's Disease

The innate immune system, present from birth, is the first line of host defense against enteric pathogens prior to the activation of adaptive or acquired immunity. Key functions of innate immunity have been demonstrated to play a significant role in CD: (1) epithelial barrier function and pathogen recognition and (2) autophagy (Figure 44.4a–c).

Epithelial Barrier Function

The epithelial barrier forms the interface between the luminal contents of the gut and the organ itself (Figure 44.4a). In the small bowel, four main cell types are found: enteroendocrine

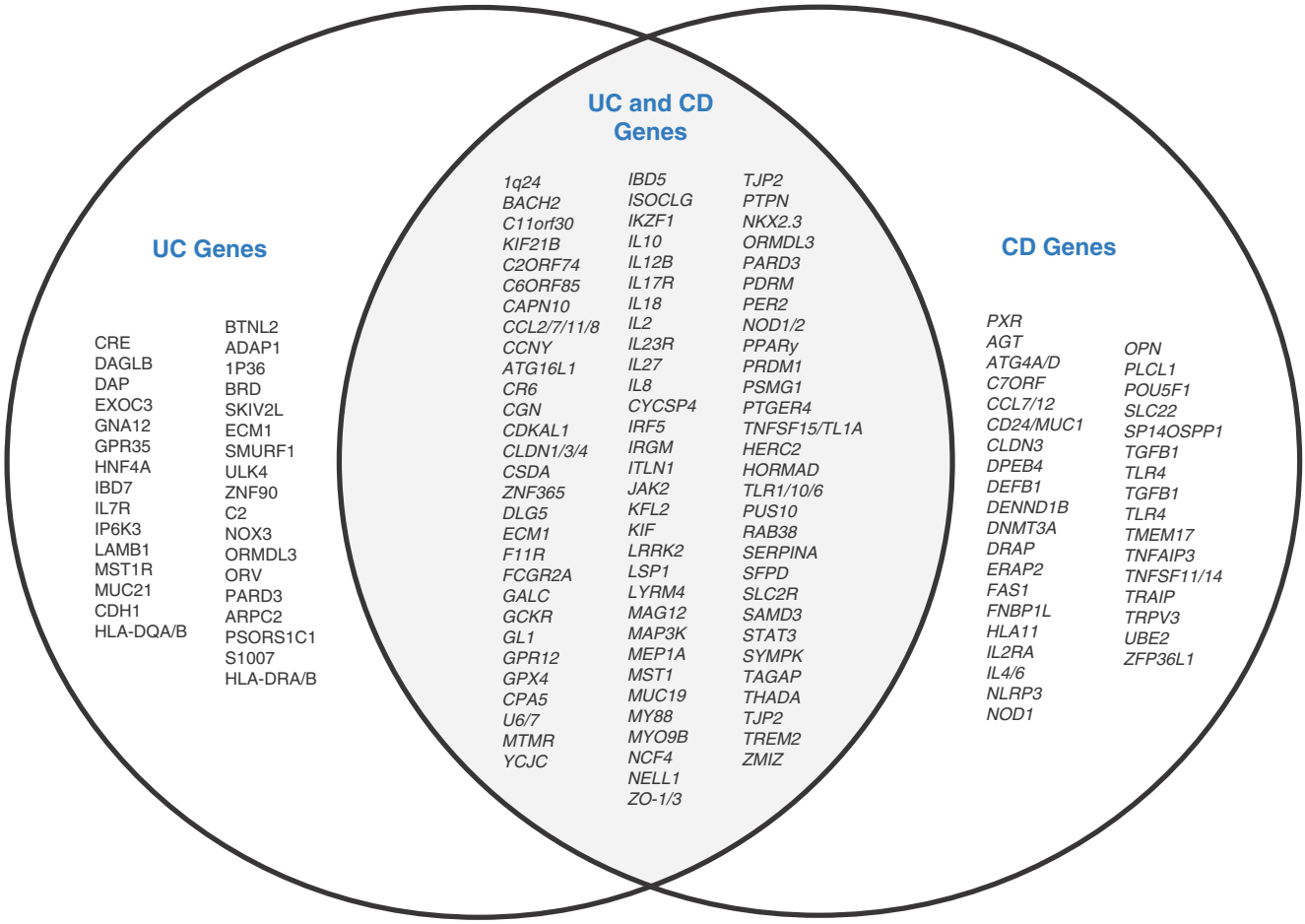

FIGURE 44-3. Genes associated with IBD. Genes associated with IBD found through genome wide association studies (GWAS) identifying single nucleotide polymorphisms (SNP) in proximity to the named genes.

cells, goblet cells, Paneth cells, and enterocytes. Goblet and Paneth cell dysfunction has been implicated in the pathobiology of CD. After differentiation, Paneth cells migrate to the base of the intestinal crypts while enteroendocrine cells, goblet cells, and enterocytes migrate to the villi. Goblet cells are interdispersed among the epithelial cells and store and secrete mucus into the intestinal lumen, thus forming a physical barrier over the intestinal mucosa to protect it from irritants and pathogens. Mucus also contains immunoglobulins such as IgA which aid in the regulation of inflammation and epithelial repair as well as binding and immobilizing enteric organisms. Paneth cells increase in number distally in the small intestine with the maximum concentration found in the ileum [77]. These cells are the main source of antimicrobial peptides in the small intestine and form a chemical epithelial barrier for pathogens [78]. Various antimicrobial peptides exist including lysozyme a phospholipase A2 and αdefensin, a hydrophobic peptide that forms pores in bacterial membranes resulting in lysis and death [79]. Decreased production of these peptides has been documented in CD involving the small intestine [80].

Epithelial cells contain cation transporters that move charged ions in and out of the cell to maintain homeostasis. How disease is caused by the altered movement of such cations between the intestinal lumen and tissue in IBD is unclear, but mutations in cation transporter genes have been associated with both CD and UC.

Junctions between adjacent epithelial cells control permeability across the intestinal mucosa and thus are necessary to avoid the passage of microbes from the intestinal lumen into the systemic circulation through these paracellular routes. The most commonly studied component of these junctions in IBD is the tight junction which is comprised of transmembrane proteins that interact with the intracellular actin cytoskeleton via plaque proteins which are under the control of several molecules. Tight junction abnormalities in IBD patients facilitate the uptake of antigens leading to inflammation and the release of cytokines such as interleukins, TNFα, and IFNɣ which in turn further propagate tight junction permeability (Figure 44-4b) [81]. Interestingly, abnormal tight junction function has been demonstrated in CD patients before the onset of disease and in unaffected family members

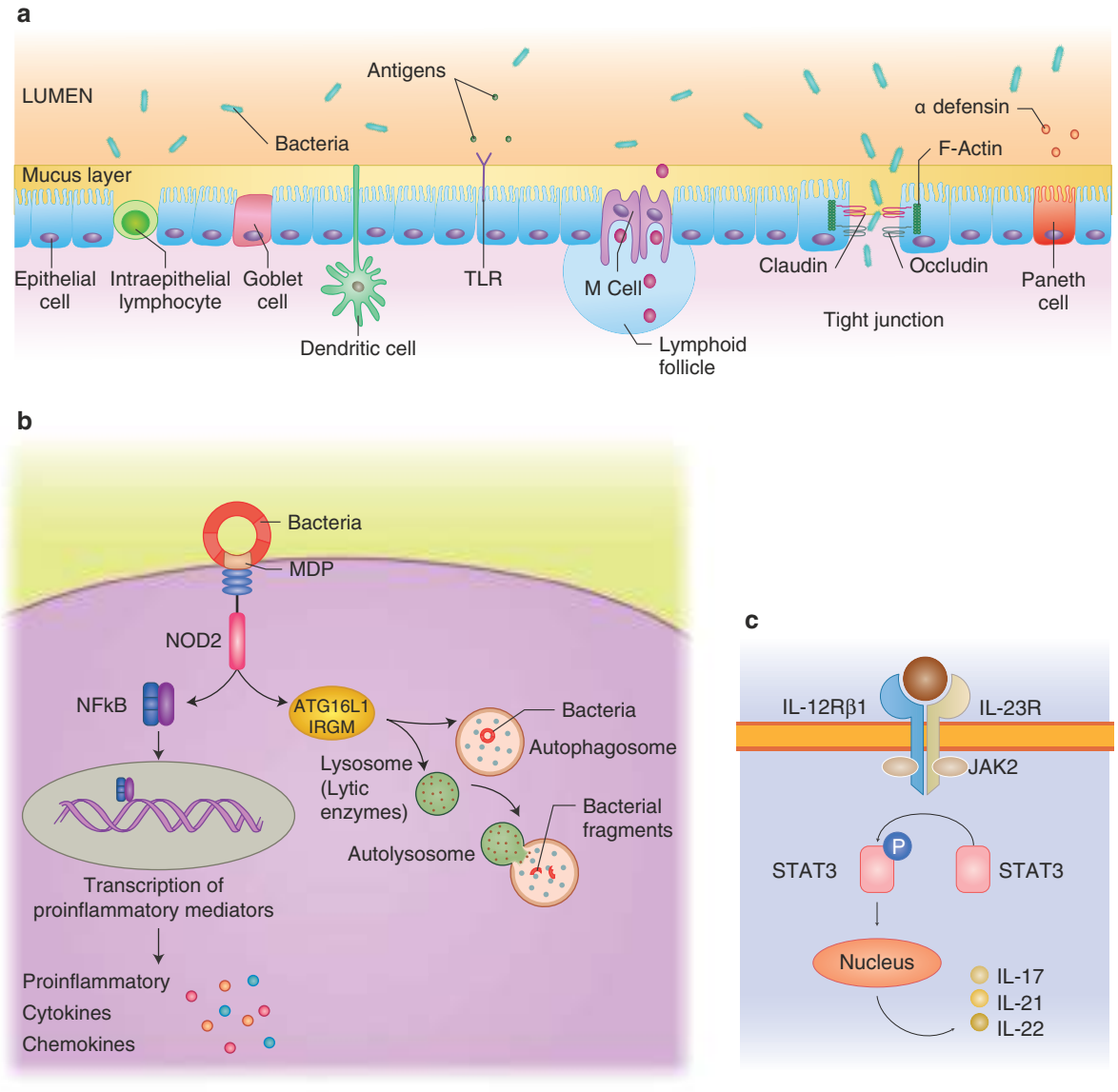

FIGURE 44-4. (**a**) The Epithelial Barrier. The epithelial barrier comprises the interface between the luminal contents of the gut and the organ itself. In the small bowel, 4 main cells types are found: enteroendocrine cells, mucous producing goblet cells, anti-microbial α defensin secreting Paneth cells and enterocytes. Additional cells of mucosal defense, include M cells shown channeling particles into the underlying lymphoid follicle and a dendritic cell reaching a dendrite between epithelial cells to make contact with lumenal antigens are depicted. The tight junction joining neighboring epithelial cells is comprised of transmembrane proteins that interact with the intracellular actin cytoskeleton is also depicted. In IBD, tight junction abnormalities allow the entry of antigens leading to inflammation and the release of cytokines such as interleukins, TNFa, INFy, which in turn further worsen tight junction permeability. (**b**) Autophagy and NOD2. The recognition and digestion of self and non self particles through autophagy is key to immunity. The figure shows the fusion of a lysosome with a bacteria-containing auto phagosome. This is in part dependent on functioning ATG16L1 and IR6M pathways. The NOD2/CARD15 pathway is also depicted, showing the recognition of MDP on the bacterial wall ultimately leading to NFkB activation that then results in changes in nuclear transcription of relevant inflammatory genes. (c) JAK/STAT PATHWAY STATs remain latent in the cell cytoplasm until, in response to signals from growth factors and cytokines through all sorts of receptors, become activated by receptor -associated tyrosoine kinases from the Janus kinase (JAK) family. STATs then dimerize, translocate into the cell nucleus and activate the transcription of inflammatory modulators.

suggesting a preexisting susceptibility to pathogen invasion due to baseline-altered permeability in CD patients [82].

Autophagy

In addition to providing an intact barrier, the healthy innate immune system also allows for the congenital ability to recognize certain antigens as foreign with subsequent "autophagy" or autodigestion and the recycling of either invading organisms or destroyed native cellular components [27]. Molecular signatures from a luminal pathogen (pathogen-associated molecular patterns or PAMPs) or from cellular debris resulting from cell stress or injury (damage-associated molecular pattern or DAMPs) are bound by pattern-recognizing receptors (PRRs) located on effector cells. This interaction activates a series of inflammation-inducing pathways including the adapter protein myeloid differentiation factor 88 (MyD88)-dependent pathway [83]. Downstream IgA production and release, epithelial cell proliferation and/or initiation of proinflammatory cascades results. Such PRR recognition of PAMPs and DAMPs is key to distinguishing "self" from "non-self."

Toll-like receptors (TLRs), the most commonly studied PRRs in IBD, are located within endosomes and on epithelial cell surfaces where they transverse the cell membrane. Although over a dozen TLRs are known, TLR2 and TLR4 have been demonstrated to play the most prominent roles in IBD [84]. TLR2 detects bacterial proteins while TLR4 detects an outer membrane component of gram-negative bacteria known as lipopolysaccharide (LPS) and functions primarily through the MyD88 pathway. However, TLR4 can also more directly activate inflammatory mediators such as tumor necrosis factor alpha (TNFα) and interferons (IFNs) through a MyD88-independent pathway.

Through the efficient degradation and recycling of cellular components, the process of autophagy is an energy-conserving mechanism for nutrient supply to the cell (Figure 44-4b). Autophagy is also involved in the adaptive immune system through the differentiation of T and B cells and the suppression of inflammation through mechanisms that have not yet been elucidated [85, 86]. During autophagy, the material for degradation is engulfed by the autophagosome. The autophagosome then fuses with a lysosome for degradation followed by presentation of the resultant peptide particles to HLA class II molecules for further processing. The main site of autophagy is the small intestinal Paneth cell; thus autophagy plays a stronger role in the pathobiology of CD than UC [78]. Mutations within several genes involved in this pathway are among the most highly replicated IBD-associated genes (NOD2/CARD15, ATG16L1, IRGM), providing evidence for the key role of dysregulated autophagy in the pathobiology of both diseases. These genes are discussed in further detail below in the Genetic Correlates section.

Macrophages

Macrophages are immunoregulatory cells involved in the pathobiology of IBD through two main mechanisms, proinflammatory cytokine secretion and phagocytosis. High levels of proinflammatory cytokines including IL-18 and IL-1 are produced and secreted by macrophages [86]. Secretion of these cytokines activates natural killer (NK) cells which then secrete interferon gamma (INFy) leading to dendritic cell (DC) activation. Once activated, DCs secrete TNFα, resulting in the recruitment of more inflammatory cells to the area [79]. IFNγ and IL-8 production leads to the maturation of macrophages and the formation of multinucleated giant cells [19] which are the key components of the granulomas characteristic of CD. Further release of proinflammatory cytokines potentiating T cell activation and further inflammation occurs when the granulomas themselves then present antigens to the T cells perpetuating the cycle of inflammation [79].

Macrophage and neutrophils are also recruited to the site of antigen presentation for phagocytosis. When levels of chemokines, cytokines (including IL-1 and TNFα), and leukotrienes are elevated, leukocytes traveling within blood vessels are signaled to cross the endothelial surface to reach the site of inflammation. Integrins, which are receptors on the surface of neutrophils, bind to factors such as mucosal addressin cell adhesion molecule-1 (MAdCAM-1) on the endothelium facilitating this margination and homing process [79, 87]. These integrins are the targets of some of the newest pharmacological treatments for IBD (See Chap. 46 on IBD treatment) [87].

APCs: The Bridge Between the Innate and Adaptive Immune Systems

Antigen-presenting cells (APCs) recognize both host enteric and foreign peptides. In the gut, APCs either travel to the location where a pathogen has breached the epithelial barrier or, alternatively, extend long armlike dendrites to reach through the tight junction between two epithelial cells to bind to intraluminal antigens. Dendrites also interact with M (or microfold) cells, specialized small intestinal cells that transport antigen directly from the lumen to APCs and T cells in a basolaterally located pocket via endocytosis [86] (Figure 44-4a). After antigen binding, APCs return to lymphoid tissue for presentation to T cells in a process guided by homing molecules. Such homing molecules include $\alpha_4\beta_{7,}$ present on effector T cells, and its ligand mucosal addressin cell adhesion molecule-1 (MAdCAM-1) which is expressed by small intestinal endothelial cells and colonic lamina propria cells [88]. A smaller role has also been demonstrated for the vascular adhesion molecule ELAM-1 (endothelial leukocyte adhesion

molecule-1) in both UC and CD [89]. In CD, the CCL25 chemokine and its receptor CCR9 have been demonstrated to contribute to small intestinal homing [87, 88].

Dendritic cells (DCs) are the APCs most implicated in the pathobiology of IBD (Figure 44-4c). One theory on the inappropriate response to self or foreign antigens and/or lack of tolerance to normal flora in IBD is that a "leaky" epithelial barrier may allow increased DC-antigen contact and an overstimulation of the systemic immune system [85]. Several DCs subsets have been found, some of which are involved in tolerance and others which are proinflammatory. IL-2 secreting DCs have been implicated in both UC and CD pathobiology [90]. IL-12 is a key cytokine involved in T cell function and is a driver of differentiation of naïve T cells to the IL-2 secreting Th1 subset thought to play a major role in CD [78, 91] (Figure 44-5).

Adaptive Immunity in Crohn's Disease

Together, the T and B lymphocyte response to the presence of antigen comprises the adaptive immune response. T and B lymphocyte activation results in the elimination of pathogens through direct killing, cytokine-mediated pathways, and antibody-mediated killing. T cell-mediated adaptive immune responses are better characterized in the pathobiology of IBD than the B cell response. T cells are predominantly located in the lamina propria and are divided into two main categories: CD4/memory T cells (which play a more predominant role in IBD) and CD8/cytotoxic T cells (whose main role is the production of IFNɣ). The secretion of the key immunological defense molecule, IgA, is the main function for B cells in IBD elucidated to date [87, 92].

Once bound with antigens on the surface of their major histocompatibility complexes (MHCs), APCs travel through the lymphatic vessels to the gut-associated lymphoid tissue (GALT), including the mesenteric lymph nodes and the intestinal lymphoid islands known as Peyers' patches. The antigen is then presented to the naïve T cell, and in the presence of costimulatory molecules, T cell activation followed by T cell subset differentiation occurs. Differentiation into one of four major subsets is guided by the influence of cytokines in the cellular milieu (Figure 44-5). A bias toward Th1 (T helper one) cell differentiation with associated TNF and IFNγ production is the main pathway of differentiation in CD [76, 93]. Abnormal Tregs (T regulatory cells) are well documented in CD. This relatively newly discovered T cell subset has an anti-inflammatory role through the promotion of tolerance to dietary antigens and gut microbiota and the suppression of immune responses through involvement in the production of the anti-inflammatory cytokine, IL-10 [94]. IL-17 secreting Th17 cells have been associated with both CD and UC but have a slightly stronger association with CD [76, 93, 95].

Cytokine Signaling

Several cytokines play a role in the pathways involved in IBD. Some maintain these pathways while others induce or disrupt them. Several of these cytokines are mentioned in the above sections. Key cytokines with genetic correlates associated with IBD are highlighted below in the Genetic Correlates of IBD section.

Innate Immunity in Ulcerative Colitis

The epithelial barrier plays a greater role in the pathobiology of UC as opposed to CD since the inflammation of UC is limited to the mucosa of the colon and rectum [96]. UC is characterized by a loss of epithelial integrity and damage to the goblet cells, enteroendocrine cells, and enterocytes. Unlike small intestinal CD, where these cells migrate to the villi, in UC, affected cells are found on the surface of the colon (as no villi are present in the colon). Paneth cells are only found in the small intestine; thus they do not play a role in the pathobiology of UC.

The role of the tight junction has been the focus of much research in UC [97]. Impaired tight junction permeability has been associated with an increase in proinflammatory cytokines even in quiescent IBD [98]. Autophagy is also involved in the pathobiology of UC but is more studied in CD [86, 99]. As granulomas are not found in UC, the role of macrophages in UC is likely limited to the production of proinflammatory cytokines [86] and the activation of NK and dendritic cells. Integrin mediators on the surface of neutrophils including MAdCAM-1 are also implicated in UC [79, 87, 100], and targeting of these molecules has also been shown to be effective in the treatment of UC (See Chap. 46 on IBD treatment) [87].

Studies on the role of DCs in IBD have more commonly focused on CD than UC. The luminal projection of DC dendrites may be affected by variations in tight junction permeability in UC, however [101]. Recent in vitro studies on DCs by Ueno et al. have suggested that exposure to cigarette smoke may affect DC function and be a key driver of T cell differentiation toward Th1 cells in CD and Tregs in UC [102], a potential explanation for the smoking paradox in UC vs. CD described above.

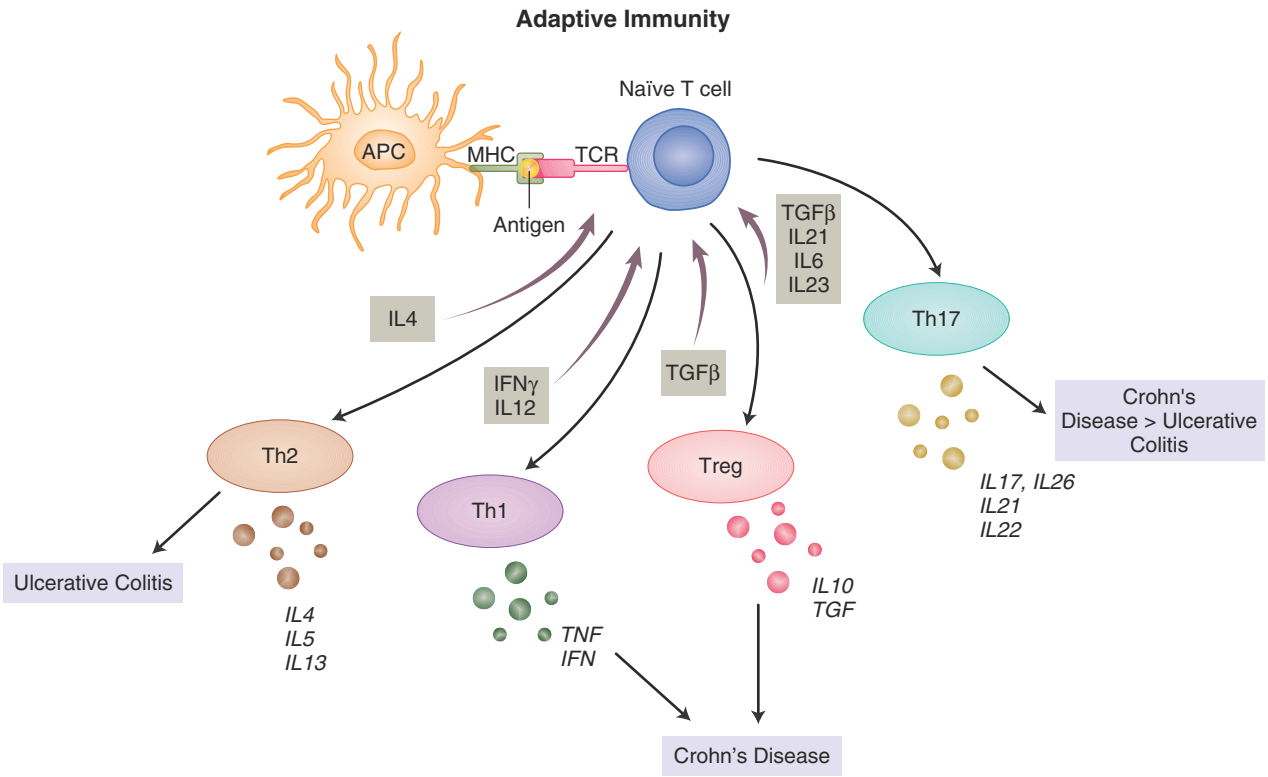

FIGURE 44.5. Adaptive immunity in Crohn's disease.

Adaptive Immunity in Ulcerative Colitis

T cell activation and differentiation is described in detail above. During differentiation, a Th2 cell bias leading to increased production of IL-4, IL-5, and IL-13 has been associated with UC (Figure 44-5). Th17 cells and their IL-17 secretion have also been associated with UC but to a lesser extent than CD [76, 93, 95].

Genetic Correlates Suggesting Mechanisms of Disease in IBD

Innate Immunity

Epithelial Barrier

The MUC family of glycoproteins is the main component of intestinal mucus. MUC2 is the most abundant glycoprotein and as such has been the main MUC gene of interest in IBD. Murine MUC2 knockout models develop an IBD-like colitis with features of both CD and UC [103]. Similarly, decreased expression of three members of the MUC family of genes, MUC2, 3, and 4, has been demonstrated in colonic tissue from UC patients when compared with control tissue while MUC19 polymorphisms have been associated with CD in humans [27, 104].

Anti-inflammatory prostaglandins are involved in epithelial mucosal repair. Prostaglandin E receptor 4 (PTGER4) SNPs have been associated with the development of CD [27]. A similar association has not been found in UC.

Polymorphisms in several cellular transport genes have been associated with IBD by GWAS; however, their roles in the pathobiology of IBD are not clear. This is true of the cation transport molecules OCTN1 (organic cation/carnitine transporters, also known as the solute carrier family 22, member 4/ SLC22A4) and OCTN 2 (also known as SLC22A5) located on chromosome 5. Mutations within both genes have been associated with UC and CD. These associations have been highly replicated through multiple GWAS studies [105]. Polymorphisms have also been associated with colonic involvement and anal disease in CD [105]. The mechanism for this association has not been elucidated, however.

Claudin and occludin are transmembrane bridging proteins found within tight junctions. Both are linked to the actin cytoskeleton via interactions with scaffolding proteins including the Zo (zona occludens) family [106, 107]. Claudin protein expression levels have been demonstrated to correspond to severity of inflammation in Crohn's colitis [108]. An absence of Zo-1 has been seen in experimental murine colitis models [109, 110]. When the ratio of claudin to occludin expression was studied, a significant increase in the ratio was demonstrated in diseased UC colon compared to

non-diseased UC colon and normal colon. In CD, the ratio did not vary with disease status, suggesting a greater role for these proteins in UC [96].

A number of IBD-associated genes including signal transducer and activator of transcription molecules (STATs), the intelectin-1 (ITLN1) and Drosophila discs large 5 (DLG5), domain class 5, also known as the octamer-binding transcription factor 4 (OCT4) and laminin beta 1 subunit (LAMB1), can be grouped together under the umbrella term "miscellaneous epithelial integrity genes." STATs remain latent in the cell cytoplasm until, in response to signals from growth factors, cytokines (including IL-2, IL-3, IL-5, and IL-7), thrombopoietin, and erythropoietin, they become activated by receptor-associated tyrosine kinases from the Janus kinase (JAK) family. STATs then dimerize, translocate into the cell nucleus, and activate transcription and the expression of various proteins (Figure 44-4c) [111–113]. STAT3 has been implicated in IBD but has a paradoxical effect in the innate and adaptive immune systems. When activated in innate immune cells (e.g., intestinal epithelial cells, neutrophils, and macrophages), mucosal barrier function is enhanced [114]. Conversely, when activated in T cells, an exacerbation of colitis is seen [115].

ITLN1 gene's protein product is expressed in the brush border of enterocytes and plays an important role in membrane stabilization and protection of the glycolipid barrier from pathogens [115]. SNP variants have been associated with IBD by GWAS, however. No studies on the functional consequences of these polymorphisms in IBD have been performed to date. Similarly, polymorphisms within the DLG5 gene, a guanylate kinase family member located at the cell-cell junction, have been associated with both CD and UC by GWAS [116] and replicated in smaller studies [117]. Functional studies have been limited to UC and have shown an increased expression of the protein in UC tissue vs. healthy control tissue [118].

Two genes POU5F1 and LAMB1 are exclusively associated with UC, again suggesting a greater role in epithelial barrier function in UC vs. CD. Similar to many IBD-associated genes, the POU5F1/OCT4 gene has been previously associated with other immune-mediated diseases such as toxic epidermal necrolysis [119] and psoriasis [120]. POU5F1's protein product is involved in stem cell pluripotency in the embryo and renewal in the adult. The gene has been associated with colonic adenomas and colorectal cancer (CRC) [121–123], perhaps by inhibiting dividing progenitor cells from differentiating [124]. Yasuda et al. demonstrated decreased expression in UC tissue with CRC vs. UC tissue with inflammation only [123]. Interestingly, this gene has also been associated with patient satisfaction after IPAA in a quality of life study inclusive of over 140 patients. Two SNPs within this gene were associated with poor emotional well-being, which may be the result of a more severe disease phenotype. An SNP within another immune-mediating gene, TNFSF14, was also associated with overall poorer quality of life, worse bowel symptoms, and poorer emotional well-being [125].

Laminin is a key component of the basement membrane and acts as an anchor for the single-layered intestinal epithelium and thus has a role in pathogen defense and cell adhesion [126]. LAMB1 codes for a subunit of laminin. Its expression has been demonstrated to be downregulated in colonic tissue samples from UC patients vs. controls [126]. This downregulation has been associated with distortion of the colonic basement membrane in UC [127].

Genetic correlates with macrophage and DC homing have been associated with CD only. Neutrophil homing genes have been associated with both CD and UC. Such polymorphisms within the peritoneal phagocytosis-inducing macrophage stimulating 1 (MST1) gene have been associated with CD in multiple large GWAS [128, 129]. The homing receptor chemokine receptor 6 (CCR6) is expressed by immature dendritic and memory T cells and has also been associated with CD on GWAS [115]. The expression of the neutrophil homing mediator, mucosal addressin cell adhesion molecule-1 (MAdCAM-1), has been demonstrated to be overexpressed in the gut epithelium during active CD and UC [79, 87, 100]. This discovery has led to the use of MAdCAM-1 and other related integrins as therapeutic targets for some newer IBD pharmacological treatments (see Chap. 46 on IBD treatment) [87].

Pathogen Recognition and Autophagy

NOD2/CARD15

Genes within the autophagy pathway were the first genes to be associated with IBD. The identification of these genes and further study into their functional roles in the pathobiology of IBD linked the fields of microbiology, immunology, and genetics. The most commonly studied autophagy-associated genes in IBD are nucleotide-binding oligomerization domain-containing protein 2 (NOD2, also known as caspase recruitment domain-containing protein 15 or CARD15), autophagy-related protein 16-like 1 (ATG16L1), and immunity-related GTPase family M protein (IRGM). Generally, a stronger association with CD vs. UC with these genes has been demonstrated.

The first step in autophagy is antigen recognition. Functional studies have demonstrated significantly higher expression of the PRR, TLR4 within the intestine of both UC and CD patients when comparing inflamed colonic mucosa with non-inflamed controls [130]. NOD2/CARD15, located on chromosome 16, was the first gene discovered to be associated with IBD in 2001 [66, 131]. To date, it has the strongest, most commonly replicated gene association with IBD, especially CD [132]. The NOD2/CARD15 gene is expressed in several cell types involved in the pathobiology of IBD including intestinal epithelial cells, Paneth cells, dendritic cells, and monocytes. The CARD15 protein is

involved in the recognition and binding of muramyl dipeptide (MDP, a bacterial cell wall component) at the protein's leucine-rich repeat nucleotide-binding domain [132]. Thus CARD15 is a PRR. Two main pathways, the nuclear factor kappa B (NFκB) and mitogen-activated protein kinase (MAPK) pathways, are activated when NOD2/CARD15 is activated through the binding with MDP [27]. NF-κB plays a key role in the regulation of several genes responsible for the production of proinflammatory factors, cytokines, chemokines, adhesion molecules, and growth factors including interleukins1β, 8, 6, and 12 and TNFα, a potent proinflammatory cytokine highly involved in IBD pathogenesis. TNFα is a critical target of a whole class of biologic drugs that bind both free and cell-associated TNFα, known as TNF antagonists which are highly effective in both UC and CD (see Chap. 47 on treatment). MAPKs are heterogeneous enzymes which phosphorylate serine and threonine amino acids causing the propagation of downstream inflammatory signals [133].

Despite having the strongest IBD association, not all IBD patients have a NOD2/CARD15 mutation. In fact, the three most commonly IBD-associated SNPs or single-base substitutions within the NOD2 gene (R702W, G908R and 1007 fs) are rarely found in Asian CD patients and is only found in, at most, 40 % of European and North American CD patients vs. 10–15 % of the non-IBD population [134]. Interestingly, these three SNPs are all located either near or directly within the leucine-rich repeat sequence area of the gene where MDP is detected. The presence of any one of these SNPs has been demonstrated to cause impaired activation of the NFκB pathway and the subsequent production of inflammatory cytokines [135].

Besides activating the second messengers NFκB and MAPK, NOD2/CARD15 also recruits the autophagy-associated protein, ATG16L1, to the cell membrane [131, 132]. Both NOD2/CARD15 and ATG16L1 must be functional in dendritic cells for autophagy to occur [86]. Found on chromosome 2q37, ATG16L1's protein product is expressed by APCs, T cells, intestinal epithelial cells, and macrophages and is involved in the formation of the autophagosome. Paneth cell abnormalities, an impaired ability to breakdown intracellular bacteria, and increased levels of inflammatory cytokines have been demonstrated in both CD patients with mutations in ATG16L1 and ATG16L1 murine knockout models [19, 86]. Although more commonly associated with CD, meta-analysis has shown a small, but statistically significant, association with UC although with an odds ratio of only 1.08 [136].

An association between the IRGM gene and IBD was discovered at the same time as ATG16L1. Located on chromosome 5, IRGM encodes immunity-related GTPases required for the IFNγ-mediated clearance of intracellular pathogens. Similar to ATG16L1, the knockdown of IRGM in animal models has been shown to result in defective autophagy and the survival of several pathogens including *Toxoplasma gondii*, *Listeria monocytogenes*, and *Mycobacterium tuberculosis* [137, 138]. Three IRGM SNPs (rs13361189, rs4958847, and rs10065172) have been associated with IBD in early GWAS and confirmed in CD but not UC in a 2013 meta-analysis of 25 studies inclusive of 20,590 IBD cases and 27,670 controls. When stratified by ethnicity, a significantly increased CD risk was demonstrated in Europeans vs. Asians [139]. The presence of SNPs in the IRGM gene has been associated with earlier disease recurrence after ileocolectomy in CD [140].

The Adaptive Immune System

The human leukocyte antigen (HLA), also known as the MHC, involved in the presentation of antigen to T cells has been the focus of much study in IBD with a particular focus on HLA-DR subtypes. Although these genes are conventionally thought of as UC associated, subtypes of HLA genes such as DRB3, DR7, and DQ4 have also been associated with CD [141–144]. An association with DR2, DR9, and DRB1 and UC has been demonstrated by meta-analysis [142]. The HLADRB1 gene has been associated with the extraintestinal manifestations of IBD [141].

Several known IBD-associated genes including tumor necrosis factor superfamily member 15 (TNFSF15, also known as the TNFSF ligand 1A/TL1A and vascular endothelial growth inhibitor/VEGI), signal transducer and activator of transcription (STAT5), and T cell activating Rho GTPase-activating protein (TAGAP) are involved in T cell differentiation which occurs after activation [95]. The TNFSF15 gene, found on chromosome 9q32, is one of the earliest genes associated with both CD and UC through GWAS which has been subsequently confirmed with smaller studies [94]. TNFSF15's protein product, tumor necrosis factor (TNF)-like cytokine 1A (TL1A), is expressed in macrophages, endothelial cells, and gut lamina propria lymphocytes [145] and acts as a ligand binding the death domain receptor 3 (DR3) which is mainly expressed on T lymphocytes [94, 145]. Interestingly, TNFSF15/TL1A also has a regulatory, angiostatic effect in the vasculature [146]. Roles in apoptosis and the induction of metalloproteinases involved in intestinal barrier function have also been demonstrated [147, 148]. Stimulation occurs through the NFκB pathway. Downstream effects in IBD patients include an enhanced IFN gamma and IL-2 production by T cells [149, 150] and a preferential differentiation into Th1 and Th17 subsets [94, 149, 151]. Additionally, overexpression of TL1A in T cells has also been associated with a dysregulated immune response with increased numbers of Tregs noted [147, 152]. Interestingly, SNPs in this gene have also been associated with surgical diverticulitis [153].

The STAT5 gene encodes a protein member of the STAT family of transcription factors which are described above in the innate immunity/epithelial barrier function section. In contrast to TNFSF15, STAT5 inhibits differentiation into

Th17 and Tregs subsets and is associated with dysregulation of Th1 cells through the alteration of the IL-2 receptor and enhanced proinflammatory IL-4 secretion by mast cells [112, 154–159]. A key role for STAT5 in the functions of both the innate and adaptive immune systems, namely, tight junction permeability and mucosal healing [158] and the development of T, B, and NK cell [112, 159], has been demonstrated in STAT5 knockdown animal models.

The TAGAP gene, which is co-regulated with the proinflammatory cytokine IL-2 [160], plays a role in both T cell migration and activation [161–163]. Originally believed to be exclusively associated with CD, Toedter et al. demonstrated variations in TAGAP expression (as well as several other genes) before and after anti-TNF treatment in the colonic tissue of UC patients [164]. TAGAP's protein product is a member of the Rho GTPase–activating protein (GAP) family. This class of molecules is involved in several immune-modulating processes including actin formation. Actin formation affects cell motility, the establishment of cell-cell contacts, and the formation of the immunological synapse [165]. Interestingly, TAGAP propagates the inactive form of the Rho molecule [163, 166], thus impairing its interaction with downstream effectors resulting in changes in the T cell cytoskeleton which are critical to cell shape, movement, and contractility [167]. Like POU5F1 and several other IBD-associated genes, the TAGAP gene is also associated with other immune-mediated diseases such rheumatoid arthritis, celiac disease, and type 1 diabetes mellitus [160]. It has also been associated with anal Crohn's disease and has been shown to vary its expression along the course of the colon [168, 169].

Several cytokines are involved in the pathways involved in IBD. Some maintain these pathways while others induce or disrupt them. Several of these cytokines are mentioned in the above sections. The most well-known IBD-associated cytokine is IL-10. This cytokine is unique since it has anti-inflammatory properties. Therefore, mutations within the gene or its receptor which disrupts its function result in inflammation which is often very severe. IL-10 receptor (IL-10R) gene mutations were famously associated with extremely severe, early onset medically refractory CD with severe anal involvement at the Royal Free Hospital in 2009, a discovery which has since been replicated [170, 171]. This small cohort of patients with IL-10R mutations responded well to bone marrow transplantation suggesting the possibility of an actual cure for CD, by effectively reversing the specific genetic defect responsible for the disease in this highly unique subpopulation of patients.

IL-23 is secreted by DCs, monocytes, and activated macrophages and is involved in the Th17 differentiation of naïve T cells and the release of other proinflammatory cytokines including TNFα, IL-1, and IL-6 from monocytes and macrophages, also known as the IL-23–Th17 axis [172]. The IL-23 receptor (IL-23R) is a key linking molecule between the innate and adaptive immune systems. IL-23R is expressed by NK, memory T, and cytotoxic T cells. Particularly high levels are found in Th17 cells [92]. Binding of IL-23 to the IL-23R activates the JAK2 protein leading to the downstream recruitment and dimerization of the two subunits of the transcription activator, STAT3. STAT3 is then able to translocate into the cell nucleus and promote the transcription of proinflammatory mediators as described as above [172].

The IL-23 signaling pathway also activates an additional pathway with a key role in T helper cell differentiation, the retinoic acid-binding orphan receptor-γt (ROR-γt) pathway. The cytokines produced when this pathway is activated (IL-17A, IL-17F, IL-6, and TNFα) are proinflammatory and propagate naïve T cell differentiation into Th17 cells [172]. This pathway is particularly important in the pathogenesis of IBD as multiple polymorphisms located within several genes in this pathway are associated with the disease [92, 173]. The IL-23 gene is also associated with other immune-mediated diseases including rheumatoid arthritis and ankylosing spondylitis [92] as well as extraintestinal manifestations in UC [174].

The Molecular Basis of Malignant Degeneration

Both UC and CD patients are at an increased risk of developing CRC. An earlier onset of CRC and an increased risk of synchronous and metachronous neoplasia are found in both UC and CD patients when compared to the general population. Risk is significant and generally underappreciated by caregivers since up to 15 % of IBD patients die from CRC [175]. Despite the demonstrated increased risk of UC-associated CRC and the poor performance of colonoscopic surveillance protocols, no genetic or serological marker has been identified or shown to be effective in clinical practice; thus colonoscopy, including chromoendoscopy, continues to be the mainstay of surveillance practice.

Inflammation is a known risk factor for dysplasia, metaplasia, and progression to carcinoma. Thus IBD-associated dysplasia and CRC are found predominately in tissues with evidence of current or past inflammation [175–179], and risk is therefore also related to disease extent and duration [175]. Typically, inflammation progresses to low-grade dysplasia (LGD) with which it shares pathologic features. LGD then progresses to high-grade dysplasia (HGD), with shared features with CRC and then to CRC. In IBD, however, this progression is unpredictable and, unlike sporadic CRC which typically takes 10 years to develop, varies in rate and does not always occur in the aforementioned order [176, 179–183].

Like sporadic CRC, IBD-associated CRC involves p53 and adenomatous polyposis coli (APC) mutations and microsatellite instability. However, the sequence of these mutations in progressive malignant degeneration is different between IBD-associated malignancy and conventional CRC (Figure 44-6) [184, 185]. APC mutations are involved in the

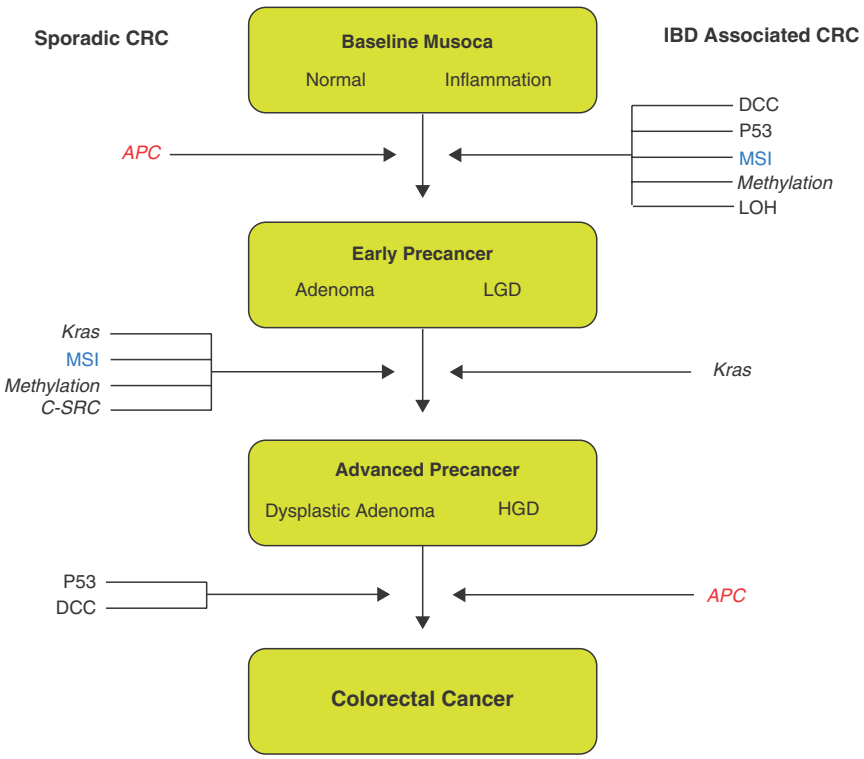

FIGURE 44-6. Malignant degeneration in the setting of IBD vs. sporadic colorectal cancer.

first step of progression from normal tissue to sporadic cancer. However, APC mutations are involved relatively late in the progression from inflammation to IBD-associated cancer. An increased frequency of p53 mutations in LGD in UC and decreased frequency of APC mutations in UC-associated CRC patients compared with sporadic neoplasia patients were demonstrated in an early study of 33 UC-associated neoplasias and 23 sporadic neoplasias [186].

The discovery of a genetic predictor of progression to CRC in IBD could potentially affect surveillance regimens and provide the opportunity to offer a prophylactic colectomy to patients at high risk [187]. To date, only a few small studies have been performed in this field of research, and results are conflicting [188, 189]. An SNP within the OCTN1 genes (discussed above in the Genetic Correlates section) was found to be associated with UC, UC-associated CRC, and early onset of sporadic CRC in a large cohort of over 600 Italian patients. However, only two genes (OCTN1 and OCTN2) were investigated [190]. In a study of over 300 known IBD-associated SNPs comparing carefully matched UC and UC-neoplasia patients, no correlation between any of these IBD SNPs and neoplasia was found suggesting a stronger role for sporadic CRC-associated mutations [191].

A more significant association with UC-associated cancers (57 %) vs. sporadic cancer (36 %) has been demonstrated in cases of promoter region methylation of the e-cadherin encoding gene CDH1 gene which is involved in epithelial junctions [192]. Houlston et al. subsequently demonstrated an association between CDH1 and both sporadic CRC and UC, suggesting a link between the two pathologies. However, UC-associated CRC patients were not included in the study [193, 194]. The process of methylation is the best studied epiphenomena in IBD-associated CRC [195]. Interestingly, methylation levels have been demonstrated to be higher in human UC-CRC vs. sporadic cancer [189], and known key mediators of IBD-associated inflammation including IL-6 and IFNγ have been shown to induce DNA methylation, possibly explaining why the risk of cancer increases with the duration of UC inflammation [189]. Mouse models of colitis have demonstrated the presence of DNA methylation prior to tumor development [188, 196]. However, though methylation in UC-associated cancer appears to play a potentially significant role, utilizing this to identify patients at risk for UC-associated CRC has not been done.

Surgical Genetics in IBD

The novel field of "surgical genetics" utilizes clinical and genotype data to predict operative outcomes [197]. Due to the unpredictable nature of IBD both in surgical outcome and disease recurrence, the identification of specific genetic factors that might predict surgical outcome is attractive. Other examples could include the identification of patients that will fail medical treatment, require repeat segmental resections for Crohn's, or experience severe or develop debilitating pouchitis after ileal pouch-anal anastomosis for UC. Some early studies have been performed that identify possible genes of relevance to the surgical management of IBD patients.

There are several gene alleles that suggest a predisposition to early surgery in IBD. Increased expression of the drug efflux pump, multidrug resistance (MDR) gene in peripheral blood lymphocytes, was associated with failure of corticosteroid treatment and the need for surgery in a study of over 200 IBD patients [198]. A TNFα polymorphism (308A allele) was associated with an OR of 2.1 for requiring surgery due to medical failure in pediatric IBD patients [199]. In the largest surgical genetics study to date, utilizing genotyping results from greater than 70 known IBD loci in over 1000 CD patients, Dubinsky et al. associated three loci, IL-23R, IL-12B, and chromosome 11 open reading frame 30 (a regulator of transcription), with the requirement for early surgery (within 5 years of IBD diagnosis) [200].

Utilizing an SNP array with over 70 IBD-associated SNPs, the presence of the IRGM SNP rs4958847 was associated with the more frequent need for repeat ileocolectomy [140]. In a study evaluating only three NOD2 SNPs in 80 small bowel CD patients, the 1007 fs variant was associated with a the requirement for surgery for stenotic disease in over 60 % of patients with the variant [201]. SNPs in the PTGER, NOD2, and TNFSF15 have also been associated with Crohn's-like pouch complications (i.e., fistula, abscesses) and severe pouchitis after IPAA [202–204]. Much like the increasing role of genetic determinants in defining chemotherapy for CRC, genetic alleles will likely soon be used to assist the surgeon in deciding the type and timing of operative intervention in IBD patients.

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45
IBD Diagnosis and Evaluation

Matthew M. Philp and Howard M. Ross

Key Concepts

- Familiarity with modes of clinical presentation of ulcerative colitis and Crohn's disease allows the clinician to promptly select the most efficient combination of tests.
- Knowledge of histologic findings of ulcerative colitis and Crohn's disease facilitates discussion with other physicians of the care team and tailors specific medical and surgical therapies.
- Serologic tests such as ASCA, pANCA, and fecal markers such as calprotectin are increasingly becoming utilized for diagnosis and treatment effectiveness monitoring.
- High definition images, chromoendoscopy, confocal laser endomicroscopy, and double balloon enteroscopy add to the ability to diagnose and treat ulcerative colitis and Crohn's.
- Capsule endoscopy, computerized tomography and computerized tomography enterography, magnetic resonance imaging, and magnetic resonance enterography provide previously unimagined ability to visualize disease and are revolutionizing the care of the IBD patient.

Inflammatory Bowel Disease: Diagnosis and Evaluation

Historical Context

The purpose of this chapter is to describe modalities and points of information that will aid the surgeon in the diagnosis and evaluation of the inflammatory bowel diseases.

Crohn's disease and ulcerative colitis are collectively referred to as inflammatory bowel diseases. Inflammation plays a significant role in each entity. Though largely different in the distribution of disease and the manner in which inflammation affects the gastrointestinal tract, occasionally the diseases overlap both in behavior and in their responses to similar treatments.

The consideration of ulcerative colitis and Crohn's disease together as inflammatory bowel diseases is beautifully described in a historical review in the Mt. Sinai Journal of Medicine, "Although clinical descriptions of diarrhea with or without blood go back thousands of years, clear distinctions between enteritis and ulcerative colitis were possible only in the nineteenth century." [1] The term "ulcerative colitis" was mentioned in 1888 by Dr. Hale-White in his paper, "On simple ulcerative colitis and other rare incidental ulcers" [2]. As described by Dr. Lockhart Mummery in 1905, the introduction of the electric sigmoidoscope made it possible to make proper diagnosis of ulcerative colitis and distinguish it from infective dysentery, membranous mucous or catarrhal colitis, and nervous diarrhea [3]. The entity now known as Crohn's disease has a politicized origin. Drs. Ginzburg and Oppenheimer "in conjunction with Dr. Burrill B. Crohn" presented a definitive paper, "Non-specific Granulomata of the Intestine," on May 2, 1932, to the American Gastro-Enterological Association and the paper "Regional Ileitis: A Pathologic and Chronic Entity," under the authorship of Crohn, Ginzburg, and Oppenheimer," was published later that year [4].

Ulcerative Colitis

The classic presentation of ulcerative colitis is the new passage of bloody diarrhea. The work-up must include a careful history. The importance of rapidity of onset, fecal consistency, frequency of defecation, continence, and exposure to infectious agents, weight loss, other concurrent associated symptoms, and family history are all important and may hint at diagnosis. The goal of investigation is to make a specific, prompt diagnosis to facilitate early treatment. Past medical history is always crucial. Patients with prior immunosuppression, foreign travel, or antibiotic use may be more likely to have an infectious colitis and prior perianal infection may suggest Crohn's disease. Physical exam is important to evaluate signs of toxicity that might mandate prompt surgical

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TABLE 45-1. Extra-intestinal manifestations of ulcerative colitis [6]

Site	Manifestation	% of UC patients
Skin	Erythema nodosum	3
	Pyoderma gangrenosum	1.4–5
	Aphthous stomatitis	4
Hepatopancreatobiliary	Primary sclerosing cholangitis	5
	Cholangiocarcinoma	Rare
	Primary biliary cirrhosis	Rare
	Autoimmune hepatitis	Rare
	Portal vein thrombosis	Rare
	Pancreatitis	Rare
Musculoskeletal	Peripheral arthritis	20–40
	Axial	5
	Metabolic bone disorders	2–40
	Myopathy	Rare
Ocular	Episcleritis	Rare
	Uveitis	Rare
	Scleritis	Rare
	Optic neuritis	Rare
Hematologic	Anemia	8–73
Vascular	Venous thromboembolism	Rare
Genitourinary	Urolithiasis	Rare
Pulmonary	Bronchiolitis	Rare
Cardiac	Pericarditis	Rare

evaluation and treatment. Evaluation of vital signs is critical looking for tachycardia specifically. Careful abdominal examination and rectal exam must be performed. External anal examination should be performed evaluating signs of anal Crohn's disease (waxy thickened skin tags, fistulae). Rectal tone should be evaluated and documented. The nature of the anus should receive focus. Is there any sign of anal structuring or fibrosis, or is the musculature supple? Is there a mass? The contents of the rectal vault should be noted for stool consistency and the nature of the bleeding.

Infectious colitides that mimic ulcerative colitis must be evaluated via stool culture. Shigella, Salmonella, Yersinia, Clostridia *difficile*, and Cytomegalovirus must be specifically queried (see Chap. 52 for further details about infectious colitides).

The colon must be evaluated by colonoscopy. The extent of disease and characteristics of the mucosa are critical. Classically, ulcerative colitis begins in the distal rectum and extends proximally. The inflammation progresses in a confluent manner and affects only the mucosa, without fissuring, or skip areas. An activity index for ulcerative colitis is seen in Table 45-1 [5]. Extra-intestinal manifestations can be associated with both ulcerative colitis and Crohn's disease (Table 45-2) [6].

TABLE 45-2. A simple clinical colitis activity index. Scoring system for the Powell-Tuck Index [5]

Symptoms and signs		Score
Symptoms		
Bowel frequency	3–6	1
	>6	2
Stool consistency	Formed	0
	Semi-formed	1
	Liquid	2
Abdominal pain	Before/after bowel motions	1
	Prolonged	2
	Anorexia	1
	Nausea/vomiting	1
General health	Normal	0
	Slightly impaired	1
	Activities restricted	2
	Unable to work	3
Extracolonic manifestations	One/mild	1
	More than one/severe	2
Signs		
Abdominal tenderness	Mild	1
	Marked	2
	Rebound	3
Body temperature (°C)	<37.1	0
	37.1–38	1
	>38	2
Blood in stool	Trace	1
	More than trace	2
Sigmoidoscopy	Non-hemorrhagic	0
	Friable	1
	Spontaneous bleed	2

Crohn's Disease

Crohn's disease can affect anywhere in the digestive tract from the mouth to the anus and the inflammatory process of Crohn's involves the full thickness of the bowel wall.

TABLE 45-3. Macroscopic features used for the diagnosis of IBD [13]

	Ulcerative colitis	Crohn's disease
Localization GI tract	Especially colon and rectum	Whole GI tract
Ileum	Not except in backwash ileitis	Often involved
Colon	Left > right	Right > left
Rectum	Commonly involved	Typically spared
Distribution GI tract	Diffuse (continuous)	Segmental (discontinuous)
Ulcers	Superficial ulcers	Aphthoid ulcers, confluent deep linear ulcers
Pseudopolyps	Common	Uncommon
Skip lesions	Absent	Present
Cobblestone pattern	Absent	Present
Deep fissures	Absent except in fulminant colitis	Present
Fistulae	Absent except in fulminant colitis	Present
Mucosal atrophy	Marked	Minimal
Thickness of the wall	Normal	Increased
Fat wrapping	Absent	Present
Strictures	Uncommon	Present

These properties contribute to the clinical behavior of the disease and the varied manners of presentation.

The most common site of Crohn's disease is an ileocolic distribution though anal, intestinal, or colonic disease alone are also regularly seen. As Crohn's disease involves the full thickness of the bowel wall, stricture and obstruction, fistula formation, and abscess formation are important sequelae that might result in presenting symptoms, point to diagnosis, and might mandate intervention. Discontinuous skip areas of involvement are common and a clear differentiating behavior from ulcerative colitis.

The work-up of Crohn's disease begins similarly to ulcerative colitis. History and physical exam provide evidence of the diagnosis.

IBD Histology

A basic knowledge of the histological features in inflammatory bowel disease is essential for the practicing colorectal surgeon. The combination of clinical disease activity, endoscopic findings, and histology generates accurate diagnosis. Communication with an experienced IBD pathologist is vital for making correct treatment decisions in many situations.

Ulcerative Colitis

The classic macroscopic finding in ulcerative colitis (UC) is contiguous mucosal inflammation extending from the rectum proximally for a variable distance in the colon. Other portions of the gastrointestinal tract are not involved. Macroscopic features of UC are shown in Table 45-3. Clinicians should be aware of certain instances where macroscopic inflammation in UC may not be in a continuous pattern. These situations are often confused with Crohn's disease. The cecal cap or patch is an isolated area of inflammation surrounding the appendix [7, 8]. Backwash ileitis is contiguous ileal inflammation in UC from reflux through the ileocecal valve. It is correlated with severity of cecal inflammation. The incidence of backwash ileitis is decreasing, likely due to improved medical management and reductions in severe right-sided colitis [9]. Patchy or noncontiguous ileal involvement should raise suspicion for Crohn's disease. Rectal mucosal sparing is often thought to result from enema topical therapy. Among medically treated UC patients, both oral and per rectum, 33–44% have been shown to have some patchy distribution of inflammation [10].

The hallmark of microscopic ulcerative colitis is widespread crypt distortion in a continuous pattern of inflammation (Figure 45-1). The severity of inflammation is worse distally in the colon. It is mucosal limited, with occasional extension into the superficial submucosa. In situations of fulminant UC, ulcer penetration to the muscularis propria with serositis can occur, making it difficult to discriminate from Crohn's disease. Crypt abscesses occur more frequently in UC (41%) than in Crohn's disease (19%) [11]. Mucin depletion is much more common in UC than in Crohn's [12]. Basal plasmacytosis is an early feature of UC and can be used to help differentiate it from infectious colitis [13].

Crohn's Disease

Crohn's disease (CD) can affect any portion of the gastrointestinal tract. Mostly commonly the ileocolon is involved. "Creeping fat" at the mesenteric edge of the bowel is due to transmural inflammation and is strongly correlated with Crohn's. "Creeping fat" is nonspecific and is found in other inflammatory conditions, including diverticular disease [14]. Aphthous ulcers are one of the early gross mucosal findings in Crohn's. Ulcers are often surrounded by edematous, but otherwise normal tissues. Coalescence and spread of the ulcers leads to the classic cobblestoned mucosal appearance (Figure 45-2). Inflammatory pseudopolyps caused by inflammation and

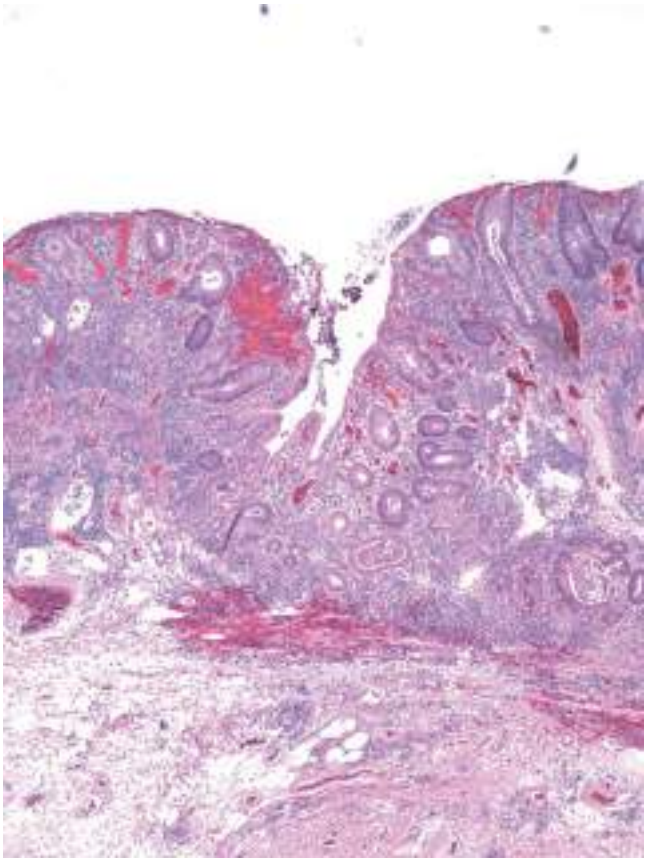

FIGURE 45-1. Low-power view of ulcerative colitis showing inflammatory infiltrate confined to the mucosa.

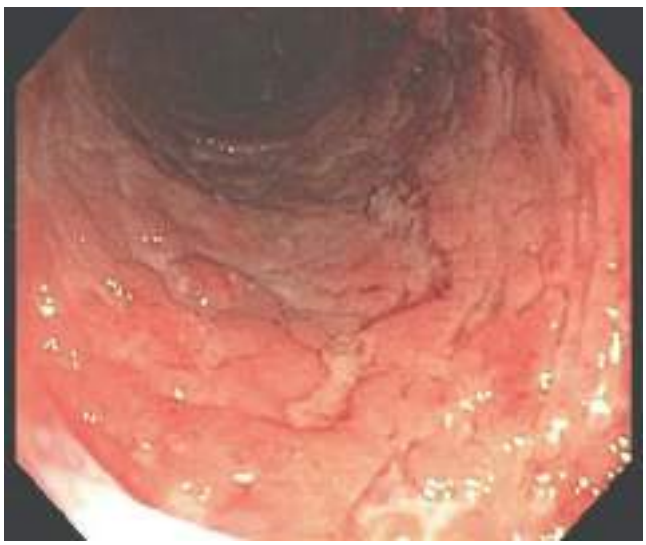

FIGURE 45-2. Crohn's disease with cobblestone appearance of the mucosa.

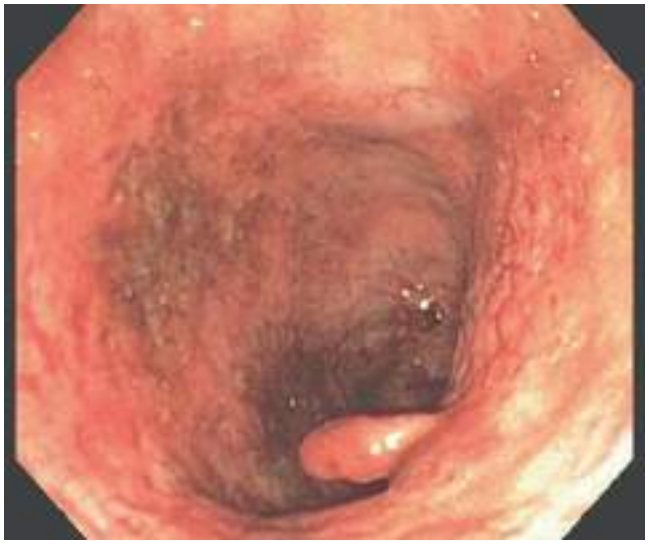

FIGURE 45-3. Pseudopolyp in Crohn's disease.

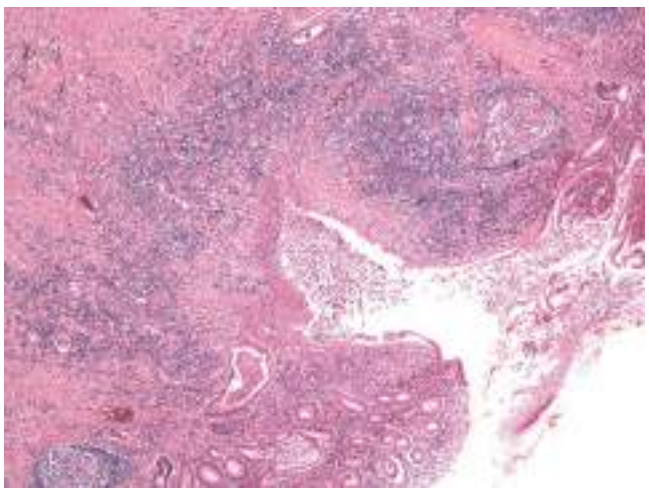

FIGURE 45-4. Low-power view of Crohn's disease with lymphocytic infiltration and mucosal ulceration.

reactive hyperplasia, although more common in UC, also occur in Crohn's colitis (Figure 45-3).

Focal chronic inflammation, granuloma, and localized crypt distortion are some of the commonly accepted microscopic features in Crohn's. Plasma cells and lymphocytes in the lamina propria are hallmarks of colonic inflammation (Figures 45-4 and 45-5). Lymphoid aggregates are common and transmural. Granulomas, although highly suggestive, are not specific for Crohn's, being present in a few as 18% of samples in some studies (Figure 45-5) [11]. Granulomas can

occur at the site of ruptured crypts in UC and are also found in infectious colitis and intestinal tuberculosis. Microscopic differences between UC and CD are listed in Table 45-4.

Indeterminate Colitis

Often the clinical and histologic features of a patient's disease course may share that of both UC and Crohn's. One common situation is fulminant UC mimicking CD with deep transmural inflammation. Indeterminate colitis (IC) was first described by Kent in 1970 [15] and more formally by Price in 1978 [16]. The Montreal Working Party recommended that the term indeterminate colitis should be reserved only for those cases where colectomy has been performed and pathologists are unable to make a definitive diagnosis of either CD or UC after full examination [17]. The term "inflammatory bowel disease, type unclassified" (IBDU) is suggested for patients in whom there is evidence on clinical and endoscopic grounds for chronic inflammatory bowel disease affecting the colon, without small bowel involvement, and no definitive histological or other evidence to favor either CD or UC [17].

The distinct delineation of disease carries becomes surgically relevant when considering a patient with an IC or IBDU diagnosis for a restorative proctectomy. Higher rates of pelvis sepsis, pouch fistula, and pouch failure have been reported in patients with IC undergoing ileal pouch-anal anastomosis (IPAA), compared to a UC cohort [18]. When the patients ultimately diagnosed with CD were excluded, outcomes for the IC patients were similar to the UC group. Functional status and quality of life have been reported to be similar between IC and UC patients post-IPAA, along with similar pouch failure rates [19].

Ultimately, most patients with an initial IC diagnosis will be found to have UC [20]. In the absence of current or historical clinical features of Crohn's disease, most IC patients could be considered for IPAA, with expectations of functional outcome and pouch retention rates similar to that of UC patients [21].

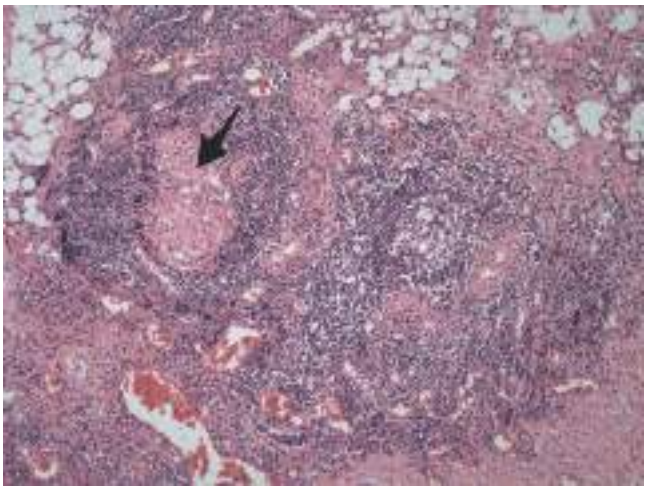

FIGURE 45-5. Crohn's disease with full-thickness inflammatory change and lymphocytic infiltration into the serosa and granuloma (*arrow*).

Serology and Markers of Disease

ASCA and pANCA

Anti-*Saccharomyces cerevisiae* antibodies (ASCA) and perinuclear anti-neutrophil cytoplasmic antibodies (pANCA) have been extensively studied as biomarkers in IBD. Due to

TABLE 45-4. Microscopic features used for the diagnosis of IBD [13]

	Ulcerative colitis	Crohn's disease
Crypt architectural irregularity	Diffuse (continuous)	Focal (discontinuous)
Chronic inflammation	Diffuse (continuous) Decrease proximally	Focal (discontinuous) Variable
Patchiness	Uncommon	Common
Localization	Superficial Transmucosal Sometimes in submucosa	Transmural
Serositis	Absent except in fulminant colitis	Present
Lymphoid aggregates	Frequent in mucosa, submucosa	Common, transmural
Granulomas	Absent, except with ruptured crypts	Present
Acute inflammation	Diffuse (continuous)	Focal (discontinuous)
Crypt epithelial polymorphs	Diffuse (continuous)	Focal (discontinuous)
Crypt abscesses	Common	Uncommon
Mucin depletion	Present, pronounced	Uncommon, mild
Neuronal hyperplasia	Rare	Common
Muscular hypertrophy	Absent	Present
Paneth cell metaplasia	Present	Uncommon
Pyloric gland metaplasia	Rare	Present

their presence in other inflammatory conditions, such as vasculitis or rheumatoid arthritis, they are not useful as screening measures. pANCA-positive values range from 2 to 28% in CD patients, while 20–85% of UC patients are positive for pANCA, resulting in a sensitivity of 56% and a specificity of 89% in UC patients [22]. ASCA positivity is found in 39–69% of CD patients and in 5–15% of UC patients [22]. One clinical situation where biomarkers could be extremely useful would be in indeterminate colitis. Unfortunately, in one study of 97 IC patients nearly half (48.5) were ASCA−/pANCA−, thus providing no useful clinical information [23]. ASCA+/pANCA− status was able to predict CD in 80% and ASCA−/pANCA+ predicted UC in 63.3%. One small study of IPAA patients showed ASCA+/pANCA− patients had 44% of developing postoperative fistulas and were more likely to have their diagnosis changed to CD [24]. Elevated levels of pANCA in UC patients undergoing IPAA have been shown to predict the incidence of chronic pouchitis. The cumulative risk of developing chronic pouchitis among patients with high-level pANCA (56%), defined as >100 EU/ml, before IPAA was significantly higher than in patients with medium level (22%), low level (16%), and those who were pANCA−ANCAsi [25].

Fecal Markers

Calprotectin is a small calcium-binding protein, found in abundance in neutrophilic granulocytes, in which it accounts for 60% of the cytosolic fraction, as well as in monocytes and macrophages [26]. Calprotectin is stable in feces for up to 7 days at room temperature and is homogenously distributed [26]. The presence of calprotectin in stool implies mucosal inflammation, which is nonspecific, and can also occur with mucosal bleeding. This can occur in non-IBD situations like NSAID damage or malignancy. Lactoferrin is similar to calprotectin in that it is neutrophil derived and found in the stool. Like calprotectin, it can be measured by commercial ELISA. Lactoferrin testing tends to be more affordable than calprotectin [27]. Calprotectin has been used in a variety of clinical situations for IBD patients, including diagnosis, prediction of clinical course, monitoring response to therapy, and postoperative surveillance. Although primarily assayed via stool sample, measurement via serum samples has been studied, but correlation to stool values is weak [28].

Initial use of fecal calprotectin was in attempting to differentiate between patients with IBD and irritable bowel syndrome, a non-inflammatory condition. This has been fairly extensively studied in both the adult and pediatric populations, with a goal of reducing the need for invasive testing. A meta-analysis showed good sensitivity (93%) and specificity (96%) of fecal calprotectin to diagnose IBD in adult patients, although specificity (76%) was much lower for pediatric patients [29]. The authors calculated in a hypothetical population of 100 adults with suspected inflammatory bowel disease (and an overall mean prevalence of 32%) three patients without the disease would go on to have endoscopy and two patients with the disease would be missed [29]. They conclude that increased fecal calprotectin levels could be used to guide more urgent endoscopic evaluation, but caution that negative values in a patient with persistent rectal bleeding do not exclude the presence of IBD.

There is mounting evidence that mucosal healing is a better target in IBD treatment, rather than clinical symptom control, as it can alter the course of disease, reducing hospitalizations and rates of future surgery [30]. Calprotectin would be a desirable marker for following mucosal healing, as repeated endoscopic evaluation is not practicable for patients. One study of IBD patients in clinical remission with normalized calprotectin levels showed 38 of 45 had complete mucosal healing [31]. Data from the STORI trial showed that of CD patients in stable remission on infliximab and immunomodulator who stopped biologic treatment, 43.9% would relapse at 1 year [32]. Fecal calprotectin ≥300 μg/g was shown to be predictive of relapse on multivariable regression (hazard ratio 2.5). In general, fecal calprotectin has been more effective in predicting the clinical course of UC patients or in CD patients with colonic involvement [26].

Fecal calprotectin has also been studied in the surgical IBD cohort. In a prospective study of 90 patients admitted with acute UC, calprotectin was shown to be predictive of the need for colectomy [33]. All patients received high-dose steroid therapy, with 23% receiving infliximab. 34.4% of patients required colectomy due to failure of medical management. Fecal calprotectin was significantly higher in patients who had failed medical therapy compared to those who escaped surgery (1200.0 vs. 887.0 μg/g; $P=0.04$). Using a cutoff point of 1922.5 μg/g at mean follow-up around 1 year, 87% of patients required colectomy. In post-resection CD, fecal calprotectin >200 μg/g has been shown to be predictive of endoscopic recurrence after 12 months [34]. Recurrence after surgical resection for CD may also be predicted by calprotectin levels. In a prospective study, levels of calprotectin greater than 100 μg/g indicated endoscopic recurrence with 89% sensitivity and 58% specificity and a negative predictive value of 91% [35]. Calprotectin was superior to CRP and a clinical disease index (CDAI) for detection of recurrence and monitoring response to treatment. Serial calprotectin measurement may represent a less invasive and costly method for the postoperative management of CD patients.

Inflammatory Markers

C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and albumin are three common serum measures of the acute phase of inflammation. IBD intestinal inflammation is clearly a trigger for elevation of these measures, but remains nonspecific, as other inflammatory conditions can

elevate them as well. Albumin has a long half-life (5 days), limiting its clinical usefulness. CRP is made by hepatocytes, and a primary trigger for release is IL-6. CRP has a short half-life (19 h) compared with other acute-phase proteins and will therefore rise early after the onset of inflammation and rapidly decrease after resolution of the inflammation [36]. CRP tends to be elevated more in CD, rather than UC [37]. ESR is the rate at which erythrocytes settle in the plasma. ESR is an indirect measurement of plasma acute-phase protein concentrations and can be greatly influenced by the size, shape, and number of erythrocytes, as well as by other plasma constituents such as immunoglobulins or fibrinogen [38]. Compared with CRP, ESR will peak much less rapidly and may also take several days to decrease, even if the clinical condition of the patient or the inflammation resolves [36].

These inflammatory markers have been studied in a variety of clinical IBD situations. They allow for excluding IBD diagnosis in patients with functional bowel disorders without invasive study, in whom there may be some overlap of clinical symptoms. One study of patients presenting with abdominal symptoms showed elevations in CRP and ESR in all patients eventually diagnosed with CD and in 50% of those eventually diagnosed with UC [39]. No patients with functional bowel disorders had elevated inflammatory markers. A more recent study showed a cutoff value of 2.3 mg/l had a sensitivity of 100% and a specificity of 67% in differentiating functional disease from new cases of IBD [40]. CRP tends to be a less reliable predictor of endoscopic disease in the postoperative CD patient [35, 41].

Genetic-Based Testing

In 2001, two groups simultaneously reported on NOD2/CARD15 gene mutations on chromosome 16 that conferred susceptibility to Crohn's disease [42, 43]. NOD2 plays a role in the nuclear factor NF-κβ pathway that is responsible for the cellular response to bacteria. This has provided a genetic model for the dysregulated response of the immune system that occurs in IBD. In retrospective clinical studies, NOD2 mutations have been shown to be more frequently associated with ileal CD and severe pouchitis in UC patients after IPAA [44, 45]. NOD2/CARD15 mutations are actually quite common in asymptomatic patients, with prevalence between 2.4 and 11.5% in a white population, with wide geographic variability [46]. Even patients with double NOD2/CARD15 mutations did not have elevated risk of IBD [46]. This underscores the fact that genetics in conjunction with environmental exposure is necessary for the clinical expression of IBD. In fact, another burgeoning area of genetic research in IBD involves the microbial environment of the gut [47]. Although the clinical utility of genetic testing remains limited currently, it is clear that research in this field will shape the future of IBD diagnosis and treatment.

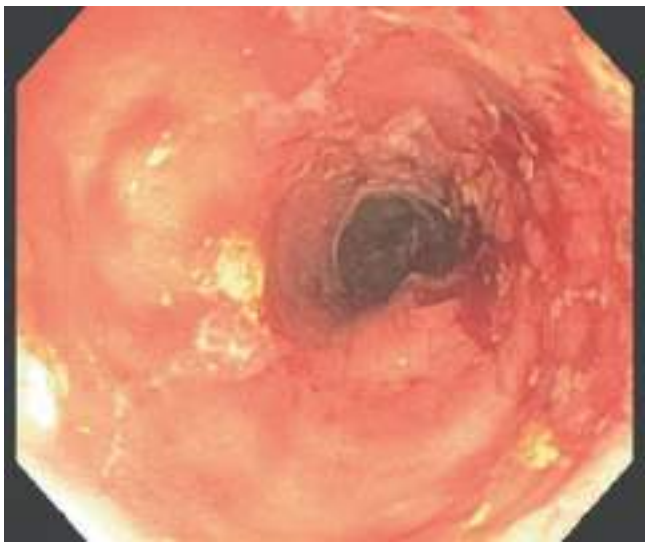

FIGURE 45-6. Crohn's colitis of transverse colon.

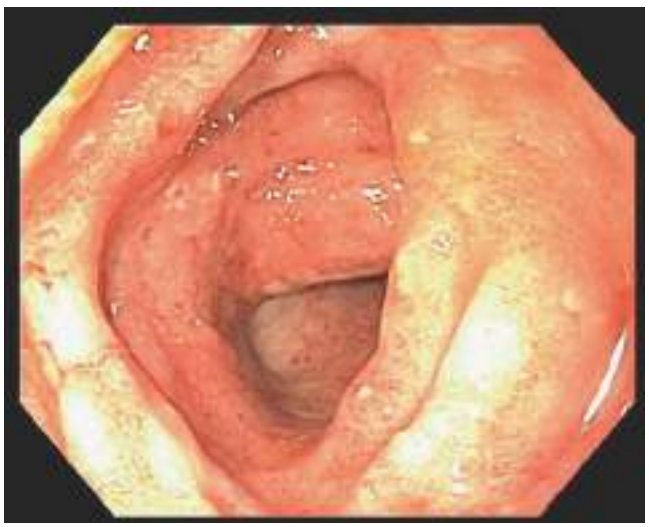

FIGURE 45-7. Sigmoid colon in ulcerative colitis.

Endoscopy in IBD

Flexible Endoscopy

Flexible endoscopy remains a gold standard technique in the initial diagnosis and follow-up management of patients with suspected or established inflammatory bowel disease. Figures 45-6 and 45-7 show the endoscopic appearance and subtle differences between Crohn's colitis (patchy) and ulcerative colitis (diffuse and contiguous). Endoscopy allows for mucosal inspection and, importantly, tissue sampling for histology. Therapeutic interventions, such as balloon dilations of strictures, can also be performed. Patients with symptoms suggestive of IBD should undergo colonoscopy. Intubation and biopsy of the terminal ileum is especially

important in patients with suspected Crohn's disease. Endoscopically abnormal areas of the colon should be sampled. Biopsy of normal areas is important as well, as presence or absence of microscopic colitis can aid in differential diagnosis. Particular attention should be made in areas of colonic stricture, with historical studies showing 24% of UC and 6% of CD strictures may be malignant [48, 49]. Colonoscopy is overall a safe procedure, but it is invasive and carries risk of serious complications. IBD patients are known to carry higher risks of procedural complications. This is especially true in patient with advanced age, severe colitis, or during therapeutic interventions. Risk of perforation in one national database study for IBD patients was 1%, with age, female gender, and therapeutic dilation being predictors of complication [50]. Upper endoscopy plays a role in the smaller subset of Crohn's patients who present with esophagogastroduodenal involvement. Newer techniques of single and double balloon enteroscopy allow advanced endoscopists to reach far into the small bowel, in both antegrade and retrograde directions. Double balloon enteroscopy has been shown to be similar to CT enterography for the evaluation of Crohn's small bowel disease [51]. Double balloon enteroscopy is invasive, however, and carries risk of perforation, with major complication rates of around 1% and interventional procedure complication rates of 4–5% [52]. One major advantage is that it can be used for stricture dilation or retained video capsule removal, with relatively good rates of success [53, 54]. Double balloon enteroscopy remains an advanced endoscopic technique and may not be available in all centers.

Beyond initial diagnosis, endoscopy is used for evaluating the response of IBD to medical therapy, for monitoring recurrence after surgery, and for dysplasia surveillance in UC. There are no specific guidelines for routine colonoscopy during medical therapy for IBD [55]. Colonoscopy is indicated when there is a major change in symptoms. It is debated whether colonoscopy should be done for the clinically asymptomatic patient. It is well established that clinical symptoms and endoscopic findings may not be congruent, and clinicians are often poor at predicting disease extent based on symptoms alone. Colonoscopy is useful in the decision to withdraw medical therapy in stable CD [55]. Endoscopic mucosal healing has been shown to reduce twofold the risk of relapse after infliximab withdrawal in CD patients on immunosuppression with steroid-free remission [32]. Colonoscopy is recommended 6–12 months after surgery for CD, as anastomotic recurrence (Figure 45-8) is common (60–90% at 1 year) [55]. Fecal calprotectin may be a useful screening trigger to prompt earlier colonoscopy (see Fecal markers section) [55]. Early medical intervention in the postoperative CD setting is associated with lower rates of endoscopic recurrence and higher rates of complete mucosal healing [56]. There are a number of endoscopic grading systems used to describe mucosal findings in CD, including the Crohn's Disease Endoscopic Index of Severity (CDEIS) and the Simple Endoscopic Score for Crohn's Disease (SES-CD) [57, 58]. None are widely or routinely used outside of research settings. However, it is important to standardize endoscopic reporting including severity, location and extent of inflammation, and presence of strictures or other lesions. The Rutgeerts endoscopic score (Table 45-5) has been shown to predict the recurrence of symptoms and need for repeat surgery based on the endoscopic appearance of the neoterminal ileum and ileocolonic anastomosis [59]. 85% of patients with i0 or i1 lesions 6–12 months postoperatively will have no endoscopic progression at 3 years [60]. i3 or i4 patients had progressive or very severe endoscopic progression 92% of the time [60]. Clinical recurrence occurred in less than 5% of patients with i0/i1 lesions, 15% with i2, 40% with i3, and >90% with i4 [60]. There are at least 9 endoscopic scoring systems described for UC [30]. Two of the most commonly used are the Baron and Mayo scores (Table 45-6) [61, 62]. The Baron score relies on the assessment of mucosal bleeding during colonoscopy, and the Mayo score evaluates the overall appearance of the mucosa, with respect to erythema, vascular pattern, friability, bleeding, erosions, and ulcerations.

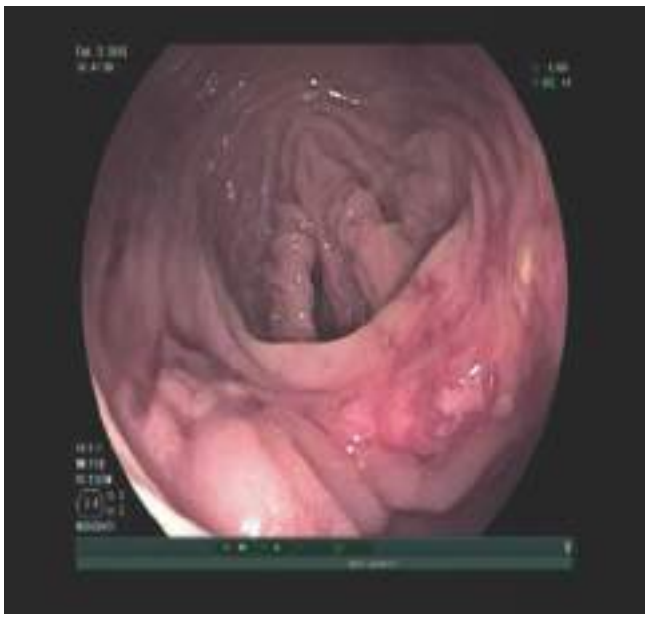

FIGURE 45-8. Anastomotic recurrence 2 months after ileocolic resection.

Colonoscopy is recommended for patients with chronic colitis for dysplasia surveillance. The risk of colorectal cancer surpasses that of the general population after 8–10 years of disease [63]. It is important to note that this period begins at the onset of symptoms, rather than time of histological diagnosis. Although a meta-analysis demonstrated the cumulative risk of colorectal cancer for UC patients to be 2.1% at 10 years, 8.5% at 20 years, and 17.8% at 30 years, population-based series have reported lower annual incidence rates of 0.06–0.2%. Despite this, it is generally

TABLE 45-5. Rutgeerts score of postoperative endoscopy for CD [59] and corresponding CTE scoring system for postsurgical examination [92]

Rutgeerts	Endoscopic findings	CTE	CTE findings
i0	No lesion in the neoterminal ileum	CTE0	No findings
i1	<5 aphthoid ulcers	CTE1	Minor mucosal irregularities with slight wall thickening and mural contrast enhancement
i2	>5 aphthoid ulcers with normal mucosa in between, or skip areas or larger lesions related to anastomosis	CTE2	Mucosal hyperdensity with distinct bowel wall thickening, no stenosis, or stenosis without prestenotic dilatation
i3	Diffuse aphthoid ileitis, with mucosa extensively inflamed	CTE3	Major mucosal abnormalities, distinct bowel wall thickening with target sign and extravisceral signs such as perienteric stranding, comb sign, fibrofatty proliferation, stenosis with prestenotic dilatation, and/or the presence of complications
i4	Diffuse inflammation, large ulcers, nodules, and/or stenoses		

TABLE 45-6. Baron and Mayo scores for ulcerative colitis

	Baron score	Mayo score
Score 0	Normal mucosa, ramifying vascular pattern clearly visible throughout, no spontaneous bleeding, no bleeding to light touch	Normal or inactive disease
Score 1	Abnormal but not hemorrhagic: appearances between "0" and "2"	Mild disease (erythema, decreased vascular pattern, mild friability)
Score 2	Moderately hemorrhagic: bleeding to light touch, but no spontaneous bleeding seen ahead of instrument on initial inspection	Moderate disease (marked erythema, absent vascular pattern, friability, erosions)
Score 3	Severely hemorrhagic: spontaneous bleeding seen ahead of instrument at initial inspection, and bleeds to light touch	Severe disease (spontaneous bleeding, ulceration)

accepted that chronic UC is associated with an increased risk of malignancy [64]. Studies on dysplasia and cancer in UC are more widely available than those on CD; thus surveillance and treatment paradigms are often similar in the two groups despite the differing disease pathophysiology [65]. The Crohn's and Colitis Foundation of America (8–10 years), the American College of Gastroenterology (8–10 years), and the American Society of Colon and Rectal Surgeons (8 years) all have similar recommendations for initial surveillance colonoscopy in chronic colitis [64, 66, 67]. After a negative study, most recommend 1–2 year interval for repeat examination. After two negative exams, follow-up time can be 1–3 years. After 20 years of disease, recommendations are again every 1–2 years [66]. Patients with primary sclerosis cholangitis (PSC) have higher rates of malignancy and should undergo yearly evaluation [68].

The traditional recommendation for endoscopic biopsy for dysplasia surveillance is four-quadrant sampling every 10 cm [64, 66]. Particular attention should be paid to raised lesions or strictures, with sampling of any normal surrounding areas to allow for histologic comparison. Significant pseudopolyposis may make surveillance unreliable by obscuring the mucosa or being too numerable to sample [67]. Particularly in UC, consideration of sampling every 5 cm in the distal colon is reasonable given the worsening severity of inflammation and higher rates of malignancy in this area [66]. A typical endoscopic biopsy samples 0.05% of the mucosal surface [69]; accordingly multiple samples must be taken for adequate sampling. A minimum of 33 random biopsies has been shown to result in 80–90% sensitivity for detecting dysplasia, with 64 required for 95% [70].

Recent advances in endoscopic technology are changing how dysplasia surveillance is performed. The American Society for Gastrointestinal Endoscopy (ASGE) has recently made strong recommendations that high definition video equipment be used when using traditional white-light colonoscopy [71]. One retrospective study showed twice as many dysplastic lesions were detected with high definition equipment rather than standard definition [72]. Chromoendoscopy involves the use of dye applied to colonic mucosa to improve epithelial surface detail and allow for targeted sampling. Diluted indigo carmine and methylene blue are the two most commonly used dyes. Two prospective tandem colonoscopy studies have shown the increased ability of chromoendoscopy to detect dysplastic lesions, being 1.8–3.5 times more likely positive than conventional four-quadrant biopsy technique [71, 73, 74]. One study found no dysplasia in 2904 non-targeted biopsies, versus 9 in 157 chromoendoscopy-targeted biopsies [73]. The improvement in efficiency using chromoendoscopy is clear. It is not clear that this has had any effect on reducing rates of progression to cancer. The St Mark's Hospital recently reported on the outcomes of their UC surveillance screening program originating in 1971. From 2002 to 2012 twice as many dysplastic lesions were found using chromoendoscopy (8.4%) vs. white-light colonoscopy (4%) [75]. The post-colonoscopy colorectal cancer rate was lower following chromoendoscopy compared with white-light endoscopy, although this did not reach statistical significance [75]. Chromoendoscopy has been given a strong recommendation over white-light colonoscopy by the ASGE [71]. Currently there is no evidence to support routine use of digital enhancement techniques, such as narrow band imaging (NBI).

One study of NBI vs. white-light colonoscopy actually found fewer total dysplastic lesions were detected with NBI [76].

Confocal laser endomicroscopy (CLE) is a newly introduced modality which captures images of "virtual histology" of the gastrointestinal mucosa during endoscopy [77]. At present, CLE can be performed with two devices: one integrated into an endoscope (Pentax, Tokyo, Japan) and one as a mini-probe through the scope (Cellvizio, Mauna Kea Technologies, Paris, France) [77]. Confocal microscopy consists of focusing a laser ray onto the mucosal surface and filtering the returned light by means of a small pinhole which rejects out-of-focus light [77]. This technology allows for real-time interpretation of histology and, in theory, could eliminate the need for endoscopic biopsy. It can also detect microscopic evidence of ongoing inflammation in normal appearing colonic mucosa. One study found 4.75-fold more dysplastic lesions using chromoendoscopy-guided CLE with 50% fewer biopsy specimens [78]. This technique will require further investigation and study before it can be considered for integration into screening paradigms.

Capsule Endoscopy

Video capsule endoscopy (VCE) was introduced in 2001 as a noninvasive method to evaluate the small bowel that remains outside the reach of contemporary flexible endoscopy [79]. The technique consists of a pill-sized device with self-contained lighting, video capture, and transmission capability. After a 12 h fast, the patient consumes the camera with a sip of water. Bowel preparation regimens are variable, but a meta-analysis showed a combination of polyethylene glycol and simethicone provided optimum image quality [80]. Patients should abstain from NSAIDs for a month prior to examination, as these can induce mucosal ulcerations and confound image interpretation. Patients wear image capture sensors and belt, avoid consumption of fluids for 4 h, and do not have to limit physical activity. The capsule itself passes naturally with bowel movement and is usually excreted within 24–72 h [79].

For the IBD patient, evaluation of small bowel CD is the most common indication for VCE. Meta-analysis has shown VCE to have higher diagnostic yield than colonoscopy, push enteroscopy, conventional enterography, and CT enterography [81, 82]. VCE was found to be similar to MR enterography in those same reviews. One important consideration in many VCE studies is that patients with suspected or known structuring CD were excluded, due to fear of capsule retention. Capsule retention is a rare, but feared, complication of VCE. Reported rates of capsule retention in CD patients are around 13%, with one review showing that established CD diagnosis increased the risk of capsule retention ninefold [83, 84]. A slowly dissolvable patency capsule exists (Agile PC, Given Imaging) and is intended to assess patency of the small bowel prior to VCE [79]. The European Society of Gastrointestinal Endoscopy (ESGE) has recommended that VCE be done if deemed necessary to change management in CD and only after cross-sectional imaging and patency capsule evaluation are done to exclude stricture [83].

FIGURE 45-9. Fluoroscopic enterography study showing terminal ileal stricture in Crohn's disease.

Radiology in IBD

Plain Radiography

Plain radiographs remain a standard for rapid assessment of the IBD patient presenting with acute abdominal symptoms. Free air from hollow viscus perforation, toxic megacolon, or small bowl obstruction from stricture or adhesion are diagnoses that can rapidly and inexpensively be confirmed. Fluoroscopic gastrointestinal imaging, once the gold standard for IBD evaluation, has rapidly been supplanted by advanced imaging techniques and flexible endoscopy. In the 1960s and 1970s, before CT or MRI, single contrast and then double contrast enema imaging was the primary method to evaluate both the upper and lower GI tracts. Historically, small bowel follow-through (SBFT) studies have been the standard approach to assess active disease [85]. Early mucosal changes and strictures can be seen with fluoroscopic studies (Figure 45-9). Although well-supervised SBFT studies allow for excellent visualization of the bowel mucosa, small bowel enteroclysis offers a more sensitive and accurate assessment of mucosal abnormality and strictures [85]. Standard enteroclysis is typically performed with placement of a nasojejunal tube with fluoroscopic guidance. Barium along with air or methylcellulose, for double contrast, is instilled to provide opacification and distension of the small bowel [86].

Computed Tomography

Computed tomography (CT) imaging has revolutionized the diagnosis and management of abdominal diseases. Findings of small and large bowel mural thickening, abscess, and

fistulae were evident on the earliest generation of CT scanners in early studies of IBD patients [87]. CT imaging for UC patients is mostly limited to situations of severe or fulminant colitis. CT for CD allows non-interventional assessment of the small and large bowel, as well as possible extra-intestinal manifestations of disease. In addition to standard axial image acquisition, CT enteroclysis and enterography are also possible. CT scanning is a primary modality for image-guided percutaneous biopsy of abscesses in CD. A study using a nationwide database showed 29% of CD abscesses were treated with percutaneous drainage in 2007, up from 7% in 1998 [88]. In that same time period, surgical drainage fell from 59 to 32%.

CT enterography (CTE) requires specialized preparation. Neutral intraluminal contrast agents (such as water) are required to enable adequate visualization of enhancing mucosal lesions which would otherwise be masked by positive contrast agents such as barium [85]. Because luminal collapse can mimic bowel wall thickening, large volume ingestion is necessary. A typical prep consists of 1 L of a polyethylene glycol solution followed by 1 L of water. This can be consumed orally (enterography) or via nasojejunal tube (enteroclysis) given 1 h before scanning. Intravenous contrast is given to enhance inflammatory changes in the mesentery and bowel wall. Anti-spasmodics are often given to reduce bowel motion artifact.

CTE has been shown to be as specific as conventional enteroclysis in diagnosis of Crohn's small bowel lesions, with somewhat less sensitivity [89]. Enteroclysis can pick up some early changes of disease (thickened folds, aphthoid ulcers) that CTE does not have the resolution to identify, and there may be clinical situations where a combination of the techniques is helpful. CTE has been shown to alter clinical decision making in CD. One cohort study of 273 established or suspected IBD patients showed CTE changed management in 51% of cases [90]. Of those with established disease, 48% had management change, including 24% with medication changes. Another study showed poor correlation between CTE findings and clinical assessment of IBD symptoms [91]. 16% of CTE identified strictures in this study were not suspected by expert clinical assessors. No scoring systems for CTE are in wide use, but one has been developed for imaging postsurgical resection [92] (Table 45-5). This has been evaluated prospectively, and been shown to accurately predict need for reoperation, similar to Rutgeerts endoscopic score [93].

MRI

Magnetic resonance imaging (MRI) allows for acquisition of images, similar to CT, but does so by manipulating the nuclear properties of hydrogen atoms and thereby avoids exposing the patient to the ionizing radiation that CT requires. MRI also allows for obtaining images with specific contrast profiles to allow for differentiation between inflammation and fibrosis or suppressing surrounding fatty tissues. One issue with MRI is increased complexity, longer time for image acquisition, and generally more limited availably, when compared to CTE. The increased soft tissue resolution delivered by MRI over CT has made it the preferred imaging technique when imaging is required for complex fistulizing perianal CD.

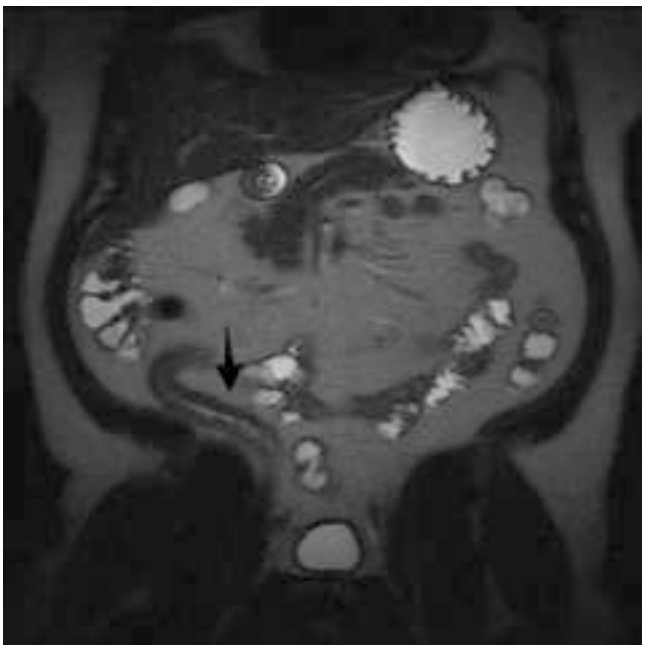

FIGURE 45-10. MRE in Crohn's disease. Coronal T2-weighted images demonstrate segmental mural thickening of the terminal ileum (*black arrow*).

Patient preparation for MRE is similar to that of CTE. Oral purgatory solution and large volume negative contrast solution are consumed. MR enteroclysis can be performed, but enterography is preferred by patients and has been shown to produce similar image quality [94]. Gadolinium is used as an IV contrast medium. MRE is much more sensitive to motion artifacts than CTE, so 1 mg of glucagon is often used. Multiple image acquisition sequences are taken including T1, T2, and diffusion weighted (Figures 45-10, 45-11, and 45-12). Breath holding is necessary for most sequences and the entire time of image acquisition takes around 30–35 min [94].

The presence of bowel wall thickening in conjunction with asymmetric mural hyperenhancement is essentially pathognomonic for Crohn's disease images (Figure 45-10) [95]. The "comb sign" refers to engorgement of the vasa recta and is highly suggestive of active inflammation [95]. The ability of MRE and CTE to detect Crohn's lesions is similar. One study showed sensitivity of MRE to be 90.5% and 95.2% in CTE for detecting active small bowel Crohn's disease [96]. In this study, MRE image quality scores were rated significantly worse than CTE, underlying the increased technical challenge of image acquisition for MRE. Three indexes of activity based on adequate external references have been proposed: the

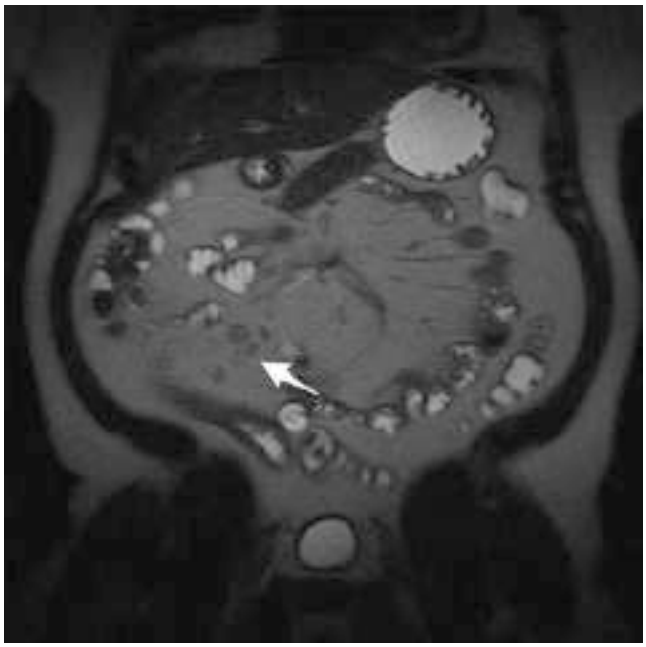

FIGURE 45-11. MRE in Crohn's disease. Coronal T2-weighted images with surrounding fibrofatty proliferation and ileocolic lymph nodes (*white arrow*).

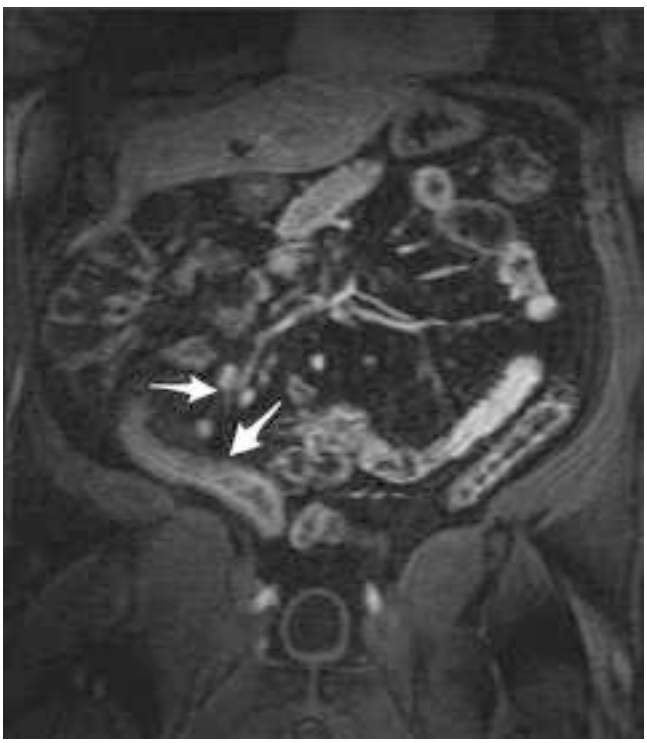

FIGURE 45-12. MRE in Crohn's disease. Gadolinium-enhanced coronal T1-weighted image demonstrate mucosal hyper-enhancement as well as enhancement of the ileocolic lymph nodes, indicative of active Crohn's disease (*arrows*).

Magnetic Resonance Index of Activity (MaRIA) score, the Crohn's disease MRI Index (CDMI) score, and the Nancy score [97]. The MaRIA and CDMI scores are the most commonly used in research settings, but neither has yet transitioned to routine clinical practice [97]. The accuracy of the MaRIA, CDMI, and Nancy scores for detecting inflammatory activity is in the range of 80–90%, with MaRIA accuracy of predicting mucosal healing being 83% [97].

Ultrasound

Ultrasound (US) could, in theory, represent an ideal imaging technique for the IBD patient. US is widely available, is relatively low cost, is noninvasive, and does not require ionizing radiation. However, US is a highly operator-dependent imaging method and correct interpretation of sonographic findings requires adequate experience in abdominal and bowel sonography [98]. Both oral and intravenous contrast agents are available to enhance images. Bowel wall thickness >3–5 mm detected with US is the primary cutoff for postoperative CD recurrence in many studies, with a wide range of sensitivity and specificity reported [99]. One study looked at bowl wall thickness of the anastomosis in postoperative CD, showing patients with thickness >3 mm had twice the risk of further surgical intervention [100].

Nuclear Medicine

Currently nuclear medicine plays a limited role in the initial imaging assessment of patients with CD, depending on local practice [85]. Radiolabeled white cells have been used to quantify degree of bowel inflammation, but are limited by poor anatomical correlation and failure to detect strictures and fistulae [85]. PET/CT has also been evaluated in CD, with higher standardized uptake values (SUV) correlating with worsening inflammation [101]. One small study of 13 patients showed the addition of PET to CTE was able to detect additional areas of inflammation or fistula in 23% of patients [102]. In general, concerns over radiation exposure have limited the use of many nuclear medicine techniques in routine clinical practice.

Evolving Role of CTE and MRE

There has been recent concern among medical professionals and the media regarding increasing exposure of patients to ionizing radiation and subsequent risk of malignancy. IBD patients represent a cohort at particular risk for repeated studies employing ionizing radiation. The young IBD patient represents a particular concern. Younger patients are inherently more radiosensitive and have longer life spans for radiation-induced cancers to develop [103]. One retrospective study looking at radiation exposure in children with IBD

estimated that 60% would exceed 50 mSv by age 35 [104]. There is direct evidence from epidemiologic studies that organ doses in the range of 30–90 mSv result in an increased risk of cancer [103]. Given the similar clinical usefulness of both CTE and MRE, many advocate for the use of MRE in most situations where imaging is required, especially in the adolescent IBD patient. Surgeons, gastroenterologists, and emergency medicine physicians caring for IBD patients should be particularly aware of this issue and coordinate care so that unnecessary radiologic studies can be avoided.

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46
Medical Management of Chronic Ulcerative Colitis

Stefan D. Holubar and Mattias Soop

Key Concepts

- CUC is highly prevalent in North America and Europe, and its incidence is increasing globally.
- CUC has an unknown etiology, but the pathogenesis is believed to be multifactorial, with an impaired mucosal immune regulation and unknown environmental conditions or trigger(s).
- The incidence of colorectal cancer in CUC is increasing, and the presence of low-grade dysplasia is an indication for colectomy given an unacceptably high rate of synchronous or metachronous cancers.
- Surgeons must be familiar with the numerous medical treatments for CUC, including their side effects.
- Mild-to-moderate CUC is typically treated in a bottom-up manner with oral aminosalicylates, and if steroids are required for flares, then the patient is transitioned to AZA/6MP or a biologic agent to wean the steroids.
- Moderate-to-severe disease is typically treated in a top-down manner with combination therapy with a biologic agent and immunomodulator, often under the cover of temporary steroid treatment.
- Medical patient who may require surgery should be aggressively optimized in terms of anemia, malnutrition, and VTE prophylaxis.
- Pouchitis is common and responds promptly to oral antibiotic use. Patients with "Crohn's-like" picture of the pouch (indeterminate pouchitis) may benefit from additional medical therapy.

Electronic supplementary material: The online version of this chapter (doi:10.1007/978-3-319-25970-3_46) contains supplementary material, which is available to authorized users.

Part 1: Defining CUC

Introduction

Chronic ulcerative colitis (CUC) is an idiopathic, recrudescent chronic disease of colonic mucosal ulceration (Figure 46-1) with a prevalence of well over 600,000 affected persons in North America [1]. CUC is one end of the spectrum of idiopathic inflammatory bowel disease (IBD) (Figure 46-2). Although the etiology of CUC remains idiopathic, it is generally accepted that the pathogenesis of CUC is multifactorial, with an impaired mucosal immune regulation and unknown environmental conditions or trigger(s) playing complementary roles.

The vast majority of patients with CUC will require multiple medications to control disease over the course of their lifetime. Surgeons managing patients with IBD must be intimately familiar with medical management as the risks and benefits of surgery must be weighed against those of continued medical treatment in both elective and acute settings. In this chapter, in Part 1 we will discuss the definition and severity classifications of CUC, and we will review the epidemiology. Part 2 will review the armamentarium of medications currently available. In Part 3 we will present an algorithmic approach to CUC treatment based on severity and extent, as well as that of pouchitis. This chapter, intended for a surgical audience, aims to be a pragmatic clinical overview with clinical pearls rather than being an exhaustive review.

Wilks & Moxon at Guy's Hospital, London, originally described CUC in 1875. Symptoms include chronic diarrhea, often bloody, accompanied by tenesmus and defecatory frequency and urgency. The urge incontinence that many patients experience is one of the more troubling symptoms, and CUC patients will often report needing to "run to the bathroom" and knowing the location of "every bathroom on the interstate." Other common disease manifestations including anorexia related to spasmodic/crampy abdominal pain and systemic signs such as weight loss, fever, arthralgia, and

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fatigue/malaise related to anemia and disrupted sleep patterns due to diarrhea. Extra-intestinal manifestations are numerous and summarized in Figure 46-3.

Diagnosis

CUC is diagnosed using a combination of history, physical exam, and colonoscopic and histologic appearance (Figure 46-4). History should include baseline bowel function and continence or prior anorectal manifestations that may suggest Crohn's disease (both these could obviate future IPAA). Other conditions that should be ruled out include irritable bowel syndrome, celiac sprue, and the other colitides seen in Figure 46-2. Family history is important, as it is generally appreciated that although IBD is not a genetic disease, there is clearly an "auto"-inflammatory component, with haplotype B27 and other similar genes leading to a predisposition. Relatives and siblings of patients with IBD may also have either CUC or Crohn's disease. Physical exam should assess for anemia, malnutrition, stigmata of CD, abdominal tenderness and scars, rectal tone, masses, and pelvic floor dysfunction. Pelvic floor dysfunction should be treated with physical therapy preoperatively as it can result in suboptimal IPAA function.

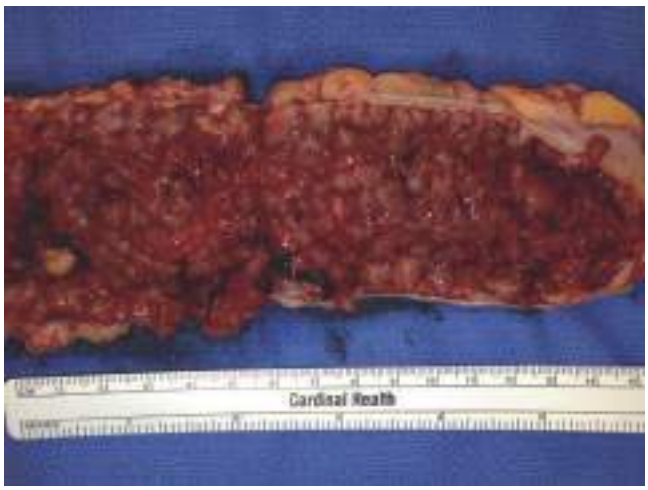
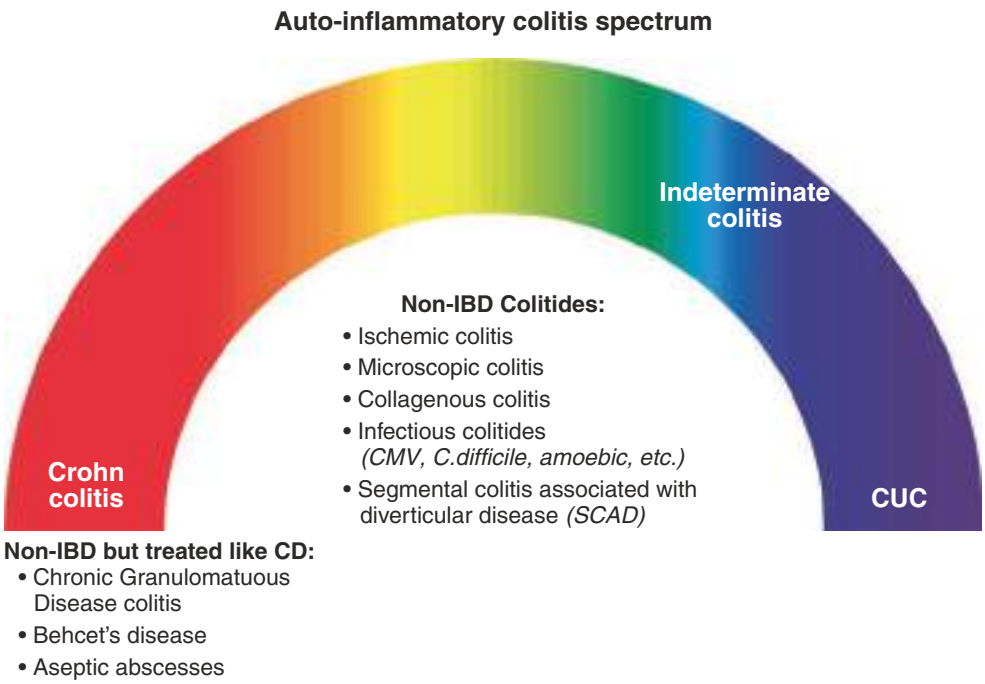


FIGURE 46-1. Operative specimen, gross photo. Note ulcerated, hemorrhagic mucosa with severe pseudopolyposis and exposed muscularis, slightly (chronically) thickened bowel wall.

Colonoscopy

Mucosal assessment is crucial to diagnosing CUC, with continuous (i.e., no skip areas) mucosal inflammation starting in the rectum (not the anus) and progressing proximally a variable distance, from only the rectum, to pancolitis with backwash ileitis. Inflammation may be mild, with a granular mucosa with contact bleeding, to more severe with linear ulcerations, to fulminant with severe pseudopolyposis characterized by "islands of mucosa in a sea of muscularis" (Figure 46-1). In patients with long-standing disease, the colon may be foreshortened, ahaustral ("lead-pipe colon"), and although a mucosal only disease, there may be full-thickness hypertrophy and even strictures. Biopsies will

FIGURE 46-2. Auto-inflammatory colitis spectrum.



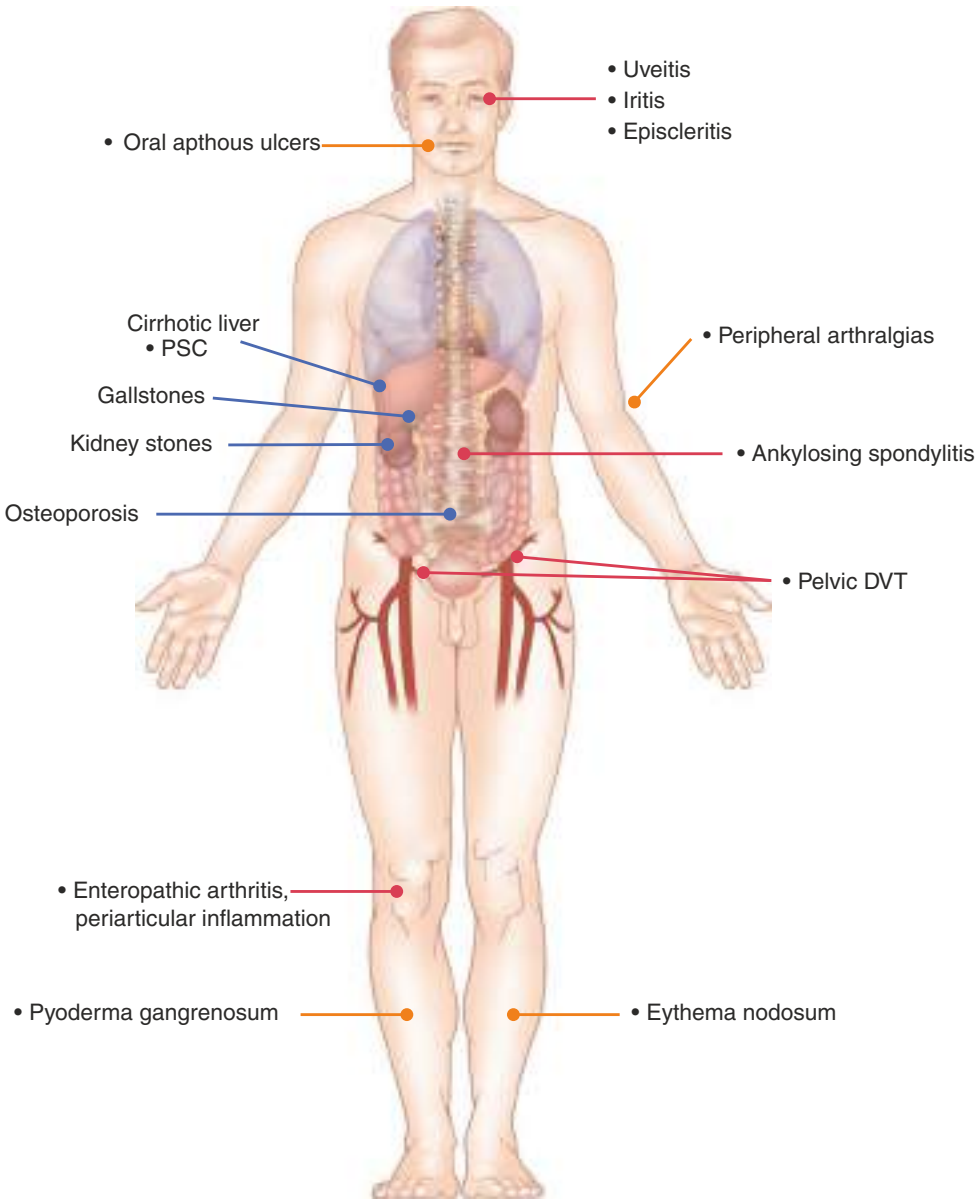


FIGURE 46-3. Schematic representation of common extra-intestinal manifestations in CUC.

demonstrate inflammatory acute and/or chronic colitis, with inflamed lamina propria and distorted crypt architecture. The presence of granuloma on biopsies indicates CD (Figure 46-4: photomicrograph of CUC vs. CD with granuloma). Regarding the role of colonoscopy in CUC surveillance, please see below colorectal cancer section.

Imaging

Cross-sectional imaging is part of the standard initial work-up of patients suspected of having IBD. These may include fluoroscopic small bowel follow-through, magnetic resonance enterography (MRE, Figure 46-5), computed tomographic enterography (CTE, Figure 46-6), or occasionally capsule endoscopy (Video 46-1) to evaluate the small intestine for stigmata of Crohn's disease. CTE and MRE and will typically also demonstrate the extent and severity of colitis. Inflamed bowel will typically demonstrate an edematous, thickened rectal and colonic wall with mucosal hyperenhancement, as well as lead-pipe changes.

MRE is preferred given long-term concerns over harmful levels of cumulative radiation exposure for patients with IBD [2]. MRE has the added benefit of the additional sequences in which the enteric contrast can be made to appear as either positive contrast or negative contrast to enhance visualization of mucosal detail. Of note both CTE and MRE use a larger than standard volume of enteric contrast. MRE uses IV gadolinium which is slightly more nephrotoxic than CT IV contrast, and patients with chronic diarrhea should be well hydrated to prevent contrast-induced nephropathy associated with either CTE or MRE.

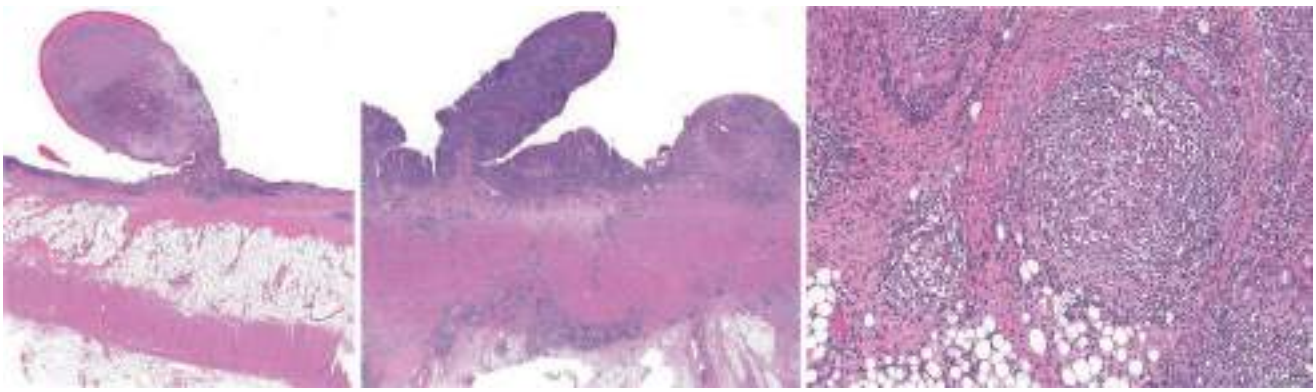


FIGURE 46-4. Photomicrograph of CUC vs. CD. H&E stain. *Top panel* shows severe transmural inflammation and granulomas consistent with Crohn's Disease.; *middle panel* shows severe mucosal ulceration consistent with ulcerative colitis; *bottom panel* shows mucosal inflammation and a pseudopolyp consistent with ulcerative colitis. Courtesy of Dr. Anthony Senagore.

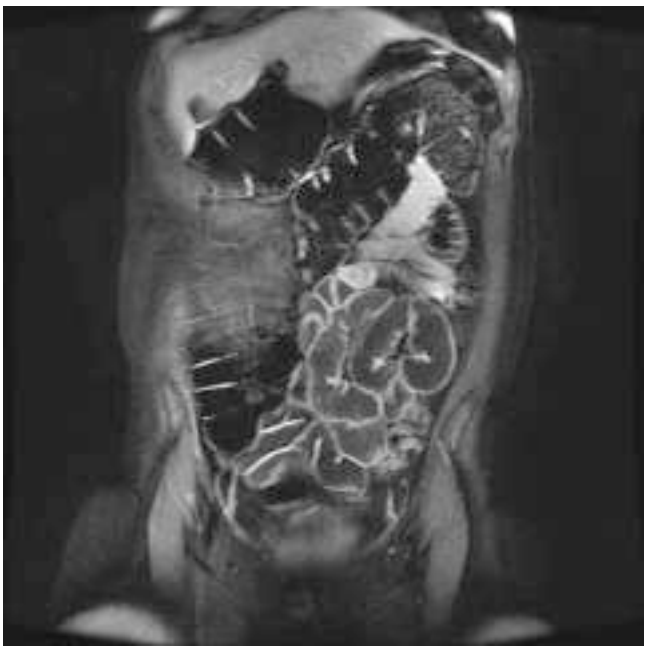


FIGURE 46-5. Magnetic resonance enterography, LAVA sequence 70 s post-contrast. Note the normal appearance of the small bowel wall in a CUC patient prior to total colectomy. Specifically the small bowel wall is of normal thickness, and the lack of mucosal or bowel wall hyper-enhancement, with no demonstrable fistula, strictures, or abscesses. This patient also had marked proximal colonic dilation due to left-sided CUC.

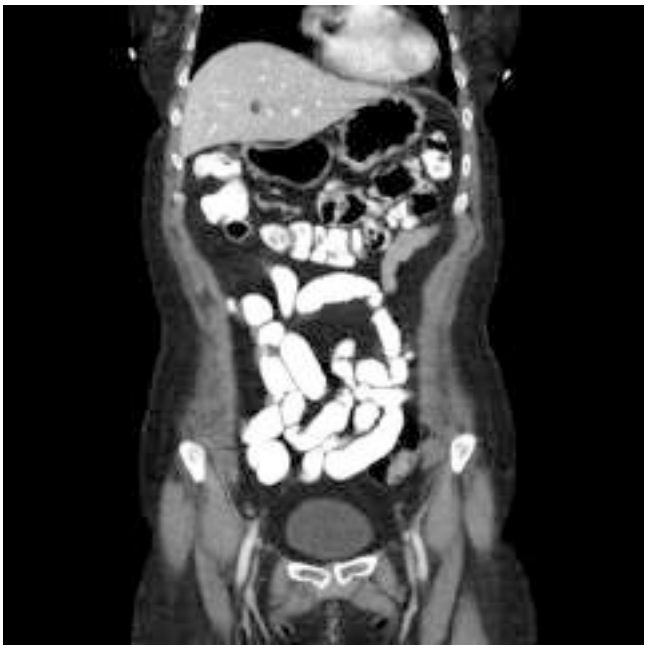


FIGURE 46-6. Computed tomographic enterography. Note the normal appearance of the small bowel wall in a CUC patient prior to total colectomy. Specifically the small bowel wall is of normal thickness, and the lack of mucosal or bowel wall hyper-enhancement, with no demonstrable fistula, strictures, or abscesses.

Serology

Ancillary studies include serial measurement of nonspecific serologic inflammatory markers including white blood cell count (WBC), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). Both ESR and CRP are sensitive markers of inflammation, inexpensive, and available in most centers. The main difference is ESR's longer half-life. More recently, fecal calprotectin, a measure of colonic mucosal macrophage activity, used in conjunction with ESR and CRP can predict and follow the trajectory of disease flares, and a falling calprotectin can predict mucosal healing [3].

Often clinicians are confronted with IBD patients who are difficult to diagnose with IBD or who do not fit nicely into the category of CD or CUC. In these patients, Prometheus® antigen testing panel has been used as a diagnostic aid. Now in its fourth generation the panel assesses nine antigens, Prometheus testing is reserved for helping to diagnose

cases that are difficult to classify based on traditional testing. Prometheus testing is most helpful in ruling out IBD, but may also have a role in differentiating between CUC vs. indeterminate colitis vs. CD, although it may not have adequate specificity for that indication [4]. As additional antigens are added to the panel, this test is likely to become more clinically useful in the near future.

Infectious Work-up

For newly diagnosed patients with bloody diarrhea, and especially for those with severe disease activity, it is crucial to rule out infectious colitides. These include standard stool studies for ova and parasites mainly to assess for *Giardia lamblia* (more common in those with a history of hiking/camping). Others include cryptosporidium (more common in immunosuppressed patients). *Clostridium difficile* is seen with increased frequency in IBD, and may be related to prior antibiotics or to immunosuppression, and can be assessed by endoscopic appearance (Figure 46-7) or molecular testing. Assays can detect either *C. difficile* antigens or toxins (toxin A and/or toxin B). Cytomegalovirus (CMV) colitis (Figure 46-8) with its characteristic "punched-out" ulcerations is also seen with increased frequency and may also be related to immunosuppression; CMV colitis is usually diagnosed by colonoscopic biopsy. Both C. diff and CMV are more common in patients with CUC who are already on immunosuppressive medications, and these coinfections should be ruled out prior to proceeding to surgery.

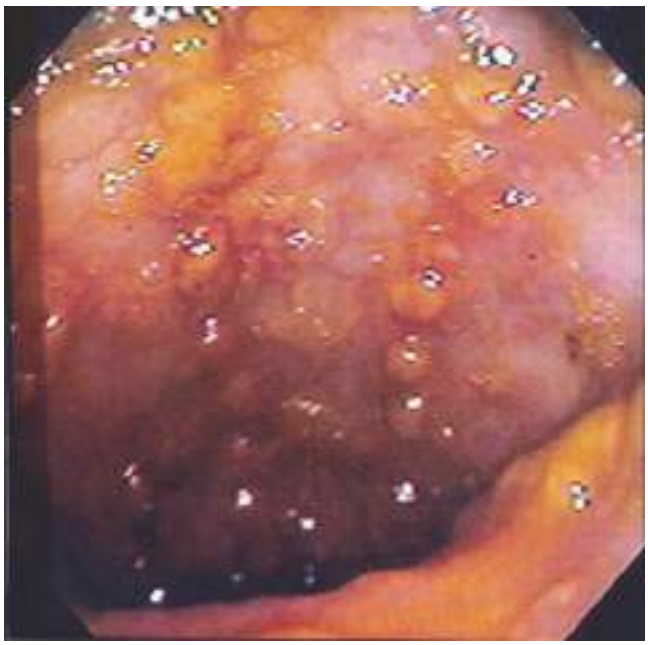


FIGURE 46-7. Colonoscopic appearance of pseudomembranous (*Clostridium difficile*) colitis. Courtesy of Dr. Anthony Senagore.

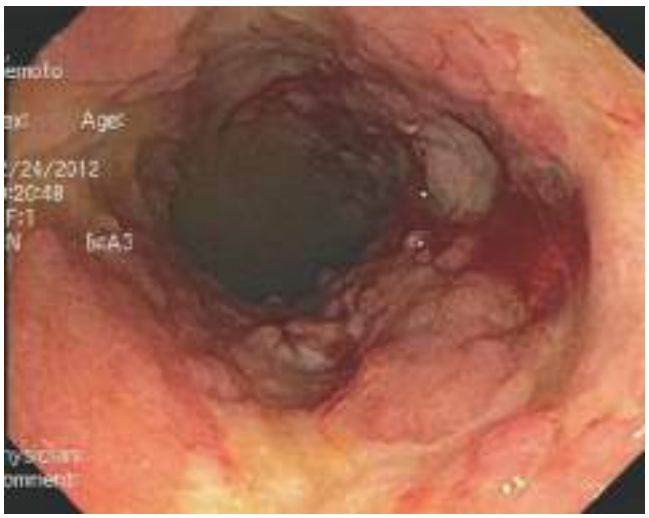


FIGURE 46-8. Colonoscopic appearance of CMV colitis in a patient with CUC. Note the classic "punched-out" ulcerations (bottom center of photo) in a background of peudopolypsis. Courtesy of Dr. Anthony Senagore.

Epidemiology

The epidemiology of CUC is relatively well defined. North America has a relatively high incidence of 8–15 cases per 100,000 persons per year [5]. It is estimated that 50,000 new individuals are diagnosed in these regions yearly, and it has an estimated point prevalence of more than 600,000 persons at any given time in the North America. The incidence of CUC in Western societies continues to rise, lending indirect support to the hygiene hypothesis of pathogenesis of CUC (see below). Furthermore, since CUC does not typically shorten the life span of patients, the prevalence continues to rise as well. Risk factors for CUC are summarized in Table 46-1.

Overall, approximately 70–75% of CUC patients will never require colectomy. Some 50% of those who do not undergo colectomy are in remission, and 50% have active disease. Unfortunately, the proportion of patients with prolonged remission is only 10%, highlighting the recrudescent, waxing and waning nature of this illness. Approximately 1% of patients live with continuously active disease [6].

Hygiene Hypothesis and Fecal Microbiome

Although the etiology is as yet undefined and CUC remains idiopathic, mounting evidence suggests that the hygiene hypothesis may pull together many epidemiological features of the disease into a unified theory [7]. This hypothesis, which may also apply to other autoimmune/auto-inflammatory diseases such as diabetes and asthma, suggests that lack of exposure to environmental pathogens sets the stage for future development of hypersensitivity to normally harmless pathogens by lack of tolerance induction. This hypothesis is supported by a number of findings, including

TABLE 46-1. Epidemiologic risk factors for development of CUC

Category	Risk factor(s)	Comments
Age	Median age of diagnosis = 33 years	Larger studies have disproven bimodal distribution
Gender	Slight male preponderance	–
Genetics	Monozygotic twin concordance = 14–19%, dizygotic concordance 0–7%	If one sibling with CUC, other sibling(s) with 7–17 relative risk of CUC
Geography	Higher prevalence in Northern, developed countries but is worldwide	Highest risk areas appear to be North America, UK, Northern Europe, Scandinavia; rising incidence of CUC in developing countries typically precedes that of CD by 1–2 decades
Race/ethnicity	Caucasians, Ashkenazi Jewish ("Jews of Europe"); incidence rising in Asians and Hispanics	Migration studies suggest that geography is a more important risk factor than race as low-risk groups who migrate to higher prevalence areas and then develop a higher prevalence independent of race
Socioeconomic status (SES)	Possible association between increased SES and increased risk of CUC	–
Cigarette smoking	Highly characterized strong, inverse relationship current smokers @ 40% risk reduction for development of CUC	Current smokers with CUC less likely to require hospitalization or colectomy relative to nonsmokers
Appendectomy	Highly characterized strong, inverse relationship with patients who have had appendectomy with a 70% risk reduction for development of CUC	Patients who have had appendectomy who do develop CUC may have less severe disease
Antibiotics	Oral antibiotics in prior 2–5 years modestly increase the risk of IBD development	Probable dose–response relationship, i.e., the more prescriptions for prior antibiotics, the higher the likelihood of developing IBD
Oral contraceptives	No significant relationship for CUC	Earlier studies suggested a modest increased risk for CUC if prior oral contraceptives
Diet	No significant relationship for CUC	Some studies suggested a link between refined sugar and CD not CUC
Infection	No significant relationship for CUC	Conflicting data for CD but no effect for CUC

Adapted from Loftus EV, Epidemiology of inflammatory bowel disease [76]

geographic variation in incidence (more developed countries having increased incidence), socioeconomic status, migration studies (which show that persons who migrate from low-incidence areas to high-incidence areas are at increased risk), and others, the penultimate being a correlation to clean households.

Another area of intense research at this time that may lead to etiologic clues focuses on the characterization of the fecal microbiome (the mass of colonic bacteria in the colonic lumen and on the mucosa) in individuals with and without IBD [1, 8]. At this time, it is unknown whether observed differences in microbiomes between affected and unaffected individuals are etiologic in nature or *secondary* to the disease and/or its treatment. Nevertheless, manipulating the fecal microbiome is a promising line of inquiry.

Colorectal Adenocarcinoma

Aside from confirming the clinical diagnosis, severity, and extent of CUC, colonoscopy also has an important role in surveillance. Patients with CUC are at increased risk of developing colorectal cancer. A rule of thumb is the risk of developing colorectal cancer (CRC) in CUC is 0.5–1% per year after the first 10 years of disease. Currently it is recommended that surveillance should commence 8–10 years after onset of colitis (rather than the time of diagnosis) [2, 9]. However, some 20% of cancers in CUC occur within the first 8 years of disease, emphasizing the importance of early colonoscopy and continued vigilance and low threshold for repeating endoscopy as the clinical situation demands [3, 10]. A number of factors increase the risk of dysplasia and cancer development and hence should inform the frequency of surveillance colonoscopy. These include young age at diagnosis, longer disease duration, severity and extent of inflammation, family history of CRC, and presence of primary sclerosing cholangitis (PSC) [4, 11]. Of note patients with CUC with neoplasia and PSC are also at increased risk for pouchitis after IPAA. The importance of timely surveillance cannot be underemphasized, as the incidence of colorectal adenocarcinoma in CUC appears to be increasing over the last 40 years [5, 12].

For patients with multiple diarrheal bowel movements per day, less bowel preparation is needed, and the patients should be aware *a priori* that multiple mucosal biopsies will be taken. The endoscopist should intubate the terminal ileum for a minimum of 5–10 cm in order to evaluate for backwash ileitis versus Crohn's ileitis. The mucosa and any lesions are biopsied, as is the mucosa in multiple segments, such as eight biopsies from the right colon (and labeled as such), eight from the transverse colon, and eight from the left colon.

A more sensitive approach to neoplasia surveillance is chromo-endoscopy and narrow-banding imaging (NBI). Chromo-endoscopy uses dilute methylene blue sprayed onto mucosa using a standard endoscope, while in NBI a filter narrows the white light to blue. The resulting increased contrast facilitates detection of subtle, especially flat lesions not visible to white-light endoscopy, and directed instead of random biopsies. Although more time-consuming, chromo-endoscopy has a higher adenoma detection rate in CUC [6, 13].

Patients with low-grade dysplasia in flat or non-polyp-like lesions (formally called dysplasia-associated lesions or masses—DALMs) should be advised to undergo colectomy due to a 20–30% risk of these patients already harboring unrecognized colorectal adenocarcinoma and >50% risk of developing cancer within 5 years of the diagnosis of low-grade dysplasia [7, 14].

Classification of CUC

The severity and extent of CUC ultimately is what directs the treatment, so in this section we will review the different methods of assessing disease activity. Historically, disease activity was measured by the criteria outlined by Truelove & Witts in their landmark 1955 study of corticosteroid therapy for the treatment of CUC [15]. These widely used criteria, based on signs, symptoms, and ESR, are shown in Table 46-2.

More recently the Montreal classification of IBD, a revision of the Vienna classification, has become the preferred way to specify disease activity, both in clinical usage and in research studies (Figure 46-9) [16]. The advantage and utility of this system is that it stratifies patients not only by disease severity but also by extent:

Severity

- S0 = clinical remission
- S1 = mild disease: <4 bowel movements per day, no serologic or systemic signs of inflammation
- S2 = moderate: >4 stools per day, some signs of inflammation
- S3 = severe: >= 6 bloody stools daily, pulse >90 beats per minute, temperature >37.5 °C, hemoglobin <10.5 g/100 ml, and ESR >30 mm/h)

TABLE 46-2. Modified Truelove and Witts Criteria

Variable	Mild disease	Severe disease	Fulminant disease
No. of stools/day	<4	4–10	>= 10
Blood in stool	Intermittent	Frequent	Continuous
Temperature	Normal	>37.5	>37.5
Pulse	Normal	>90	>90
Hgb	Normal	<75% of normal	Requiring transfusions
ESR (mm/h)	Normal =< 30	>30	>30
Abdominal X-ray	Normal	Edema/thumbprinting	Dilation
Abdominal pain	None	Mild diffuse tenderness	Distension and tenderness

Note moderate disease with features of mild and severe disease
Adapted from Mahadevan Clin Colon Rectal Surg 2004 [75]

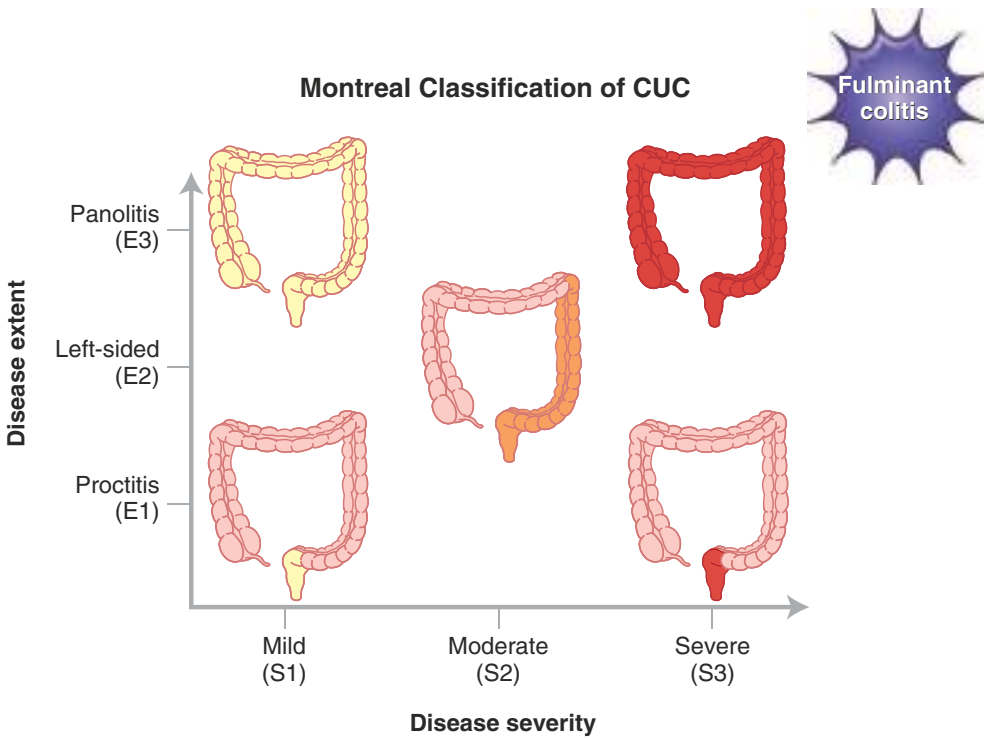


FIGURE 46-9. Diagrammatic representation of the Montreal classification of CUC disease severity and extent.

Extent

- E1 = ulcerative proctitis
- E2 = left-sided colitis
- E3 = pancolitis

Other recommendations of the Montreal Working party was that the clinical term *indeterminate colitis* should be renamed *IBD-unclassified (IBDU)* and that use of the term indeterminate colitis should be reserved for use in the post-colectomy patient in which the pathologist cannot categorize the colitis as either CD or CUC.

Endoscopic classification is facilitated by the Mayo Severity Index (also called the Mayo Clinic Score and Disease Activity Index, Table 46-3). This assesses symptoms, the degree of mucosal inflammation, and the physicians' global assessment of patient well-being [17]. The Simple Clinical Colitis Activity Index (SCCAI, Table 46-4) is also useful clinically for following patient's symptoms over time [18].

Treatment Endpoints

The goals of medical therapy for CUC include induction of remission, avoiding steroids, and improving quality of life (QoL), while avoiding toxicity and preventing neoplasia. Remission is defined as an absence of symptoms that typically accompanies mucosal healing. Maintenance of remission often requires ongoing medical therapy. Symptomatic improvement can objectively be assessed using the above scores, but can also be assessed by measuring quality of life (QoL). Instruments to assess QoL may include measures of overall QoL (such as the SF-36 or EuroQoL 5D VAS [Figure 46-10]), disease (IBD-Q), or symptom-specific (FISI/FIQL) QoL. These can be used both clinically and for research studies.

Cost Considerations

Both the direct and indirect costs of therapy for CUC have been studied and must be considered when determining the optimal treatment for CUC. Overall CUC is known to be a costly disease with medical patients consuming on average $6,586 dollars per year, increasing to $15,732–$20,131 in the years prior to surgical intervention [19, 20]. The cost-effectiveness of surgery for CUC compared with biologic therapy has also been studied, and early colectomy was found to be a cost-effective treatment compared to maximal medical therapy [21]. A subsequent study, including the long-term costs of medical and surgical complications, did find that infliximab (IFX) therapy was initially cost-effective. However, as shown in Table 46-5 (a sensitivity analysis of a model of the effect of time in years on the cost-effectiveness of infliximab and surgery for severe CUC), after 2 years of IFX therapy surgery became the dominant strategy (more effective and less costly), increasingly so as time goes on towards age 70 years [22].

Part 2: Specific Treatments

Bottom-up Versus Top-Down Strategies

An overview of available medical therapy is shown in Table 46-6. In general, there are two competing therapeutic strategies, namely the traditional "bottom-up" (additive) therapy in which less expensive, less effective medications are sequentially added until the desired clinical endpoint is achieved. An emerging approach is the "top-down" (subtractive) strategy in which patients are initially placed on the more aggressive therapies in order to achieve rapid remission, and then agents are sequentially weaned.

TABLE 46-3. Mayo severity index

Variable	Points (Range 0–12)			
	0	1	2	3
BM frequency	Normal	1–2 BM > normal	3–4 BM > normal	>= 5 > normal
Bleeding	None	Streaks < 50% of BM's	Obvious blood with most BM's	Blood alone
Endoscopy	Normal	Mild: Erythema, decreased vascularity, mild friability	Moderated: marked erythema, lack of vascular pattern, friability	Severe: Spontaneous bleeding, ulceration
Physicians Global Assessment (PGA)	Normal	Mild	Moderate	Severe

Adapted from Schroeder NEJM 1987 [17]

TABLE 46-4. Simple clinical colitis activity index

	Points (range 0–15)				
Symptom(s)	0	1	2	3	4
Daytime BM frequency	1–3	4–6	7–9	>9	
Nocturnal DM frequency	None	1–3	4–6		
Fecal urgency	None	Hurry	Immediately	Incontinence	
Bloody stools	None	Trace	Occasional frank	Usually frank	
General well-being	Very well	Below average	Poor	Very poor	Terrible
EIM's	1 point per extra-intestinal manifestation				

Adapted from Walmsley 1998 [18]

FIGURE 46-10. EuroQoL 5-D Visual Analog Scale, an example of a rapid, easily administered, and interpretable instrument which assesses global health-related quality of life. © Stichting Euroqol Research Foundation.

TABLE 46-5. Sensitivity analysis of the effect of duration of disease on the cost-effectiveness of infliximab and surgery for severe ulcerative colitis

Model length	Dominant strategy	Cost of IFX strategy (US dollars)	Cost of surgery strategy (US Dollars)	Effectiveness of IFX strategy*	Effectiveness of surgery strategy
1 year	IFX	$26,698.45	$63,721.15	0	0
2 years	IFX	$63,648.51	$74,090.32	0.78	0.76
3 years	Surgery	$91,515.26	$82,364.24	1.51	1.50
4 years	Surgery	$112,938.29	$90,277.08	2.19	2.21
5 years	Surgery	$129,786.88	$97,911.94	2.84	2.89
10 years	Surgery	$179,816.82	$132,325.91	5.65	5.98
Lifetime	Surgery	$305,691.59	$270,477.74	16.58	18.34

Quality-adjusted life years based on EuroQoL-5D Visual analog scale

Reproduced with permission from Holubar SD, Piazik B, Xu Kathleen, Dulai P, Tosteson A, Siegel C, Finlayson S. Cost-effectiveness of infliximab versus colectomy for severe ulcerative colitis: A Markov analysis: P-108. Inflamm Bowel Dis. 2012 May 7;18:S57–8. © Wolters Kluwer [22]

*Quality-adjusted life years based on EuroQoL-5D Visual analog scale

An example of top-down therapy would be inducing the patient on a biologic and a thiopurine and then attempting to remove the biologic after the patient is clinically improved.

Aminosalicylates (5-ASA Moieties)

Sulfasalazine is the prodrug of the 5-ASA class of medications. Multiple forms of 5-ASA medications have been developed, mainly in an attempt to reduce side effects. 5-ASA medications are administered via enteral (e.g., tablets or time-release "caplets") or topical (e.g., Canasa® suppositories) formulations. There are three release mechanisms: pH (e.g., Asacol®, Lialda®), time release (e.g., Pentasa®), and bacterial cleavage release (e.g., Azulfadine®), and these mechanisms dictate the target area of bowel (ileum, colon, or rectum). To determine the proper dose for a given 5-ASA product, the prescribing provider must the calculate "5-ASA delivered dose." Doses are typically in the 2–4 g by mouth per day range.

Oral 5-ASA products have been shown to be effective for induction of remission in mild-to-moderate CUC (see Part 3 below) [23]. Overall no difference in remission rates was demonstrated between the different preparations. These findings support the conclusion that use of an *adequate* dose is

TABLE 46-6. Overview of clinical pharmacotherapy for CUC

Class (effect)	Indication	Examples	Dose
5-aminosalicylates (enteric/topical anti-inflammatory)	Induction *and* maintenance of remission for mild-to-moderate colitis/proctitis	Sulfasalazine	4–6 g PO daily
		Mesalamine	PO: 2.4–4.8 g PO daily
		Canasa®suppositories	PR: 500 mg–1 g per rectum daily
		Olsalazine	1.5–3 g PO daily
		Balsalazide	6.75 g PO daily
Topical corticosteroids (anti-inflammatory)	Maintenance of remission for mild-to-moderate colitis	Budesonide	9 mg PO daily; rectal foam now available
Thiopurine immunomodulators (block purine metabolism)	Induction *and* maintenance of remission for moderate-to-severe colitis	Azathioprine (AZA) 6-MP	AZA: 2.5 mg/kg PO daily (50–150 mg PO q24)
			6MP: 1.5 mg/kg daily
Biologics agents (block TNF or leukocyte rolling and adhesion)		Anti-TNF-alpha Antibodies	IFX: 5–10 mg/kg, weeks 0, 2, 6 then every 4 weeks
			Adalimumab: 160 mg week 1, 80 mg week 2, then 40 every other week
		Anti-integrin Antibodies	Golimumab: 200 mg week 0, then 100 mg every other week
			Vedolizumab: 300 mg IV weeks 0, 2, 6, then every 8 weeks
Systemic corticosteroids (anti-inflammatories)	Rescue therapy for severe colitis[a]	Prednisone	5–40 mg PO daily
		Hydrocortisone	20–300 mg IV daily
Calcinurin inhibitors (immunosuppressives)	Rescue therapy for steroid refractory severe colitis[a]	Cyclosporine	2–4 mg/kg daily
		Tacrolimus	0.05 mg/kg twice daily

[a]indicated for induction of remission *not* maintenance of remission. Inability to wean from these agents is an indication for surgery

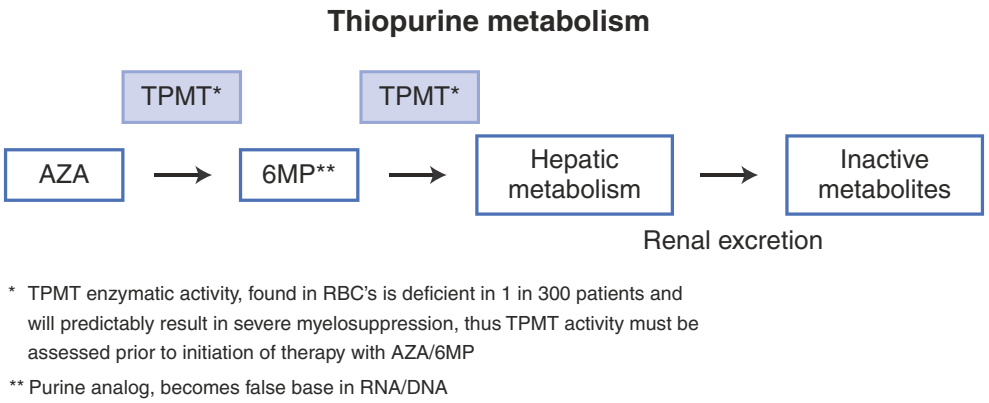


FIGURE 46-11. Schematic representation of in vivo thiopurine metabolism.

more important than preparation, emphasizing the concept of "5-ASA delivered dose." Overall it appears high-dose oral 5-ASA, which is associated with increased side effects, is *not* more effective at induction of remission than moderate dose in CUC patients [23]. Regarding the maintenance of remission, 5-ASA medications are effective for maintenance, but only by maintaining, not lowering the dose. Despite their efficacy in inducing and maintaining clinical remission, 5-ASA class medications are not protective for development of colorectal cancer [24]. "Bidirectional therapy" with both enteral and per rectal preparations is well known to be more effective than either alone and makes clinical sense as essentially all CUC patients have distal disease. However, patients are often resistant to the daily use of suppositories or enemas.

Side effects, which are dose dependent, are mainly dermatologic and gastrointestinal toxicity. Sun exposure can lead to severe sunburn as sulfa moieties can be found in the dermis and can be activated by sunlight.

Immunomodulator Therapy (6-MP, Azathioprine)

Azathioprine (AZA) is the prodrug of 6-mercaptopurine (6-MP), and both act as immunomodulator or weak immunosuppressant. Thiopurines (TPs) are metabolized as shown in Figure 46-11. In summary, the prodrug AZA is first converted by the enzyme TPMT into 6MP, which in turn is then converted by TPMT into other metabolites.

It is important to understand the TMPT metabolic pathway in order to prevent severe toxicity, including life-threatening leukopenia, pancreatitis, and hepatitis [25]. Specifically, the TMPT genes, expressed in red blood cells, are present either in its wild-type form (normal metabolizers) or as deficient genes (prevalence 1 in 300 persons). In TMPT-deficient patients, active metabolites are not efficiently degraded resulting in supra-therapeutic AZA concentrations, frequently leading to myelosuppression.

Thus, TMPT testing is an integral part of initiating TP therapy, and CBCs are monitored for signs of myelosuppression [26]. Since TPs are immunosuppressive, any active infections must be treated prior to initiating therapy. Other side effects include hypersensitivity reactions such as fever, nausea, pancreatitis, and influenza-like symptoms. Finally, immunomodulator therapy may be associated with a marginally increased risk of lymphoma, but the absolute risk is small [27]. It should be noted that IBD patients are at baseline-increased risk of lymphoma due to their chronic inflammatory state (see IFX side effects below for additional discussion).

TPs are effective steroid-sparing medications. They are seldom used by themselves and are often started upfront with steroids (top-down or step-up therapy) to induce remission in a top-down manner. The steroids are then weaned, and the TP used as a maintenance drug. TPs have also been used in combination with biologic agents as they are known to increase biologic efficacy; the increased efficacy of "SONIC-style" combination therapy may be due in part to prevention of anti-TNF immunogenicity [28]. Thiopurines, in the setting of combination therapy, may also represent an "exit strategy" from chronic biologic therapy [29].

Biologic Agents

Anti-TNF-Alpha Antibodies

Infliximab (Remicade®)

IFX is chimeric mouse/human monoclonal anti-Tumor Necrosis Factor (NTF) alpha antibody. IFX was FDA approved for CUC in 2005 and is now indicated for the treatment of mild-to-severe UC in both adults and children. In the ACT-1 and ACT-2 randomized trials assessing the efficacy of IFX for inducing and maintaining remission (defined as reduction of Mayo score by 3 points), 60–69% of patients have successful induction, compared with 29–37% response for placebo [30]. The typical loading dose is 5 mg/kg IV at week 0, 2, and 6, switching to maintenance dose of 5 mg/kg IV every 8 weeks starting at week 14. If a loss of responsiveness occurs and symptoms flare, then the IFX dose can be increased to 10 mg/kg IV every 4–8 weeks. Serum drug trough levels are monitored to assure proper dosing, ensuring adequate trough levels may be associated with increased efficacy and decreased risk of colectomy. The best outcomes of IFX therapy are seen in combination with other medications such as TPs as demonstrated by the UC-SUCCESS trial with 40% of patients achieving a steroid-free remission, compared with only 2% on monotherapy with either agent; similarly mucosal healing was observed in 63% of combination therapy patients compared with 55% on IFX alone [31].

The most widely recognized side effect of IFX is activation of latent infections most notably TB. Thus, prior to initiation of IFX therapy patients are screened with the QuantiFERON® gold assay [32]. IFX can also make active infections worse and can exacerbate hepatitis B. Other adverse reactions include infusion reactions, which can result in flash pulmonary edema or hypersensitivity including anaphylaxis; thus, these patients must be administered the drug in an infusion center. Demyelinating central nervous system disorders and other neurologic side effects such as optic neuritis and multiple sclerosis have been reported, and *young males receiving combination TP therapy may be at increased risk of hepatocellular T-cell lymphoma, an otherwise rare, lethal disease*. It is unknown whether IFX independently increases the risk of other forms of lymphoma as IBD patients IBD are generally at increased risk due to their chronic inflammatory state [33].

It is highly controversial whether or not biologic agents, and IFX in particular, increase the risk of surgery. Both Mayo Clinic and Cleveland Clinic have shown increased perioperative risk in patients on biologics, and the Crohn's and Colitis Foundation has recently published a position paper regarding perioperative management [34–36]. One consideration is the half-life of the agents (Figure 46-12). This schematic, which *assumes first-order elimination pharmacokinetics*, may provide some guidance for timing of surgery for patients requiring elective surgery.

Adalimumab (Humira®)

The second in class, this humanized form represents an attractive alternative to infliximab.

Similar to IFX albeit less powerful, adalimumab is indicated for induction and maintenance of remission in adults with moderate-to-severe CUC; an additional indication is loss of response to IFX. The ULTRA-1, 2, and 3 trials demonstrated that in patients with moderate-to-severely active CUC, adalimumab is efficacious in both short-and long-term

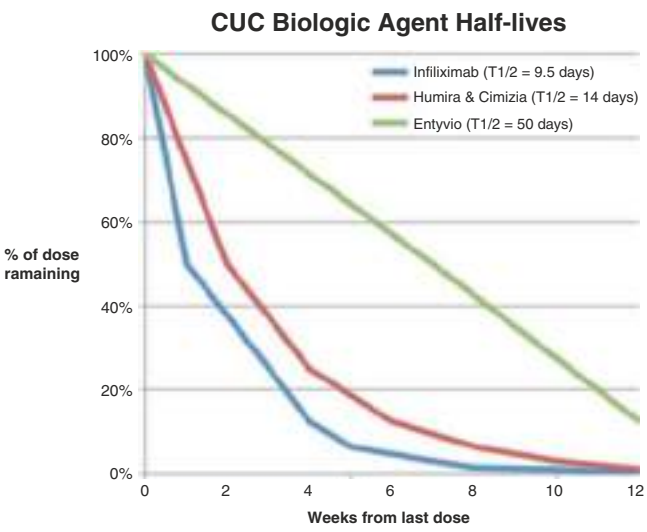


FIGURE 46-12. Graphical representation of the theoretical in vivo half-lives of biologic agents used to treat CUC. Note this graph assumes first-order elimination pharmacokinetics.

maintenance of remission for up to 4 years in 60% of patients. Loading doses are used (week zero 4 shots = 160 mg, week two 80 mg, maintenance week four 40 mg SQ every other week subcutaneously). If a suboptimal response is observed the dosing interval is often increased to weekly. As in IFX, trough levels can be used to monitor and optimize therapy, such as by increasing the dose to 40 every week or 80 every other week. Also as in IFX, the best outcomes are seen with combination therapy with TPs. Humira may be more convenient for patients since they self-administer, but some patients may be less compliant because patients may not be self-medicating.

The humanization of the antibody has greatly reduced the side-effect profile of this medication relative to IFX. Adverse reactions are generally similar to those of IFX and also include local, injection-site reactions and loss of responsiveness.

Certolizumab Pegol (Cimzia®)

This was the third in class of anti-TNF-Ab agents indicated in IBD in adults. It is a partially humanized Fab' fragment of an anti-TNF antibody, which is PEGylated (the pegol acts as a carrier for the Fab' fragment which is lacking the Fc fragment). Presently it is FDA approved for CD (and RA), *but not approved for CUC*. Patients with CUC refractory to other agents may be offered this medication on-study or off-label.

Golimumab (Simponi®)

Simponi is another humanized anti-TNF-Ab which was FDA approved for CUC in 2013 for the induction and maintenance of remission in adults and for patients with loss of responsiveness to IFX and Humira. In the PURSUIT-SC study, Golimumab has been shown to be effective for the induction of remission in moderately-to-severely active CUC with >51% of patients achieving remission compared with 30% of placebo patients, and over 47% of patients maintaining remission, compared with 30% in the placebo arm [37, 38]. Dosing is usually 200 mg subcutaneously at week zero and then 100 mg subcutaneously every other week. Trough level assays are not yet available.

Anti-Integrin Antibodies

Vedolizumab (Entyvio®)

Entyvio is an intravenously administered monoclonal antibody to integrin **α**4**β**7, also known as lymphocyte Payer's patch adhesion molecule 1 (LPAM-1). Blocking this receptor results in the upregulation of anti-inflammatory pathways [39]. In 2014 it was FDA approved for the induction and maintenance of remission of both CUC and CD in adults and also for patients with loss of responsiveness to the above medications. In the GEMINI-I and -II studies, vedolizumab resulted in the induction of remission in 47% of patients, compared with 25% of placebo and maintenance of remission in 41% vs. 15% with placebo [40]. Dosing, which is intravenous, is 300 mg IV at week 0, 2, 6 and then every 8 weeks, and trough levels are not yet available. The adverse drug reactions are similar to IFX and also include a warning regarding the potential the risk of PML (see natalizumab below).

Natalizumab (Tysabri®)

In May 2015, natalizumab is only FDA-approved biologic agent for the treatment of CD. Although *not FDA approved for the treatment of CUC patients at this time*, but it presented here as (a) some patients refractory to the other biologic agents may be offered treatment on- or off-trial (off-label), and (b) natalizumab may become approved for CUC in the future. Given the lack of FDA approval at this time, and the potential for PML, the role of natalizumab for CUC is off-label and unclear. Some experts, in patients with inflammatory bowel disease refractory to other strategies, have used natalizumab to induce remission and, once remission has been achieved, transition the patient to vedolizumab or other non-first-line biologic agent [41].

Natalizumab is associated with JC virus activation or infection that can be a lethal neurological condition progressive multifocal leukoencephalopathy (PML). PML is caused by the JC virus, although an immunocompetent immune system will typically prevent disease development. Prior to initiation of treatment with natalizumab, serologic testing for JC virus is performed. If a patient has negative serologic testing, then the risk of developing PML with treatment is approximately 1 in 10,000. However, if a patient has positive JC virus serology, then the risk increases by two orders of magnitude to the range of 1 in 500 and as high as 1 in 100 with prolonged treatment. Given the severity of the PML illness, this is real cause for concern and the patient must be counseled carefully. Thus, main contraindication to it use is known or suspected PML [32].

"Rescue" Therapy

Corticosteroids

Corticosteroids represent the mainstay of rescue therapy for otherwise medically refractory CUC. Their mechanism of action is that of nonspecific immunosuppression and immunomodulation. Steroids are associated with significant side effects and they should not be used for maintenance therapy. Corticosteroids are glucocorticoid steroid hormones that bind to glucocorticoid receptors, which are ubiquitous in all animal (vertebrate) cells [42]. After binding they result in anti-inflammatory protein upregulation and downregulation of pro-inflammatory proteins. They are metabolized in the liver and excreted in the urine. Various formulations are converted to hydrocortisone equivalent doses using readily available online conversion calculators.

Effects of steroids include adrenal suppression, water retention, moon-like facies, psychological distress (ranging from agitation and insomnia to frank psychosis), rosacea, buffalo-hump, abdominal striations, and osteoporosis. One of the most serious and potentially nonreversible adverse effects is osteoporosis, which may not be responsive to calcium or vitamin D supplementation. Patients on repeated courses of corticosteroids need bone density monitoring with dual-energy X-ray absorptiometry (DEXA) scans.

Enteric or topical budesonide has been shown to be effective for CUC. The CORE-1 study showed that budesonide MMX 9 mg was effective at indication of remission in mild-to-moderate CUC but more limited in maintenance of remission [43]. Newly available Budesonide foam, released February 2015, was shown to decrease symptoms [44]. Long-term (2 years) Budesonide use was shown to be safe based on bone density and protective if steroid naive [45].

Oral forms are typified by prednisone. Most patients with CUC respond to oral steroids, with only 16% not responding acutely [46]. However, systemic steroids have no role for maintenance of remission due to their relatively severe side-effect profiles. Long-term (>1 year) corticosteroid treatment is contraindicated and the inability to wean off chronic steroids represents an indication for surgery.

IV steroids are indicated for those refractory to outpatient medical therapy. Maximum-effective dose is 300 mg hydrocortisone per day. An estimated 60% of patients will respond, usually within 5–7 days. Please see "Severe CUC" section below.

Oral or intravenous (IV) steroids can also be used to prevent immune hypersensitivity to the antigens of infliximab. Effective IV steroid premedication for infliximab dosing was shown to be single dose of 300 mg [47].

Tapering, also called weaning, is done to prevent Addisonian crisis after times of physiologic stress. Rapidity of weaning depends on the duration of use—in general patients treated with steroid for only days to a few weeks can be weaned rapidly (50% reduction per day), while patients on more long-term steroid therapy must have slow tapers of 5–10 mg per week. A common scheme for patients on 40 mg prednisone equivalents per day is 40 for 7 days, 30 for 7 days, 20 for 7 days, 10 for 7 days, then 5 for 7 days, and if no symptoms of withdrawal (lethargy, sluggishness) then off versus 5 every other day or 2.5 every day for an additional 1–2 weeks. Finally, patients weaning from steroids should anticipate symptoms of physical and emotional withdrawal from the steroids such as decreased energy and mood.

Regarding the perioperative management of steroids, a recent Cochrane analysis found no evidence for or against a protective effect for stress dose steroids [48]. Although case reports have identified cases with Addisonian crisis, based on more recent data, no stress-dose steroids are needed [49]. However, clinicians opting not to use them should still monitor these patients for signs and symptoms such as fever, tachycardia, and fluid-resistant hypotension in the perioperative period and treat accordingly.

Some centers advocate for Vitamin A (60,000 IU PO, IV, or IM per day for 5 days) supplementation immediately postoperatively to optimize wound healing. It has been shown in animal studies to prevent the inhibition of collagen-cross-linking and the obvious deleterious effects on wound healing. Although the level of evidence is weak, this treatment is both safe and inexpensive; thus, the potential benefits outweigh any risks.

Cyclosporine/Tacrolimus

These drugs, used for prevention of graft rejection in solid-organ transplantation, are calcinurin inhibitors. These medications bind to a T-cell receptor, inhibiting calcineurin-mediated cytokine release, essential to promote T-cell-mediated immune-competency.

Given its position as a major immunosuppressive agent, calcinurin inhibitors are reserved for use as a rescue agent for severe, otherwise medically refractory CUC [50]. Please see the "Severe Colitis" section below.

These medications carry a risk of opportunistic infections and are associated with a host of specific adverse reactions. These latter include constitutional and gastrointestinal symptoms, and they are potentially nephrotoxic, hepatotoxic, and neurotoxic and exacerbate hypertension and hyperlipidemia. Finally, they are potentially carcinogenic; these drugs taken long term can increase the risk of skin squamous cell carcinoma.

Methotrexate

Methotrexate (MTX) is an anti-metabolite, specifically inhibiting folic acid metabolism by competitive inhibition of dihydrofolate reductase (DHFR). Since folic acid metabolites such as tetrahydrofolate are a required cofactor for DNA synthesis and repair, blockage of this path inhibits rapidly dividing or growing cells. MTX undergoes extensive hepatic metabolism and are renally excreted. Aside from being hepatotoxic and myelosuppressive, MTX is also an FDA Category X drug, meaning it is teratogenic, resulting in birth defects, and has been used as an abortifacient.

Given its success in rheumatoid arthritis and psoriasis, MTX held promise as an alternative to biologics or corticosteroids for IBD. Although MTX may be used in the treatment of CD, at present there is *no evidence supporting the use of MTX for induction or maintenance of remission in CUC* [51, 52]. Current trials are under way (MERIT-UC and METEOR) which may further define its role in CUC.

Part 3: Medical Management of Mild-to-Severe CUC

Mild-to-Moderate Distal Colitis/Proctitis (Figure 46-13)

Topical mesalamine is the first-line treatment for both inducing and maintaining remission of distal mild or moderate colitis [53]. The formulation chosen is tailored to the extent of disease: suppositories are appropriate for proctitis without proximal involvement, foams reach the sigmoid colon, and enemas may even reach the splenic flexure, but compliance can be an issue. Although oral aminosalicylates are less effective than topical mesalamine [53], most patients prefer oral formulations. In moderately severe cases, combining topical and oral therapy is more effective than topical mesalamine alone in both achieving and maintaining remission [54]. Clinical effects of oral aminosalicylates are apparent after 2–4 weeks and overall some 60–80% of patients have a response [55].

Topical corticosteroids have similar efficacy in achieving remission in active disease and are an alternative to topical mesalamine. They should not be used for maintenance, however. The roles of oral corticosteroids, TPs, and biologics in cases where aminosalicylates fail to induce or maintain remission in distal colitis are similar to those in extensive colitis, as discussed below.

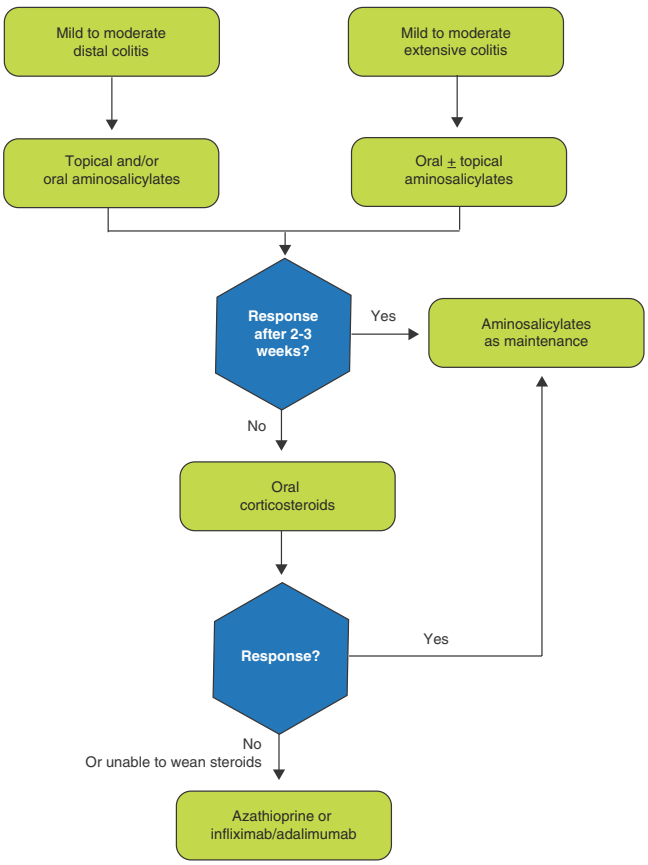


FIGURE 46-13. Standard "Bottom-up" approach to the management of mild-to-moderate CUC (based on the American College of Gastroenterology 2010 Practice Guidelines).

Mild-to-Moderate Extensive Colitis (Figure 46-13)

For mild or moderate colitis, oral salicylates induce clinical improvement in 60–80% of cases within 4 weeks of therapy [55]. Efficacy is dose related, but due to common adverse effects such as nausea and anorexia, and the risk of less common but severe adverse effects such as hepatotoxicity, pancreatitis, and nephrotoxicity, daily doses of sulfasalazine are commonly started at 1–2 g and increased as tolerated up to 4–6 g. Non-sulfonamide aminosalicylates, such as mesalamine, are more expensive but may be better tolerated [17]. The highest recommended dose for these compounds is 4.8 g daily.

In either distal or extensive colitis not responding to 4 weeks of aminosalicylate therapy, a course of oral steroids is indicated. This is usually started at 40–60 mg of prednisone per day. When a clinical response has been achieved, the dose is tapered over several weeks, typically reducing the daily dose by 5–10 mg every week until a daily dose of 20 mg is reached, and by 2.5–5 mg thereafter. Due to its well-known and wide-ranging acute and chronic toxic and adverse effects, corticosteroid therapy should be used judiciously and is only indicated for active colitis. Although the response rate is around 70%, some 20% overall develop steroid dependency and cannot be weaned without relapse of symptoms [46].

In nonresponders, and in patients who become steroids dependent, a third-line therapy should be started to aid in weaning of prednisone. The two main options at this stage are TPs and biologics. Azathioprine is effective in inducing and maintaining remission, but its effects are slow with the time of onset measured in months, requiring overlap with an extended course of oral prednisone.

Infliximab has been well studied in steroid-refractory mild and moderate colitis. Trials have established the efficacy of the 5 mg/kg intravenously administered dose at 0, 2, and 6 weeks in inducing remission, and every 8 weeks to maintain remission [30]. Some 69% of patients respond to induction treatment. The drug is discontinued in nonresponders after two doses, as later response is very unlikely. Co-administration of infliximab and azathioprine may be associated with an increased clinical response rate and mucosal healing in moderate and severe steroid-refractory colitis compared to monotherapy with either drug [31]. Synergy may be due to the thiopurine-related inhibition of hypersensitivity reactions against the biologic agent's antigens. However, such patients may be at increased risk of immunosuppression-related infections.

Remission in mild and moderate extensive colitis can be maintained either by oral aminosalicylates, TPs, or inflix-

imab. Alternately, patients with a single episode of mild disease may opt for clinical observation alone. The choice of maintenance therapy is chiefly determined by the method by which remission was induced. Responders to aminosalicylates or oral steroids are typically subsequently maintained on oral aminosalicylates. These can be given as sulfasalazine or a non-sulfonamide derivative, although recent evidence does not support any benefits of those more expensive derivatives either in efficacy or adverse events [23]. Overall, some 59% of patients remain in steroid-free remission at 12 months on oral aminosalicylates [23].

When treatment with infliximab or azathioprine, or a combination, is used to induce remission, the same therapy is continued as maintenance. Infliximab is infused every 8 weeks. In initial responders who develop symptoms during maintenance therapy, a dose increase to 10 mg/kg is often effective. Some 74% of patients will require one or more additional courses of oral corticosteroid over a maintenance period of 54 weeks [30]. Steroid-free remission during 12 months is achieved in some 56% of patients on azathioprine on meta-analysis of randomized trials [56]. Long-term efficacy of a combined TP and biologic therapy is unknown. Similarly, the rationale of switching from infliximab to a newer anti-TNF drug such as adalimumab or golimumab is unclear.

Severe Colitis (Figure 46-14)

Most patients with severe colitis require hospitalization for stabilization and a course of intravenous corticosteroids, regardless of the extent of disease. Selected patients with severe disease who partially have responded to oral medications and, importantly, are systemically well with no signs of toxicity can be started on infliximab as outpatients [30]. A course of intravenous steroids has been the standard therapy for severe ulcerative colitis since the 1950s [15] and is currently given in a daily dose of 300 mg hydrocortisone or equivalent. A course of 3–5 days is given with close clinical observation. Ideally consultation with a colorectal surgeon and a stoma therapist is advisable during this stage, so that the patient can be in a position to make an informed decision about the next steps by day 3–5 should steroid therapy fail, especially since overall some 20–40% of patients with severe UC will fail to improve on IV corticosteroids. Persistence of colonic or systemic manifestations after this period is labeled steroid-refractory disease and mandates surgical consultation.

During these first days, several additional measures need to be taken to reduce morbidity and prepare for so-called rescue therapy should this be necessary. In addition to initial fluid and electrolyte resuscitation, patients with significant weight loss will often need supplemental parenteral nutrition support. Continued oral diet is encouraged in most patients, due to the theoretical advantages of short-chain fatty acid provision to the colon. However, bowel rest may be indicated if bowel movements are excessive.

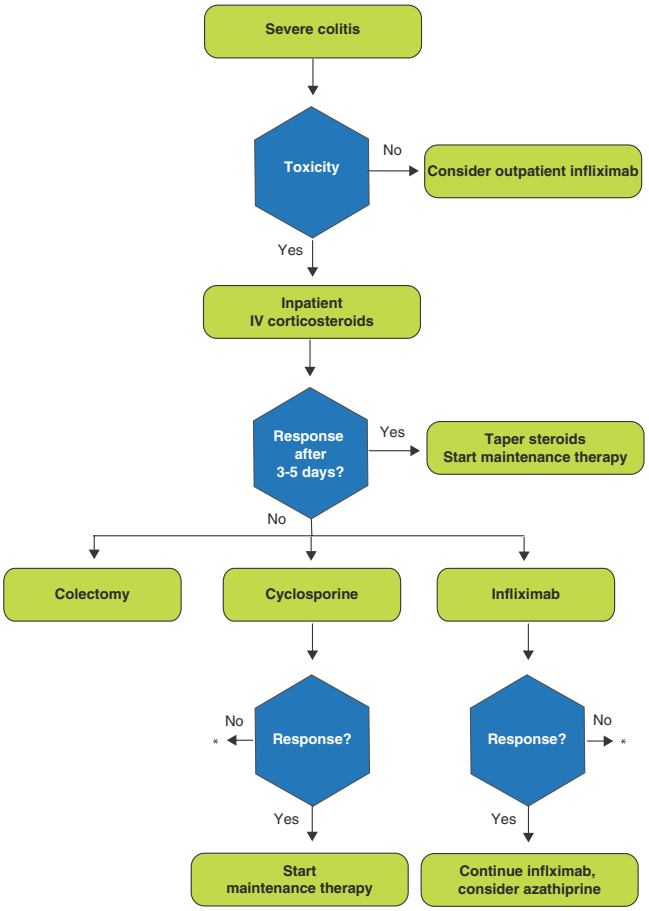


FIGURE 46-14. Standard "Bottom-up" approach to the management of severe CUC (based on the American College of Gastroenterology 2010 Practice Guidelines).

Thromboembolic prophylaxis is routinely given and anticholinergic and opioid medications are avoided.

Importantly, gut infections may exacerbate ulcerative colitis and treating those aggressively is thought to facilitate induction of remission. Stool samples are therefore cultured for *Salmonella*, *Yersinia*, and *Shigella* and tested for *C. difficile* toxin. Some 25–36% of patients with steroid-refractory UC have CMV disease in colonic biopsies [57]. Colonic CMV disease is best demonstrated by immunohistochemistry of classic "punched-out" mucosal ulcer biopsies obtained on flexible sigmoidoscopy, although leukocyte CMV PCR is sometimes used as a surrogate marker. Importantly, positive CMV antibody titers merely signal current or previous CMV infection (worldwide prevalence of CMV is in the order of 50%), but negative IgM titers means that the patient is highly unlikely to carry CMV and sigmoid biopsies are not required. CMV colitis is usually treated with IV ganciclovir at 5 mg/kg q12 h × 14–21 days and then transitioned to 5 mg/kg daily or 1000 mg PO three times daily.

Broad-spectrum antibiotics are often given to patients with toxicity over fear of bacterial translocation. There are no data to support this, and it is known that portal or venous bacteremia is rare in severe UC even during colectomy [58].

Patients with megacolon (often defined as colonic dilatation to a diameter >6 cm) require additional caution. Oral intake is stopped, abdominal signs are closely monitored, and daily plain abdominal films obtained to assess progression. In this subgroup of severe CUC, failure to respond to corticosteroids is an indication for urgent colectomy already after 24–48 h, as is progressive dilatation. Fulminant colitis is the advanced form of severe, acute colitis and is typically defined as toxic colitis, i.e., colitis with signs of systemic toxicity such as peritonitis, hypotension, impending perforation, and/or end-organ damage such as renal failure.

Rescue therapy for steroid-refractory severe UC falls into three main categories. In historical order, these are colectomy, cyclosporine, and infliximab. For a complete discussion on the indications and technical aspects of colectomy in this context, please refer to Chap. 48.

In randomized trials and large uncontrolled studies, intravenous cyclosporine is highly effective in steroid-resistant severe UC, with response rates of up to 82–83% [59, 60]. On the other hand, it has proven difficult to maintain remission in responders, with up to 54% of patients subsequently requiring colectomy [60]. Responders are typically started on maintenance azathioprine, often with the addition of an oral aminosalicylate. The issue of recrudescence of colitis following rescue therapy with cyclosporine, in combination with a significant toxicity profile, has led to a reduction in its usage in the biologic era, and presently it is only offered at select centers.

More recently, infliximab has emerged as a widely used rescue therapy in the recent decade, despite support by relatively small studies, with response rates in the 50–71% range [61, 62]. One important advantage is that infliximab can be continued long term to maintain remission. A direct comparison confirmed that both cyclosporine and infliximab have high initial response rates when used as rescue therapy in steroid-refractory severe colitis (85 vs. 86%), and in this trial colectomy rates were also similar at 3 months (18 vs. 21%) [63]. Selected patients who fail either cyclosporine or infliximab may respond to the alternate therapy, although this is associated with risks and should only be undertaken in selected patients in specialized IBD units [64]. Specifically two other alternative rescue therapies that have been used anecdotally with success include cigarette smoking and hyperbaric oxygen, the latter of which is under study.

Preoperative Optimization of the Medical CUC Patient

When a patient is refractory to maximal medical therapy, or has CUC-associated neoplasia (colorectal cancer or high-grade dysplasia), or patient refusal of additional medical therapy, then surgery is indicated. Note we use the term "refractory to maximal medical therapy" in lieu of "failure of medical therapy" as the latter has negative connotations for both the patient and referring gastroenterology provider. Overall medically refractory disease is the indication in 88% of colectomies for CUC, while neoplasia the remaining 12% [65]. A third category, not frequently indicated, is colorectal cancer prophylaxis (without dysplasia).

Given the overall success of medical therapy for CUC, surgery has often been relegated to a therapy of last resort. This is often due to patient and (referring) physician concern over surgical complications and fear of permanent ileostomy. However, a recent population-based study from the UK demonstrated that the strategy of surgery as last resort may actually increase CUC-related mortality [66]. Furthermore, delay in surgery has been shown to increase postoperative complications [67]. Clearly surgery should not be relegated to this position, and ideally at the time of CUC diagnosis, referring gastroenterologists should refer patients to colorectal surgery not just for surgery but also for appropriate education in the event that they ultimately do require surgery. Demystification of surgery, and in particular of ostomy-related and post-IPAA lifestyle/functional concerns, can dramatically change patient perception of surgery and make it a more acceptable option. In addition to local or regional colorectal surgeons and Wound and Ostomy Care nurses, resources for patients include the Crohn's and Colitis Foundation of America literature, including camp Oasis for children and young adults with IBD, the American College of Surgeon's Ostomy Education series (available on YouTube®), as well as the recently developed CUC Medical Therapy and CUC Surgical Therapy (Emmi Solutions, Inc.) online educational modules.

VTE Prophylaxis

Perioperative venous thromboembolism (VTE) is known to be particularly prevalent in patients undergoing surgery for IBD due to decreased mobility and a pro-inflammatory state. The perioperative incidence is 2.7% in this population and is higher than the incidence among patients having colorectal resection (2.1%) [68]. Randomized studies support the use of extended VTE prophylaxis postoperatively after abdominopelvic cancer [69, 70]. The authors' preference is prophylaxis with enoxaparin 40 mg once daily for a total of 4 weeks postoperatively.

However, it is also well recognized that hospitalized *medical* CUC patients are also at increased risk of VTE, and there can be little doubt that some CUC patients who come to surgery bring to the table unrecognized preoperative VTE [71]. It is important that medical teams, including colorectal surgeons, who are caring for CUC patients are aware of this significantly increased risk and treat appropriately with aggressive ambulation and chemo-prophylaxis *before* surgery.

Anemia

Patients with CUC are also at increased risk for anemia, and similar to VTE represents an opportunity for preoperative prevention of postoperative complications. Oral ferrous sulfate (325 mg PO, two to three times daily) given with concurrent vitamin C (500 mg PO, two to three times daily) doubles the rate of iron absorption. Other adjuncts for oral anemia treatment in CUC include folic acid (1–2 mg per day PO), thiamine, or multivitamin supplements daily. For more severe cases, intravenous iron (Venofer, 100–300 mg per infusion) or transfusion of packed cells may be indicated. Erythropoietin is generally not indicated and may also be prothrombotic. Auto-transfusion is also typically not recommended because it will worsen the patients' existing anemia. In addition to the above treatments, nutritional optimization will aid in reversal of anemia. New, more effective forms of supplemental iron are expected in the very near future.

Nutrition

Protein-calorie malnutrition represents another preoperative comorbidity, which CUC patients may bring to the table that is recognizable, and usually treatable, in medically treated CUC patients. The most readily available markers of malnutrition include history of weight loss, serial office-based weight, and clinical indicators such as temporal wasting. Unfortunately, all of these may be confounded by steroid-induced water-weight gain; thus, serologic assessment has an increased role of importance in this patient population. Serum markers such as prealbumin and albumin are acute phase reactants and thus fluctuate based on the underlying inflammatory state. In the near future, radiographically assessed sarcopenia (lack of skeletal muscle) assessment using traditional MR or CT images with additional semi-automated tissue compartment assessment is likely to become an additional, practical tool (e.g., Slice-o-matic®, Materialize®, others) for use in this patient population.

For malnourished patients who are able to tolerate PO, nutritional supplementation 2–4 times per day with formulations for several weeks may stabilize and or reverse mild-to-moderate malnutrition. For patients with severe disease who may not be able to tolerate enteric supplementation, parental nutritional therapy is indicated. For the pre-surgical patient, peripherally inserted central access catheters (PICC) placed for TPN, especially if dual lumen, can be maintained and used for perioperative access as well; patients should be aware of the risk of line-sepsis and upper extremity DVT.

Medical Therapy for the Postsurgical Patient: Ileostomy and Pouch issues

A significant number of readmissions after surgery for CUC are for dehydration. Dehydration is more common in ostomates who are age >50 or who required diuretics prior to discharge [72]. Recent work has shown that ileostomy discharge carepaths, including educational materials and access to Wound and Ostomy Care Nurses, discharge coordinators, and social workers, can successfully decrease readmissions for dehydration [73]. A practical pathway of educations instructions to "thicken it up, and slow it down" using fiber, a BRAT diet, and over-the-counter Imodium, as well as instructions to eat salty foods and drinks, such as "potato chips and Gatorade®." The patient and family should also be educated about signs and symptoms of dehydration.

Pouchitis is an acute inflammatory state of the pouch that typically responds to oral antibiotics therapy. In some cases, pouchitis can be antibiotic dependent, and in others antibiotic refractory. Pouchitis must be differentiated from several other medical conditions: cuffitis, which is inflammation limited to the anal canal mucosal cuff left behind and which typically responds to topical Canasa, Crohn's enteritis—which is typically obvious endoscopically, and irritable pouch syndrome, which may be due to a fixed pelvic pouch or primary or secondary pelvic floor dysfunction. For additional pouch-related complications, please see Chap. 51.

A meta-analysis of treatments for pouchitis found that both ciprofloxacin and metronidazole were effective for inducing and maintaining remission of pouchitis in most patients [74]. There is some evidence that probiotics in the form of VSL#3 are effective for maintaining antibiotic-induced maintenance.

Pouch surveillance with flexible pouchoscopy is recommended annually to biannually, but pouch neoplasia is exceptionally rare, and its utility may be more for early diagnosis of Crohn's-like pouch changes; for patients with a Crohn's-like picture of the pouch, the authors prefer the term "*indeterminant pouchitis*". Random biopsies of the pre-pouch ileum, pouch body including afferent and efferent limb, and pouch-anal anastomosis and anal transition zone are recommended. Mild-to-severe pouch-anal anastomotic strictures can be dilated at the time of pouchoscopy with sedation, using either Hagar dilators or via pneumatic balloon dilation (Video 46-2).

Summary

Medical therapy will continue to be the mainstay of treatment for the vast majority of patients, and we should expect new, more efficacious agents, with varying side-effect profiles, to be released in the near future, as the etiology of CUC is elucidated.

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47
Medical Management of Crohn's Disease

Scott A. Strong

Key Concepts

- Crohn's disease is classified by age at diagnosis, disease location, and disease behavior.
- Disease severity is stratified using a clinical or endoscopic scheme that assesses symptoms and signs or endoscopic appearance, respectively.
- Medical therapy (e.g., 5-aminosalicylate compounds, glucocorticoids, immunomodulators, and biologic agents) should be approached in a "step-up" or "top-down" manner to balance efficacy and toxicity.
- 5-aminosalicylate compounds are of limited value in the induction and maintenance of remission.
- Glucocorticoids can successfully induce remission, but short- and long-term adverse effects largely limit their usage to management of acute episodes.
- Immunomodulators are of limited use for induction of remission, but successfully maintain remission in many patients.
- Biologic agents can induce and maintain remission in patients with moderate-to-severe disease, but the efficacy and safety varies among the different medications.
- Disease prophylaxis after surgery should be individualized according to the patient's risk for recurrence.

Introduction

The appropriate treatment of Crohn's disease includes a combination of medical and surgical therapy to safely resolve inflammation, lessen symptoms, improve quality of life, and minimize the risk for short- and long-term complications. Therapy is usually guided by the age of the patient, anatomic extent of inflammation, disease behavior, symptom severity, treatment response, and risk for adverse effects. Treatment can be intended to induce remission in patients with active disease or maintain remission in others. Operative intervention is generally reserved for patients with disease-related complications or disease that is refractory to medical therapy with the later indication being quite common. Consequently, it is important for the surgeon to understand the indications, dosing, benefits, and risks of the various types of medications used to treat intestinal Crohn's disease.

Disease Classification

Initial attempts to classify Crohn's disease were fraught with problems that instigated a World Congress of Gastroenterology Working Party to develop the Vienna classification [1] and its modification, the Montreal classification [2–4]. The Vienna scheme was prospectively designed to be a simple phenotypic classification system based on objective and reproducible clinical variables that include age at disease diagnosis, anatomic location of disease, and disease behavior. However, controlled trials showed that experts could not independently agree on disease phenotype using the Vienna classification [5]. Therefore, the Montreal classification introduced modifications within each of the variables, but did not alter the three primary categories (Table 47-1).

This newer classification system introduced a subgroup for patients with early onset of disease (i.e., ≤16 years of age) because several centers have demonstrated that specific genotypes or serotypes are more frequently found in early-onset Crohn's disease.

With respect to disease location, ileal disease is defined as involvement limited to the lower third of the small bowel with or without involvement of the cecum. Colonic disease is disease between the cecum and rectum without ileal disease. Ileocolonic disease is understood to be disease of the terminal ileum and colon. Upper gastrointestinal disease represents disease located proximal to the terminal ileum. Moreover, the upper gastrointestinal disease description can be used alone or as a modifier of the ileal, colonic, or ileocolonic subgroups because upper gastrointestinal disease is recognized to coexist with more distal disease.

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TABLE 47-1. Vienna and Montreal classification for Crohn's disease

	Vienna	Montreal
Age at diagnosis	A1 below 40 years	A1 below 16 years
	A2 above 40 years	A2 between 17 and 40 years
		A3 above 40 years
Location	L1 ileal	L1 ileal
	L2 colonic	L2 colonic
	L3 ileocolonic	L3 ileocolonic
	L4 upper	L4 isolated upper disease[a]
Behavior	B1 non-stricturing, non-penetrating	B1 non-stricturing, non-penetrating
	B2 stricturing	B2 stricturing
	B3 penetrating	B3 penetrating
		p perianal disease modifier[b]

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[a]L4 is a modifier that can be added to L1–L3 when concomitant upper gastrointestinal disease is present

[b]"p" is added to B1–B3 when concomitant perianal disease is present

The behavior variable is defined as inflammatory, stricturing, or penetrating behavior. Perianal disease is a separate subgroup because experts recognize that perianal fistulizing disease is not exclusively associated with intestinal penetrating disease.

Initial application of the Vienna classification to clinical practice showed that phenotype evolves over time for an individual patient [6–9]. Specifically, 80% of individuals with inflammatory disease ultimately exhibit stricturing or penetrating behavior, whereas only 15% of patients experience a change in anatomic location. Although the Montreal classification has demonstrated significant potential because of good interobserver agreement [10, 11], a system that combines genotype and phenotype characteristics will likely emerge as we better understand genetic linkages associated with Crohn's disease [12].

Disease Severity

Crohn's disease is caused by immune dysregulation that leads to chronic intestinal inflammation manifesting itself as symptoms including abdominal pain, bleeding, and diarrhea and signs such as anemia. Although medical therapy is targeted towards controlling inflammation, disease activity is commonly assessed by composite indices that largely measure symptoms and signs with the former preferred in everyday clinical practice. The traditional approach to monitoring therapy accordingly relies on the consequences instead of the causes of inflammation. The problem with this strategy is that substantial overlap exists between the symptoms of Crohn's disease and other conditions, such as adhesive disease, bacterial overgrowth, bile salt diarrhea, irritable bowel syndrome, and steatorrhea. Some clinicians now argue that the newer goals of therapy should include induction and maintenance of mucosal and histologic healing.

The Crohn's Disease Activity Index (CDAI) has long been the primary outcome measure used in clinical trials to study the impact of new medications for the treatment of Crohn's disease. Regressing 18 clinical items against a 4-point global rating of disease activity created the CDAI [13]. Eight independent predictors were identified including liquid/soft stool frequency, abdominal pain severity, general well-being, extraintestinal symptoms, need for antidiarrheal drugs, presence of an abdominal mass, hematocrit, and body weight. Regression coefficients for each of the eight predictors were ascertained to generate an overall CDAI score that ranges from 0 to 600. Benchmarks for disease activity were established as follows:

Clinical remission	CDAI <150
Mild disease	CDAI 150–219
Moderate disease	CDAI 220–450
Severe disease	CDAI >450

Clinical response has been subsequently defined as a reduction from the baseline score of more than 70–100 points. The majority of the CDAI score stems from items recorded in a symptom-based, 1-week diary (i.e., stool frequency, pain, well-being). Further studies have proven that the CDAI can be simplified to these patient-reported variables without a significant compromise in the instrument's responsiveness [14, 15].

The Harvey–Bradshaw Index (HBI) was derived to simplify calculation of the CDAI. The HBI consists of five descriptors including general well-being, abdominal pain, number of liquid stools, abdominal mass, and complications. Remission has been defined as a score of <5 [16]. A 3-point change in the HBI correlates with a 100-point change in the CDAI. An HBI ≤4 corresponds with a CDAI score ≤150 [17].

Clinicians have more recently attempted to use mucosal healing as a marker of disease activity with the thought that mucosal inflammation often precedes the onset of clinical symptoms. The Crohn's Disease Endoscopic Index of Severity (CDEIS) was accordingly created using regression modeling and weighting of independent items that correlated with the global evaluation of lesion severity [18]. Four descriptors (i.e., superficial ulceration, deep ulceration, ulcerated stenosis, and non-ulcerated stenosis) are summed with the estimated extents of both ulcerated and diseased areas in each examined segment (i.e., ileum, right colon, transverse colon, left colon, rectum). The total CDEIS score ranges from 0 to 44. Complete endoscopic remission has been somewhat arbitrarily defined as a score of <3, endoscopic remission as a score of <6, and endoscopic response as a decrease of >5 points [19]. Mary and others (1989) have argued different scores, and the tool remains incompletely validated with an undefined responsiveness to change despite being associated with a high level of interobserver agreement [20].

Just as the CDAI can be cumbersome for measuring clinical disease activity, the CDEIS has been argued as awkward. Consequently, a Simple Endoscopic Score in Crohn's Disease (SES-CD) was developed to overcome the unwieldy nature of the CDEIS [21]. The four descriptors selected from the CDEIS for use in the SES-CD are ulcer size, proportion of surface covered by ulcer, proportion of surface covered by other lesions, and stenosis. Each descriptor is graded 0–3 and is scored in five segments (i.e., ileum, right colon, transverse colon, left colon, rectum). The total score is calculated as the sum of all the items in each segment and can range from 0 to 60. The SES-CD demonstrates a high degree of interobserver agreement and well correlates with the CDEIS. Benchmarks for disease activity have been described as follows:

Remission	0–2
Mild inflammation	3–6
Moderate inflammation	7–16
Severe inflammation	>16

Unfortunately, both the CDEIS and SES-CD demonstrate a weak correlation with the CDAI [21–23], and legitimate grading of disease activity remains an unresolved issue. This shortcoming is underscored by concerns that no valid patient- or clinician-reported outcome instruments have yet been created according to criteria established by the US Food and Drug Administration. In fact, the Food and Drug Administration recently indicated that the CDAI is no longer acceptable as a measure of disease activity in clinical trials related to Crohn's disease [24].

Medications

Probiotics, antibiotics, 5-aminosalicylate compounds, glucocorticoids, immunomodulators, and biologic agents are all therapies approved by the US Food and Drug Administration for the treatment of Crohn's disease depending upon the clinical scenario. Each drug within these therapeutic groups is distinguished by dosing parameters, short- and long-term side effects, and expected response intervals. Before initiating therapy with any medication, patients should be comprehensively counseled about these characteristics. Moreover, objective criteria for disease response should be initially discussed and then measured after a reasonable time interval. If the desired response is not achieved, prohibitive side effects ensue, or noncompliance transpires, the drug has failed, and another medication should be trialed. When all suitable medical management has proven unsuccessful, operative intervention is generally indicated. The continuation of ineffective drug therapy risks the development of further disease complications that may adversely impact surgical outcome.

Some patients will instead seek an operation before trialing all available medical modalities because they have concerns regarding the alternative drug(s). Interestingly, a survey of outpatients with Crohn's disease, gastroenterologists, and colorectal surgeons quantified this behavior [25].

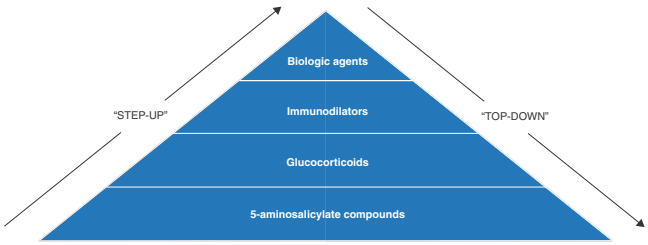

FIGURE 47-1. "Step-up" versus "top-down" models of therapy.

Participants were interviewed to measure their preferences for six scenarios by using a prospective preference measure, and significant differences were seen between patients and gastroenterologists for three of six scenarios. Although 72% of gastroenterologists were willing to gamble life expectancy to avoid a laparoscopic ileocolic resection, only 36% of colorectal surgeons and 37% of patients were willing to similarly gamble. Conversely, 85% of patients were willing to gamble to avoid a proctocolectomy and permanent ileostomy compared to 75% of surgeons and 91% of gastroenterologists.

The current model for the medical treatment of Crohn's disease is referred to as "step-up" therapy whereby patients are initially managed with drugs associated with fewer side effects, but might not be as effective as more potent medications linked with greater potential for toxicity. If the initial treatment fails, therapy will be escalated using stronger drugs with the process repeated until the disease is adequately managed or an operation is warranted. The patient's relative severity of disease dictates which therapeutic group is initially trialed. However, debate exists as to whether an alternative approach should be employed. The "top-down" method is predicated on the hypothesis that using more effective medications from the outset may alter the natural history of Crohn's disease while reducing the likelihood for disease exacerbations, hospitalizations, and operations. As we gain an enhanced understanding of the disease and identify risk factors associated with a more aggressive disease behavior, we will be better positioned to use an individualized approach that finds an acceptable balance between efficacy and toxicity (Figure 47-1).

Probiotics

Probiotics are beneficial microorganisms that can potentially impact the gut's microbiota composition, metabolic activity, and immunomodulation to confer host benefit. These bacteria and fungi can alter microbial diversity through competitive inhibition of other microbes, enhance mucosal barrier function via the production of short chain fatty acids, and interact with intestinal dendritic cells to instigate an anti-inflammatory response. The microorganisms must be of human origin, nonpathogenic, and able to survive the gastrointestinal transit in

order to be beneficial. Unfortunately, recent meta-analyses suggest that probiotics are ineffective for both the induction and maintenance of remission in patients with Crohn's disease [26–28].

Antibiotics

Antibiotics are felt to benefit patients with Crohn's disease through the inhibition of pathogenic bacteria and reduction of overall bacterial burden. The principal shortcomings associated with antibiotic therapy include lack of specificity associated with therapy, poor insight as to which bacteria should be targeted, and the potential for antibiotic resistance. The majority of studies demonstrate improvement with antibiotics only when disease is limited to the colon [29]. Metronidazole, which is active against anaerobic bacteria and some parasites, and ciprofloxacin, especially active against *Enterobacteriaceae* and *Escherichia coli*, are the most frequently used antibiotics. Multiple randomized clinical trials employing metronidazole or ciprofloxacin for induction of disease remission have suggested that metronidazole is effective for active colonic and ileocolonic disease, but not upper gastrointestinal tract inflammation [30]. Five randomized controlled studies evaluating the efficacy of ciprofloxacin alone or in association with metronidazole for active Crohn's disease have yielded mixed results [30].

A recent meta-analysis reviewed trials that compared antibiotic therapy prescribed for at least 3 months duration with placebo; outcomes were defined as remission in patients with active disease and relapse in patients with inactive disease [31]. Sixteen trials examining 13 treatment regimens in 865 patients were included. Three trials of nitroimidazoles demonstrated benefit with a combined odds ratio of 3.54 [95% confidence interval (CI), 1.94–6.47] and four trials of clofazimine had an odds ratio of 2.86 (95% CI, 1.67–4.88). For patients receiving nitroimidazoles, the number needed to treat was 3.4 (95% CI, 2.3–7.0) and 6.1 (95% CI, 5.0–9.7) for patients with active and inactive disease, respectively. The corresponding numbers for clofazimine were 4.2 (95% CI, 2.7–9.3) and 6.9 (95% CI, 5.4–12.0). A separate review found that rifamycin derivatives, which are minimally absorbed and active against gram-positive and gram-negative bacteria either alone or in combination with other antibiotics, have a significant impact related to inducing remission in active Crohn's disease [32]. None of these antibiotics are specifically approved by the US Food and Drug Administration for the treatment of Crohn's disease.

Metronidazole therapy is associated with several side effects that are dose dependent and occur in up to one-half of patients. These include gastrointestinal intolerance, headaches, metallic taste, and vertigo. Peripheral neuropathy is a rare complication, but may be irreversible. Side effects linked to clofazimine include abnormal pigmentation, gastrointestinal upset, and pruritus from clofazimine crystal deposits. Rifaxamin has been associated with gastrointestinal intolerance, headaches, and rectal tenesmus.

5-Aminosalicylate Compounds

A number of 5-aminosalicylate (ASA) compounds are available with active 5-ASA released at various locations throughout the intestinal tract depending on the design of each specific drug. These compounds work by activating a class of nuclear receptors involved in the control of apoptosis, cell proliferation, inflammation, and metabolic function. These gamma forms of the peroxisome proliferator-activated receptors are found at particularly high levels in colon epithelial cells, where their expression appears to be at least partially stimulated by gut bacteria. Sulfasalazine is the original 5-aminosalicylate and is compromised of 5-ASA bound to a sulfapyridine moiety that detaches when the drug reaches the bacteria of the colon. Sulfasalazine has a number of side effects due to the sulfapyridine moiety, including symptoms such as gastrointestinal upset and headaches. Rare side effects include bone marrow suppression, fever, hemolytic anemia, hepatitis, hypersensitivity reactions, pancreatitis, pneumonitis, and rash. Patients who take sulfasalazine must also take folic acid (1 mg daily) because the medication depletes folic acid stores.

These agents were once a mainstay in the medical management of Crohn's disease, but are now rarely recommended for disease treatment [33, 34]. A recent meta-analysis looked at six placebo-controlled randomized controlled trials with standard criteria in defining clinical remission (CDAI < 150) [35]. The trials included 910 patients with active Crohn's disease treated by 5-ASA compounds for 6–17 weeks. Remission of disease was not achieved in 68% of 5-ASA group compared to 74% of patients allocated to placebo (relative risk of failure: 0.89; 95% CI, 0.80–0.99). The number needed to treat to obtain clinical remission was 11. Furthermore, the role of 5-ASA as a maintenance medication is equivocal at best and clearly of no benefit in patients with glucocorticoid-induced remission [36]. In the previously mentioned meta-analysis, 11 trials of 5-ASA compounds versus placebo or control therapy in quiescent disease revealed 53% of the 5-ASA patients relapsed compared with 57% of the controls (relative risk: 0.94, 95% CI, 0.87–1.01) [35].

Glucocorticoids

Glucocorticoid drugs were first used for the management of Crohn's disease several decades ago and their benefit originates from an ability to modulate the immune response, inhibit expression of adhesion molecules, and decrease trafficking of inflammatory cells to the intestine. However, the traditional glucocorticoids are associated with significant

short- and long-term adverse effects that limit their usage to management of acute episodes. Budesonide, a glucocorticoid with an extensive first-pass metabolism, was consequently developed because it maximizes the amount of glucocorticoid locally available in the distal ileum and proximal colon, but theoretically has minimal systemic accessibility making it ideal for the treatment of ileocolonic Crohn's disease.

Prednisone is generally prescribed in dosages of 40–60 mg daily for 2–6 weeks to induce remission, although no appropriate dose-ranging studies have been performed. The daily prednisone dose is then tapered by 5–10 mg/week until a level of 20 mg daily is reached. The daily dosage is thereafter reduced by 2.5–5 mg weekly until discontinuation of the medication. Budesonide is started at 9 mg daily for up to 8 weeks with courses repeated for recurring episodes of active disease. Once symptoms are controlled, the drug is tapered to 6 mg daily for maintenance tapering to complete cessation attempted if symptom control is maintained for 3 months.

Resistance and dependency are major concerns when treating patients with glucocorticoids. On average, one-half of patients treated for active symptoms with a glucocorticoid will be "steroid resistant" or "steroid dependent" [37, 38]. Studies further suggest that younger patients, smokers, and those with colonic disease are at highest risk of becoming dependent on glucocorticoid therapy [39]. The occurrence and severity of most side effects are related to the dose and duration of treatment. Common findings include abdominal striae, acne, cataracts, fluid retention, glaucoma, hyperglycemia, hypertension, insomnia, mood disturbances, moon facies, and weight gain. Musculoskeletal complications, such as myopathy, osteonecrosis, and osteoporosis, are additional side effects. Lastly, adrenal suppression can occur during the course of treatment and contribute to physiologic dependence.

A recent meta-analysis limited to randomized controlled trials identified two trials using standard oral glucocorticoids to induce remission in active Crohn's disease that included a total of 267 patients [40]. Overall, 53 of 132 patients (40%) assigned to oral glucocorticoids failed to achieve remission compared with 93 of 135 (69%) prescribed placebo. Moreover, the number needed to treat to achieve remission in one patient with standard glucocorticoids was 3 (95% CI, 2–11). The same analysis reported the effect of budesonide on active disease after reviewing two trials involving 458 patients with ileal, ileocolonic, or right-sided colonic disease [35]. They found that 192 of 351 patients (55%) randomized to budesonide failed to achieve remission compared with 81 of 107 (76%) receiving placebo. The number needed to treat with budesonide to achieve remission in one patient was 5 (95% CI, 3–9). One trial reported the rates of adverse events that were thought to be glucocorticoid related; identical proportions (26%) in both treatment arms experienced an event. Another six trials directly compared standard glucocorticoids to budesonide in patients with active disease involving the ileum, ileocolon, or right colon. Overall, 116 of 304 patients (38%) receiving standard oral glucocorticoids failed to achieve remission compared with 173 of 365 (47%) managed with oral budesonide. The number to treat with standard oral glucocorticoids compared with budesonide to achieve remission in one patient was 11 (95% CI, 6–50). However, 62% of patients treated with standard glucocorticoids experienced glucocorticoid-related adverse events compared with only 37% of patients prescribed budesonide; the number needed to harm was 4 (95% CI, 3–6).

Although traditional glucocorticoids are not used for maintenance therapy, the role of budesonide has been evaluated in selected patients. Budesonide has been compared to placebo in five randomized controlled trials containing 559 patients with at least 70% of patients afflicted with isolated ileal disease [40]. Overall, 200 of 319 patients (63%) randomized to oral budesonide experienced a relapse of disease activity compared to 167 of 240 (70%) receiving placebo. When the efficacy of budesonide 6 mg daily was compared to 3 mg daily, no benefit was seen with the higher dose (59% versus 63%, respectively). In addition, the relative risk of glucocorticoid-related adverse events was significantly higher in budesonide-treated patients with a number needed to harm of 6 (95% CI, 4–25). Therefore, it appears that budesonide at any dose to maintain remission is no more effective than placebo, but significantly more toxic [41].

Immunomodulators

The thiopurines and methotrexate are immunomodulators that can be used to induce remission in patients with active disease, allow glucocorticoid tapering in patients with "steroid-resistant" or "steroid-dependent" disease, and maintain remission in patients with quiescent disease.

Thiopurines Azathioprine and 6-mercaptopurine (6-MP) are thiopurines with azathioprine being the precursor of 6-MP. Although their exact mechanism of action in patients with Crohn's disease is uncertain, they are known to cause immunosuppression by interfering with nucleic acid metabolism in the immunological sequence that follows antigenic stimulation. Azathioprine is prescribed at 2.0–2.5 mg/kg and 6-MP is dosed at 1.0–1.5 mg/kg for daily maintenance therapy. Clinical benefit may not be evident until 6–12 weeks after initiation of therapy, but tends to be durable. Genetic polymorphisms of thiopurine methyltransferase (TPMT), the primary enzyme responsible for 6-MP metabolism, have been identified and drug metabolite levels can be measured. These clinical assays allow monitoring and dosing of the medications according to measurements of the metabolites 6-thioguanine and 6-methylmercaptopurine. Prior to starting thiopurine therapy, TPMT enzyme activity or genotype should usually be determined because the drugs should be avoided in patients with TPMT deficiency. Patients with heterozygous genotype of intermediate activity should begin

therapy at reduced doses that are one-half the usual recommendations. If TPMT activity or genotype cannot be assayed in advance of initiating treatment, the drugs should be cautiously dosed at the outset with careful monitoring for leukopenia.

While the most common side effect linked to azathioprine and 6-MP is nausea, adverse events associated with these drugs include liver function abnormalities, leukopenia, and pancreatitis. Pancreatitis typically presents during the first 8 weeks of therapy, and reintroduction of either agent should be avoided because pancreatitis will likely recur. Routine monitoring of complete blood counts is recommended at 1–2 week intervals initially and subsequent to a dose change and then at least every 3 months thereafter to detect evidence of acute or delayed bone marrow suppression. Rare hypersensitivity reactions characterized by fever, liver dysfunction, and rash may occur. A slightly increased risk of lymphoma has also been reported [42, 43].

A recent review addressed the role of immunomodulators in inducing and maintaining remission in patients with Crohn's disease [44]. Five randomized controlled trials containing 380 patients compared azathioprine or 6-MP with placebo for the induction of remission [45]. The majority of studied patients had ileal or ileocolonic disease for at least 3–4 years and had previously received medical therapy or undergone an intestinal operation. Tapering doses of glucocorticoids were generally prescribed in both groups. Compared with placebo, thiopurine therapy showed a trend towards fewer failures to achieve remission at 12–17 weeks (relative risk: 0.87; 95% CI, 0.71–1.06).

Three randomized controlled trials evaluated maintenance of remission with azathioprine continuation versus azathioprine withdrawal. More patients maintained remission in the group that continued therapy than in the group that ceased treatment (relative risk of failure to prevent disease relapse: 0.39; 95% CI, 0.21–0.74) [31]. This translates into 201 fewer disease relapses per 1000 patients for those continuing azathioprine compared with azathioprine withdrawal.

Data related to the risk of serious infections were obtained from a large prospective, observational cohort study of 6273 patients with a mean follow-up of more than 5 years [46]. On multivariate analysis, thiopurine therapy was associated with a trend towards an increase in serious infections (adjusted odds ratio: 1.23; 95% CI, 0.96–1.57). Patients treated with thiopurines had ten more serious infections per 1000 patients compared with patients who were not managed with thiopurines.

Methotrexate Methotrexate and its polyglutamate metabolites are folic acid analogues that demonstrate inhibitory activity against many enzymes in the metabolic pathway of folic acid. Chronic low-dose methotrexate therapy inhibits the production of thymidylate, purines, and methionine and leads to the accumulation of adenosine, a potent anti-inflammatory purine nucleoside. These actions decrease formation of antibodies, inhibit cellular proliferation, and reduce the production of inflammatory mediators. Methotrexate (25 mg) is weekly administered by subcutaneous or intramuscular injection. Folic acid (1 mg daily) should be concomitantly prescribed. After remission has been achieved, a dose of 15 mg weekly may be effective. The most frequent side effects reported with methotrexate are gastrointestinal upset and stomatitis. Leukopenia can also occur, but much less frequently than seen with thiopurine therapy. Rare complications of methotrexate therapy include hepatic fibrosis and hypersensitivity pneumonitis.

Two randomized controlled trials have compared methotrexate with placebo for the induction of remission. Compared with controls, a trend towards fewer failures of remission was seen with methotrexate versus placebo (relative risk: 0.82; 95% CI, 0.65–1.03) [45]. Accordingly, methotrexate therapy results in 143 fewer failures per 1000 patients compared to placebo. Another two randomized controlled trials examined the utility of methotrexate in patients with quiescent disease. A pooled analysis reported that methotrexate therapy was associated with fewer relapses (relative risk: 0.74; 95% CI, 0.54–1.0), and methotrexate therapy would result in 168 fewer relapses compared with placebo. Unlike the experience with thiopurines, there is insufficient data to determine the risk of infection and lymphoma in patients with Crohn's disease treated with maintenance methotrexate.

Three small randomized controlled trials have compared methotrexate with thiopurines for the induction of remission. In general, methotrexate failed to show or exclude a beneficial or detrimental effect on failure of remission at 24–36 weeks (relative risk: 1.17; 95% CI, 0.82–1.67) [47]. However, methotrexate therapy would be expected to produce 68 more failures of remission per 1000 patients compared to thiopurine treatment.

Moderate quality evidence indicates that methotrexate at a dose of 15 mg weekly is superior to placebo for maintenance of remission in Crohn's disease and appears to be safe [48]. Conversely, low-dose oral methotrexate (12.5–15 mg/week) does not appear to be effective for maintenance of remission.

Biologic Agents

Anti-tumor necrosis factor (TNF) agents The anti-TNF agents are designed to block the effects of TNFα, and three such medications (i.e., infliximab, adalimumab, certolizumab pegol) are currently approved for the treatment of Crohn's disease. Infliximab is permitted for the treatment of moderate-to-severe Crohn's disease that does not respond to standard therapies. Adalimumab is accepted for the treatment of moderate-to-severe disease that does not respond to con-

ventional medications and for patients who have lost response to or are intolerant of infliximab. Certolizumab was approved for therapy in patients with moderate-to-severe disease who have failed conventional treatment.

Infliximab (5 mg/kg) is parenterally administered and usually well tolerated. After the initial infusion of infliximab, patients are generally administered another dose 2 and 6 weeks later and then at consistent 8-week intervals. If patients lose their initial response to infliximab, the medication dose can be increased (10 mg/kg) or the interval between infusions can be decreased (every 6 weeks). Infusion reactions are not uncommon, and most are successfully managed without discontinuing the infusion or preventing further use of infliximab.

Adalimumab (40 mg) is given as a single subcutaneous injection every other week after an initial induction regimen of four injections the first week and two during the third week. Although adalimumab may prove highly effective in the initial treatment stages, some patients lose response over time and the medication may need to be administered each week. Certolizumab (400 mg) is indicated for inducing or maintaining a clinical response in patients with moderate-to-severe disease who have had an inadequate response to conventional therapy. The drug is given by subcutaneous injection initially and at weeks 2 and 4. If the disease responds, the injections continue every four weeks.

Side effects associated with the anti-TNF agents are well recognized and include an increased risk of infections, such as tuberculosis, as well as autoimmune reactions, heart failure, liver dysfunction, lymphoma, and multiple sclerosis. Ongoing infection is an absolute contraindication to treatment with any TNF inhibitor. Prior to initiating treatment with an anti-TNF agent, patients should be screened to assure that they do suffer from occult infection secondary to hepatitis B or tuberculosis.

Integrin receptor antagonists Natalizumab is indicated for inducing and maintaining clinical response and remission in patients with moderate-to-severe Crohn's disease who have demonstrated an inadequate response to or are unable to tolerate conventional therapies and anti-TNF agents. Natalizumab (300 mg) is intravenously infused every 4 weeks. If patients have not experienced a therapeutic benefit by 12 weeks of induction therapy or cannot discontinue glucocorticoids within 6 months of starting therapy, the drug should be discontinued. Natalizumab should not be used in combination with immunomodulators or anti-TNF medications due to the risk of developing progressive multifocal leukoencephalopathy.

Vedolizumab is another integrin receptor antagonist indicated for patients with moderate-to-severe who have failed glucocorticoid or immunomodulator therapy. After an initial infusion of vedolizumab (300 mg), patients are administered another dose 2 and 6 weeks later and then at consistent 8-week intervals. If patients have not experienced a therapeutic benefit by 14 weeks of induction therapy or cannot discontinue glucocorticoids within 6 months of starting therapy, the drug should be discontinued.

A recent systematic review of randomized controlled trials compared these biologic agents with placebo or one another for inducing and maintaining clinical remission in patients with moderate-to-severe disease [48]. Of the 17 randomized controlled high-quality trials comparing six biologic agents with placebo in biologic-naïve patients, network meta-analysis revealed that infliximab and adalimumab, but not certolizumab pegol, natalizumab, and vedolizumab, were more likely to induce remission than placebo. Similar results were observed for maintenance of remission (Table 47-2). Infliximab showed the greatest probability of being ranked as the most effective agent for induction of remission and adalimumab for maintenance of remission at 86% and 48%, respectively. Unfortunately, few comparative efficacy studies exist.

TABLE 47-2. Pooled relative risk of inducing and maintaining remission with biologic agents in biologic-naïve patients with moderate-to-severe disease

		Remission induction		Remission maintenance	
Biologic agent	Usual maintenance dose	Relative risk	95% CrI	Relative risk	95% CrI
Infliximab	5 mg/kg IV every 8 weeks	6.11	2.49–18.29	3.31	0.98–14.01
Adalimumab	40 mg SQ every 2 weeks	2.98	1.12–8.18	5.16	1.78–18.00
Certolizumab	400 mg SQ every 4 weeks	1.48	0.76–2.93	2.26	0.38–13.57
Natalizumab	300 mg IV every 4 weeks	1.36	0.69–2.86	4.26	0.71–25.49
Vedolizumab	300 mg IV every 8 weeks	1.40	0.63–3.28	2.20	0.37–13.54

SQ subcutaneous, *CrI* credible interval, *IV* intravenous

With permission from Singh S, Garg SK, Pardi DS, Wang Z, Murad MH, Loftus EV Jr. Comparative efficacy of biologic therapy in biologic-naïve patients with Crohn disease: a systematic review and network meta-analysis. Mayo Clin Proc. 2014;89:1621–35. © Elsevier 2014 [47]

Induction and Maintenance of Remission

Several guidelines have been published that detail recommendations for the induction and maintenance of active Crohn's disease based on disease location and severity [33, 49–52]. As discussed earlier, the long-term use of glucocorticoids, including budesonide, is associated with unacceptable side effects and they cannot be safely used for chronic therapy. Thiopurines and methotrexate should not be offered as monotherapy, but may be added to glucocorticoid therapy when two or more disease flares have occurred in a 1-year period or the glucocorticoid cannot be tapered. Biologic agents are commonly prescribed when a patient's disease is steroid resistant or dependent. In most instances, anti-TNF therapy should be used only after active disease has been objectively confirmed by laboratory tests (e.g., C-reactive protein), imaging studies, or endoscopy.

A recent meta-analysis identified 39 randomized controlled trials comparing thiopurines, methotrexate, infliximab, adalimumab, certolizumab, vedolizumab, or combined therapies with placebo or an active agent for the induction and maintenance of remission in patients with Crohn's disease [53]. They reported that infliximab, the combination of infliximab plus azathioprine, adalimumab, and vedolizumab were superior to placebo for the induction of remission in active disease. In comparisons of anti-TNF agents, infliximab plus azathioprine and adalimumab alone were superior to certolizumab for induction of remission. In addition, all treatments were superior to placebo for maintaining remission, except for the combination of infliximab plus methotrexate. Infliximab, infliximab plus azathioprine, and adalimumab were superior to a thiopurine alone for maintenance of remission. Infliximab plus azathioprine and adalimumab alone were superior to certolizumab, and adalimumab was superior to vedolizumab.

Induction of Remission

Mild disease Mildly active Crohn's disease limited to the ileum is best managed with budesonide (9 mg daily); mesalamine and antibiotics in this setting are associated with minimal and no benefit, respectively. Some selected patients with ileal disease and only mild symptoms can be appropriately managed with no medical therapy. For mild disease of the colon or ileocolon, sulfasalazine or systemic glucocorticoids can be used. Extensive upper gastrointestinal Crohn's disease should be treated with systemic glucocorticoids and immunomodulators. Patients with clinical features indicative of a poor prognosis should be offered thiopurines, methotrexate, or anti-TNF therapy used alone or in combination.

Moderate disease Moderately active disease of the ileum should be treated with budesonide (9 mg/day) or systemic glucocorticoids. Antibiotics should be added if features of localized sepsis are noted. Systemic glucocorticoids plus an immunomodulator is also a viable alternative. Anti-TNF therapy should be considered as an option for patients with active disease that has previously been steroid resistant or dependent.

Moderately active colonic disease should be treated with systemic glucocorticoids. Anti-TNF therapy with or without thiopurines or methotrexate is an appropriate option for patients who have relapsed with moderately active disease. For some patients with only occasional relapsing disease, reintroduction of glucocorticoids with an immunomodulator may be more appropriate. Before initiating anti-TNF or immunomodulator therapy, surgical options should be discussed with the patient.

Extensive, moderately active upper gastrointestinal disease should be handled with systemic glucocorticoids and immunomodulators. For patients who have relapsed, anti-TNF therapy with or without thiopurines or methotrexate is an appropriate option. Surgical management should be considered and discussed at an early stage.

Severe disease Severely active ileal Crohn's disease should be initially managed with systemic glucocorticoids. For patients who have relapsed, anti-TNF therapy with or without an immunomodulator is an appropriate alternative. However, patients with infrequently relapsing disease may be best treated with glucocorticoids in combination with an immunomodulator. Surgery is also a reasonable option for some patients and should be discussed.

Severe disease of the colon may be treated with systemic glucocorticoids. Patients who have relapsed can be appropriately handled with anti-TNF therapy with or without an immunomodulator, but glucocorticoids with an immunomodulator may be warranted if the disease is infrequently relapsing. Before initiating thiopurine, methotrexate, or anti-TNF therapy, surgical options should be discussed with the patient.

Extensive upper gastrointestinal Crohn's disease should be managed with systemic glucocorticoids and immunomodulators. For patients who have relapsed, anti-TNF therapy with or without immunomodulators is an appropriate option. Surgical alternatives should also be considered and discussed at an early stage. Patients who demonstrate clinical features predictive of a poor prognosis seem to be the most suitable candidates for early introduction of anti-TNF therapy and thiopurines.

Maintenance of Remission

If remission of an initial presentation has been achieved with a glucocorticoid, a thiopurine or methotrexate should be considered, but no maintenance treatment is an option for some patients. If a patient has a relapse, escalation of the maintenance treatment can be considered. Surgery should always be considered as an option in localized disease. Oral 5-ASA compounds have not been consistently proven effective in maintenance of remission.

Patients who relapse on thiopurine should be evaluated for therapy adherence and have their dose escalated according to 6-thioguanine and 6-methylmercaptopurine concentrations or until leukopenia develops. A change in their maintenance therapy to methotrexate or an anti-TNF agent is an alternative, and surgery should always be considered as an option in localized disease.

If remission has been achieved with an anti-TNF agent, maintenance with regular anti-TNF therapy should be offered. Patients in a scheduled-treatment regimen with regular infliximab infusions appear to do better compared to patients managed using an episodic strategy. Thiopurine monotherapy may be also considered if the patient is naïve to thiopurines. However, combination therapy with infliximab plus a thiopurine is of greater efficacy in achieving and maintaining glucocorticoid-free remission than either infliximab or thiopurines used alone in patients naïve to both medications. Some clinicians feel that patients managed with long-term anti-TNF agents should have their disease annually assessed to determine whether ongoing therapy is still clinically justified.

The relapse rate following immunomodulator cessation in patients receiving immunomodulator monotherapy for maintenance of remission is nearly 20% at 1 year [54]. In patients receiving an immunomodulator plus infliximab for at least 6 months, the relapse rate following discontinuation of the immunomodulator seems to be equivalent to the risk of relapse in patients maintained on combination therapy at 20% over 2 years. However, cessation of the anti-TNF agent in combination therapy is associated with a 50% recurrence rate after 2 years. These findings suggest that a deescalating treatment strategy should be largely limited to patients with a high risk for severe adverse events and patients in deep remission. Deep remission for a patient on maintenance thiopurine is often considered 4 years of remission, while the most appropriate duration of treatment with methotrexate or anti-TNF agents is unknown.

Medical Prophylaxis After Surgery

The cumulative risk for surgery in patients with Crohn's disease is estimated to be 16%, 33%, and 47% at 1, 5, and 10 years, respectively [55]. Endoscopic recurrence has been reported in 54% of patients at 5 years, and clinical recurrence follows endoscopic recurrence with a prevalence of 28–45% by 5 years [56]. Clinicians have accordingly attempted to use medical therapy to prevent this almost inevitable recurrence of disease, and a recent view summarized 21 trials comprised of more than 2000 patients comparing seven treatment strategies to placebo.

Antibiotics, immunomodulator monotherapy, immunomodulator plus antibiotics, and anti-TNF monotherapy but neither mesalamine nor budesonide reduced the risk of endoscopic recurrence [57]. Similarly, antibiotics, mesalamine, immunomodulator monotherapy, immunomodulator plus antibiotics, and anti-TNF monotherapy but not budesonide reduced the risk of clinical recurrence. Overall, anti-TNF monotherapy was the most effective pharmacologic intervention for postoperative prophylaxis, as evidenced by large effect sizes relative to all other strategies. Moreover, the relative risk of medication discontinuation as a result of adverse events did not significantly differ between antibiotics, immunomodulator monotherapy, immunomodulator plus antibiotics, and anti-TNF monotherapy.

Conclusions

Crohn's disease is a complex inflammatory condition of the intestine that is best managed through collaboration among the patient, physician, and surgeon. Medical therapy is commonly the first-line treatment and typically managed by the physician, but the surgeon must be familiar with the medications and their characteristics to understand when operative intervention is in the patient's best interest. While most patients are currently treated in a step-up manner, a top-down approach is gaining support in an effort to alter the disease's long-term outcome. This change in strategy coupled with the development of new medications directed at specific molecular targets will likely lead to a reduced need for operative intervention for patients suffering from this potentially debilitating disease.

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48
Anorectal Crohn's Disease

Stephen R. Gorfine

Key Concepts

- Crohn's disease is an incurable inflammatory condition of unknown cause that can involve any portion of the GI tract. Anorectal involvement is estimated to occur in 25–35 % of cases.
- Common manifestations of anorectal Crohn's disease include skin tags, abscesses, fissures, ulcers, fistulas, and strictures. Cancers, both adenocarcinomas and squamous carcinomas, are also possible, occurring with more frequency than that seen in the general population.
- Evaluation of the Crohn's patient with anorectal disease usually involves examination under anesthesia and imaging studies such as pelvic MRI or ERUS in addition to colonoscopy, enterography, and laboratory studies.
- Any undrained sepsis must be addressed promptly. Incision and drainage of abscesses and placement of drains or setons under general anesthesia are often required.
- Once sepsis has been controlled, medical therapy, which usually includes antibiotics, immunomodulators, and biologics, in combination or as single agents, is generally instituted. Corticosteroids are ineffective in anorectal Crohn's disease and should be avoided. Close collaboration with the medical team is mandatory.
- Fistulizing anorectal Crohn's disease occurs commonly. Fistulas are classified as simple or complex. Simple fistulas can often be treated by lay-open fistulotomy. Complex fistulas are usually treated medically with biologics, often in combination with immunomodulators. Surgical management of complex fistulas can include permanent seton, fibrin glue, fistula plug, endorectal advancement flap, and LIFT procedure. Surgical interventions should be used judiciously as these incur a risk of incontinence and nonhealing wounds.
- Long-standing fistula tracts and strictures should be routinely biopsied to exclude malignant degeneration. Cancers, when found, are generally treated in the same manner as those found in the general population. Total proctocolectomy is a consideration in a patient with extensive Crohn's colitis of long duration found to have a rectal adenocarcinoma.
- Diversion and/or proctectomy are required in about 10–20 % of cases.

Introduction

Crohn's disease (CD) is an inflammatory condition of unknown etiology that can affect any portion of the GI tract. The terminal ileum is most commonly involved [1] and perianal disease occurs in about 25 % of cases. Crohn's disease was first described in 1932 [2]. The first association of ileitis with perianal disease was described by Bissell in 1934 [3] and confirmed by Penner and Crohn in 1938 [4]. Crohn's disease is marked by transmural inflammation of the affected portion of the gut.

Incidence and Natural History

Perianal Crohn's disease is defined as inflammation at or near the anus. Various perianal lesions are commonly associated with Crohn's disease. These include external tags, fissures, ulcers, abscesses, fistulas, and strictures. Anal cancer, either adenocarcinoma or squamous carcinoma, may also complicate perianal CD. Symptoms of perianal CD include pain, bleeding, drainage, and incontinence. Risk factors for perianal involvement include colonic and especially rectal disease and young age at CD onset [5–7]. Hellers et al. reported that 12 % of patients with small bowel CD had perianal disease [8]. The same report showed that 41 % of patients with CD colitis with rectal sparing and more than 90 % of patients with colitis and rectal involvement had perianal disease [8]. The incidence of perianal CD occurring in the pediatric population has been estimated to be between 14 and 62 % [9].

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In the majority of cases, intestinal manifestations of Crohn's disease will precede anorectal involvement. However, in a small number of patients, perianal disease will be the first manifestation of CD [10]. The presence of perianal disease suggests a more aggressive CD phenotype [11]. The natural history of perianal CD depends upon the type of disease present. Simple fissures and ulcers are often amenable to medical treatment. Superficial fistulas can usually be resolved by simple surgical techniques. Complex fistulas, destructive ulcers, and stenosis often present therapeutic challenges that may be solved only by anoproctectomy. CD patients who have perianal involvement generally fare less well than those who do not. Perianal disease is associated with more disability [11], more frequent extra-intestinal manifestations [12], and more steroid resistance [13].

Etiology

The cause of Crohn's disease is unknown. The reason for a predilection for perianal involvement is also unclear. There appears to be an underlying autoimmune process based upon genetic predisposition and microbiota influence that is responsible for perianal involvement in CD patients. Genetic factors associated with fistulas and abscesses have been associated with specific gene variants at the susceptibility locus on chromosome 5q31 (IBD5), including OCTN [14] and IRGM [14–16]. OCTN and IRGM both play roles in the development and preservation of intracellular pathogen killing, among other functions. The association between NOD2/CARD15 genotype and perianal Crohn's disease has also been studied with no conclusive correlation established [6, 17]. The influence of various bacteria has also been studied. A variety of microorganisms have been associated with perianal disease, but none have been linked conclusively. Changes in the microbiota among patients with perianal CD may be primary phenomena or secondary changes.

Crohn's disease is characterized by a transmural inflammatory process which may lead to perforation, abscess, and fistula formation at the anus or at other intestinal locations. One postulated mechanism regarding the pathogenesis of perianal abscesses and fistulas hypothesizes that Crohn's-related inflammation causes a shallow mucosal ulceration which subsequently extends to deeper structures by the action of exposure to stool and the pressure of defecation [18]. A second hypothesis implicates infection of anal glands with penetration of the infective process beyond the intersphincteric space [19].

Anatomy

The anus is the most terminal portion of the gastrointestinal tract. It opens on the perineum distally and becomes the rectum proximally. It has two muscular layers, the internal and external anal sphincters. The internal sphincter is a continuation of the circular smooth muscle of the rectum. It is an autonomic structure, not under voluntary control. The external anal sphincter is a skeletal muscle, a continuation of the puborectalis and levator ani muscles. It is subject to voluntary control. The perianal skin is a stratified squamous epithelium, similar to hair bearing skin elsewhere on the body until it approaches the anal verge. At the anal verge, the pigmented, keratinized perianal skin of the buttocks becomes the anal canal epithelium, the anoderm, which is also pigmented and keratinized but does not have skin appendages (hair, sweat glands, and sebaceous glands). The surgical demarcation between the rectum above and the anal canal below is the anorectal ring, where the puborectalis muscle forms a sling around the posterior aspect of the anorectal junction.

The anal canal is about 4–5 cm in length. The dentate line, a scalloped demarcation formed by the anal valves at the inferior-most ends of the anal columns, is located about 1–2 cm proximal to the anal verge. The anoderm changes from stratified squamous epithelium of the perianal skin of the anal verge to the columnar epithelium of the rectum at a point just proximal to the dentate line. This area is called the anal transition zone. The anal glands, located within the intersphincteric space, drain into the anal crypts. The anal crypts are located at the distal end of the columns of Morgagni, which are 6–10 longitudinal mucosal folds in the upper part of the anal canal (Fig. 48.1).

The anal or hemorrhoidal cushions are present in the left lateral, right anterolateral, and right posterolateral positions. These cushions contain fibromuscular connective tissue as well as branches of the middle and inferior rectal arteries. The ischiorectal fossae are located lateral to the anal canal below the pelvic diaphragm. In men, the prostate and seminal vesicles and the vagina and cervix in women lie anteriorly to the anal canal separated by Denonvilliers fascia. Posteriorly the anococcygeal ligament communicates with the presacral fascia of Waldeyer. The entire anal canal is completely extra-peritoneal.

Clinical Presentation

Perianal Crohn's disease is manifest as five, often overlapping, conditions. These are anal skin tags, tissue destruction in the form of fissures and ulcers, infective complications consisting of fistulas and abscesses, anorectal strictures, and anorectal cancers. Clinical manifestations are exceedingly variable ranging from mildly bothersome anal tags to destructive perianal lesions causing sepsis and incontinence.

Diagnosis

In order to effectively manage perianal Crohn's disease an understanding of the extent of intestinal disease is required. In addition to a history and physical exam, including a thorough anorectal exam, when possible, a colonoscopy and

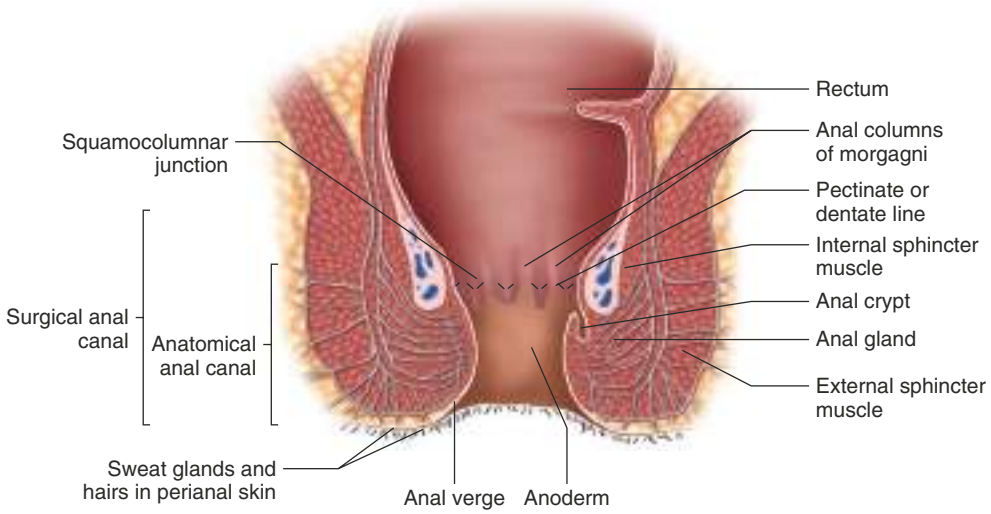

FIGURE 48-1. Anal anatomy.

small bowel evaluation, usually by CT enterography, will be required. The anorectal exam usually includes inspection of the anus and perianal areas, digital anorectal exam, and anoproctoscopy. This exam may be limited by patient discomfort and examination under anesthesia (EUA) may be required.

In the evaluation of perianal abscess and fistulous disease, a combination of magnetic resonant imaging (MRI) of the pelvis, endorectal ultrasound (EUS), and exam under anesthesia has been shown to yield 100 % diagnostic accuracy [20]. These exams, in combination, have gained increasing importance in arriving at management decisions. EUA involves inspection, palpation, and probing of fistulous tracts as well as anoproctoscopy with rigid or flexible instruments. The source of fistulous disease may be aided by the injection of dilute hydrogen peroxide into the external fistulous openings and observing the anal canal for bubbling. Alternatively, intra-operative EUS may also be augmented by injection of hydrogen peroxide.

Classification

In 1978, Hughes [18] proposed an anatomic and pathologic classification for perianal Crohn's disease (the Cardiff classification, later modified [21]) in which each major manifestation of perianal Crohn's disease (ulceration, fistula, and stricture) is graded on a scale of 0–2 (0, absent; 2, severe); fistulas are classified as low (not extending above the dentate line) or high (extending above the dentate line, sometimes to the levator muscles), and other associated anal conditions, the intestinal location of other sites of Crohn's disease, and a global assessment of the activity of the perianal disease are noted [18, 21]. Neither the Cardiff classification nor a more recent perianal Crohn's disease scoring system developed by Pikarsky and colleagues [22] has been reproduced or prospectively validated using clinically meaningful end points. These classification systems are not widely used because of a perceived lack of clinical relevance [23].

A more widely used clinical classification proposed by the American Gastroenterological Association (AGA) identifies each type of lesion [24, 25]. Ulcerations are divided into fissures and ulcers similar to the simplified Cardiff classification. Only irreversible and fibrous anorectal strictures are included in the AGA classification and may be short, annular, diaphragm-like strictures less than 2 cm in length, or longer tubular strictures arising from rectal inflammation. Anal skin tags are either type 1 (large edematous and cyanotic lesions) or type 2 corresponding to flat and broad or narrow, soft painless lesions [25].

Skin Tags

Skin tags have been classified into two types [25]. Type 1 are edematous, hard, often cyanotic, tender or not, typically arising from a healed anal fissure, ulcer, or hemorrhoid. These skin tags are caused by lymphedema secondary to lymphatic obstruction. They often occur in concert with intestinal inflammation. Type 2 lesions are raised, broad or narrow based, single or multiple, soft or firm, and painless (often referred to as "elephant ears"). Elephant ear tags (Fig. 48.2) are usually multiple and are generally asymptomatic except for patient complaints of difficulty cleaning and poor cosmesis. A study by Bonheur et al. [26] found that type 2 tags were more frequently found among CD patients when compared to patients with ulcerative colitis. There was a trend toward greater incidence of these tags among CD colitis patients compared to CD patients with ileitis and ileocolitis. These tags are fairly common among CD patients. Peyrin-Biroulet and colleagues [27] found in a population-based cohort study that the ten-year cumulative probability of developing tags from time of diagnosis was

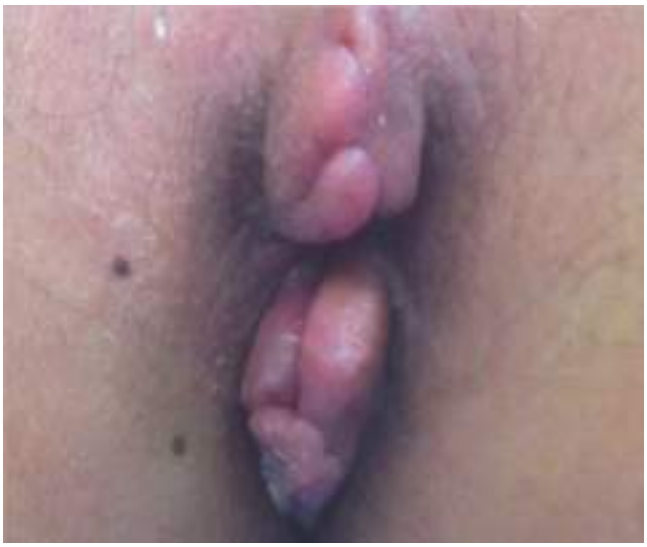

FIGURE 48-2. "Elephant Ear" tags.

18.7 %. Taylor and colleagues [28] investigated excisional biopsies of anal skin tags in 26 patients with known CD and found noncaseating granulomas in almost 30 %.

Management

Skin tags associated with CD are generally best managed with benign neglect. There is no effective medical management of these lesions. Excision in some cases can lead to non-healing, persistent surgical wounds and a substantially worse problem. The AGA Institute states that most colorectal surgeons should avoid excision of skin tags, particularly type 1, owing to problems with wound healing. Fibroepithelial polypoid tags and "elephant ear" tags can be excised locally if clinically indicated in patients experiencing difficulty with perianal hygiene and in whom there are no concerns about wound healing [25].

Hemorrhoids

Symptomatic hemorrhoidal disease is remarkably uncommon in the setting of Crohn's disease. A study by the St Mark's group [29] showed that among more than 50,000 patients treated for hemorrhoids, only 20 had Crohn's disease. Results of surgery within the CD group were uniformly poor, and the authors concluded that hemorrhoidal surgery was contraindicated in the setting of CD. A more recent report [30] showed better results following hemorrhoidectomy among CD patients with symptomatic hemorrhoids. A review found that the incidence of complications after hemorrhoidectomy or removal of tags was high among CD patients [31]. CD patients contemplating hemorrhoid surgery should be free of active anorectal involvement.

Management

Hemorrhoidal disease in the setting of CD is best managed expectantly. Dietary modifications, antidiarrheal medications, and limiting toilet time, when possible, are useful adjuncts. Topical medications or suppositories have not been proven effective, but have limited downside potential. Surgical interventions such as rubber band ligation and excisional procedures should only be undertaken when conservative measures have failed and the anorectum is otherwise free of evidence of CD.

Anal Fissure and Ulcer

An anal fissure is a cut, tear, or defect in the anoderm. In the setting of CD, anal fissures can be idiopathic, similar to those seen in non-CD patients, or "atypical," being Crohn's related. An idiopathic anal fissure is located in the anterior or posterior anal midline at the anal verge (Fig. 48.3). About 90 % of idiopathic fissures occur in the posterior midline and 10 % occur in the anterior midline, areas with a characteristically poor blood supply [32]. These fissures are located distal to the dentate line and rarely extend beyond the anal verge. The resting anal sphincter tone is generally elevated. Anal hypertonicity is thought to decrease anodermal blood flow leading to non-healing of chronic fissures [33].

Characteristically, idiopathic fissures will cause modest bleeding with BMs and cause pain for some time (usually hours) following the movement. Idiopathic anal fissures can be acute or chronic. Acute fissures have the appearance of a simple slit or cut of the anoderm. Chronic fissures will often expose the fibers of the internal sphincter muscle at the fissure base and show "heaped up" edges. A skin tag or "sentinel pile" may be present at the distal margin and an hypertrophied anal papilla may be present at the proximal margin.

Atypical fissures and ulcers are more common among patients with CD. These lesions are often located off the anterior and posterior midline. In many cases there are multiple fissures or ulcers [34]. These fissures have granulating bases and overhanging edges (Figs. 48.4 and 48.5). They can extend beyond the anal verge to the perianal skin. Large cavitating ulcers with significant tissue destruction are also seen (Figs. 48.6 and 48.7). A majority of patients with these lesions will present with anal pain and bleeding. These lesions are painful in up to 70 % of cases [34, 35]. Discharge, pruritus, and bleeding are frequent associated symptoms. Biopsy of these lesions will show non-necrotizing epithelioid cell granulomas, characteristic of CD, in up to 77 % of cases [36]. Patients with noncaseating granulomas in perineal biopsies have more severe disease [36].

These fissures and ulcers are thought to result from a direct involvement of the perianal tissues with Crohn's-related inflammation and are not related to internal anal sphincter hypertonicity. Among those patients not known to have intestinal CD, other ulcer-forming anal diseases need to

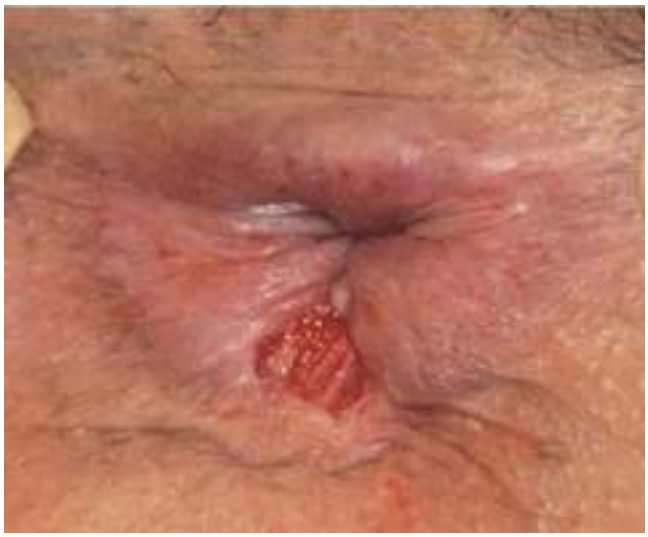

FIGURE 48-3. Idiopathic chronic anal fissure. Note "heaped up" edges and internal sphincter fibers at base.

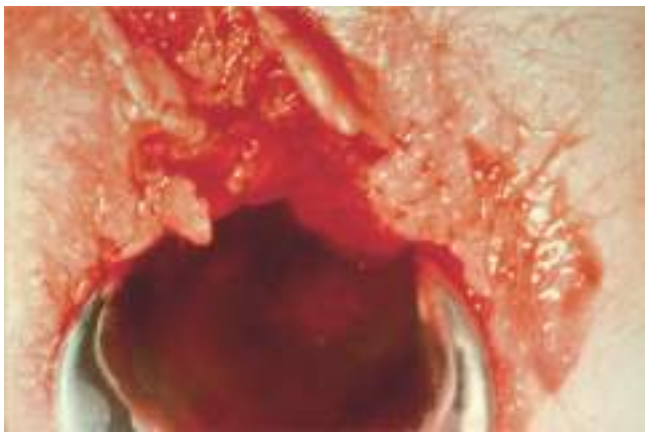

FIGURE 48-4. Fissure in Crohn's disease.

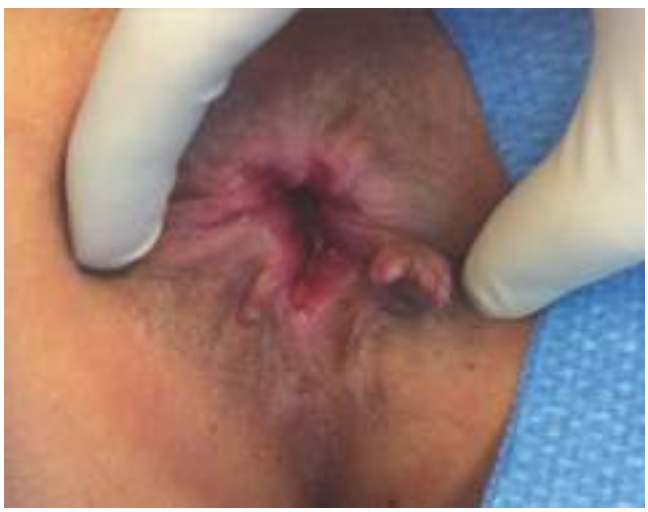

FIGURE 48-5. Chronic fissure with associated tag in Crohn's disease.

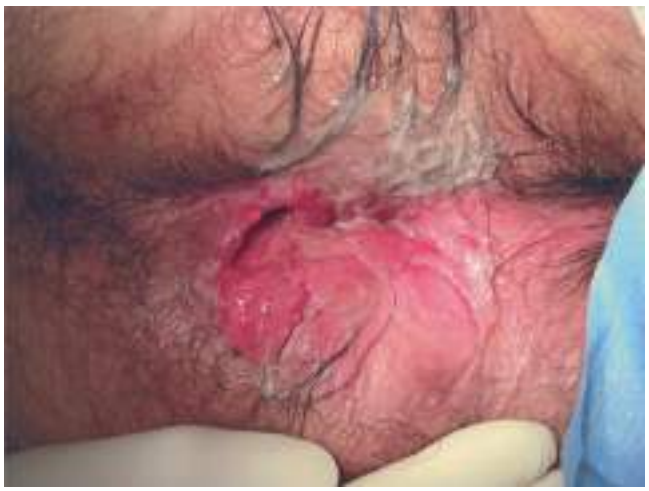

Fig. 48-6. Cavitating Crohn's disease ulcer.

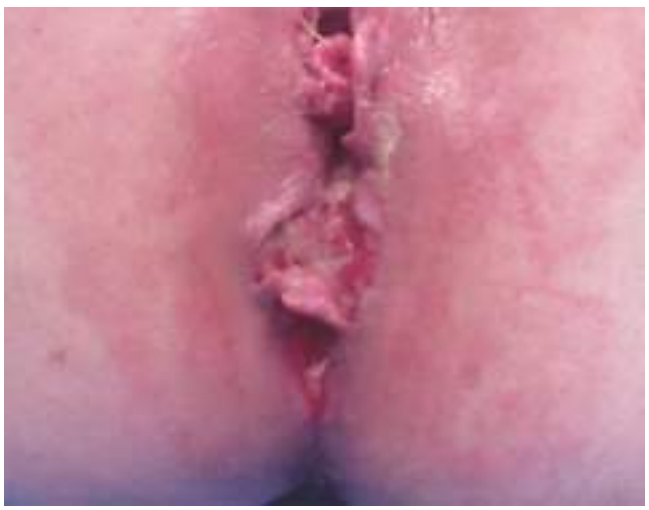

FIGURE 48-7. Crohn's disease ulcer.

be excluded. These conditions, including syphilis, herpes, acquired immunodeficiency syndrome (AIDS), *Neisseria gonorrhea*, *Chlamydia trachomatis*, tuberculosis, and leukemic infiltrates [37]. Carcinoma and prior radiotherapy may also cause anal ulcerations [37]. Biopsy and microbiologic studies may be necessary to establish the diagnosis.

Management

Idiopathic fissures in CD patients can be treated in a fashion similar to that used in non-CD patients. Limiting toilet time and use of antidiarrheal medications, when appropriate, are useful. "Chemical sphincterotomy" with topical nitroglycerin, calcium channel blockers, and injected Botulinum toxin have been used to treat chronic anal fissures [38, 39]. Control of pain has been demonstrated with the use of these agents in numerous studies involving non-CD patients [40–45]. Healing rates of chronic fissures in non-CD patients with use

of these medications are somewhat better than those seen with placebo [39]. Use in CD patients has not been studied, but the risk among these patients appears to be low.

Healing rates of idiopathic anal fissures after lateral internal anal sphincterotomy have been shown to be superior to those seen with medical management among non-CD patients [39, 46]. In a small series of CD patients, Fleshner and colleagues found that "judicious" use of lateral internal sphincterotomy appeared to be safe and more effective than medical management [34]. Surgical treatment should be reserved for CD patients with a single, "characteristic" midline fissure, elevated resting sphincter tone, and a disease-free rectum.

Crohn's associated fissures and ulcers present more of a therapeutic challenge. Topical treatments have been used with varying degrees of success. Topical metronidazole 10 % showed improvement in the Crohn's Disease Activity Index and improvement with regard to pain, discharge, and induration at 4 weeks in an open-label study [47]. Similarly, topical tacrolimus 0.1 % was shown to improve these lesions in early studies (Fig. 48.8) [48].

Systemic medications including corticosteroids, antibiotics, aminosalicylates, and 6-mercaptopurine have been studied as treatments for CD perianal ulcerations [35, 49–51]. Improvement of these lesions has been inconsistently observed. None of the clinical studies of thiopurines in perianal Crohn's disease have examined perianal Crohn's disease as the primary efficacy endpoint [52]. Thalidomide [53], cyclosporine [54], and hyperbaric oxygen [55] as well as local infiltration of infliximab [56] and granulocyte colony-stimulating factor (GM-CSF) [57] have also been used effectively in small uncontrolled studies.

Infliximab and potentially other anti-TNF antibodies have become the "gold standard" in the treatment of perianal CD. In a recent large retrospective study 42.5 % of patients with ulceration had a complete clinical response after anti-TNF induction [58]. Resolution of symptoms, including anal pain and soiling, occurred rapidly after initiation of infliximab therapy.

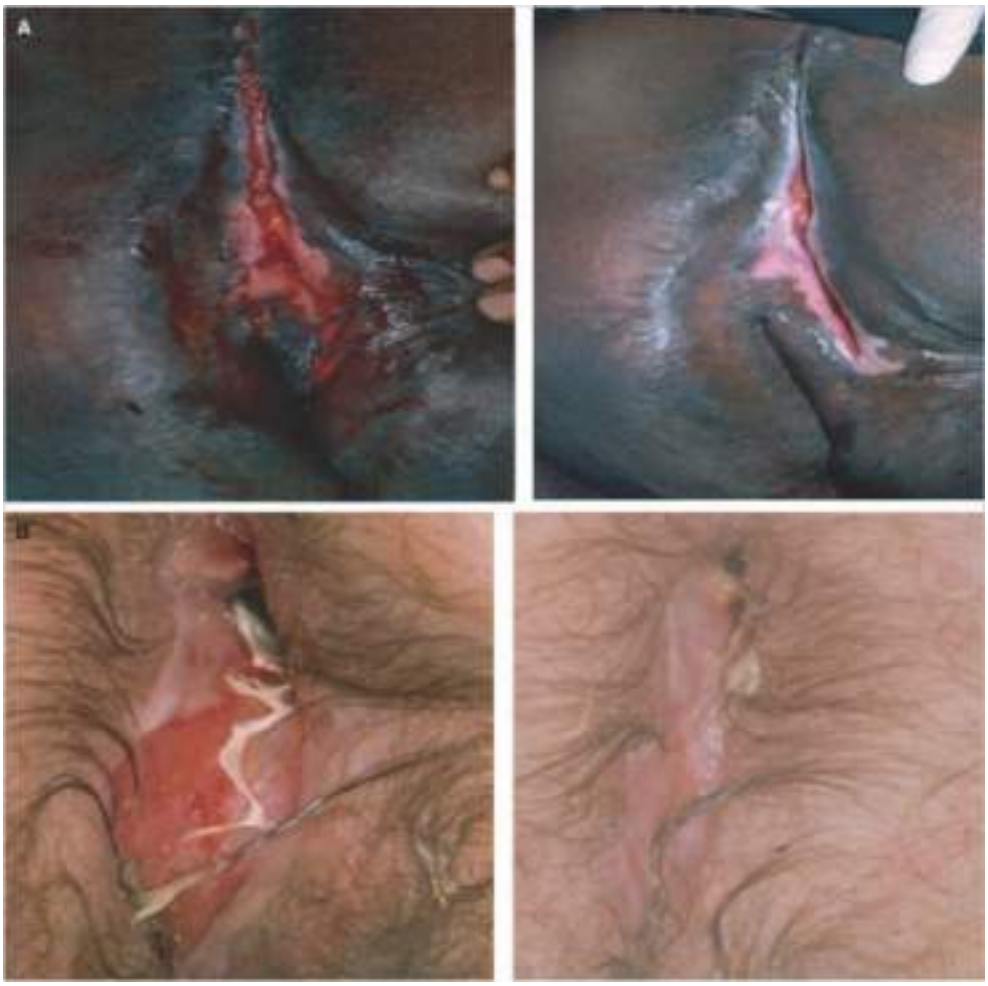

FIGURE 48-8. Response to topical tacrolimus for two separate patients (**a** and **b**). Before *left*, after treatment on *right. With permission from Hart AL, Plamondon S, Kamm MA. Topical tacrolimus in the treatment of perianal Crohn's disease: exploratory randomized controlled trial. Inflamm Bowel Dis 2007; 13(3):245-253 (49) © Wolters Kluwer 2007.*

After a median follow-up period of 175 weeks, healing of ulcers was maintained in 73 % of cases [58]. Anti-TNF therapy should be considered as first-line therapy for cavitating ulcers as the long-term outcome is poor, with the risk of anoproctectomy approaching 83 % in some studies [59].

Abscess and Fistula

Abscess

Perirectal and perianal abscesses can be expected to occur in up to 80 % of CD patients [60]. Abscesses about the anus and rectum can form in four distinct anatomical locations. These are the perianal space, the ischiorectal (or perirectal) space, the intersphincteric (or submucosal) space and the supralevator space (Fig. 48.9). The majority of abscesses involve the perianal and ischiorectal spaces. The patient will often present with constant anorectal pain, worsened by sitting, coughing, walking and bowel function. Fever, chills and signs of systemic sepsis may also be present. Physical exam shows erythema and swelling of the affected side. The diagnosis of perianal abscess (Fig. 48.10) and ischiorectal abscesses (Fig. 48.11) is usually fairly easy to establish, whereas submucosal and supralevator abscesses may require imaging studies, such as MRI [61], computed tomography (CT) [62] or endorectal ultrasound [63]. Induration and tenderness are common findings. Fluctuance is generally a late sign. Examination under anesthesia is often required for diagnostic and therapeutic purposes.

Management

When the diagnosis of an abscess has been established, surgical drainage is indicated. Unless the abscess is quite superficial, this is usually best accomplished under general anesthesia in the operating room. Superficial perianal abscesses can be drained under local anesthesia in the clinic or emergency department. A cruciate incision will often prevent premature closure of the skin edges. Recovered purulence may be sent for microbiologic cultures, although growth of mixed flora is the rule rather than the exception [64]. Cultures are more useful when there is extensive surrounding cellulitis. Antibiotic therapy is often added, but is not a substitute for adequate surgical drainage.

The site of incision for drainage of an ischiorectal abscess should be placed on the buttock, just outside the sphincter complex. Most of these abscesses will result in fistula formation, and an incision site closer to the anorectum results in a shorter fistula tract. Placement of a mushroom or Malecot catheter or a draining seton, if the internal opening of a causative fistula is found, is preferred. "Packing" the abscess cavity is contraindicated in virtually all cases, as the packing actually impedes drainage.

Submucosal abscesses can be successfully drained into the anorectum by incising the overlying mucosa and internal

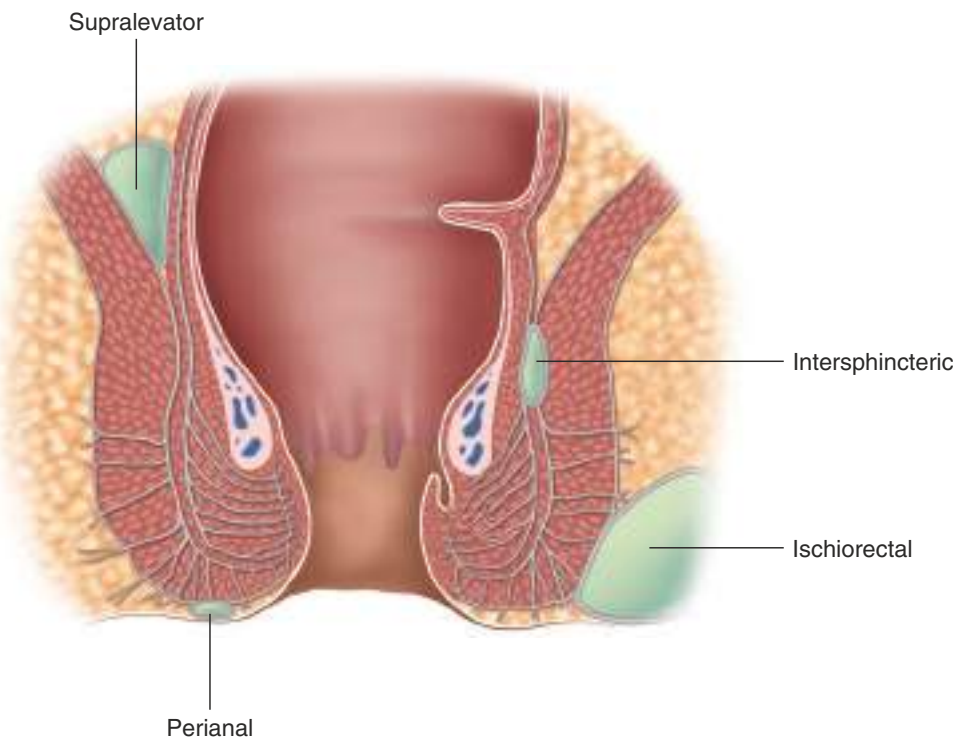

FIGURE 48-9. Location of abscesses.

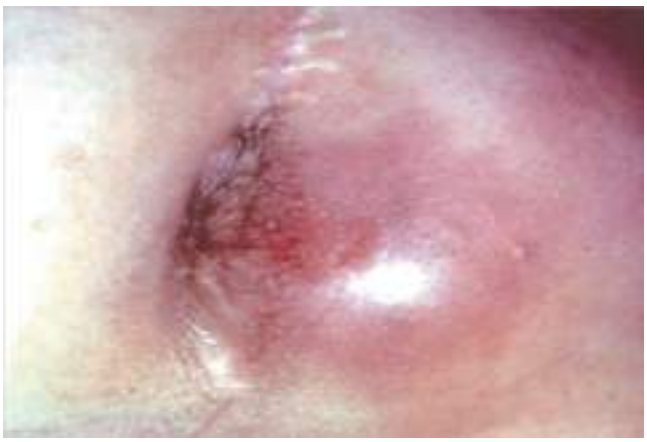

FIGURE 48-10. Perianal abscess.

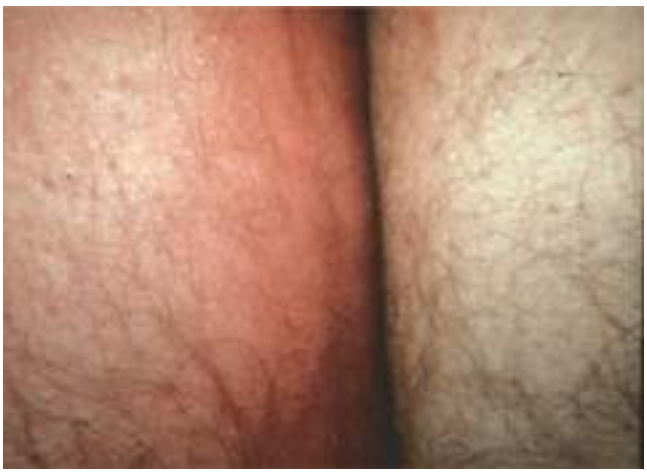

FIGURE 48-11. Left perirectal or ischiorectal abscess. Notice *left*-sided erythema and fullness.

anal sphincter muscularis. Division of the internal sphincter, however, may result in impaired anal continence. This potential complication should be explained to the patient before surgery. Supralevator abscesses may originate from a cryptoglandular focus or from an intra-abdominal source. Every effort should be made to differentiate the origin of this type of abscess. Supralevator abscesses originating within the abdominal cavity can be successfully drained into the rectum. Supralevator extensions of abscesses of cryptoglandular origin should be drained with a mushroom catheter via a perineal incision (Fig. 48.12) [65]. Non-palpable supralevator abscesses may require drainage by interventional radiology under CT or MRI guidance or by the surgeon under EUS guidance [63]. Abscesses will often lead to anorectal fistulas, whether drained surgically or not.

Fistula

A fistula is an abnormal communication between two epithelial lined surfaces. Fistulas arising from the anus or rectum can terminate on the perianal or buttock skin, the vagina and

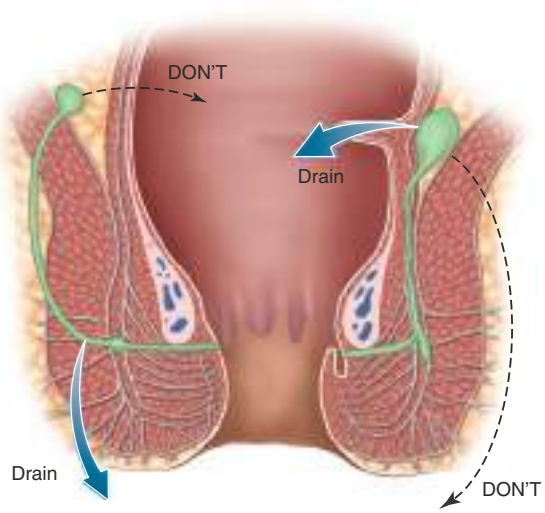

FIGURE 48-12. Drainage of supralevator abscess.

labia, the scrotum and penis, or the thighs, groins, and even further from the anus. Fistula formation is probably the most common complication of perianal CD. After 10 years of CD, the cumulative incidence of anal fistulas is reported to be up to 33 % and after 20 years it is about 50 % [66]. Among CD patients presenting with perineal disease, 29 % will have anal fistulas without antecedent abscesses [59].

Various classification schemes have been devised for perianal fistulas. Parks' classification [67] is perhaps most descriptive but also the most complicated. CD patients often have complex, branching, and interconnected series of fistulas that are not easily defined, much less objectively classified. A simpler scheme devised by Bell and colleagues [68] divides fistulas into two groups: simple and complex. A simple fistula has a low intersphincteric or transphincteric location, and a single, short tract (Fig. 48.13). The internal opening is at or caudad to the dentate line, and the external opening is near the anal verge. Vaginal involvement and abscess are not present. A complex fistula has a single internal opening above the dentate line or multiple internal or external openings. A complex fistula is present when any one or more of a vaginal extension, an abscess, multiple openings, an anorectal stricture, or active anorectal CD are present (Figs. 48.14 and 48.15) [25, 68]. Goodsall's rule, which predicts the tract of a fistula and the location of the internal opening within the anorectum based upon the relationship of the external fistulous opening to a transverse anal line, is notoriously inaccurate in the setting of perianal CD. Combining modalities such as EUA with MRI or EUS increases diagnostic accuracy [20] which can aid in therapeutic decision making. Transperineal ultrasonography is an alternative to EUS when EUS is not tolerated [69]. CT and fistulography are considered inferior studies for these purposes [70, 71].

Management

The goals of management of perianal fistulous disease include preservation of continence, complete healing, a reduction in the number of septic events, and improvement

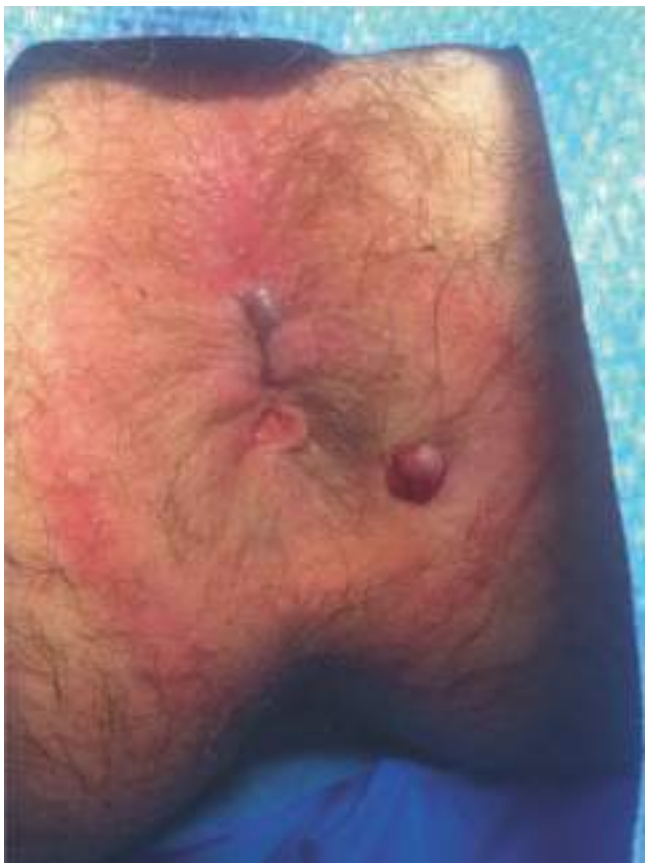

FIGURE 48-13. Simple Crohn's disease fistula.

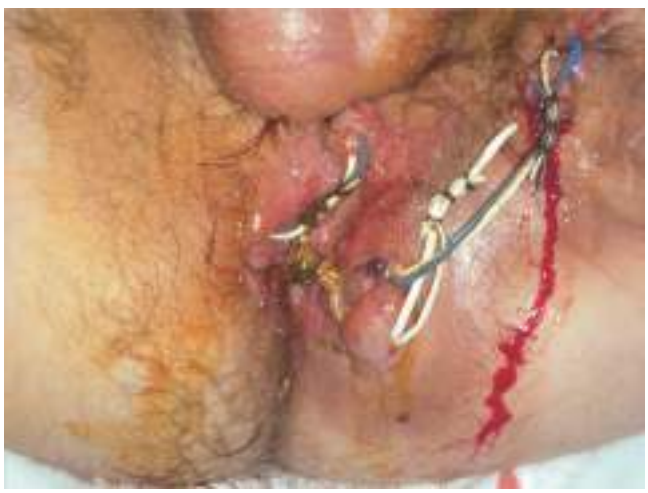

FIGURE 48-14. Complex Crohn's disease fistula.

in the patient's quality of life. Obviously, these goals are not always met. As a general rule, control of diarrhea, perianal hygiene by showers or sitz baths, and application of protecting barrier creams are always appropriate [72]. Successful treatment will often involve a close collaboration among surgeons, gastroenterologists, and radiologists, among others.

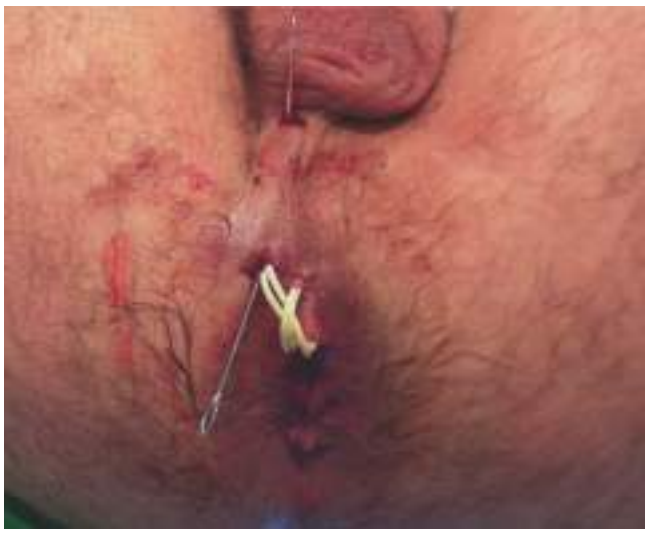

FIGURE 48-15. Complex Crohn's disease fistula.

Medical Therapy

Aminosalicylates and Corticosteroids

Clinical data suggest that aminosalicylates are more effective than placebo in achieving remission of mildly to moderately active intestinal CD [73, 74]. Their effectiveness, however, is influenced by the site of disease activity. Similarly, corticosteroids have been considered first-line treatment in patients with moderately to severely active CD. This approach is based largely on the findings of large clinical studies demonstrating the efficacy of steroids in mild-to-moderate intestinal CD [73, 74]. Despite these findings, there is no evidence that aminosalicylates play any role in the treatment of perianal CD. Steroids are similarly ineffective and may be contraindicated in the setting of fistulizing perineal disease.

Antibiotics

Despite a lack of convincing evidence, antibiotics are often used as initial treatment in the setting of CD-related fistulous disease [25]. In a small study, Bernstein and colleagues [75] treated CD patients with metronidazole at relatively high doses. More than half of these patients had complete healing with rapid onset of symptom resolution. Decreased pain and tenderness were noted in all study patients. However, long-term treatment with metronidazole was associated with a variety of adverse reactions including nausea, peripheral neuropathy, and paresthesias. Symptoms recur when metronidazole therapy is discontinued [76]. Ciprofloxacin has also been studied in the setting of perianal CD. In a small pilot study comparing ciprofloxacin and metronidazole to placebo, CD fistula response and remission rates were greater among those patients treated with ciprofloxacin [77]. The difference, however, did not reach statistical significance. A recent meta-analysis of 15 randomized, placebo-controlled trails of the efficacy of antibiotic treatment in CD found, that compared to placebo, ciprofloxacin exhibited significant clinical benefits in patients with perianal fistulas [78]. Antibiotics are

perhaps best used as an effective bridge to immunosuppressive therapy [79].

Immunosuppressives

Immunosuppressive medications used in the treatment of fistulizing perianal CD include 6-mercaptopurine (6-MP), azathioprine, methotrexate, cyclosporine, and tacrolimus. There are no controlled clinical trials in which the efficacy of immunosuppressants in treating fistulizing perianal CD was considered the primary end point [80]. Several small studies have assessed perineal healing by azathioprine and 6-mercaptopurine as secondary endpoints. A meta-analysis of this data found that significantly more patients responded to these immunosuppressants than those responding to placebo [52].

Tacrolimus and cyclosporine are calcineurin inhibitors that suppress T-cell activation and interleukin-2 production. Tacrolimus was compared to placebo in a randomized, controlled study where fistula closure was defined as either the absence of spontaneous drainage or the ability to express drainage with "gentle compression" [81]. The authors concluded that oral tacrolimus is effective for fistula improvement, but not fistula remission, in patients with perianal CD. Significant adverse events were also noted in the tacrolimus group. In another small, exploratory series, Hart and colleagues [48] found that topical tacrolimus was ineffective in treating CD-related perineal fistulas. Multiple small studies have shown value in treatments with cyclosporine A and thalidomide [54, 82–85]. However, use of these agents is limited owing to significant side effects.

Biologics

Tumor necrosis factor alpha (TNF-α) antagonists specifically target the elevated concentrations of TNF-α that contribute to the pathological inflammation in CD. Anti-α4 integrins belong to a newer class of drugs which also show promise in treating CD.

Infliximab

Infliximab is a chimeric monoclonal antibody to TNF-α. It is administered by intravenous infusion. Infliximab is the best studied of all the biological agents. Efficacy of infliximab in the treatment of fistulizing perineal CD has been demonstrated in multiple randomized, controlled studies. In the first published study, Present and colleagues [86] randomized 94 patients (85 with perianal fistulas) to receive either 5 mg/kg of infliximab or 10 mg/kg of infliximab or placebo at weeks 0, 2, and 6. The primary end point was a reduction of 50 % or more from base line in the number of draining fistulas observed at two or more consecutive study visits. A secondary end point was the closure of all fistulas. At the end of the study 55 % of the patients assigned to 5 mg/kg of infliximab had a closure of all fistulas, compared with 13 % of the patients assigned to placebo. Sands and colleagues [87] demonstrated the superiority of infliximab over placebo in maintaining long-term fistula healing. Despite these positive results, 11 and 15 % of patients enrolled in these trials developed abscesses during the study period. This was probably due to an early closure of the cutaneous opening of the fistula tract. To minimize this complication, a combined surgical and medical approach has been proposed. Small studies [88, 89] reported a better response rate, a lower recurrence rate, and a longer time to recurrence among patients who had a seton placed prior to infliximab treatment when compared with patients receiving infliximab alone. The seton is removed after the second infliximab infusion. Although the initial response to infliximab tends to be very good, the median duration of fistula closure is approximately three months and repeated intravenous infusions of infliximab are usually necessary. Long-term maintenance therapy (as opposed to episodic therapy) may be necessary to prevent fistula relapse [90]. Despite impressive rates of patient improvement, radiographic evidence of complete fistula healing occurs in a minority of patients [91]. Patients who received surgery and infliximab had a shorter time to fistula healing and a longer mean time to relapse compared to those who received infliximab or surgery alone. Discontinuation of infliximab therapy is associated with fistula recurrence.

Alessandroni and colleagues [92] reported a small series of CD patients with complex fistulas treated by core-out fistulectomies plus local injections of infliximab. Results were generally good, but long-term closure of fistulas was observed in a minority of patients.

Adalimumab

Adalimumab is a completely humanized monoclonal antibody to TNF-α. It is administered by subcutaneous injection. The CHARM study [93] was a 56-week, randomized, double-blind, placebo-controlled trial with a 4-week open-label induction period. Patients successfully completing CHARM could enroll in an open-label extension, the ADHERE study [94]. In the ADHERE study, fistulas were assessed for spontaneous drainage or drainage with gentle compression at each study visit. Complete fistula healing was defined as the absence of drainage under both of these circumstances. Of 117 enrolled patients (113 with perianal fistulas), adalimumab therapy was associated with progressive increases in fistula closure over time. Rates of complete closure differed between placebo and adalimumab groups as early as 2 weeks after randomization and reached statistical significance at 16 weeks. Baseline immunosuppressant or CD-related antibiotic use had no apparent effect on the rates of fistula closure in patients receiving adalimumab or placebo at weeks 26 or 56. In addition, whether patients were naive to or experienced with TNF antagonists before receiving adalimumab did not appear to effect fistula healing. Adalimumab was effective in patients who were infliximab nonresponders or had become infliximab refractory [94]. In the CHOICE trial [95], patients receiving adalimumab had draining fistula counts decrease by 41.3 % at the last visit compared with

baseline and approximately 38.6 % of patients had complete fistula healing at the last visit.

Certolizumab Pegol

Certolizumab pegol is the PEGylated Fab' portion of a recombinant humanized monoclonal antibody to TNF-α. It is administered by subcutaneous injection. Certolizumab pegol has also been shown to be effective in the treatment of CD in a number of well-controlled clinical trials [96–99]. Schreiber and colleagues [100] reported on a series of patients with CD fistulas from the PRECISE 2 [99] study. After open-label induction with certolizumab pegol at weeks 0, 2, and 4 responders were randomized at week 6 to receive either certolizumab pegol or placebo every 4 weeks. At week 26, 36 % of the patients in the certolizumab pegol group had fistula closure compared to 17 % among the placebo group; however, protocol-defined fistula closure was not statistically significant between the two groups. The authors concluded that when compared to placebo, continuous treatment with certolizumab pegol improves the likelihood of sustained perianal fistula closure.

Natalizumab

Natalizumab is a humanized monoclonal antibody against the cell adhesion molecule, α4-integrin. It is administered by intravenous infusion. Natalizumab is indicated for both induction of remission and maintenance of remission for moderate to severe Crohn's disease [101]. Natalizumab is largely reserved for CD patients with extensive ileocolonic disease who have failed conventional immunosuppressants and at least two anti-TNF-α agents [102]. Data concerning fistula healing is limited to open-label, retrospective studies [102]. Fistula disease responded to natalizumab in about half of treated patients [102]. Data concerning this agent is limited because of the association with the rare but usually fatal condition, progressive multifocal leukoencephalopathy (PML). Natalizumab should not be combined with an immunosuppressant or prolonged corticosteroids, because this may increase the risk of PML.

Vedolizumab

Vedolizumab is a humanized monoclonal antibody specifically designed to inhibit gut $\alpha_4\beta_7$ integrins. Blocking the $\alpha_4\beta_7$ integrin results in gut-selective anti-inflammatory activity [103]. It inhibits adhesion and migration of leukocytes into the gastrointestinal tract by preventing the $\alpha_4\beta_7$ integrin subunit from binding to mucosal addressin cell adhesion molecule-1 (MAdCAM-1). Because MAdCAM-1 is preferentially expressed on blood vessels in the intestinal tract, vedolizumab is theoretically more gut specific and therefore a more targeted form of immunosuppression. Vedolizumab is indicated for the treatment of moderately to severely active CD in patients who have lost response to biologic agents, immunosuppressive agents, or corticosteroids. A large randomized trial showed that vedolizumab was more effective than placebo in achieving remission but not a Crohn's Disease Activity Index-100 (CDAI-100) response, at week 6 [104]. There is no data concerning the use of vedolizumab in the treatment of CD fistulas. The risk of progressive multifocal leukoencephalopathy with this agent is thought to be less than that seen with natalizumab [105].

Surgical Therapy

Surgical therapy for fistulizing perianal disease needs to be tailored to each individual patient. While there are a variety of approaches available to the surgeon, it must be borne in mind that surgical interventions in CD patients can result in non-healing perineal wounds, incontinence, and significantly diminished quality of life. Surgical management of perianal CD should control perianal sepsis without resort to more extensive procedures when possible.

Seton

Placement of a loose, draining seton is often used as the first step in the management of fistulizing perianal CD. A silastic vessel loop passed through the fistula tract and tied to itself outside the anus works well (Fig. 48.16). The goal of the seton is to promote drainage and prevent recurrence of an abscess. Placement of the seton does not require division of the sphincter complex; hence the seton itself has essentially no impact on continence [106]. Draining setons are generally well tolerated by patients. Cutting setons should be avoided, as not only are they painful, but they can also lead to impaired control [107].

In the presence of active rectal CD, a seton can be used for many months [108] as a temporizing measure while medical therapy is instituted. Some authors advocate an "indwelling or permanent" seton for patients with CD-related complex fistulas [109].

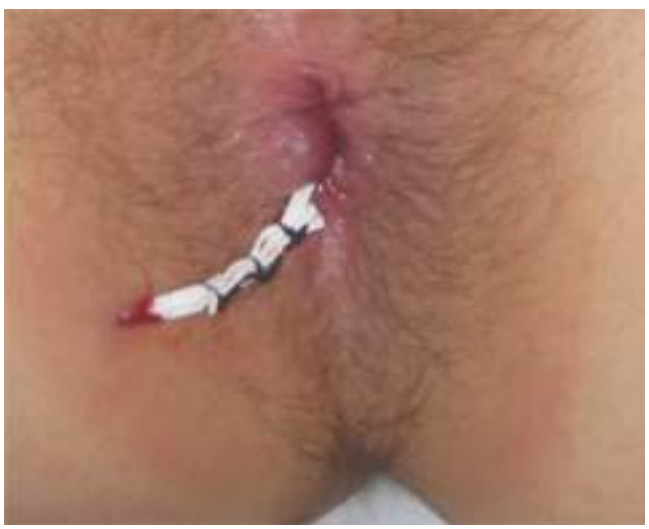

FIGURE 48-16. Silastic seton.

Fistulotomy

Lay-open fistulotomy should be reserved for simple Crohn's fistulas. These will be either low transphincteric or intersphincteric fistulas (Figs. 48.17 and 48.18). The anorectum should be free of disease. This surgery is usually performed under general or spinal anesthesia with the patient in the lithotomy, left lateral decubitus, or prone jackknife position. A probe is passed from the external to internal opening and an estimate of the amount of muscle encompassed within the fistula tract can be estimated by palpating over the probe. Care must be taken to ensure that very little to none of the sphincter mechanism is involved. Granulation tissue at the base of the fistulotomy site is removed by curettage and the edges of the wound are then sewn to the edge of the fistulous tract with a running, locked absorbable suture. Healing rates between 80 and 100 % have been reported [25]. Healing rates are substantially worse when active proctocolitis is present [110].

Complex fistulas require a more cautious surgical approach. Muscle division in these cases carries a high risk of incontinence and non-healing perineal wounds [111]. Surgical alternatives to lay-open fistulotomy include a variety of surgical techniques with varying rates of observed success.

Fibrin Glue

Instillation of fibrinogen and thrombin causes a fibrin clot to form within the fistula tract. The clot is thought to promote hemostasis and angiogenesis while acting as "scaffolding" upon which fibroblasts can migrate, effectuating healing. This procedure is generally performed under general anesthesia. The fistula tract is gently curetted of granulation tissue and the fibrinogen/thrombin mixture is instilled into the fistula tract with a special, two-barreled catheter.

Despite promising healing rates shown in initial reports for patients with cryptoglandular fistulas [112], later results, especially among the CD population, have been disappointing. In a randomized, prospective, multicenter trial, Grimaud et al. [113] compared fibrin glue instillation to seton removal alone among 77 highly selected CD fistula patients. Forty-one patients had simple fistulas and 36 had complex fistulas. All patients had no recent surgery or biologic drug use and no evidence of local sepsis. Evaluation at 8 weeks showed clinical remission (absence of purulence with gentle compression) in 38 % of the fibrin glue group compared with 16 % in the observation group. Simple fistulas seemed to respond better than complex ones. At 16 weeks, two of 13 responders in the glue group experienced fistula recurrences. Fibrin glue injection was generally very well tolerated with no difference in the frequency of adverse effects between the fibrin glue and control arms. Incontinence did not occur in either group. The authors concluded that fibrin glue appears to be a simple, effective, and well-tolerated therapeutic option in the treatment of CD perianal fistulas. Neither the addition of antibiotics to the sealant [114] nor closure of the internal opening with sutures or a flap [115] has substantially improved results. It appears that fibrin adhesive achieves fistula healing in a minority of CD cases. However, given the minimal risk of incontinence it could be used in an attempt to avoid more invasive surgery or as an alternative to permanent seton placement.

Anal Fistula Plug

An anal fistula plug (AFP) is either a cone-shaped device made from lyophilized, rolled, porcine small intestinal submucosa (Cook®, Biodesign®) or a tubular, multi-legged, button made from bio-absorbable polymers (Gore® Bio-A®). As with fibrin sealant, the absorbable plug is designed to provide a matrix allowing for the in-growth of collagen producing fibroblasts. AFP is generally inserted under general anesthesia. The plugs are inserted through the fistula tract with the broad or button end inside the anorectum and the tapered end or legs through the tract. The end of the plug within the anorectum is designed to be fixed in place with

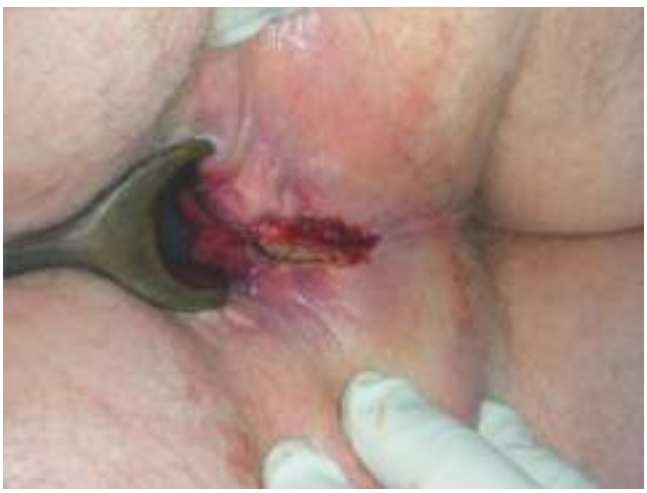

FIGURE 48-17. Simple fistulotomy.

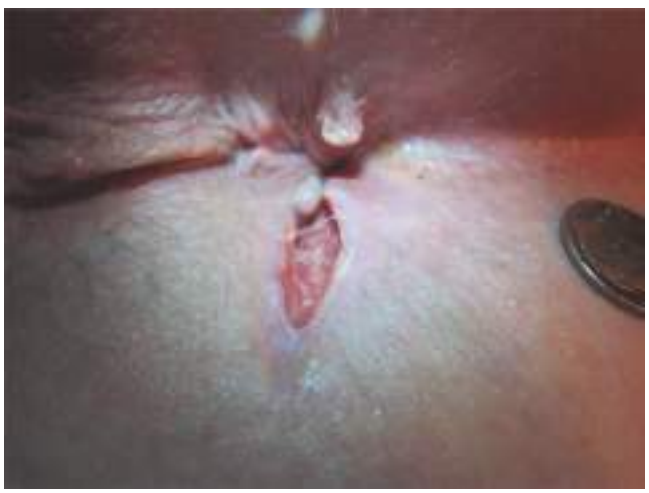

FIGURE 48-18. Simple fistulotomy.

sutures and covered with mucosa. Of the two devices, the porcine plug is better studied.

Results with both plugs are variable and data is scant among CD patients. Garg and colleagues [116] performed a systematic review of the then available literature. A total of 25 studies were extracted and 12 (317 patients) were finally included in the systematic review. Fistula plugs were noted to have patient cure rates ranging from 24 to 92 % during follow-up periods between 3.5 and 12 months. Prospective studies among patients with complex fistulas yielded successful outcomes in 35–87 %. The success rate in patients with Crohn's disease was 29–86 %. Failure, often attributed to plug extrusion, occurred in 4–41 % of cases. More recent studies using the polymeric plug included only four patients with CD fistulas [117, 118]. It would appear that for CD patients the AFP procedure is safe and at least as effective as fibrin glue. The risk of incontinence and abscess appears to be minimal.

Adipose Tissue-Derived Stem Cells

Use of autologous adipose tissue-derived mesenchymal stem cells (ACSs) to treat CD-related fistulous disease was first described in a case report in 2003 [119]. The procedure involves injection of the fistula with stem cells recovered from the patient or a healthy donor, in the case of allogenic transplant. ACSs are recovered through a rather elaborate purification and cell culture process [120]. ASCs are cryopreserved until used. The ASC product consists of a cellular suspension of living adult stem cells. After curettage of the tract, the cells are injected into the fistula tract walls [120] and, additionally, in some studies, instilled into the tract with fibrin glue [121, 122]. ACSs are considered a promising tool for cell therapy due to their immunomodulatory capacity [123, 124].

A phase two trial reported healing of complex perianal fistulas in 71 % of 24 patients who received adipose stem cells mixed in fibrin glue [121]. A more recent, open-label multicenter study [122] involved 43 CD fistula patients. Tracts were curetted and irrigated and the internal openings were closed with sutures. ASC was injected into the fistula walls and the tract was filled with ASC mixed with fibrin glue. Fistula healing was assessed at 8 weeks after final treatment. Patients without complete closure of their fistulas at 8 weeks received a second injection of ASCs containing 1.5 times more cells than the first injection. A modified per-protocol analysis showed that complete fistula healing occurred in 27 of 33 patients (82 %) at 8 weeks after injection. Of the 27 patients with fistula healing, 26 completed an additional observational study for 1 year. Twenty-three of 26 patients (88 %) had maintained closure at the end of 1 year. There were no adverse events reported. The authors concluded that ASC injections for patients with Crohn's fistulas were well tolerated and showed a favorable and sustained 1-year outcome [122]. Other authors reported that over a longer, mean follow-up of 38 months, only seven of 21 patients (33 %) remained healed [125]. Longer follow-up also failed to report any instances of anal incontinence. While long-term study has reaffirmed a very good safety profile of ASC treatment, only a third of fistulas remained healed at a mean interval of about 3 years. These results suggest that ASC could be an effective, short-term treatment option for CD fistulas, but more evidence concerning durability of results is required.

Ligation of Intersphincteric Tract

First described by Rojanasakul [126], ligation of the intersphincteric fistula tract (LIFT) is a novel approach to anal fistulas. This procedure, usually performed under general or spinal anesthesia, approaches the fistula tract via an intersphincteric incision. Outpatient surgery is possible. The fistula tract, once isolated, is divided in the intersphincteric space at both the internal and external sphincters. The distal portion of the external tract is then curetted out, and the external opening is widened at the skin. Lastly, the skin incision overlying the intersphincteric groove is closed (Fig. 48.19a–f). In several small series, the LIFT procedure has been effective in healing 57–83 % of cryptoglandular fistulas [127, 128]. Incontinence has not been reported [129]. Failures are usually manifest as persistent drainage from the intersphincteric surgical site [130]. The procedure has been modified to include insertion of a bioprosthetic graft in the intersphincteric space (BioLIFT). In small series of non-CD patients, this technique reported healing rates of 60 and 94 % [131, 132].

Gingold and colleagues [133] enrolled 15 CD patients with trans-sphincteric fistulas in a prospective study of the LIFT procedure. Fistula healing and two validated quality-of-life indices were assessed two and 12 months after surgery. LIFT site healing and fistula closure were seen in nine patients (60 %) at 2-month follow-up. No patient developed fecal incontinence. LIFT site and fistula healing were seen in eight of the 12 patients (67 %) with complete 12-month follow-up. Patients who had successful operations also significantly improved their mean quality-of-life scores. The authors concluded that fistulas among CD patients may be successfully treated by LIFT with minimal perianal wound creation and sphincter injury [133].

Endorectal Advancement Flap

Treatment of CD fistulas by endorectal advancement flap is an attractive and well-studied option for CD fistula patients without anorectal stricture or inflammation. This procedure can often be accomplished in the outpatient setting under general or regional anesthesia. Advancement flap often will be performed after seton drainage of the fistula has allowed the tract to "mature." The internal opening of the fistula is identified within the anus and a "U"- or square-shaped incision is made in the mucosa around it. A flap of anoderm, submucosa, and a small portion of the internal sphincter is raised proximally so that the flap reaches beyond the

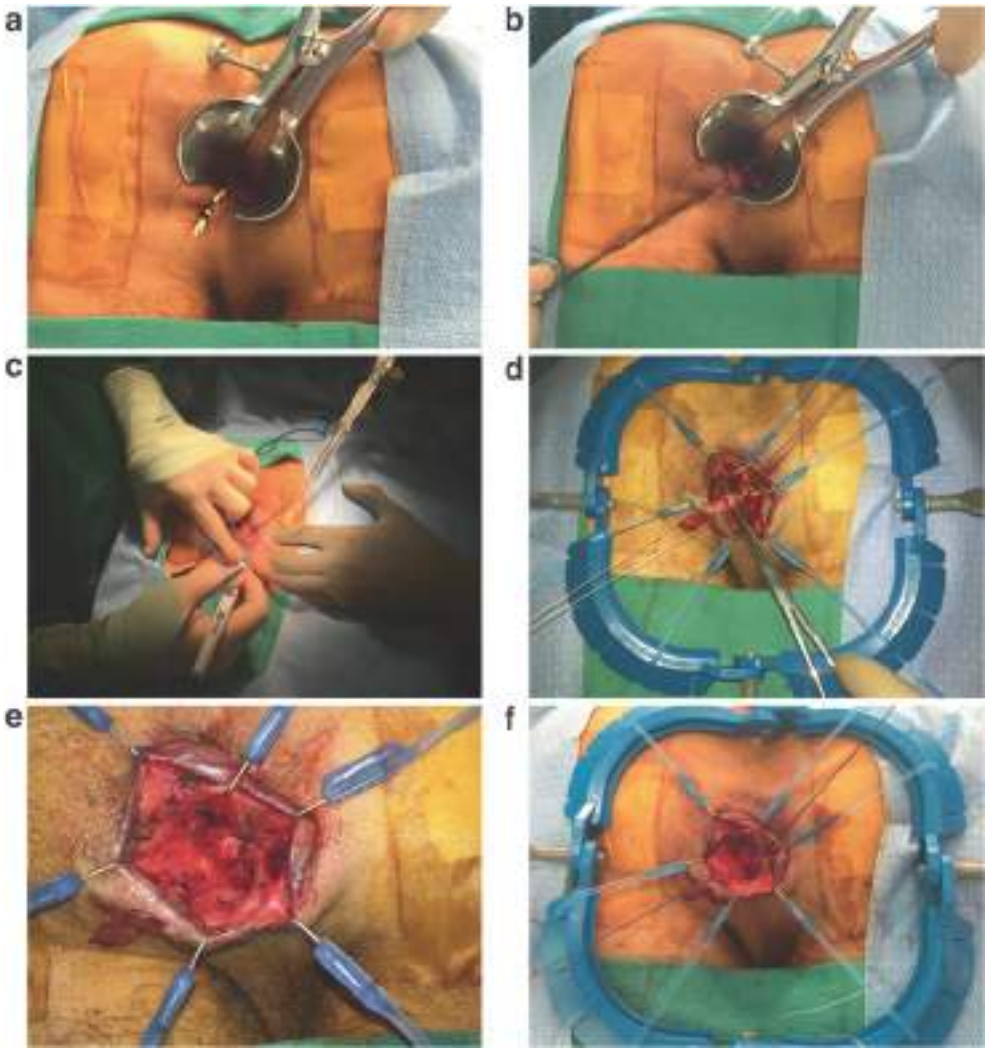

FIGURE 48-19. (**a**) LIFT: Seton in the fistula tract.; (**b**) LIFT: Identification of internal opening; (**c**) LIFT: Dissection in the intersphincteric groove. (**d**) LIFT: Isolation of the tract. (**e**) LIFT: Suture ligation of the tract. (**f**) LIFT: Ligation of the external sphincter.

muscular internal opening with no tension. The internal opening in the sphincter is closed with absorbable sutures. The distal end of the flap containing the mucosal internal opening is trimmed and the flap is sutured to the remaining anoderm (Fig. 48.20a–e).

Small series have demonstrated fairly good fistula healing rates after advancement flap in CD patients, but less than those seen in cryptoglandular disease [134]. In a systematic review of the then available literature, Soltani et al. [135] found 35 studies dealing with endorectal advancement flaps used in the treatment of CD and cryptoglandular fistulas. Of these, 23 consisted of retrospective case series, eight were prospective studies, and three were randomized clinical trials. Of 1654 patients available for pooled analysis, 91 had CD-related fistulas. Endorectal advancement flaps were more successful in cryptoglandular than in CD fistulas with weighted success rates of 80.8 % (range, 24.1 % to 100 %) in the cryptoglandular group and 64.0 % (range, 33.3 % to 92.9 %) in the CD group. The weighted average rate of incontinence was noted to be 13.3 % (range 0–35 %) in patients with cryptoglandular disease and 9.4 % (0–28.6 %) in patients with CD.

There are several reports concerning the effectiveness of endorectal advancement flap in rectovaginal fistulas with short-term healing rates reported between 42 % and 68 % [136–140]. The failure rates among CD-related rectovaginal fistula patients after endorectal advancement flap alone or in combination with levatorplasty were both about 50 % [141]. Successful trans-vaginal flap repairs of ano-vaginal fistulas have also been reported [142–144].

A retrospective, non-randomized study of patients with high anal fistulas of cryptoglandular origin initially treated with seton drainage demonstrated superiority of endorectal advancement flap over LIFT procedure [145]. In a multi-center, randomized trial of endorectal advancement flap versus anal fistula plug among non-CD patients, no differences

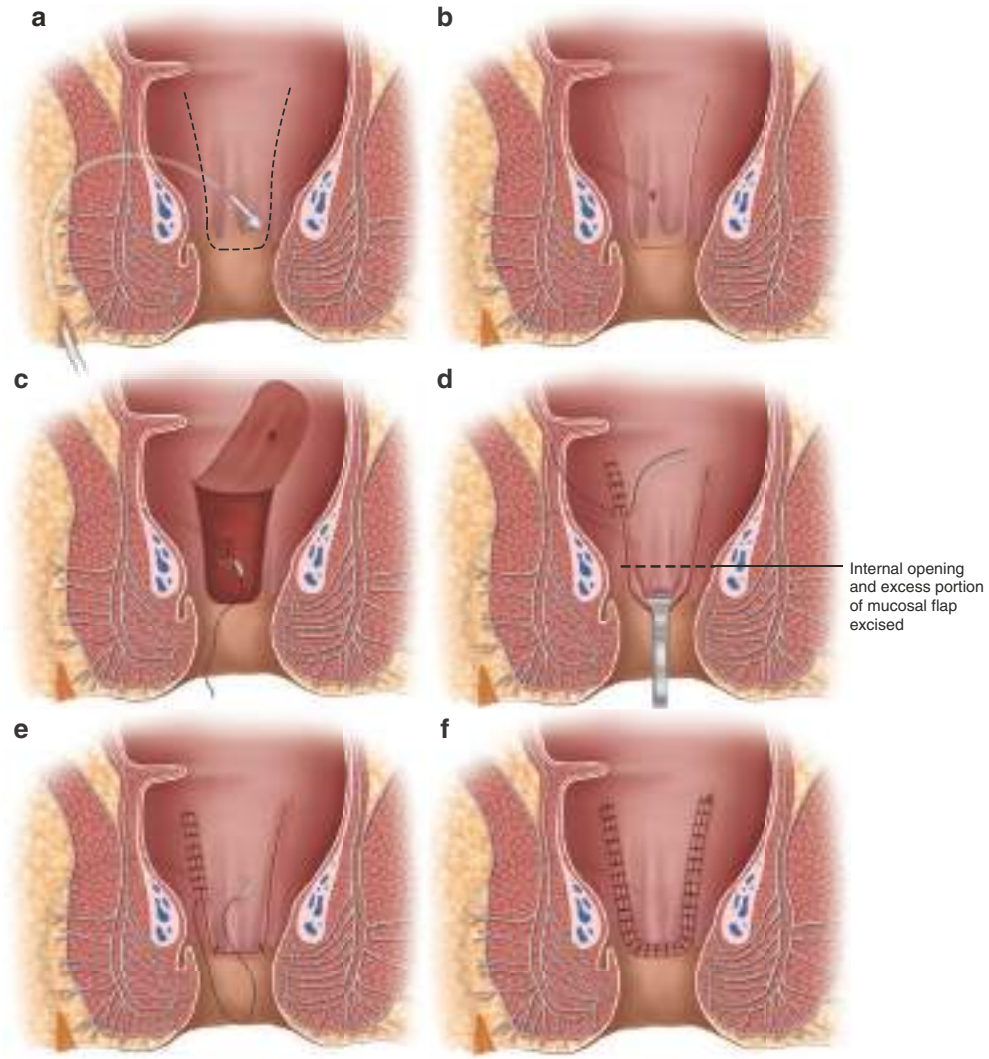

FIGURE 48-20. Endorectal advancement flap. (**a**) The probe or seton through the tract and the external opening is widened (**b**) The internal opening. The flap and area of excess mucosa that will be resected are marked. (**c**) The flap is constructed and the internal opening is closed (**d**) Excess mucosa resected overlying the fistula (**e**, **f**) Mucosa is sewn in place in a tension-free manner.

were found in healing rates or continence scores [146]. At a median follow-up of 11 months the recurrence rate was 71 % in the anal fistula plug group and 52 % in the advancement flap group [146].

While some advocate that endorectal advancement flap is a good option for patients with complex CD anal fistulas [134], others point out that surgical outcome for complex CD fistulas remains disappointing, and recurrence is unpredictable [147].

Diversion

In situations where combined medical and local therapy is ineffective in controlling the symptoms of perianal Crohn's disease, fecal diversion, either on a temporary or permanent basis, has a role in patient recovery [148–151]. Ileostomy and colostomy have both been utilized for this purpose. Diversion of the fecal stream from the anorectum allows healing of those structures as well as amelioration or complete healing of perianal complications (Figs. 48.21 and 48.22a, b).

In a small, nonrandomized study [151] 13 of 39 patients underwent fecal diversion as treatment of severe perianal CD. At an average of 5 years follow-up, 11 of these patients (85 %) had complete resolution of their fistulas and only two (15 %) required proctectomy. In contrast, after local surgical procedures, only five of 26 patients (19 %) had complete resolution of perianal disease. Intestinal continuity was restored in six patients and three of these patients remained disease free. The authors concluded that fecal diversion was a viable treatment option for severe, perianal Crohn's disease and diversion may be associated with a higher rate of resolution than local surgical treatments alone [151]. Despite encouraging local control by diversion, only a minority of diverted patients ever achieve restoration of intestinal continuity.

In a recent report of 138 diverted patients [152], only 30 (22 %) came to stomal closure and 63 (45 %) underwent proctectomy with a permanent stoma. No particular treatment, including biological therapy, was associated with an improved outcome among these patients [152, 153]. While diversion usually causes the perineal disease to become quiescent, leaving the unused and diverted rectum in place as a Hartmann pouch poses its own set of risks. Cancers have been reported under these circumstances despite ongoing surveillance [154]. Proctectomy is strongly recommended in instances where the rectum is unlikely to be restored to continuity.

Proctectomy

In some instances, perineal CD is so severe that proctectomy with permanent diversion is the only viable option. About ten to 20 % of cases will require this intervention [155]. The presence of anal stricture and active colonic CD is associated with increased risk of proctectomy and permanent diversion [156]. This procedure usually involves two surgical fields, abdominal and perineal. Whenever possible, the perineal approach should utilize an intersphincteric dissection so as to lower the risk of non-healing of the perineal wound. Primary closure of the perineal wound is generally indicated [157–159]. Perineal wound problems can be expected to occur in up to 35 % of cases after abdominoperineal resection (Fig. 48.23) [160]. Non-healed perineal wounds have been managed with a variety of techniques including skin grafting [161], gracilis [162], and rectus abdominis myocutaneous flaps [163]. As perineal disease can be extensive, a staged approach is often warranted. Abdominal proctectomy with rectal transection at the level of the levators will allow perineal disease to heal or improve and permit a subsequent, second-stage, perineal anoproctectomy of a more limited scale [164].

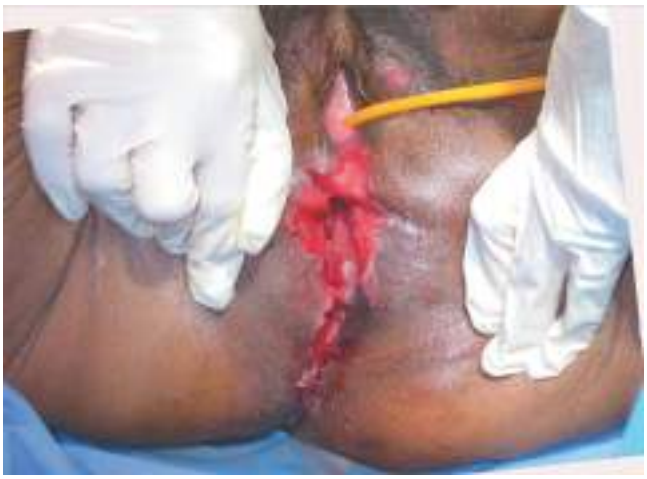

FIGURE 48-21. Perineal wounds before diversion.

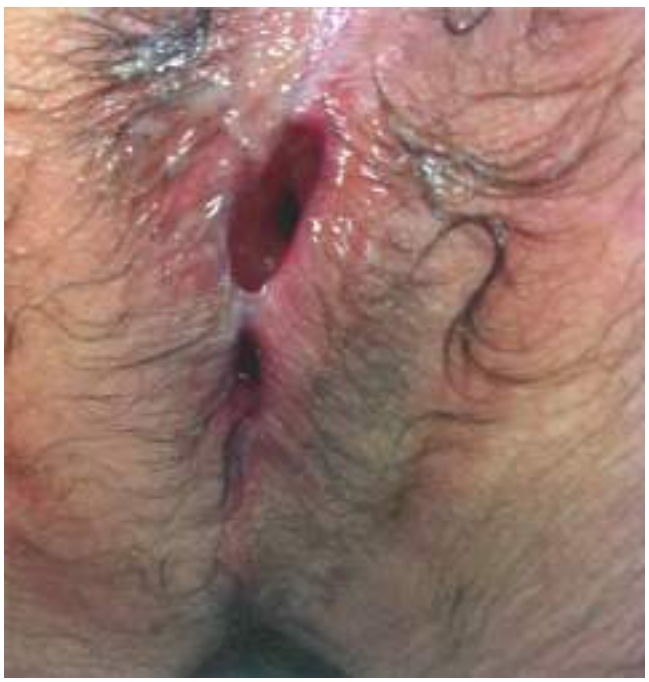

FIGURE 48-23. Non-healed perineal wound 4 years after surgery.

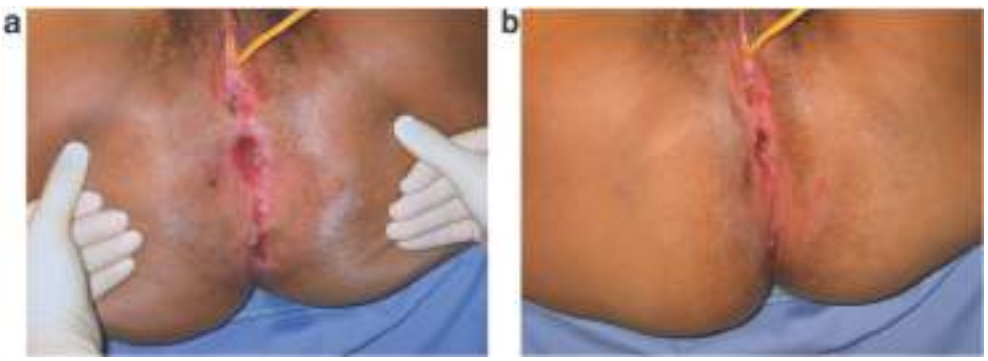

FIGURE 48-22. (**a**) Perineal wounds after diversion (**b**) Near complete healing a few months later.

Anorectal Stricture

Anal or rectal strictures are thought to arise as a consequence of transmural inflammation occurring in those structures. Stricture of the anorectum has been reported in 17 % of patients with perineal CD [59]. Linares and colleagues [165] reported on 44 patients with CD-related strictures of the anorectum. Of 48 strictures, 22 were in the rectum, 15 were in the anus, and 11 were anorectal. Proctitis and perianal disease were present in nearly all of these patients. While some strictures may be asymptomatic, the most common reported symptoms were hematochezia, constipation, perineal pain, and incontinence [165]. The diagnosis is often easily established by digital exam or anoproctoscopy.

Management

Asymptomatic strictures require no specific therapy. Any associated proctitis should be treated medically with systemic and/or rectal preparations. Symptoms of obstructed defecation often can be managed with dilatation using the finger, coaxial balloon, or Hegar dilators [165]. Effective management by rectal sleeve advancement has also been reported [166]. Despite these measures, about half of these patients will eventually come to proctectomy [156, 165].

Anal Cancer

Patients with Crohn's disease are at greater risk for colorectal carcinoma [167]. Long-standing perianal disease increases the risk of both anal squamous [168] and adenocarcinomas [169]. These lesions can occur within the anal canal or within chronic fistula tracts (Fig. 48.24). Diagnosis is made by biopsy. Cancers are relatively uncommon, but are often discovered late [170]. For this reason, routine, periodic biopsy of all persistent, perianal lesions is highly recommended [167]. A change in drainage or increased pain in a persistent fistula tract should raise suspicion of malignant degeneration. Physical exam is often unrewarding and misleading in these cases as scarring, induration, and distorted anatomy are often coexistent.

Management

Management of anorectal cancers in CD patients should follow generally accepted practices applicable to any patient. Pretreatment evaluation should include appropriate imaging studies to rule out metastatic spread. Squamous cancers generally are best treated with combined chemoradiation (Fig. 48.25). Wide local excision is possible if the lesion is small. Adenocarcinomas may require neo-adjuvant chemoradiation and then abdominoperineal resection. Consideration should be given to total proctocolectomy in these situations.

Summary

Perianal Crohn's disease is an all too common problem. Early treatment of perineal sepsis is required in all cases. Simple problems such as tags, hemorrhoids, and simple fistulas can often be managed in routine fashion if the anorectum is otherwise free of CD inflammation. More complicated problems will usually require combined medical and surgical therapy. Thorough understanding of the anatomy and extent of disease and expected risks and benefits of therapy are mandatory. Close collaboration between the surgeon and gastroenterolo-

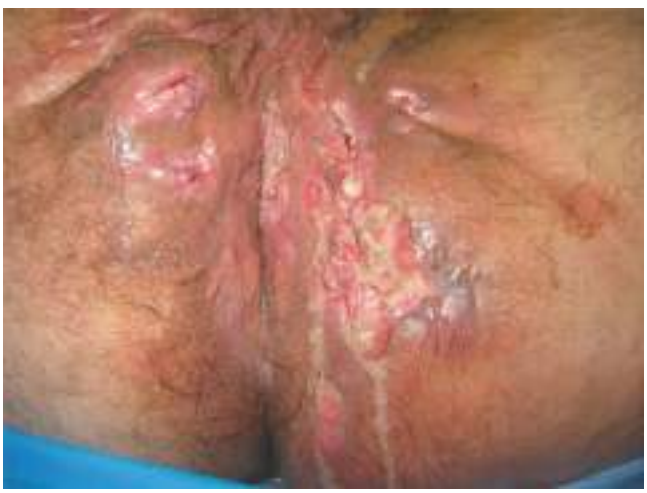

FIGURE 48-24. Squamous carcinoma in multiple fistulous tracts.

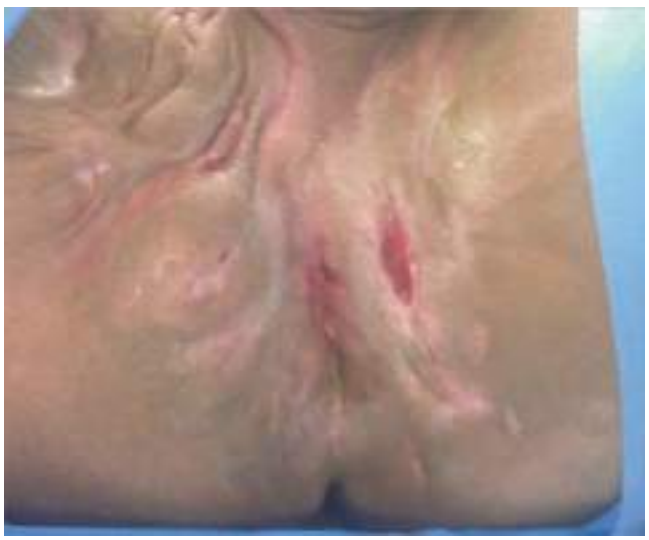

FIGURE 48-25. Squamous carcinoma in multiple fistulous tracts after chemoradiation.

gist, as well as other specialists, is essential. Crohn's disease is not curable. Therapy of perianal disease should be directed toward complete healing when possible, maintenance of rectal function and continence, elimination of sepsis, and overall improvement in quality of life. An algorithm of suggested management is presented in Fig. 48.26.

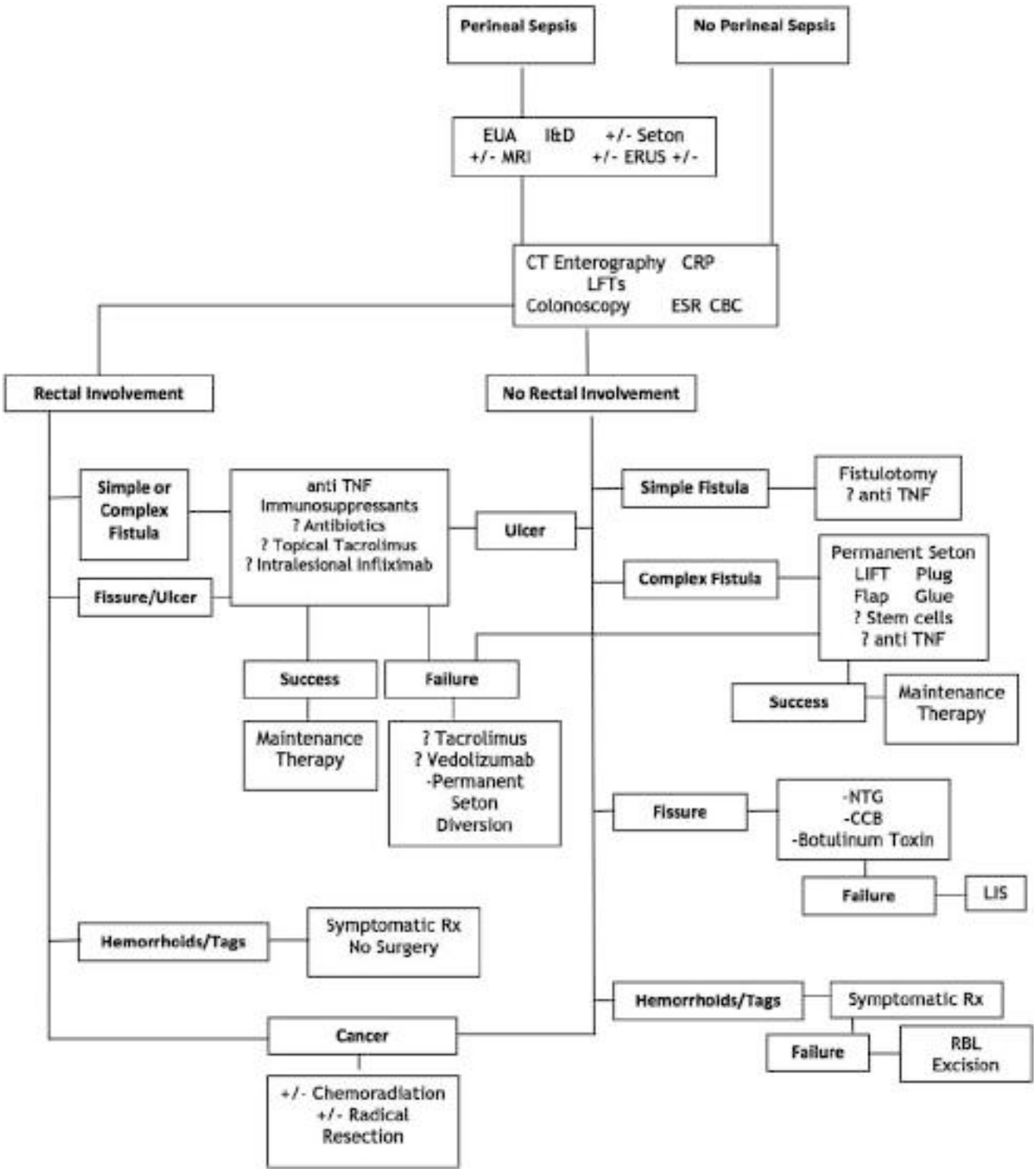

FIGURE 48-26. Algorithm for the management of perineal Crohn's disease. (*EUA* Exam under anesthesia, *I&D* incision and drainage, *MRI* magnetic resonant imaging, *ERUS* endorectal ultrasound, *CT* computed tomography, *CRP* C-reactive protein, *LFTs* liver function tests, *ESR* erythrocyte sedimentation rate, *anti-TNF* anti-tumor necrosis factor, *LIFT* ligation of intersphincteric tract, *NTG* nitroglycerin, *CCB* calcium channel blocker, *LIS* lateral internal sphincterotomy, *RBL* rubber band ligation).

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Crohn's Disease: Surgical Management

Roberta Muldoon and Alan J. Herline

Key Concepts

- Crohn's Disease is a chronic inflammatory bowel disease which primarily affects the terminal ileum and colon; however, it can involve all portions of the GI tract.
- Surgery is utilized in the treatment of Crohn's disease when medical therapy fails to control the disease or when there are complications from the disease (obstruction, perforation, fistulization, bleeding).
- Preoperative evaluation including appropriate imaging, nutritional assessment, as well as consideration of current medications and comorbidities will play a key role in operative planning and potential surgical outcome.
- Surgical intervention for Crohn's Disease should seek to alleviate symptoms while preserving small bowel length whenever possible.
- An ileocolic resection is the most common operative procedure performed on Crohn's patients.
- In cases of toxic colitis, aggressive medical therapy includes corticosteroids and/or rescue infliximab. If the patient fails to respond, total colectomy with end ileostomy is necessary. Delay in treatment can have dire consequences.

Surgery in the Treatment of Crohn's Disease

Crohn's disease is a chronic transmural inflammatory condition that primarily affects the terminal ileum and colon; however, it can involve all portions of the gastrointestinal tract. The course that the disease takes is variable, often manifesting acute attacks on a chronic underlying potentially debilitating condition. The severity of the disease is also variable ranging from a few flares with long periods of remission to constant unrelenting crippling symptoms. The transmural inflammation leads to the complications that are attributed to this disease including strictures, obstructions, fistula, and abscesses. Although Crohn's disease, at this time, is not curable, the goal of treatment is to induce and maintain remission of the disease to control symptoms as well as decrease the complications from this disease. This is accomplished primarily through medications; however, surgery plays an important role in the treatment of this disease. The specific goals of surgery are to determine the ideal timing of surgery and avoid delays in treatment, maximize patient conditioning to decrease postoperative complications, preserve as much small bowel as possible, and decrease recurrence rates. This complex disease does require thorough planning and preparation to have the best outcome from surgery. Special attention needs to be given to the patient's preoperative state including their overall health status, nutritional status, and current medication, as all of these factors can affect the outcome of surgery. The location of the disease, severity of disease, effect on the surrounding organs/tissue, and the patient wishes will all affect which procedure will be in the best interest of the patient. Surgery can have a profound effect on the well-being of the patient with >90 % of patients having significant relief or complete resolution of their symptoms after surgery [1].

Changing Trends in the Era of Immunomodulators and Biologics

There have been significant advances in the diagnosis and treatment of Crohn's disease over the past few decades. This has included an improvement in our ability to diagnose the disease at earlier stages with the use of CT enteroclysis and MRI. In addition to this, there have been significant advances in the medical therapies used to treat the disease over the years including the use of immunomodulators as well as

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biologics. Studies have not only looked at this effect with regard to the natural history of Crohn's disease, but also how these medications have influenced surgical intervention.

Overall, there has been an increase in the incidence and prevalence of Crohn's disease over the last five decades [2]. The highest incidence of Crohn's disease has been reported in Northern Europe, the United Kingdom, and North America [2, 3]. The incidence of Crohn's disease in Olmsted County, Minnesota, was 5.8/100,000 from 1940 to 1993; however, it increased to 7.9/100,000 from 1990 to 2000 [4, 5]. In Northern Denmark, the incidence rate for women with Crohn's disease increased from 4.1/100,000 in 1978–1982 to 10.7/100,000 in 1998–2002. For the same time period, the incidence for men with Crohn's disease increased from 3.2/100,000 to 8.5/100,000 [6]. The incidence rates for North America between 1981 and 1999 ranged from 3.1/100,000 to 14.6/100,000. The prevalence of patients with Crohn's disease in North America ranged from 26 to 198.5 cases per 100,000 from 1988 to 1999 [7]. Again, we see an increase in the prevalence over the years. The prevalence of Crohn's disease in 1991 in Olmsted, Minnesota, was 133 per 100,000, which was 46 % higher than that seen in 1980 [4]. The rate continued to increase in 2001 to 174 cases per 100,000 [5]. The prevalence in northern Denmark was 151 per 100,000 in 2002.

The rate of surgical intervention for Crohn's disease has also changed over the years. Prior to 1995, the reports of Crohn's patients requiring operations ranged from 35 to 78 % with the majority of the resections being done within the first year of diagnosis [8–14]. Ramadas et al. studied the natural history of Crohn's disease in a population-based cohort from Cardiff, Wales. They compared the incidence of surgery for Crohn's disease between three groups based on the year of diagnosis: Group A: 1986–1991, Group B: 1992–1997, and Group C: 1998–2003. The rate of surgery was 59 %, 37 %, and 25 %, respectively [15]. Jess et al. reviewed the population-based cohort of patients from Copenhagen, Demark. Three cohorts of patients were identified: those diagnosed with Crohn's disease during 1962–1987, 1991–1993, and finally 2003–2004. They found that the time from onset of symptoms to diagnosis was significantly longer in the first cohort compared to the second or third cohort. This difference may be due to the introduction of better imaging allowing earlier diagnosis of the disease. Interestingly, they also found the crude rate of intestinal resection was 35 % in cohort 1 versus 28 % in cohort 2 and only 12 % in cohort 3. They attributed this to a more aggressive medical therapeutic approach for the third cohort compared to the first cohort [16]. A similar study was performed in Denmark. Patients in cohort 1 (1979–1986) had a 50.3 % risk of surgery compared to those patients in cohort 4 (2003–2011) who had a 23.3 % risk of surgery [17]. Reported rates of surgical intervention for treatment of Crohn's disease after 1995 range from 20 to 44.3 % [1, 17–21].

A number of studies have looked at the cumulative risk of surgery for Crohn's disease over time. Bernell et al. performed a retrospective population-based study with a cohort of 1936 patients who were diagnosed with Crohn's disease between 1955 and 1989. They found 73.6 % of patients required at least one bowel resection. The absolute cumulative frequency of surgery was 44 % (95 % CI, 42–47 %), 61 % (95 % CI, 59–63 %), and 71 % (95 % CI, 69–73 %), at 1, 5, and 10 years after diagnosis [9]. Vester-Anderson et al. studied patients with Crohn's disease in a prospective population-based study in Denmark. All patients diagnosed with CD between January 2003 and December 2004 were included and then followed through to December 2011. They found 29.1 % of the patients required surgery within the follow-up period. The cumulative risk of first resection during that time period was 14.6 %, 24.6 %, and 28.5 % for 1, 5, and 7 years, respectively [18]. Similarly, in Norway, the cumulative probability of surgery was 13.6 %, 27 %, and 37.9 % for 1, 5, and 10 years, respectively [20]. Comparable numbers were seen in France with cumulative probabilities of first Crohn's disease-related abdominal surgery at 6.5 %, 25.9 %, and 44.3 % for 1, 5, and 9 years, respectively [19]. These studies demonstrate that the longer a patient has the disease the more likely they are to need surgical intervention.

Further evaluation of the natural history of Crohn's disease with regard to surgery revealed that there are factors associated with a higher risk of requiring surgery. Patients who are younger than 40 years of age at the time of diagnosis are more likely to require surgical intervention for treatment of their Crohn's disease [8, 20, 22]. Also, patients with terminal ileal or ileocecal disease are more likely to require surgery compared with those who present with colonic disease [9, 10, 12, 20]. Bernell et al. found that patients with small bowel disease or solely ileocolic disease have a relative risk of 3.2 for undergoing surgery compared with those patients with colorectal disease [9]. Lastly, those with a stricturing, penetrating pattern of disease are more likely to require surgery [20]. Sands et al. evaluated 345 patients who had surgical procedures for Crohn's disease. The study revealed that 20 % of patients required surgery with 50 % of those needing it within the first 6 months after diagnosis. Factors that were found to be associated with earlier need for surgery included smoking, disease of the small bowel without colonic involvement, nausea, vomiting, and abdominal pain at presentation, neutrophil count, and steroid use in the first 6 months of diagnosis [21].

Great strides have been made in the medical treatment of Crohn's disease. The question raised is: have these medications changed the need or the timing of surgery for the treatment of Crohn's disease? Numerous studies have been done, looking at the effect these new medications have had on the outcome of the disease. D'Haens et al. performed a randomized trial including centers from Belgium, Holland, and Germany from 2001 to 2004. They compared patients who received conventional therapy, which was considered treatment with corticosteroids followed by azathioprine followed by infliximab, to those who received combined infliximab and azathioprine. They found that at week 26, 60 % of those in the combined immunosuppression group were in

remission without steroids or surgery compared to 35.9 % in the conventional group [23]. Other studies also support this finding that the long-term use of anti-TNF therapy does decrease the risk of surgery for the treatment of Crohn's disease [19, 24]. Not all studies support this finding. Burke et al. reviewed the national trend of intestinal resection in Ireland. They found that the rate of small bowel or right side resection as well as proctectomies remained the same. The rate of left colon procedures decreased, while the rate of total colectomies increased. This shift may be more a reflection of a change in practice rather than an effect of medication [25]. If one looks at the population-based studies before and after the induction of anti-TNF medication, one will find that the rate of surgical procedures before anti-TNF ranged from 27–61 % at 5 years compared to 25–33 % at 5 years in the era of anti-TNF, suggesting a modest to no decrease [26].

There has been a significant decrease in the need for surgery for the treatment of Crohn's disease since it was first described in 1932; however, the largest drop predates the introduction of biologics and is reflective of the increased use of corticosteroids for treatment of the disease. The continued decrease seen over time is more likely multifactorial. Though there is some data that suggests that immunomodulators and biologics have decreased the need for surgery, the data available needs to be viewed carefully as many studies have short follow-up, include patient that have had the disease for a long period of time prior to starting the anti-TNF, or have already had one or more surgical procedures. All of these factors can complicate data analysis. In addition to this, over the years, we have seen improved diagnostics, which have led to earlier detection of the disease. With earlier detection, the disease may be diagnosed in a milder state and thus not be as likely to need surgical intervention. Earlier detection would also lead to earlier treatment, which could decrease the complications developed from the disease and thus decrease the need for surgical treatment. Continued study of large population-based cohorts with long follow-up will help to shed more light on the effect of biologics on the natural history of the disease.

Indications for Surgery

Crohn's disease is a very complex and heterogeneous disease. Surgeons are called upon to treat Crohn's disease in both the emergent and elective settings. The timing is critical. A multidisciplinary approach including the gastroenterologist, radiologist, and colorectal surgeon is ideal. Non-emergent indications for surgery include failure of medical therapy, chronic obstruction, fistulas, abscesses, cancer, and occasionally quality of life issues. The most common of these is failure of medical therapy to adequately control symptoms. Emergent indications include acute obstruction, perforation, hemorrhage, and toxic colitis.

Failure of Medical Management

Thirty-three to 47 % of patients have surgery for Crohn's disease due to failure of medical management [14, 27]. There are numerous medications used to treat Crohn's disease including corticosteroids, 5-aminosalicylate products, antibiotics, immunomodulators, and biologics. Each of these medications has benefits, but also carries with it risks and side effects. They each also have different time frames to reach maximum effectiveness. When one medication fails, others are tried. Ultimately, when medical options are exhausted, surgery is considered. Failure of medical therapy, therefore, not only includes failure of the medications to control symptoms, but also includes those patients who have symptom control but are experiencing unacceptable side effects or reactions from the medications. Inability to wean off corticosteroids within 3–6 months is also considered failure of medical management [28]. In a population-based study, 173 patients were evaluated with 43 % being treated with steroids. Twenty-eight percent of these patients were found to be steroid dependent at 1 year [29]. It is important to strike a balance between exhausting medical management and avoidance of surgery. Often patients are so determined to avoid surgery that they ultimately suffer with a severe decline in their overall general health and well-being. Timing is important to avoid a worsening health status, development of malnutrition or weight loss, or need for escalating steroid dosages, which all could have significant deleterious effects on surgical outcomes. Scott et al. surveyed patients to evaluate the timing of surgery from the patient perspective. Seventy-four percent stated that they would have preferred the surgery to have been carried out at an earlier time. The reasons given were severity of disease in 97 %, ability to eat normally after the resection in 86 %, feeling of well-being after the resection in 62 %, and cessation of drugs in 43 % of the cases [30].

Obstruction

Approximately 20–25 % of surgeries for Crohn's disease are secondary to obstruction [14, 27, 31]. Transmural inflammation causes bowel wall thickening which over time can fibrose and cause scarring. This stricturing can lead to a chronic obstructive type picture. Since these strictures develop slowly over time, the bowel slowly accommodates to the obstruction. The patients may experience intermittent crampy pain, bloating, and intolerance to certain foods. With repeat acute attacks the scarring worsens, leading to a fibrotic stricture with potential worsening symptoms. Other etiologies of obstruction in Crohn's patients include anastomotic strictures or cancer.

When a patient presents with obstructive symptoms, it is beneficial to try to determine the etiology of the obstruction. Evaluation with CT scan is helpful. It is important to try to

differentiate between an inflammatory stricture, a fibrotic stricture, and an anastomotic stricture. An inflammatory stricture may respond to steroids with symptomatic improvement of the patient without emergent surgical intervention. Once the patient has recovered, they should be reassessed for a possible fibrotic component which may require elective surgical intervention to prevent further episodes of obstruction. Fibrotic strictures are more likely to require surgical intervention. If the obstruction is secondary to an anastomotic stricture, endoscopic dilation may be employed if in the elective setting.

Endoscopic balloon dilation can be considered as part of the therapeutic options for treatment of Crohn's obstructions secondary to strictures. Ajilouni et al. evaluated 83 strictures in 37 Crohn's patients. Thirty-one strictures were anastomotic with the remaining being primary in nature. Ninety percent of the strictures were successfully dilated with 77 % of patients requiring only a single dilation. Fifty percent of those who required a second dilation required no further intervention at 20 months. They found a high success rate (84 % per patient), low complication rate (3 %), low rate of recurrent symptomatic strictures (26 %), and low rate of subsequent surgery (13 %) [32]. Ferlitsch et al. evaluated balloon dilation for treatment of 46 Crohn's patients with strictures. Seven of the 46 were not successfully dilated (15 %) leaving 79 dilations in 39 patients to be evaluated. Ileocolonic anastomosis accounted for 59 % of the strictures with 41 % being primary Crohn's strictures. Two patients experienced perforation, requiring surgery for repair (5 %), and one patient experienced severe bleeding requiring transfusion, but ultimately resolved spontaneously. Thirty-one percent of patients were treated with a single dilation and did not require any further dilation or surgery. Sixty-two percent of patients required repeat intervention with a need for surgery in 33 % of the cases during the 21-month follow-up [33]. These studies do suggest that consideration of endoscopic dilation as a treatment option for Crohn's stricture is feasible, if there is a capable endoscopist to perform the procedure.

Perforation

Perforation is a rare indication for surgery for Crohn's disease occurring only 1–3 % of the time. When this does occur, it is usually associated with a complete obstruction or toxic colitis. Patients are often septic and require immediate surgical treatment. The location of the perforation will depend on the etiology of the perforation. If the perforation is associated with a complete obstruction secondary to a stricture of the small bowel, the site of perforation may be just proximal to the stricture. This is best treated with resection and primary anastomosis, with consideration of a proximal diversion. If however the etiology is a colonic stricture, the site of perforation may be in the cecum due to the thinness of the bowel wall in that location. This is best treated with total abdominal colectomy with end ileostomy. If the perforation is associated with toxic colitis, the perforation will be located at the site of necrosis of the bowel wall. This also should be treated with total abdominal colectomy with end ileostomy.

Bleeding

Massive hemorrhage is a rare event in Crohn's disease accounting for only 2–13 % of surgical indications for operations for Crohn's disease [27, 34–38]. The evaluation and treatment of this complication is similar to other etiologies of gastrointestinal bleed. At presentation, the patient should be resuscitated and stabilized. Next, an attempt to localize the source of the bleed is undertaken. This is typically done with endoscopic evaluation, bleeding scans, or the use of selective angiography. Identification of the source is particularly important in this group of patients so that excessive and unnecessary bowel resection is not performed. Localization with angiography is successful in 40–45 % of cases [35, 37].

Because of the rarity of this indication, there is limited literature on the rates and outcomes of massive hemorrhage in Crohn's patients. Most of the literature is from case reports of small cohorts of patients. Two of the larger studies do give us a glimpse at the seriousness of this complication. Robert et al. found that of the 1526 Crohn's patients treated at The Mount Sinai Hospital between 1960 and 1986, 21 patients presented with severe gastrointestinal hemorrhage. Six of these patients (28.5 %) were treated medically and had no further episodes of bleeding. Ten patients (48 %) were treated with surgical resection and did well. One patient treated initially with surgery rebled and required a second surgery. Thirty percent of those initially treated medically rebled. Of those, one required surgery and ultimately rebled and exsanguinated. Of those patients treated surgically, there was a 15 % incidence of rebleeding [35].

Cirocco et al. had similar findings. They evaluated their four patients in combination with 34 other cases found in the literature for a cohort of 38 patients who had severe hemorrhage with Crohn's disease. Five of the 38 patients exsanguinated (13 %). Excluding these patients, 91 % of patients required surgical intervention to control the bleeding. Ileocolectomy was the most frequent procedure performed in 53 % of the cases with a rebleeding rate after resection of 3.5 % [37].

Since localization of the source of bleeding is so important in these cases, there have been some recommendations regarding methods that can be employed to increase the chances of success. Leowardi et al. suggested leaving the angiocatheter in place and injecting isosulfan blue in the operating room to identify the bowel segment that needs to be resected [1]. Remzi et al. reported the use of provocative angiography with highly selective methylene blue injection to localize an occult small bleeding site. This may help to

identify the segment that needs to be resected when multiple diseased segments are present [39]. Finally, the addition of vasopressin to stop bleeding has been attempted; however, definitive cessation of bleeding has not been reliably accomplished. However, this drug may help to temporize, so that full resuscitation can occur prior to moving forward with definitive surgical treatment.

Abscesses

Abscesses are another common indication for surgery in the Crohn's patient. This accounts for 7–25 % of surgeries performed on Crohn's patients [27, 40–44]. The abscess forms as a result of a microperforation that originates from the transmural inflammation of the diseased bowel. The most common location in the abdomen for these abscesses to occur is the ileocecal region [31]. The size and location of the abscess will determine the best course of treatment. If an inflammatory "mass" is seen on CT or MRI, it first must be determined if the "mass" is an abscess versus a phlegmon. If there is an abscess, evaluation for possible percutaneous drainage should be considered. The majority of patients who develop a spontaneous abscess will ultimately require surgery to resect the diseased portion of bowel since 40 % of these abscesses will have an associated fistula [31]. If the abscess is too small, or not amenable to percutaneous drainage, then a trial of antibiotics could be attempted.

Garcia et al. evaluated 51 patients who presented with intra-abdominal abscesses secondary to Crohn's disease over a 10-year period. Of these patients, 10 were treated medically, 7 were treated with percutaneous drainage, and 34 patients underwent surgery to treat their abscess. Two patients died during the initial hospitalization, one in the percutaneous group and one in the surgical group, and were not included in the analysis. Recurrence of the abscess in each group was 50 %, 67 %, and 12 %, respectively. Fifty percent of those treated non-operatively ultimately required surgery whereas only 12 % treated with surgery required reoperation during the follow-up period [45].

Percutaneous drainage plays a critical role in the treatment algorithm. It is advantageous because it allows for clinical improvement of the patient as well as the possibility of converting an emergent surgery to an elective surgery. Ideally the abscess is drained with resolution of the infection prior to surgical intervention to remove the diseased segment of bowel. In addition, if the abscess is successfully controlled with percutaneous drainage, there is a significant decrease in the risk of septic complications following surgery. Over 90 % of percutaneous drainage procedures are technically successful and over 50 % of patients avoid surgery in the short term [31, 46]. Postoperative abscesses are also seen. These abscesses are more likely to be successfully treated with percutaneous drainage alone than spontaneous abscesses [46]. Multiple abscesses are more likely to require surgical intervention. If the patient either fails drainage or fails to improve, surgery intervention will be needed.

Fistula

It is not surprising that fistulas are associated with Crohn's disease being that it is a transmural inflammatory process. Interestingly, Steinberg found a 17 % incidence of fistula in his series. There is a decreasing trend when comparing his findings with other series that have been published in the past [41, 42, 47, 48]. This trend is potentially the result of heightened awareness regarding the disease as well as the advancement in the medical treatment of the disease. Fistulas can be internal or external. The internal fistulas may be enteroenteric but can also be from bowel to any surrounding structure or organ such as the bladder, vagina, or retroperitoneum. Enterocutaneous fistulas are considered external fistulas. Often there is a stenotic area in the bowel wall distal to where the fistula originates which increases the intraluminal pressure. This circumstance predisposes to the formation of these fistulas [1]. Only fistulas that are symptomatic require treatment. For example, a fistula that extends from terminal ileum to a closely adjacent loop of small bowel would not necessarily require treatment. However, a fistula that bypasses a long segment of bowel such as a gastrocolic fistula would more likely cause complications and require such intervention. Fistulas account for 15–24 % of surgeries performed for Crohn's disease [14, 27].

Enteroenteric fistulas are the most common type of abdominal fistula found in Crohn's disease with majority originating from the terminal ileum [1, 31]. The fistulas originate from the disease portion of bowel; however, these can penetrate into normal surrounding tissue. Ileosigmoid is the most common of this type of fistula [1, 27]. These are typically treated with excision of the diseased bowel, excision or division of the fistula tract, and repair of the non-inflamed bowel wall. Patients can also present with a psoas abscess which is the result of a blind ending fistula from the ileum to the retroperitoneum. These require excision of the inflamed bowel to treat and prevent recurrence [1].

Enterocutaneous fistulas can occur either spontaneously or as a result of prior surgery. These fistulas can be quite detrimental to the patient causing dehydration, metabolic abnormalities, and skin damage as well as interfering with daily activities secondary to uncontrolled output. The etiology of these fistulas determines the best treatment as well as the likelihood of success. Seventy-five to eighty-five percent of enterocutaneous fistulas occur in the post-op period and are secondary to either anastomotic leaks or inadvertent injuries to the bowel. Because this bowel is healthy, the fistula is more likely to close with conservative measures. Fifteen to twenty five percent are spontaneous enterocutaneous fistula

which is due to abnormal bowels which have been affected by Crohn's disease, radiation, or cancer. These types of fistulas are unlikely to heal without surgical intervention [31, 49, 50].

Poritz et al. did a retrospective review of 51 patients with Crohn's disease who underwent surgery for fistula between 1983 and 2000. They found that 64 % had enterocutaneous fistula, 21 % had colocutaneous fistula, and 14 % were associated with a prior anastomosis. The onset of the fistula was postoperative in 23 %, post-abscess drainage in 27 %, and recurrent disease in 50 %. Seventy two percent of the patients were treated conservatively first, in an attempt to control sepsis and inflammation. Eight of the 51 patients (16 %) had a recurrence of the fistula with a mean time to recurrence of 27.0 ±9.0 months with majority being farther out from surgery suggesting recurrence of disease [51].

Cancer and Dysplasia

Patients with Crohn's disease have an increased risk of developing cancer in their lifetime. A recent meta-analysis by Laukoetter et al. evaluated 20 clinical studies for a total of 40,547 patients with Crohn's disease-associated cancer (CDAC). They found the overall incidence of CDAC in any Crohn's patient was 0.8/1000 person years duration (pyd) (95 %CI, 0.6–1.0/1000 pyd). This means that during a one-year observation period, 0.8 Crohn's disease patients out of 1000 developed a Crohn's disease-associated cancer. Crohn's disease-associated colorectal cancer had a pooled incidence of 0.5/1000 pyd (95%CI, 0.3–0.6/1000). The prevalence was 0.24 % (95 %CI, 0.19–0.28). The pooled incidence of CD-associated small bowel cancer was 0.3/1000 pyd (95 %CI. 0.1–0.5). The prevalence was 0.16 % (95 %CI, 0.12–0.21). They found that the incidence of a cancer arising from a CD-associated fistula was 0.2/1000 pyd (95 %CI, 0–0.4/1000) [52]. In summary, a patient with CD has a two- to threefold increased risk of colorectal cancer compared to the general population [52, 53]. With regard to small bowel cancer, there is an 18.75-fold increase [52]. Von Roon et al. in their meta-analysis also found an increased risk of development of small bowel and colon cancer in patients with Crohn's disease; however, interestingly they did not see an increased risk of rectal cancer [54].

A number of studies have found a male predominance in the development of cancer in Crohn's disease [55, 56]. Studies have shown that the average age at diagnosis of CDAC was 49–56 years which is about 10–15 years younger than the average age for sporadic bowel cancers [24, 55, 57]. The mean duration of disease from the onset of Crohn's disease to diagnosis of cancer is 20 years [55]. Ribeiro et al. evaluated 30 patients with 33 adenocarcinomas of the large bowel. Fifty percent of the patients had ileocolitis, 27 % had colitis, and 23 % had ileitis only. Five patients had cancer in excluded bowel. They found that 73 % of the cancers were distal to the splenic flexure. Interestingly, 58 % of the cancer occurred in areas of active disease, whereas 42 % occurred in areas that were distant from active disease. Thirteen percent were associated with a fistula and synchronous cancers were found in 10–20 % of patients [55, 57].

Survival seems to be worse for patients with Crohn's disease. Overall five-year survival was 41.3–44 % [24, 55]. A subgroup analysis looked at the difference in survival for those cancers that were found in bypassed bowel versus those found in bowel that was in continuity. Five-year survival of those patients with cancer in bowel that was in continuity was 56 % compared to 0 % for those cancers in bypassed bowel [55]. Literature supports that there is a higher risk of developing cancer in bypassed bowel and that it comes with a poor prognosis. It is for this reason that bypass surgery should be avoided and that defunctionalized rectal stumps should be removed if there is no plan for the patient to be placed back in continuity. Lastly, there is an increased risk of developing cancer in the area of a stricture. Levasz et al. found the mean overall CRC incidence rate to be 7.73 per 10,000 patient years; however, this incidence rate increased to 56.9 per 10,000 patient years when the patients presented with stenosing disease in the colon [58]. This suggests that colonic strictures need to be closely monitored if not surgically resected.

High-grade dysplasia (HGD) found in patients with ulcerative colitis is an indication for colectomy. The same is true of Crohn's disease. Kiran et al. evaluated 50 patients who had undergone colectomy for CD-associated dysplasia. The predictive value of HGD for a final HGD or cancer diagnosis was 73 %. The predictive value of LGD on biopsy for HGD in the colectomy specimen was 36 %. Forty-four percent of patients who underwent a total abdominal proctocolectomy or a subtotal colectomy had multifocal dysplasia and 40 % of cancer patients had evidence of dysplasia remote from the cancer site [59]. Studies have shown the association of HGD with colon cancers in virtually all cases [57, 60]. In addition to this, examination of 100 bowel specimens resected for noncancer-associated Crohn's disease revealed only a 2 % incidence of mild dysplasia [61]. This supports the recommendation that the presence of HGD should prompt the discussion of colectomy.

Toxic Colitis

Severe colitis is a serious and potentially life-threatening condition if not treated appropriately and in a timely manner. Patients with severe colitis typically present with a flare of their disease with signs of toxicity. Truelove and Witts characterized toxic colitis by the presence of severe diarrhea (greater than 6 bloody bms per day) in addition to fever (>37.5 °C), tachycardia (>90 bpm), anemia (<10.5 g/dl), and an elevated erythrocyte sedimentation rate (>30 mm/h) [62]. The addition of dilation of the colon (toxic megacolon) to

Table 49-1. Diagnostic criteria for toxic megacolon

Radiographic evidence of colonic distension
At least three of the following:
Fever >38 °C (101.5 °F)
Heart Rate >120 bpm
Neutrophilic leukocytosis $>10.5 \times 10^9$/L
Anemia
In addition to the above, at least one of the following:
Dehydration
Altered consciousness
Electrolyte disturbances
Hypotension

this compilation of symptoms increases further the risk of complications and could lead to a potentially fatal outcome. The most widely used diagnostic criteria for toxic megacolon was proposed by Jalan et al. (Table 49-1) [63]. A multidisciplinary approach for the treatment of these patients is critical to effectively manage these patients. Accurate assessment of the disease severity and close observation of changes in the patient's clinical status are necessary to appropriately treat this disease. If a patient presents with evidence of severe hemorrhage, intestinal perforation, or septic shock with systemic instability, then emergent surgery should be performed as soon as the patient is adequately resuscitated [64]. If these conditions are not present, aggressive medical treatment is appropriate with close observation.

Initial medical management of these patients includes efforts to resuscitate the patient, including intravenous hydration and correction of electrolyte abnormalities, in particular potassium and magnesium. These need to be kept in the normal range as hypokalemia and hypomagnesemia may predispose to colonic distention. Blood transfusions may be necessary. Though there is no proven advantage to placing patients on bowel rest and total parenteral nutrition, if there is concern for the need for urgent operative intervention, patients should be made nil per os and nutritional assessment should be made [65, 66]. Total parenteral nutrition may be necessary to optimize the nutritional status of the patient. It is important to rule out other possible causes of diarrhea including *Clostridium difficile* as well as cytomegalovirus. This can be assessed by direct evaluation of the stool for microbes, evaluation of stool for *C. difficile* toxin, or careful, limited endoscopic examination. Full colonoscopy is contraindicated as this could potentially lead to perforation. Daily abdominal films should be obtained if there is presence of abdominal distension so colonic dilation can be assessed and monitored. Anticholinergics, antidiarrheals, and narcotics should be avoided in these cases as they can lead to worsening colonic atony and dilation. In the absence of proven infection, control trials have not shown a benefit of the addition of antibiotics in the treatment of severe colitis [67, 68]. However, if an infection is suspected, it may be appropriate to treat with antibiotics. Patients with inflammatory bowel disease have a higher risk for thromboembolic disease, so special attention needs to be made for prophylaxis of this potentially fatal complication.

The mainstay of medical therapy is the administration of corticosteroids in a daily equivalent dose of hydrocortisone 300 mg (in divided doses) or methylprednisolone 60 mg (in divided doses) [69]. There is no benefit to treat with higher daily dosages, which exposes patients to a higher potential rate of side effects with no proven benefit. Patients who do not respond to steroids have limited options, which include either rescue infliximab or colectomy. Several studies have shown infliximab as an effective rescue therapy for acute severe colitis in ulcerative colitis [70–72]. Jarnerot et al. randomized 45 patients with severe colitis to receive a single infusion of infliximab (5 mg/kg) or placebo beginning four days after steroid initiation. Twenty-nine percent of the infliximab group required a colectomy within 3 months of randomization versus 67 % of those who received placebo [71].

Those patients who do not respond to medical therapy or have a decline in their clinical status within 24–72 h of initiation of treatment require emergent surgery. Delay of surgery can lead to dire consequences and increased postoperative complications [73]. Mortality rates dramatically increase in those who have suffered a perforation, increasing from 2 to 8 % up to 27 to 40 % [74, 75]. The procedure of choice for these patients is a total abdominal colectomy with end ileostomy. Emergent proctectomy is avoided if possible for a number of reasons. Emergent proctectomy in an acutely ill patient increases the morbidity and mortality of the procedure. Secondly, some patients will be candidates for a restorative procedure if the rectal and perianal region is not involved in Crohn's disease. Resection at the initial operation would obviate any possibility of reconstruction. Lastly, if there is a question as to the diagnosis, Crohn's versus ulcerative colitis, it is best to preserve the rectum for possible later restorative surgery should the patient choose that and pathology is favorable. Emergent proctectomy is rarely indicated; however, it is performed for rectal hemorrhage or rectal perforation. For those who do have a total abdominal colectomy with end ileostomy, majority will ultimately undergo a proctectomy. Harling et al. did a retrospective study looking at the outcome of the rectum after this procedure. They found that of the 84 patients they evaluated, 25 (30 %) patients ultimately underwent an ileorectal anastomosis. Of these, 16 patients (19 %) were functional at the end of the study period [76]. This suggests that a small select group of patients without rectal or perianal involvement may be candidates for a restorative procedure.

Surgical Considerations

Patients presenting with Crohn's disease, with either failure of medical management or complications from the disease, are a very heterogeneous group of patients. Their presentation may range from a simple terminal ileal stricture causing

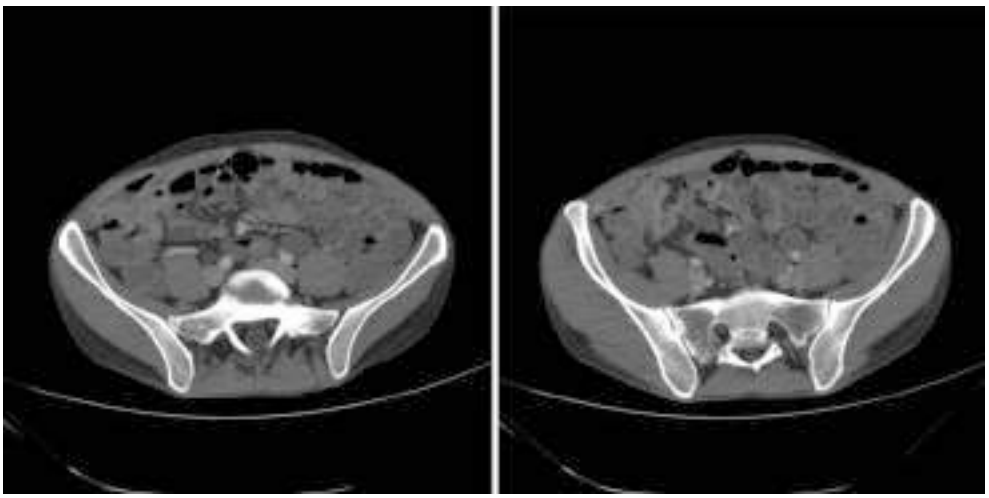

FIGURE 49-1. CT scan in a patient with Crohn's disease demonstrating fluid-filled bowel loops, thickened terminal ileum, and a subcutaneous right lower quadrant abscess.

minor obstructive symptoms, to a patient with a large inflammatory mass encompassing a significant portion of the bowel, to a patient who is hypotensive and septic from toxic megacolon. Each of these requires a different level of urgency as well as a different level of operative planning; however, all of them require careful consideration to details about the individual case as well as the optimal timing of the surgery. The basic goals of surgery in Crohn's disease are the same for all cases. Remembering basic axioms about the disease help to make sound surgical decisions when caring for these patients. Surgery for Crohn's disease is not curative, so preserving the small bowel when possible is paramount. Recurrence occurs in the majority of patients so should be considered in operative planning. Careful preoperative evaluation includes attention to the patient's overall clinical status; specific attention needs to be made of their nutritional status, current medications, prior surgeries, current disease status, as well as patient wishes.

Preoperative Evaluation

Information obtained from the history and physical, past medical, and surgical records, endoscopy, as well as imaging studies will be critical to operative planning and timing. Nutritional assessment as well as medication usage deserves special attention as this will affect healing and may increase postoperative complications. Preoperative imaging will give information regarding severity, involvement of surrounding structures, current infections, resectability, and possible risk of short bowel syndrome which will ultimately dictate what preoperative measures need to be taken as well as determine the best timing for intervention (Figure 49-1).

The amount of inflammation noted on the CT scan will help to determine the amount of bowel involved and potentially the amount that may need to be resected. When a simple fibrotic stricture is seen that is symptomatic, surgery can be scheduled without delay. On the other hand, if there is a large phlegmon with significant bowel involvement, rushing in to perform surgery may put significant amount of normal bowel at risk of injury. These patients may benefit from a period of bowel rest, steroid administration, as well as total parenteral nutrition. This will allow some of the inflammation to settle and will decrease the morbidity of the procedure. The diseased bowel will still need to be addressed; however, the benefit of waiting is to minimize the amount of normal bowel that would be at risk.

History and Physical

Initial evaluation begins with a complete history and physical. Accurate and detailed information regarding the patient's current set of symptoms is very important and helpful in deciding if surgery is indicated. Asymptomatic patients should not undergo surgery. Understanding how and when their disease flares is also helpful in understanding their disease. Questions should be queried to the patient regarding possible current or past perirectal involvement. Included in this detailed history of present illness should be specific information regarding their diet, including any dietary restrictions they have put on themselves because of the disease, as well as any change in weight. Patients will often state they are "doing well" and only on specific questioning will it become evident that they are severely limited in their dietary consumption. A complete list of current and past

medications, comorbid conditions, smoking status, as well as a complete list of any prior surgeries should be obtained. Medical and surgical records including prior endoscopies and pathologic evaluations should also be obtained. Gaining as much information about prior surgeries as possible not only sheds light on the current anatomy but also how much bowel has been previously resected. Each of these pieces of information will play a role in what operation is indicated and when the timing is appropriate.

A complete physical exam should then be performed. The vital signs will indicate the acuity of the patient and need for potential resuscitation. During the abdominal examination, special attention is paid to areas of tenderness, prior scars, evidence of draining fistula, as well as palpable masses. The rectal examination may reveal perianal Crohn's disease with visible fistula, fissures, skin tags, or abscesses. Digital rectal exam may reveal anal stenosis, scarring, or bleeding. Knowledge of rectal or perianal involvement is very important when planning operative management.

Imaging/Endoscopy

Further testing is necessary to determine the extent and severity of the disease. Endoscopic evaluation of the entire colon and terminal ileum is necessary as well as upper gastroduodenoscopy if there is concern for upper tract involvement. Biopsies of the terminal ileum should be obtained. Additional biopsies should be taken to confirm areas of inflammation as well as to confirm areas that appear to be normal. Mucosal abnormalities should also be sampled to assess for dysplasia.

CT enterography (CTE) or MRI enterography (MRE) can both be useful in assessing the extent and severity of disease. Because both of these tests cannot only give information regarding the bowel wall but also about extraenteric structures, they have essentially replaced the use of barium studies as the preferred diagnostic tool. The technique to get optimal visualization consists of having the patient drink a large volume of neutral or low-density oral contrast (enterography) which will give adequate luminal distention. In addition, an intravenous contrast agent is given which will optimize bowel wall enhancement [77]. There are specific features on CTE that can help determine whether the disease seen is active inflammatory disease versus chronic fibrostenotic disease. The former is more likely to respond to medical therapy, whereas the latter is more likely to require surgical intervention.

Enteric findings such as mural hyperenhancement, bowel wall thickening, mural stratification, and extraenteric findings such as engorged vasa recta ("comb sign") and increased attenuation of the mesenteric fat are features of active inflammatory small bowel Crohn's disease [77]. Of these, mural hyperenhancement and bowel wall thickening is the most sensitive for active disease [78]. Increased attenuation of the mesenteric fat is due to edema and engorgement of the vasa recta. The "comb sign" refers to engorged vasa recta that penetrate the bowel wall perpendicular to the bowel lumen, giving the appearance of a comb. Strictures without hyperenhancement or other signs of active inflammation as well as mucosal fat deposition, fibrofatty proliferation, and sacculations are all CTE signs of chronic fibrostenosing disease. Sacculations occur due to preferential involvement of the mesenteric side of the bowel by the inflammatory process. This causes asymmetric fibrosis on the mesenteric side of the bowel. Increased intraluminal pressure then causes sacculations on the antimesenteric bowel wall. Areas of tethering of the bowel with enhancing tracts between bowel loops or other structures suggest evidence of a fistula [77]. Abscesses are readily identified by CTE.

CT enterography and MRI enterography both have their own pros and cons and as such have different clinical scenarios in which each is the preferred test. MRI enterography also reveals information regarding the presence of active inflammatory disease versus fibrostenosing disease; however, it does this without the exposure of ionizing radiation [79]. This is particularly important since this disease affects young patients who will potentially need many of these exams over the course of their lifetime. MRE is better at demonstrating endoluminal abnormalities and ulcerations. CTE, however, is better in the emergent setting in that it takes less time, does not require the patient to be able to hold their breath to the same degree as MRE, and is better at diagnosing perforations [80]. The sensitivity and specificity of MRE for detecting small bowel Crohn's disease is 74 % and 80 %, respectively, compared to 83 % and 70 % achieved with CTE. These differences do not reach statistical significance. Abscesses are accurately detected by both modalities. The sensitivities for detecting stenosis and fistula are relatively low in both modalities. Positive predictive values for both these modalities are good; however, negative predictive value in both is low [81, 82]. Surgeons need to be mindful of this and search for additional pathology which may not have been detected on preoperative imaging at the time of exploration. Patients also need to be counseled that additional findings discovered at the time of surgery may alter the operative plan.

Nutritional Assessment and Role of TPN in Crohn's Treatment

Poor nutrition has been linked to delayed wound healing, decline in physiologic and psychiatric function, altered immune function, and increased postoperative complications. Various markers of nutrition have been evaluated including weight loss, protein depletion, serum albumin, and pre-albumin to assess their predictive value. Each of these has shown a link between malnutrition and poor surgical outcomes [83–85]. Dr. Studley, in 1936, made a pivotal

observation that linked severe preoperative weight loss and postoperative mortality. He found that a loss of >20 % normal body weight preoperatively in patients results in a 33.3 % mortality rate compared to a 3.5 % mortality rate in those who had <20 % body weight loss [86]. Seltzer et al. reviewed 4382 elective surgical patients and compared those who had a >10 lb unintentional weight loss versus those who had a <10 lb unintentional weight loss. He found the mortality to be 5.8 % versus 0.3 %, respectively [87]. Others have found that weight loss in conjunction with physiologic impairment is an even better indicator of postoperative complications [83].

Hypoalbuminemia has also been shown to be a good predictor of postoperative morbidity and mortality. Gibbs et al. performed a prospective observational study including 54,215 patients. They found that a drop in serum albumin from a concentration >4.6 g/dl to less than 2.1 g/dl was associated with an exponential increase in mortality from <1 to 29 % as well as in morbidity rates from 10 to 65 % [88]. Similarly, Lindor et al. found that patients had a complication rate of 29 % with an albumin level <3.1 g/dl compared to only 6 % when the serum albumin was in the normal range [89].

It is estimated that 80 % of Crohn's patients will have some degree of malnutrition and that weight loss has been reported in 65–76 % of patients with Crohn's disease depending on the severity of disease [90]. Total parenteral nutrition is a treatment option to improve the patient's nutritional status when enteral feeds are not possible. Ideal administration includes a balance of carbohydrates, protein, fats, and minerals. Though TPN does replenish much-needed nutrients, there is insufficient data to clearly show its benefit as a sole primary treatment of the disease. Though some studies did show initial remission, the recurrence rate was very high [91–93]. Greenberg et al. specifically studied the utility of bowel rest as a means to control Crohn's disease. Fifty-one patients were randomized to TPN, partial parenteral nutrition (PPN) plus a liquid feed of a specific formula delivered via NG tube, or PPN with a regular diet. Remission occurred in 71 % of those on TPN, 58 % of those on PPN with the addition of the specific formula, and 60 % of those on PPN with regular diet. The probability of being in remission in 1 year was 42 %, 55 %, and 56 % respectively. This did not reach statistical significance and the authors concluded that bowel rest did not contribute to primary treatment of the disease [94].

These studies found that bowel rest and TPN is not an effective primary treatment of Crohn's disease. This is not to say TPN does not have its role in the treatment of Crohn's disease. Correction of malnutrition preoperatively to lessen the risk of postoperative complications has also been studied with promising results. Rombeau et al. found that patients who received preoperative total parenteral nutrition for at least 5 days had significantly fewer postoperative complications compared to those who did not [85]. Likewise, Jacobson et al. compared 15 CD patients treated with TPN for at least 18 days with matched controls. They found that there were no significant early postoperative complications in the TPN-treated group, whereas there was a 27.6 % complication rate seen in the control group [95]. It has also been shown that those patients treated with TPN preoperatively had less bowel resected when compared to those who did not get treated with TPN [96]. These results do have to be viewed cautiously as each of these studies has a small sample size. A larger study was performed by the Veterans Affairs Group who studied 395 malnourished patients who required laparotomy or noncardiac thoracotomy. They were randomly assigned to either receive TPN for 7–15 days before surgery as well as 3 days afterward or receive no perioperative TPN. The rates of major complications as well as mortality were similar between the two groups. Those treated with TPN did have a higher infectious complication rate compared to the non-TPN group (14.1 % vs. 6.4 %, respectively.) A subgroup was studied finding that severely malnourished patients who received TPN had fewer noninfectious complications compared to the controls (5 % vs. 43 %, respectively). This would suggest a more selective approach to the use of preoperative TPN [97].

TPN is used in Crohn's disease, not only to correct severe malnutrition prior to surgical intervention but also for the treatment of intestinal fistula, treatment of short bowel syndrome, and for nutritional support when enteric feeds are not possible. Treatment with TPN does not come without its own price. Complications can be divided into those related to access, gastrointestinal, metabolic, or infectious. Access-related complications include injuries sustained during insertion of catheters (i.e., vascular injuries, pneumothorax, etc.), thrombosis, and embolization. Liver complications are the most important gastrointestinal complication related to treatment with TPN. This includes cholestasis, cholangitis, liver dysfunction, as well as elevation of transaminases. Metabolic imbalances can occur with either excess or inadequate administration of water, glucose, electrolytes, amino acids, fats, and minerals. Close monitoring is necessary to avoid such complications. Lastly, there can be infectious complications with the most common being catheter-related infections [90].

In summary, patients should be evaluated for malnutrition. Assessment of body mass index, preoperative weight loss, as well as serum albumin, pre-albumin, and transferrin should be included [84, 85, 98]. Severe malnutrition is defined as a greater than 10 % loss of body weight as well as albumin <3.5 and pre-albumin <15 mg/dl. If severe malnutrition is confirmed, administration of preoperative total parenteral nutrition should be considered. If TPN administration is not feasible either due to confounding factors or necessity of urgent or emergent surgery, then consideration should be made to either proximal divert if an anastomosis is formed or the avoidance of an anastomosis with creation of an end stoma until the time that the nutritional status can be improved.

Medication Effects on Surgical Outcomes

When Crohn's was first described, the medical treatment options were limited and included primarily corticosteroids. Though steroids remain a key medication for the treatment of acute flares, numerous other medications have been introduced to control this disease. Immunomodulators came on the scene with the thiopurines being the most commonly used and have been shown to be effective in the treatment of Crohn's disease. These include 6-mercaptopurine as well as azathioprine. These are slower acting medications so are used primarily to maintain remission [99, 100]. Antitumor necrosis factor (anti-TNF) agents were introduced in 1997 and have been shown to be very effective in the treatment of Crohn's disease [101]. Currently, there are three anti-TNF agents available: adalimumab, certolizumab, and infliximab. These agents have been shown to not only induce and maintain remission but also promote mucosal healing. A major concern with each of these medications was what, if any, effect there may be on surgical outcomes.

It is generally agreed that corticosteroids negatively affect wound healing and therefore increase postoperative complications. There have been numerous studies that have shown a deleterious effect on wound healing as well as healing of bowel anastomoses [102–104]. Stuck et al. in a meta-analysis of 71 controlled clinical trials showed an increase in the rate of postoperative infection for those patients on steroids compared to controls, 12.7 % versus 8 %, respectively. The correlation was not seen in those whose steroid doses were <10 mg/day and the rate of infection increased as the dose of steroids increased [105]. Subramanian et al. reviewed seven observational studies which included 1532 patients and found that the risk of postoperative infections was 1.6 times higher in those patients taking corticosteroids compared to control groups [106]. Lastly, Aberra et al. also found a correlation with steroid use and increased postoperative infectious complications. They did not see an increase risk of complications with the addition of thiopurine medications [107]. There have been some studies whose data did not support these findings. Bruewer et al. evaluated 397 patients who had undergone surgery for Crohn's disease at their institution. They divided the cohorts based on steroid usage: no steroids, low dose, or high dose for at least one month prior to surgery. They did not find any association between those who were given steroids and those who were steroid free [108]. Mascarenhas et al. studied 791 patients who underwent either ileocolic resection or right hemicolectomy. Ninety three of these were patients with Crohn's disease. They found that the patients with Crohn's disease did not have an increased risk of postoperative complications compared to patients without Crohn's disease even with the use of steroids and biologics in the preoperative time period [109].

With the introduction of infliximab, yet another potential contributor to postoperative complications was added to the mix. As with the other medications, numerous studies have been undertaken looking at the potential association of anti-TNF medications and postoperative complications. The majority of the studies did not find an association between the use of anti-TNF agents and increase in postoperative complications [110–112]. Kunitake et al. examined a large IBD patient cohort (413 patients) comparing the postoperative complications in those patient who had received preoperative infliximab and those who had not. They found that infliximab was not associated with an increased rate of postoperative complications [110]. Colombel et al. evaluated 270 patients who had been operated on for Crohn's disease. Of these patients, 107 had received steroids, 105 had received immunosuppressive agents (AZA, 6-MP, methotrexate), and 52 had received infliximab. Nineteen percent of patients had a septic complication. Though they found a trend linking steroid use and postoperative infectious complications, it was not statistically significant. They did not find an association between either immunosuppressive medications or infliximab with postoperative complications [111]. There have been a few studies that have either shown a trend or a statistically significant association between the use of infliximab and increased postoperative complications [113, 114]. Appau et al. studied sixty of 389 Crohn's patients who had undergone an ileocolic resection and had received infliximab. Comparison to a matched group of patients who did not receive infliximab showed that the infliximab group had a higher rate of readmission, sepsis, and intra-abdominal abscess.

The potential effect of combination therapy has also been evaluated. Brafford et al. evaluated not only single medication effect but also combination therapy. Patients who received steroids within 6 weeks of surgery, thiopurines, or anti-TNF agents within 90 days of surgery or any combination had neither higher rates of overall morbidly nor septic complications when compared with those who did not receive these medications preoperatively. The finding that steroids did not show an association may be due to the relatively low doses of steroids the patients in this series received [112]. Ali et al. performed a meta-analysis in an attempt to gain a better perspective on this issue. Twenty-one eligible studies were included (20 retrospective and 1 prospective) with 6899 patients. Interestingly, when evaluated individually, most studies failed to find an association between preoperative immunosuppressive medications and postoperative complications. Only 2/14 (14 %), 4/13 (31 %), and 1/8 (13 %) found an association between postoperative complications and preoperative anti-TNF agents, steroids, and thiopurines, respectively. In the meta-analysis, however, both antitumor necrosis factor agents and corticosteroids were found to have a higher risk of postoperative infectious complications. Anti-TNF agents were also significantly associated with wound infections and septic shock. There was no association with use of thiopurines and postoperative complications [115].

These studies do need to be interpreted with some caution. The majority of the studies are underpowered as well as being case cohorts and retrospective in design. In addition to this, there are significant confounding factors associated with this particular area of study as well as numerous intrinsic limitations. From a practical standpoint, most of the time, it is not feasible to stop these medications prior to surgery without incurring the risk associated with a potential acute flare and worsening of the clinical status of the patient. In light of this, the best approach is to wean steroids when possible keeping in mind that trying to wean them too aggressively or stopping them may cause a relapse which may increase the operative morbidity and mortality. If steroids cannot be weaned, one should consider either avoidance of an anastomosis or protect a created anastomosis with a diverting loop ileostomy. There has not been shown a clear association between postoperative complications and the use of thiopurines so these can continue up to the time of surgery. With regard to infliximab, an attempt should be made to schedule surgery just prior to the next scheduled dose (i.e., at the end of the 8-week dosing schedule) which may limit complications.

Operative Considerations: Overview

The primary goal of surgery for patients with Crohn's disease is to alleviate symptoms while preserving as much small bowel as possible. Going into surgery with as much information as possible is helpful. This includes as much information about the patient's symptoms as possible as well as the extent of disease and possible other organs that may be affected. Depending on which other organs may be involved, it may be helpful to have other specialists available. If there is significant inflammation around the ureters, ureteral stents may be helpful. Lastly, it is important to understand the wishes of the patients, especially regarding the creation of stomas, since intraoperative decision-making is frequent and changes in the operative plan may be necessary if additional pathology is discovered.

A few general principles apply when operating for Crohn's disease. First, complete exploration of the abdomen should be performed, assessing the extent of disease as well as involvement of surrounding bowel or other structures. It is critical to understand the extent of disease prior to resecting any bowel. Diseased bowel is often visible; however, the assessment can be further confirmed with palpation of the bowel and the adjacent mesentery. Involved bowel will feel thickened as will the adjacent mesentery. Normal bowel will be supple with a clearly palpable mesenteric edge. Significant inflammation in the area of the diseased bowel can affect the surrounding normal bowel loops. Every attempt should be made to preserve this uninvolved bowel. Care should be taken when handling the bowel and its mesentery because, depending on the amount of inflammation, the mesentery can be quite friable and even gentle retraction can lead to disruption of the mesentery and troublesome bleeding. Fistulas are common and arise from disease bowel. These fistulas cannot only affect other diseased bowel loops but can also extend to normal bowel loops or other nearby structures, like the bladder or vagina. Typically the diseased bowel loop will need resection while the "innocent bystander" can be preserved with its fistula site being treated with wedge resection and primary closure. Determination of extent of resection is based on macroscopic disease alone so a small margin is all that is needed. There is no need to assess microscopic margins. Fundamental principles apply when creating an anastomosis in a Crohn's patient. The bowel should be fully mobilized to assure there is no tension on the anastomosis and the bowel should be assessed for adequate blood supply.

There have been a number of studies that have compared hand-sewn end-to-end anastomosis and stapled side-to-side anastomosis in Crohn's disease in an attempt to determine if one was superior. A Cochrane Review by Choy et al. searched for randomized controlled trials comparing the stapled and hand-sewn anastomosis in ileocolic resections. Seven trials with 1125 patients were included. They found stapled anastomosis was associated with significantly fewer anastomotic leaks compared to hand-sewn (S=2.5 %, HS=6 %, p=0.03) [116]. Numerous studies looking specifically at anastomoses created in patients with Crohn's disease have shown that the stapled side-to-side anastomosis has fewer anastomotic leaks, shorter OR time, as well as lower rate of reoperation for recurrence of disease [117–119].

The notion that the type of anastomosis created could influence the rate of recurrent disease prompted more studies. Ikeuchi et al. looked specifically at the long-term effects of hand-sewn versus stapled anastomosis in a small prospective randomized trial. They found no statistically significant difference in the recurrence of Crohn's disease at the anastomosis at 5 years; however, the reoperative rate was 8 % in the stapled group versus 25 % in the hand-sewn group. This rate continues to increase to 18 % and 49 %, respectively, at the 7-year follow-up [120]. A meta-analysis comparing conventional sutured end-to-end anastomosis and stapled side-to-side anastomosis in Crohn's disease was performed. This analysis did include both randomized controlled trials and retrospective trials. They found, as others had previously found, a significant difference in both the anastomotic leak rate and the overall postoperative complication rate favoring the stapled side-to-side anastomosis. They did not find a difference between the groups with regard to recurrence or need for reoperation [121]. McLeod et al. performed a multicenter, randomized controlled trial comparing stapled side-to-side (ST) and hand-sewn end-to-end (HS) ileocolic anastomoses in Crohn's disease patients. One hundred seventy patients were included in the analysis. They found that mean operative time as well as time to create the anastomosis was significantly shorter in the stapled group.

They did not find a difference with regard to overall complication rates (24 % HS, 20 % ST, $p=0.79$), leak rates (7 % HS, 7 % ST, $p=0.86$), or reoperative rates (7 %HS, 7%ST, $p=0.86$). Endoscopic recurrence was the primary end point. After a mean follow-up of 11.9 months, the endoscopic recurrence rate was 42.5 % in the hand-sewn group and 37.9 % in the stapled group ($p=0.055$). The symptomatic recurrence rate was 21.9 % in the hand-sewn group compared to 22.7 % in the stapled group ($p=0.92$). They concluded therefore that the type of anastomosis did not affect recurrence of the disease [122].

Laparoscopic Surgery and Crohn's Disease

Laparoscopic surgery has been shown to have proven benefit over open surgery with respect to return of bowel function, hospital stay, postoperative pain, as well as cosmesis. Surgeons have questioned the feasibility of performing laparoscpic surgery on patients with Crohn's disease due to the inherent challenges of the disease. The presence of extensive inflammatory adhesions, multiple areas of disease bowel, large inflammatory masses, and the presence of fistulas and abscesses can certainly increase the difficulty of the procedure even when it is performed with an open technique. Multiple studies have shown that using the laparoscopic technique in Crohn's patients is both feasible and safe [123–127]. Additional studies compared laparoscopic versus open ileocolic resection for Crohn's disease. They found that the laparoscopic group demonstrated a faster return of bowel function and shorter hospital stay with no increase in complication rates [127–130]. These findings were also seen when laparoscopic colectomy was studied [131].

The studies mentioned above are viewed with some hesitancy since they were nonrandomized studies and many had few subjects. A bias is inherent in these studies where there is no randomization, as it may be that the surgeon is selecting out noncomplex Crohn's cases to be done laparoscopically. Rosman et al. performed a meta-analysis including 16 studies, one of which was a randomized controlled trial and the remainder were nonrandomized studies. They found that the laparoscopic surgery required more operative time but resulted in a shorter duration of ileus and a decreased length of stay. Laparoscopic surgery was also associated with a decreased rate of postoperative bowel obstruction [132]. The other meta-analysis performed by Tan et al. found similar results [133].

There are two randomized control trials that compare laparoscopic versus open ileocolic resection for Crohn's disease. Milsom et al. studied 60 patients: 31 were assigned to the laparoscopic group while the other 29 were assigned to the open surgery group. They did not find a difference between the two groups with regard to postoperative pain, return of bowel function, or rate of major complications. They did find fewer minor complications and median length of stay was 1 day shorter in the laparoscopic group [134]. Maartense et al. performed the second randomized control study. They found median operating times were longer in the laparoscopic group (115 min vs. 90 min, $p<0.003$). In addition to this, they also found a shorter hospital stay (5 vs. 7 day, $p=0.008$) and a lower complication rate in the laparoscopic group (10 % vs. 33 %, $p=0.028$) [135].

The benefits of laparoscopic surgery would be expected with simple noncomplex Crohn's cases. Goyer et al. did a prospective study assessing the feasibility of laparoscopic ileocolonic resection for complex Crohn's disease (i.e., recurrent disease, presence of fistulas or abscesses). Fifty-four patients with complex Crohn's disease (Group 1) were compared to 70 patients with non-complex Crohn's disease (Group 2). As would be expected, the operative time was higher in Group 1 (214 min vs. 191 min, $p<0.05$) as was the conversion rate (37 % vs. 14 %, $p<0.01$) The main reason for conversion was technical difficulty secondary to the presence of a complex fistula or adhesions. This compares to conversion rates in the literature which ranges from 6 to 40 %. In addition, two-stage procedure with a diverting loop ileostomy was higher in group 1 (39 % vs. 9 %, $p<0.001$). Overall morbidity (17 % vs. 17 %) and hospital stay were comparable between the two groups [124–127, 130, 131, 135–137].

There still remain some contraindications for laparoscopic surgery in the Crohn's patient. These would include patients with hypotension and sepsis, those unable to tolerate pneumoperitoneum, those with a large inflammatory mass that would require a larger incision for extraction, and those with extensive adhesion. Complex disease such as the presence of an abscess or fistula has become a relative contraindication. It is often difficult to determine preoperatively who will be a laparoscopic candidate and who will not. The key to success in these complex cases is having an experienced laparoscopist who is knowledgeable in the treatment of Crohn's disease. They must be able to recognize when it is in the best interest of the patient to convert to an open technique and accept a higher rate of conversion (Video 49.1).

Operative Considerations for Specific Locations

Upper Small Bowel Disease

Upper small bowel disease includes any involvement of the small bowel proximal to the terminal ileum. Disease in this area, when present, can be quite extensive, as this phenotype has a poorer prognosis. When the upper small bowel is involved there may be multiple areas of diseased bowel between areas of normal bowel. The number of diseased segments, as well as their proximity to each other, will determine what the best course of action is to take to treat the problem. Surgical options include resection with primary

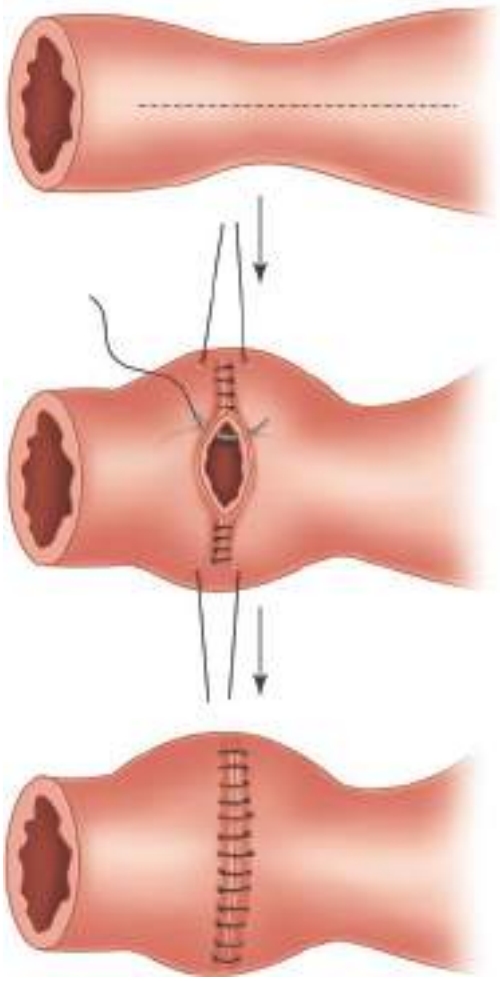

FIGURE 49-2. Heineke–Mikulicz stricturoplasty.

anastomosis, stricturoplasty, or in some instances, when there is significant distal disease present, proximal diversion. Internal bypass is rarely necessary and should be avoided if possible due to risk of bacterial overgrowth as well as higher risk of malignancy [138–140].

Resection with anastomosis is an acceptable option if the area to be resected is limited and the patient has not had significant small bowel resections in the past. Other segments of bowel that would require resection are those that have a perforation, an associated fistula or abscess, or significant inflammation. Resection may also be considered if there are multiple strictures in a short segment of bowel. Resection is carried out to gross negative margins. Fazio et al. performed a randomized control trial to evaluate the effect of surgical margins on the recurrence rates after resection for Crohn's disease. They found that recurrence rates do not increase even with microscopic evidence of Crohn's disease at the margin [141].

Since Crohn's disease is not curable and the majority of patients do undergo surgery for their disease, it is important that as much small bowel be preserved as possible. Stricturoplasty is a method by which an obstruction from a stricture in the bowel can be relieved without resecting that portion of bowel. There are multiple techniques by which this can be accomplished.

The Heineke–Mikulicz was first described by Hermann Heineke and Jan Mikulica-Radecki in 1886 for the treatment of a pyloric channel stricture. This is the most common stricturoplasty performed and is ideal for short strictures which are less than 10 cm in length. It is easy to perform with a low complication rate. This is performed by making a single longitudinal incision over the stricture with extension of the incision about 1–2 cm beyond the stricture on either side. The enterotomy is then closed in a vertical manner, thus relieving the obstruction (Figure 49-2). A variation of this type of stricturoplasty is the Moskel–Walske–Neumayer stricturoplasty and is ideal for those strictures that have a dilated proximal bowel with a stricture that is <10 cm. A "Y"-shaped incision is made over the stricture with the upper portion of the "Y" over the dilated portion of the bowel. This is then closed by advancing the dilated portion of the bowel to the base of the "Y," thus creating a "V" suture line. The advantage of this technique is that it addresses the bowel size discrepancy and is relatively easy to perform (Figure 49-3) [142, 143]

For those strictures that are slightly longer (>10 cm but <25 cm), a Jaboulay or Finney procedure is indicated. Mathieu Jaboulay, in 1892, proposed the technique of bypassing an obstructing stricture in the pylorus by performing a gastroduodenostomy. Finney later presented a modification of this technique also for the treatment of a pyloric stricture. The Jaboulay is created by folding the long strictured bowel on itself and making a longitudinal incision along the stricture on either side. These enterotomies are then sutured together. This does leave the central aspect of the stricture bypassed which can be problematic. Finney modified this technique to eradicate this bypassed segment of bowel. For the Finney technique, the strictured segment is folded on itself and a "U"-shaped incision is made along the entire length of the stricture. This is then sutured together, thus creating a large diverticulum. This may develop problems due to stasis if the created diverticulum is quite large (Figure 49-4) [142, 143].

For those strictures that are even longer (>20 cm), a Michelassi or Poggioli stricturoplasty is indicated. These, though technically more demanding, have the advantage of avoidance of resection of a significant amount of bowel without bypassing bowel or creating a blind loop. The Michelassi stricturoplasty is performed by dividing both the strictured bowel and its mesentery in the center of the stricture. The bowel is then advanced over the other end in a side-to-side manner. A longitudinal incision is made over both limbs of the stricture and sutured together (Figure 49-5) [144]. The modification to this technique that Poggioli proposed was to divide the bowel and mesentery at the distal end of the stricture. The normal bowel would then be advanced over the

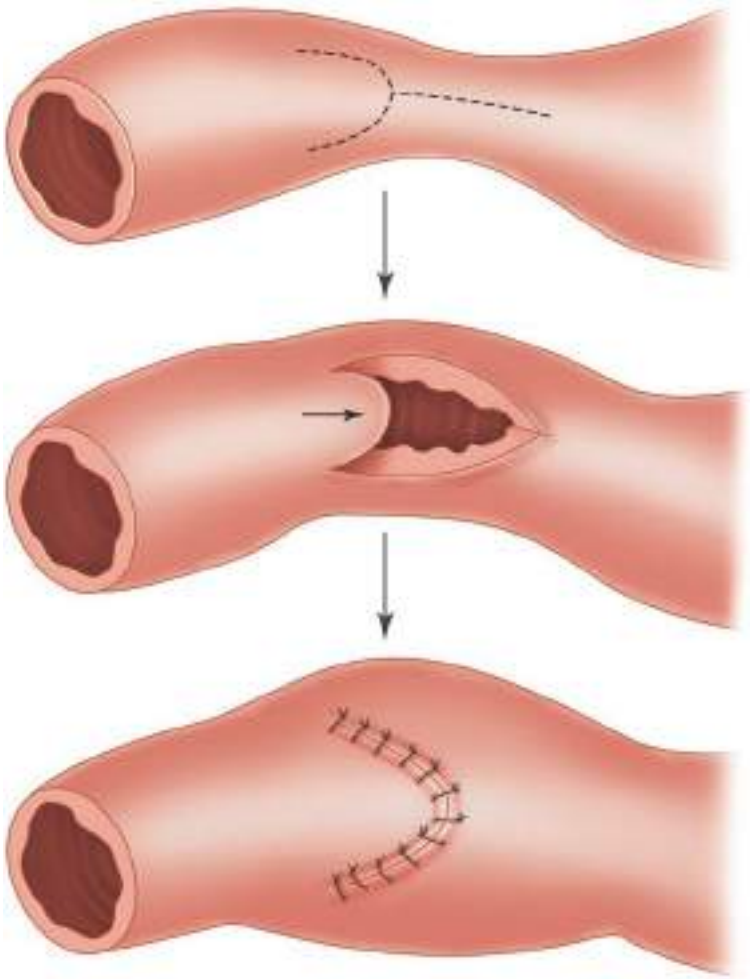

FIGURE 49-3. Moskel–Walske–Neumayer.

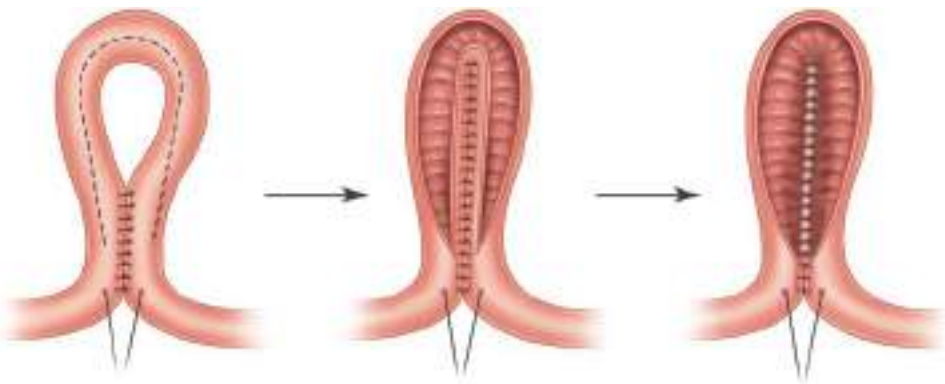

FIGURE 49-4. Finney stricturoplasty.

strictured bowel, opened via a longitudinal incision, and sutured together. This has the advantage of using normal bowel as part of the anastomosis. The normal bowel would be more pliable which may help in the execution of the stricturoplasty. It also has the disadvantage that if there is a complication, twice as much bowel will be lost, not only the strictured bowel but also an equal length of normal bowel [145, 146].

Indications for stricturoplasty include situations where there are multiple strictures involving a significant portion of bowel, previous significant small bowel resection (>100 cm), risk of short bowel syndrome, duodenal strictures or recurrent

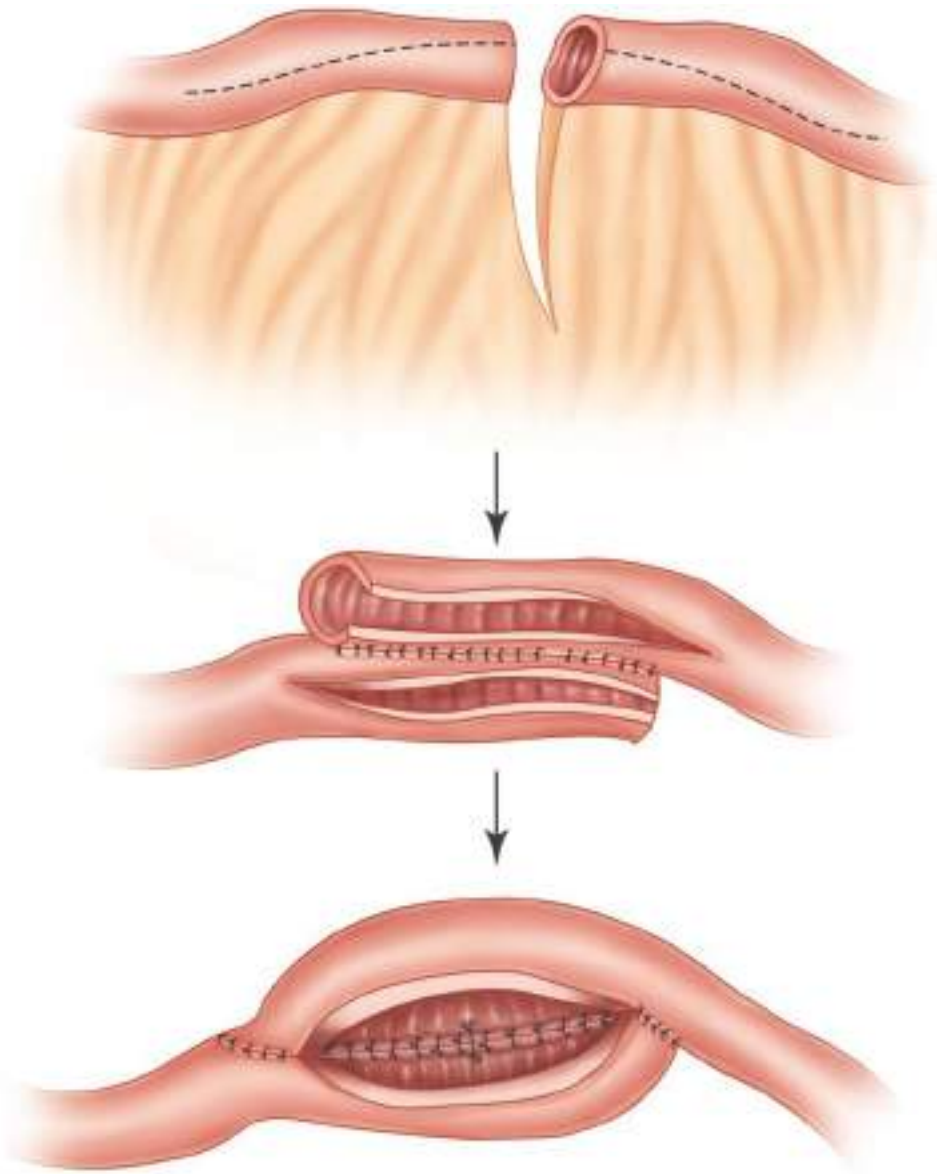

FIGURE 49-5. Michelassi stricturoplasty.

strictures, or recurrent strictures. It originally was thought unsafe to perform a stricturoplasty in a segment of bowel with active disease; however, recent studies have shown this is feasible and safe [147]. The contraindications to performing a stricturoplasty include severe inflammation, strictures associated with fistulas, abscesses, or a phlegmon, or those with diffuse peritonitis from a perforation. Stricturoplasty should also be avoided if there is concern for cancer, tension, or the area of the stricturoplasty is adjacent to an area of resection [148]. If when assessing the bowel wall, it appears to be either too fragile or thinned due to ulcerations, or so thick that there is minimal lumen left, stricturoplasty should be avoided [149].

There have been many concerns regarding performing stricturoplasties. The first is a concern regarding performing an anastomosis with bowel that is thickened and fibrosed and the potential for leaks or complications. The second main concern stems from leaving diseased bowel in situ and the potential risk of either recurrence or malignant transformation. Lastly, is it safe to perform stricturoplasties in those strictures that are >20 cm in length. Multiple studies have been done that have supported these procedures as being both feasible and safe. These studies found an overall complication rate of 5.7–20 % with a septic complication rate (fistulas, abscesses, or leak) of 2.9–6 % [148, 150–154]. A number of studies have specifically looked at the recurrence rates after stricturoplasty as well as location of recurrence when it did occur. Zuner et al. studied the effect of stricturoplasty on the recurrence rate as well as the location of the recurrence. One hundred and sixty-two patients underwent

191 operations for a total of 698 stricturoplasties (Heineke–Mikulicz 88 %, Finney 12 %). They found the five-year reoperative recurrence rate was 28 % which is comparable to what is found in the literature for reoperative recurrence rates after resection (32–53 %) [155, 156]. Multiple other studies have also confirmed comparable recurrence rate (12–36 %). In addition to that, they found a very low rate of recurrence at the site of a prior stricturoplasty (0.8–4.6 %) [149–154, 157]. Finally, Yamamoto et al., in their meta-analysis of 1112 patients found only two that had developed adenocarcinoma at the site of a prior stricturoplasty (0.02 %) [152].

In summary, it has been shown that Crohn's strictures can be safely and effectively treated with stricturoplasty using a variety of techniques based on the length of the stricture. The majority of the patients are treated with a combination of resection and stricturoplasty based on the findings at the time of operation. Of those undergoing stricturoplasty, 44–70 % of patients received at least one additional resection [142, 149, 151, 152].

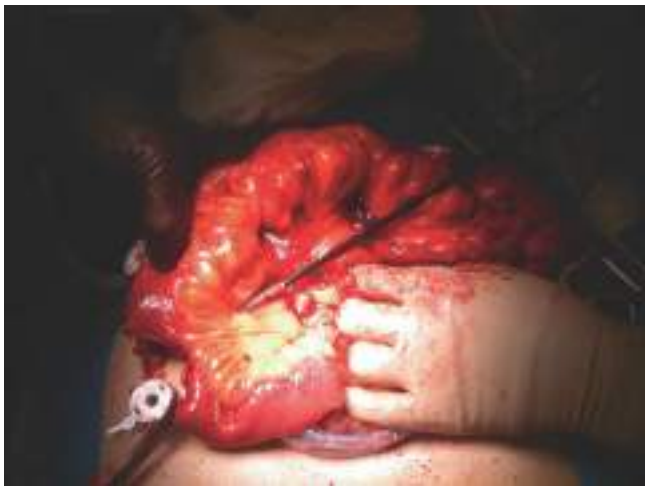

FIGURE 49-6. Following laparoscopic mobilization, an energy device is being used to divide the thickened mesentery of a patient with Crohn's disease.

Terminal Ileal Disease

Since terminal ileal disease is the most common location for Crohn's disease to occur, it is not surprising that an ileocolic resection is the most common operative procedure performed on Crohn's patients. At the start of the operation, the abdomen is explored to assess the severity and location of disease. Careful observation looking for fistulas is also important considering the most likely origin of an enteric fistula is the terminal ileum. If disease is seen in the upper small bowel, decision regarding stricturoplasty versus resection is made. For the terminal ileal disease, the cecum and terminal ileum are fully mobilized. The small bowel is assessed to determine the point of bowel division. Again, the point of division is 1–2 cm beyond the palpable thickened bowel. Microscopic negative margins are not necessary. Care should be taken when dividing the mesentery, as it often is friable secondary to both the amount of inflammation and the use of steroids. The point of division of the colon is made just proximal to the ileocecal valve, preserving as much ascending colon as possible. Once the specimen is removed, it should be opened in the operating room to assess for any indications of malignancy which may require further resection (Figure 49-6 and 49-7).

Oftentimes there will be an inflammatory mass in the right lower quadrant with normal bowel adhered to the inflamed terminal ileum with possibly the presence of enteroenteric fistula. An attempt should be made to preserve as much small bowel as possible, though sometimes the amount of inflammation will preclude separation of the normal bowel from the diseased bowel and the entire mass will need to be resected en bloc.

Once the bowel has been resected, the decision is made to either create an anastomosis +/− a diverting loop ileostomy

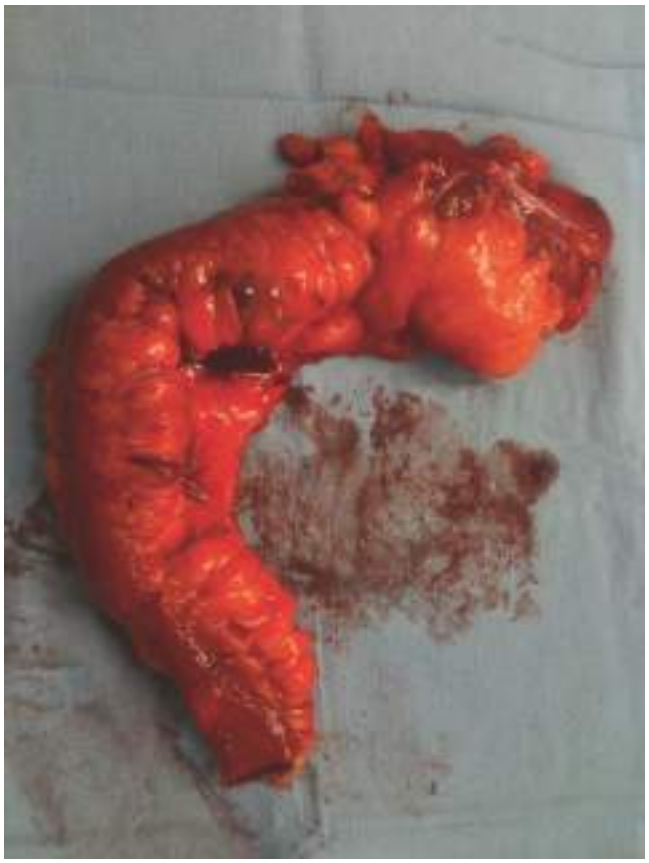

FIGURE 49-7. Ileocectomy specimen in a patient with Crohn's disease.

versus creation of an end ileostomy. This decision is made by considering the risks factors that may lead to an anastomotic breakdown. These would include the hemodynamic stability of the patient, use of high-dose steroids, malnutrition, puru-

lent or fecal contamination secondary to a perforation, and/or bowel obstruction with markedly dilated bowel. Attempts, when feasible, to create an anastomosis is preferable, since taking down a loop ileostomy has lower morbidity, compared to an exploratory laparotomy for takedown of an end ileostomy. If it is deemed necessary to create a stoma, the time lapse until takedown of the ileostomy is somewhat dictated by the indication for the stoma. The goals to attain prior to takedown should be full recovery from the first operation, weaning off of the steroids, correction of malnutrition, as well as allowing time for the acute inflammation and adhesion from surgery to resolve. This may take 3–6 months.

Colonic and Rectal Disease

The operations used to treat Crohn's disease of the colon and rectum include total abdominal colectomy with end ileostomy, total abdominal colectomy with ileorectal anastomosis, total abdominal proctocolectomy with end ileostomy, and total abdominal proctocolectomy with micro Hartman's with an end ileostomy. The decision as to which of these procedures is going to be best for the patient is made by careful consideration of the preoperative status of the patient, location and severity of disease, use of steroids, age, sexual function, and patient wishes.

Patients who present acutely ill and are requiring an emergent operation for Crohn's colitis typically will need a total abdominal colectomy with end ileostomy regardless of the presence of rectal involvement. Attempting to perform a proctectomy in this setting is dangerous and unnecessary, as it will increase the morbidity and mortality of the procedure and is not necessary to improving the patient's overall health. In this setting, the entire colon is mobilized. The terminal ileum is divided as well as the upper rectum. The terminal ileum is then fashioned into an ileostomy. The rectum will be left in situ. If the rectum has significant inflammation, oversewing the staple line will help to decrease the risk of a dehiscence at the staple line. Even if the rectum has active disease present, typically once diverted, the disease in the rectum will improve as will the patient's symptoms. The decision to leave the rectum in situ, perform an ileorectal anastomosis, or perform a proctectomy can be determined at a later date.

The decision as to which operation to perform for a patient with Crohn's colitis in the elective setting is more involved as more options are available and need consideration. Patients who present with rectal involvement in addition to their colitis are not candidates for limited resection. For those patients with good nutrition, in good health, and not immunosuppressed, a total proctocolectomy with end ileostomy is the indicated procedure. This has the advantage of treating all aspects of the disease with one operation. This procedure offers the lowest recurrence rate; however, it does have potential for complications, the most common complication being perineal wound sepsis (36 %) [158]. For those patients with poor nutrition and/or on steroids, consideration of performing a total abdominal proctocolectomy with a micro Hartmann's and end ileostomy is a viable alternative. This has the advantage of removing majority of the disease however still avoiding a perineal incision and the increased risk of wound breakdown. At a later date, when the nutritional status is improved and the steroids have been weaned, a completion proctectomy can be performed via a perineal approach. A total abdominal colectomy with end ileostomy with delayed proctectomy might be considered in younger patients who are concerned about sexual function and are in their childbearing years. Surveillance of the rectum would be necessary until the time of the proctectomy.

For those patients with Crohn's colitis with rectal sparing, a more limited resection can be entertained. Ileorectal anastomosis or segmental resection has been proposed for selective patients. Numerous studies have looked at the outcomes of each of these procedures, though all are retrospective studies, so have inherent bias present. With regard to total colectomy with ileorectal anastomosis, mortality rates range from 0 to 7 % [159–162] with an anastomotic leak ranging from 3 to 16.7 % [159, 162, 163]. Recurrence rates at 5 years were found to be 55–58 % and at 10 years cumulative reoperative rates were 48–83 % [161, 162, 164]. Though these numbers are high, 77–87 % of patients had a functioning ileorectal anastomosis at 5 years, and 61–72.2 % had a functioning ileorectal anastomosis at 10 years [159, 161, 163–165]. Not surprising, those who had rectal sparing did better than those who had this procedure done in the setting of mild to moderate proctitis [166]. Those presenting with perianal disease, as well as those presenting with small bowel disease, had a higher rate of failure [164, 165, 167]. Reasons for failure, in addition to recurrence of disease, included poor functional control after surgery. O'Riordan et al. found that 22 % of the patients in their study who had undergone an ileorectal anastomosis ultimately had a proctectomy secondary to poor functional control [163].

Segmental resection for Crohn's colitis is controversial. Again, the studies looking at this are retrospective in nature, but do shed some light on this procedure and its potential place in the armamentarium. The majority of the studies compared segmental resection to total colectomy with ileorectal anastomosis. Polle et al. followed 91 patients who underwent a segmental resection for Crohn's colitis. Median follow-up was 8.3 years. They found that only 1/3 of patients required additional surgery. Of those that did recur, 2/3 ultimately underwent a total proctocolectomy. At the end of the study, patients were more likely to have a stoma if they had undergone a left colectomy versus those who required a right colectomy [168]. Andersson et al. evaluated 57 patients: 31 underwent a segmental resection and 26 underwent a total colectomy with ileorectal anastomosis. The cumulative re-resection rate was 55.3 % for the segmental group and 41.4 % for the colectomy group. Of those patients in the segmental group that had a re-resection, 50 % had additional

surgeries. No patient in the colectomy group required more than two surgical procedures. The median time to re-resection was 2.6 years and 7.3 years, respectively. The rate of permanent stoma in each group was 13 % and 19 %, respectively. The segmental group did have statistically significant fewer symptoms, fewer loose stools, and better anorectal function [169]. Prabhakar et al. evaluated 49 patients who had undergone a colon resection without a permanent stoma. Of these patients, 33 % required additional surgery, with 89 % of the recurrences being in the colon. Of these patients, 44 % ultimately had a permanent stoma. At the completion of the study, 86 % of the patients were stoma free [170].

In summary, patients with clear rectal involvement are not candidates for limited resection. For those patients with rectal sparing, consideration can be made for colectomy with ileorectal anastomosis or in some cases segmental resection. Both of these procedures have the advantage of avoiding a stoma and segmental resection has the added advantage of better functional results over IRA. Both of these procedures though have very high recurrence rates as well as high reoperative rates. These failure rates are even higher if there is perirectal disease or if the disease was localized to the left colon.

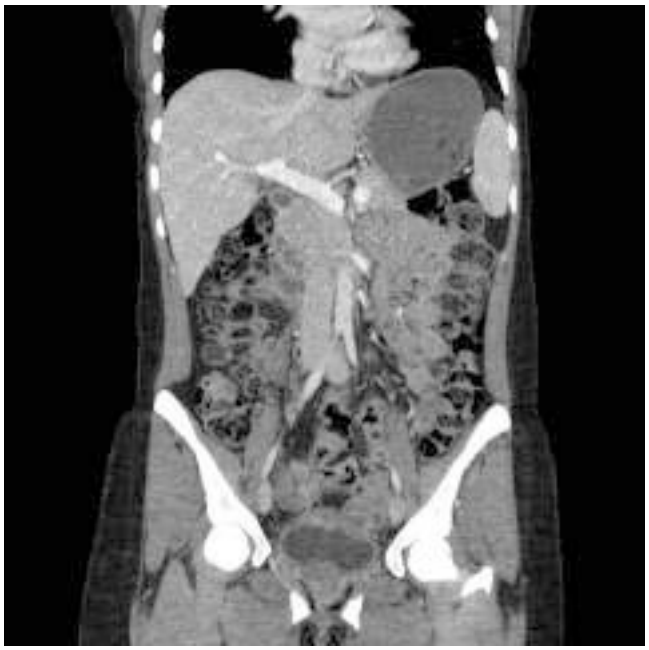

FIGURE 49-8. Coronal CT image in a patient with Crohn's disease demonstrating an ileal-sigmoid fistula from the thickened ileum to the sigmoid colon right above the level of the bladder.

Special Considerations

Ileal-sigmoid fistula

This is the most common abdominal fistula found. The origin of the fistula is from the diseased terminal ileum and ultimately the inflammation penetrates into the sigmoid colon. Most often, the sigmoid colon is not involved with Crohn's disease but happens to be adjacent to the inflamed bowel (Figure 49-8). If there is any question as to active Crohn's disease in the sigmoid colon, a flexible endoscopic exam during surgery should answer the question. In 54 % of patients, a polyp or cluster of polyps will be seen in the sigmoid colon and in no other location in the colon. This may signify the presence and location of the fistula [171]. The terminal ileum will need resection; however, the sigmoid colon can be treated with division of the fistula and primary repair of the fistula site. A wedge resection with primary repair is typically all that is needed. Occasionally, the inflammation will be so severe that wedge resection is not safe and in these cases a sleeve resection can be done to remove the short segment that has been affected.

Complex Perineal Wounds After Proctectomy

Perineal wound complications can be a devastating problem after proctectomy for Crohn's disease, leading to postoperative pain, significant wound care, and prolonged recovery. It has been estimated that the rate of unhealed perineal wounds after proctectomy for Crohn's disease ranges from 23 to 70 % [172–174]. The best approach to this problem is prevention. Strategies to prevent this complication include smoking cessation prior to surgery, improvement of the nutritional status of the patient, as well as preoperative management of sepsis. In cases of severe perianal disease, creation of a low Hartman's instead of complete proctectomy will avoid a perineal wound, yet still remove majority of the disease. This will allow resolution of the active sepsis and if necessary a perineal resection of the small rectal stump can be performed at a later time. When full resection is necessary, an intersphincteric dissection should be performed when possible. This decreases the amount of tissue removed as well as leaves well-vascularized muscle to bolster the closure.

At times, a wide excision is necessarily because of severe perianal disease, significant scarring, or the presence of cancer. In these cases, primary closure may not be possible; however, wound healing can be achieved with the use of advanced tissue flaps which bring viable healthy tissue to the wound. Various flaps have been described for this purpose including the gluteus maximus advancement flap, posterior thigh fasciocutaneous flap, chimeric posterior thigh flap, as well as the rectus abdominus myocutaneous flap. The gluteus maximus flap can be unilateral or bilateral and is ideal for smaller wounds. The posterior thigh fasciocutaneous flap is a good option for larger wounds. This provides significant soft tissue transfer as well as adequate skin for closure. The chimeric posterior thigh flap allows for two separate tissue transfers

with a single procedure. The gluteus maximus muscle can be transferred to fill dead space, while the posterior thigh flap can be used for perineal wound coverage. The most commonly used flap is the rectus abdominus myocutaneous flap. This flap provides muscle to fill the pelvic dead space as well as skin to close the perineal wound. This flap does require a laparotomy so is not used for completion proctectomies performed using the perineal approach alone [175, 176].

Recurrence of Disease

Recurrence can be described as being endoscopic, clinical, or surgical. Rutgeerts et al. followed a prospective cohort of patients and found that at 1 year, 73 % of patients had endoscopic evidence of recurrence in the neo-terminal ileum, though only 20 % were symptomatic. At 3 years, the endoscopic rate had increased to 85 % and the symptomatic rate had increased to 34 % [177]. Olaison et al. found even higher rates. They found 73 % of patients had endoscopic recurrence at 3 months, with 33 % being symptomatic. At 1 year, the endoscopic rate had increased to 93 % with a correlating symptomatic rate of 37 % [178]. Postoperative recurrence rates have been shown to be 33 % and 44 % at 5 and 10 years [9]. Frolkis et al. performed a meta-analysis of population-based studies to further evaluate the risk of second surgery in patients with Crohn's disease. They found the overall risk of second surgery to be 28.7 %. The five-year risk was 24.2 %, with the 10-year risk increasing to 35 % [179]. The rate of surgical recurrence ranged from 9.5 to 20 % at 5 years and 18.6 to 44 % at 10 years. The rate continued to increase to 57 % at 20 years [9, 14, 155, 180, 181].

Since the rate of recurrence is so high, much research has been done looking for risk factors that predict recurrence. The strongest predictor of postoperative recurrence is smoking [182–184]. Reese et al. performed a meta-analysis including 16 studies which included 2962 patients. They found that patients with Crohn's disease who smoke have a 2.5-fold increased risk of surgical recurrence and a twofold increased risk of clinical recurrence compared to patients who were nonsmokers [183]. Other risk factors that have been linked to a higher rate of recurrence include prior surgical resection and penetrating/perforating phenotypic disease type [182, 184–186]. Risk factors that have had mixed reviews in the literature regarding their predictive value for postoperative recurrence include gender and location of disease [9, 155]. Chardavoyne et al. found that patients who had the disease for 3–10 years before they underwent their first resection were more likely to have a re-resection compared to patients who had their disease for either less than 3 years or longer than 10 years [155].

As new medications become available, their usefulness in preventing postoperative recurrences is being studied. Steroids and probiotics did not show any role in the prevention of postoperative recurrences [187, 188]. Mesalamine has been shown to reduce the risk of clinical recurrence when compared to placebo in some studies but not all [189–193]. A randomized control trial demonstrated that those patients who received metronidazole for 3 months after ileocolic resection had a decrease in severity of early recurrence compared to placebo (13 % vs. 43 %) [194]. A second randomized, double-blind controlled trial investigated the effect of ornidazole (1 g/day) on clinical recurrence after ileocolic resection for Crohn's disease. The medication was given for 1 year after surgery. The clinical recurrence rate was 37.5 % in the placebo group compared to 7.9 % in the treatment group. Unfortunately, this effect was only seen when the drug was being administered and the side effects of the medication limit its prolonged administration [195]. Studies have shown a modest effect of the use of thiopurines with one study which showed that azathioprine seemed to delay endoscopic postoperative recurrence compared to historical series or placebo groups [187, 196–199].

Biologics have shown the most promise in reducing postoperative recurrence. Savarino et al. randomly assigned patients to receive adalimumab, azathioprine, or mesalamine. The endoscopic recurrence rates at 2 years were 6.3 %, 64.7 %, and 83.3 %, respectively. The clinical recurrence rate was 12.5 %, 64.7 %, and 50 %, respectively [200]. The studies on infliximab have been very promising. Regueiro et al. performed a randomized control trial investigating the effect of infliximab on postoperative recurrence and ileocolic resection. They found the endoscopic recurrence rate at 1 year was 9.1 % in the infliximab group compared to 84.6 % in the placebo group. Histologic recurrence was also lower in the infliximab group, 27.3 % compared to 84.6 % [201]. Yoshida et al. also found that infliximab had a beneficial effect. At 12 and 36 months, they showed that patients treated with infliximab postsurgery were 100 % and 93.3 % in remission, respectively, versus 68.8 % and 56.3 % in the placebo arm of the study [202]. Yamamoto et al. looked at the efficacy of infliximab on endoscopic recurrence as well as mucosal healing. Twenty-six patients who had been treated with mesalamine after surgery showed endoscopic evidence of recurrence at 6 months after surgery. These patients were treated with mesalamine, azathioprine, of infliximab. Clinical recurrence was seen in 0 % of the infliximab patients, 38 % in the azathioprine patients, and 70 % in the mesalamine patients. The rate of endoscopic improvement was 0 %, 38 %, and 75 %, respectively. Complete mucosal healing was seen in 0 %, 13 %, and 38 %, respectively [203]. These studies are relatively small but show great promise that perhaps infliximab can change the natural history of Crohn's disease. Larger randomized control trials will need to be performed to prove this.

Conclusion

In conclusion, surgery should not be viewed as a failure of treatment but rather as an integral treatment option for patients with Crohn's disease. Surgery can offer relief of

symptoms and an opportunity to return to a full and active lifestyle. Though the medical treatment has improved over the past decade, there has yet to be a significant drop in the number of surgeries performed. This may be explained by the increase in incidence of the disease. For now, surgery still plays a key role in the treatment of Crohn's disease.

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Ulcerative Colitis: Surgical Management

Mukta K. Krane, Erin O. Lange, and Alessandro Fichera

Key Concepts

- Patients with ulcerative colitis should be managed by a multidisciplinary team of gastroenterologists, surgeons, pathologists, enterostomal therapists, and nutritionists.
- Preoperative weight management, improvement of nutrition, and optimization of medical therapy before proceeding with construction of the ileal pouch anal anastomosis are critical steps to achieve optimal long-term functional results.
- Laparoscopy should be considered the standard of care for elective surgery for ulcerative colitis
- While ileal pouch anal anastomosis should be considered the standard of care in the surgical treatment of ulcerative colitis patients, the surgical plan should be individualized both in terms of staged approach and restoration of intestinal continuity.
- Long-term follow-up of patients with an ileal pouch anal anastomosis is mandatory, even though the risk of malignant degeneration remains quite low.

Introduction

Ulcerative colitis (UC) is an inflammatory intestinal condition characterized by continuous colonic inflammation extending from the rectum proximally. Patients generally present in the second or third decade of life with manifestations of the disease including abdominal pain, diarrhea, rectal bleeding, and weight loss. While medical therapy is often first-line treatment, proctocolectomy is curative and therefore surgery has a pivotal role in the therapeutic armamentarium of UC. The aim of this chapter is to highlight the indications for surgery, principles of surgical decision-making, operative techniques, and special considerations.

Indications for Surgery

Approximately 25–30 % of patients with UC will undergo surgical intervention in their lifetime, with up to 10 % of patients requiring surgery within the first year of diagnosis due to a variety of elective and emergent causes (Table 50-1) [1]. The timing of surgery depends on the indication and severity of disease.

Elective Surgery

Elective indications for surgery include failure of medical management, complications or side effects associated with medications, dysplasia or invasive cancer, extraintestinal manifestations, and growth retardation in children and adolescents. Patients with active disease despite optimization of maintenance therapy are often in better general health than patients with fulminant colitis, but may undergo surgery in order to avoid corticosteroid dependency.

A diagnosis of high-grade dysplasia (HGD), dysplasia-associated lesion or mass (DALM), or invasive carcinoma in a patient with UC is an absolute indication for surgery. The diagnosis of dysplasia or cancer can be challenging in the setting of UC; therefore, it is imperative to obtain confirmation from two experienced GI pathologists [2]. The overall rate of colorectal cancer in patients with UC is 3.7 % with a risk of 2 % at 10 years, 8 % at 20 years, and 18 % at 30 years [3]. Synchronous and metachronous dysplasia and carcinoma are more common in patients with UC than in the sporadic colorectal cancer population. Kiran et al. recently reported a 14 % synchronous cancer and 55 % synchronous dysplasia rate in 176 UC patients with colorectal cancer [4]. The recommended procedure for UC patients with colorectal cancer or HGD is therefore proctocolectomy with end ileostomy or ileal pouch anal anastomosis (IPAA).

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Table 50-1. Indications for surgery in ulcerative colitis

Elective	Emergent
Failure of medical management	Toxic megacolon
Complications/side effects of medications	Sepsis/fulminant colitis
Dysplasia	Perforation
Invasive cancer	Hemorrhage
Extraintestinal manifestations	
Growth retardation	

The need for and timing of surgery in patients with low-grade dysplasia (LGD) remains highly debated. The 5-year progression rate from LGD to HGD or colorectal cancer is reported to be as high as 54 % [5, 6]. In addition, patients may progress from LGD to colorectal cancer without intervening evidence of HGD. However, there are a number of small, observational studies which do not show a clear progression of dysplasia and have resulted in the recommendation by some that LGD can be followed with close endoscopic surveillance with surgery reserved for patients developing HGD or colorectal cancer. Recently, endoscopic mucosal resection and endoscopic submucosal dissection have emerged as possible therapeutic techniques in the treatment of UC-associated dysplasia [7, 8].

There are two widely accepted elective surgical options: total proctocolectomy with an end ileostomy or restorative proctocolectomy with ileal pouch anal anastomosis (RPC-IPAA), which may be performed in one, two, or three stages. Total abdominal colectomy with an ileorectal anastomosis is a third but rarely used option. The choice of elective procedure is individualized based on the patient and the clinical setting, and it will be discussed later in this chapter.

Emergent Surgery

Emergent indications for surgery include toxic megacolon, sepsis, or fulminant disease not responsive to medical therapy, perforation, and severe bleeding. Perforation and massive hemorrhage occur less frequently than fulminant colitis but are absolute indications for surgery, whereas toxic megacolon and severe acute flares may respond to intense medical therapy.

Toxic megacolon is a life-threatening complication of UC and there should be a low threshold for surgical intervention. An initial trial of conservative therapy with bowel rest, intravenous fluids, broad-spectrum antibiotics, and close monitoring for 24–48 h may be cautiously attempted. While infliximab and cyclosporine have been demonstrated to successfully treat toxic megacolon secondary to UC in 25–40 % of patients, associated morbidity and mortality rates are high [9]. Worsening clinical signs or evidence of increasing colon dilation with "thumb printing" or pneumatosis on radiologic imaging are indications for surgery.

Severity of UC can be characterized as mild, moderate, severe, or fulminant depending on the number of daily bowel movements, systemic symptoms, and inflammatory markers (Table 50-2) [10]. While advances in medical therapy have resulted in the avoidance or delay of surgical intervention in some patients with severe or fulminant disease, a colorectal surgeon should be consulted in these cases, particularly if the patient requires hospital admission. Early collaboration between the medical and surgical teams ensures that the patient understands that colectomy is an alternative if the colitis is refractory to medical management or if their clinical status deteriorates.

In patients admitted to the hospital with fulminant UC, steroids and other rescue therapies will often be initiated. It is important to objectively assess these patients on a regular basis by monitoring hematologic parameters, C reactive protein (CRP) levels, stool frequency, abdominal exams, and abdominal imaging. Colectomy is generally advocated for clinical deterioration or if there is no significant clinical improvement in 4–7 days [11]. Concomitant infection with cytomegalovirus or *Clostridium difficile* needs to be ruled out and appropriately treated if identified.

Critical examination of current practice reveals that the threshold for elective surgery is too high and it is important to consider surgery an alternative to medical therapy, rather than representing failed management [12]. Roberts et al. compared 3-year mortality in over 28,000 patients hospitalized for UC who had urgent or elective surgery versus medical management [13]. The elective colectomy group had the lowest mortality rate (3.7 %), while the medical management and urgent colectomy groups had similar mortality rates (13.6 % and 13.2 % respectively, $p = 0.001$). A recent review of the literature further illustrates the risks of urgent surgical intervention for severe colitis by reporting a 40.1 % morbidity rate [14].

In the emergent setting the most common procedure performed is a total abdominal colectomy with an end ileostomy, leaving the rectum in situ. Resection of the diseased colon eliminates the majority of the disease, alleviates symptoms, and usually allows the patient to discontinue immunosuppressive medications and return to an improved overall state of health. Completion proctectomy with or without an IPAA can then be addressed in an elective setting. Resection of the rectum at the time of emergent surgery should be avoided as it hinders future restoration of intestinal continuity and is associated with a higher risk of bleeding and injury to the autonomic nerves. Emergent proctectomy may also significantly increase the length of the procedure and the risk of postoperative complications.

Staged Operations

In the authors' experience, there are several indications for a staged approach to surgical therapy for UC patients (Table 50-3) and this strategy is commonly utilized in clinical practice in many major IBD centers [15]. Obesity and other patient comorbidities play a significant role in the decision tree and will be discussed throughout this chapter.

Table 50-2. Ulcerative colitis disease severity scale

	Mild	Severe	Fulminant
Number of bowel movements/day	<4	>6	>10
Rectal bleeding	Rare	Frequent	Profuse and continuous
Hemoglobin	Normal	<75 % of normal	Requiring transfusions
ESR (mm/h)	Normal	>30	>30
Body temperature (°C)	Normal	>37.5	>37.5
Heart rate	Normal	Normal to slightly tachycardic	Tachycardic

Modified from Truelove and Witts [10]

Table 50-3. Indications for a staged surgical approach

Indications for a staged surgical approach
Obesity
Medical treatment (Biologics, Steroids)
Fulminant disease/toxic megacolon
Patient comorbidities

In our practice, a two-stage approach (for both open and laparoscopic cases) includes a restorative proctocolectomy with an IPAA and diverting loop ileostomy as the first stage and reversal of the loop ileostomy at the second operation. A three-stage approach involves a total abdominal colectomy and an end ileostomy as the first stage, followed by a restorative proctectomy with an IPAA and diverting loop ileostomy as the second stage, and reversal of the ileostomy at the third and final operation.

The staged approach to pouch construction among complex UC patients seeks to decrease the incidence of pelvic sepsis, often related to a leak at the ileal-anal anastomosis [16, 17], and to minimize long-term sequelae of a postoperative septic complication including poor pouch function [18]. Pelvic sepsis is a frequent and serious complication of IPAA for UC and is reported to occur in up to 23 % of patients [19, 20]. Long-term outcomes after IPAA are worsened by the occurrence of pouch-related septic complications [16]. Although acceptable functional results can be achieved in highly motivated patients, multiple procedures are often necessary to achieve complete healing of an IPAA leak [17]. Hence efforts should be made to reduce such complications and to identify patients at risk of pouch-related sepsis.

Several risk factors have been postulated for postoperative pouch-related septic complications in UC including steroids [20, 21], infliximab [22, 23], and immunomodulators [24]. While the role of corticosteroids as a risk factor for postoperative complications has been described in various publications [16, 19–21], the role of infliximab has not been clearly defined to date [25–29]. Lim et al. reported that the use of corticosteroids was an independent risk factor for complications after IPAA in a dose-dependent fashion and concluded that patients receiving more than 20 mg/day of prednisone should undergo multistage pouch procedures [20]. Using this threshold as an indication for diversion, Gorfine et al. reported similar septic complication rates and functional results between patients on aggressive medical therapy and those taking no immunosuppressive and less than 20 mg of prednisone daily in the month preceding surgery [17, 30]. It is important to recognize that these studies were all conducted before the introduction of biologic therapy.

Since 2005, biologic therapy has become a significant component of medical therapy for many UC patients [31]. Unfortunately, aggressive medical management of acute flares of UC in the era of biologic therapy seems to be associated with increased postoperative infectious complications [23, 24], as patients are often referred to the surgeon malnourished, immunocompromised, and suffering from significant side effects of treatment.

Selvasekar et al. [23] found that UC patients treated with infliximab before IPAA have substantially increased odds of postoperative pouch-specific and infectious complications. In this study, the authors reported that anastomotic leaks ($p=0.02$) and pouch-specific ($p=0.01$) and infectious ($p<0.01$) complications were more common in the group receiving biologic therapy. Similar findings were demonstrated by Mor et al. [24]. The authors found that the odds of postoperative septic complications were 13.8 times greater ($p=0.011$) and the odds of late complications 2.19 times greater ($p=0.08$) in the group receiving biologic therapy. Although not in a standardized fashion, the surgeons involved in this study were 2.07 times more likely to perform a staged procedure for patients receiving biologic therapy ($p=0.011$) [24].

Ferrante et al. [21] reported their experience looking at 141 IPAA patients, 22 receiving biologic therapy. A moderate to high dose of corticosteroids ($p=0.003$) and an IPAA without ileostomy ($p=0.001$), but not the use of biologic therapy, were independent predictors of short-term postoperative infectious complications. However, they also noticed that patients on biologic therapy were more likely to undergo IPAA with a diverting ileostomy ($p=0.022$). Schluender et al. [22] reported that while preoperative biologic therapy alone did not significantly increase the incidence of postoperative complications, its use in combination with cyclosporine before colectomy in refractory UC was associated with higher surgical morbidity.

Finally a meta-analysis conducted by Yang et al. [32] on five studies and 706 patients found that biologic therapy increased short-term overall postoperative complications in UC, even if there was no association when analyzing separately short-term infectious and noninfectious complications,

except for a trend toward increased postoperative infections. This study was in part limited by the quality of the studies included and the small number of patients, further underpowered in the subgroup analysis.

The theoretical advantage of a three-stage approach is the opportunity to optimize the general medical condition, improve nutritional status, and wean off medical therapy during the interval following the total abdominal colectomy. While not extensively evaluated in the literature to date, this preparation period is considered important prior to attempting the more complex elements of surgical therapy, namely pelvic dissection with pouch construction and anastomosis, in order to reduce pouch-related septic complications and long-term pouch dysfunction. Recently this concept has been challenged by several authors [27, 33, 34], but this literature must be critically interpreted.

The series from Mount Sinai Hospital in Toronto concluded that preoperative treatment with TNF-alpha antagonists in IBD patients was not associated with early postoperative complications, after reporting similar rates of wound infection among patients with detectable preoperative infliximab levels compared with those with undetectable levels. However, this analysis included operations for both Crohn's disease and UC; among the 69 UC patients evaluated, only 11 pouches were constructed on patients on anti-TNF-alpha antagonists, thus limiting the validity of the conclusion for this specific subgroup [25]. Our own experience is similar: among 518 IBD surgical patients treated laparoscopically, we noted no differences in postoperative infectious complications. However, only 15 pouches (10.6 %) were constructed on patients while on infliximab [27].

In our practice, we have found that a more conservative surgical approach to UC patients with multiple comorbidities receiving aggressive medical management has allowed us to achieve excellent results with acceptable morbidity [35]. A retrospective analysis of our own prospectively collected data comparing a three- versus a two-stage approach in this population revealed no difference in overall postoperative complications. Despite significantly higher utilization of corticosteroids (96 %) and biologic therapy (43 %), as well as higher incidence of active *C. difficile* infection (14 % vs. 5.8 %) among patients in the three-stage group, we identified lower incidence of infection complications (21 % vs. 38.2 %. $p<0.05$) compared to the two-stage group [35]. In order to minimize complications, an accurate preoperative risk assessment, combined with the surgeon experience, is crucial to assign patients to the safest surgical approach. In our practice, patients receiving aggressive medical management undergo staged procedures, while single-stage pouch surgery is still offered only to the healthier, more elective group. Our interpretation of the data available in the literature suggests that by deferring the critical surgical step of the pelvic dissection with pouch construction and anastomosis to a time when patients are medically optimized, we are able to limit complications. Nevertheless, we believe that there are certain characteristics that define the group of patients who may benefit from the avoidance of a stoma and its complications [30]: young, healthy patients who are not on immunosuppressants or steroids preoperatively; surgical indication of dysplasia; uneventful operation; pouch with optimal blood supply and tension-free anastomosis. We usually leave a rectal tube in these patients for a few days to avoid pouch distension and discomfort due to the initial diarrhea and possible perianal skin irritation.

Operative Technique and Surgical Decision-Making

Once the decision is made to proceed with surgery, it is important to remember that, with UC patients, one size definitely does not fit all. In the following section, we will discuss the pros and cons of different approaches based on patient and disease characteristics and surgeon skill and judgment. While these opinions are based on the available evidence, there is a certain component of personal preference.

Preoperative Planning

The patient and family should meet with the surgical team prior to surgery to discuss the nature and necessity for the surgery, alternative options, risks and benefits of the procedure, and long-term functional outcomes. If a temporary or permanent ileostomy is planned, it is imperative that a certified enterostomal therapist evaluate the patient for preoperative marking. Preoperative anesthesia and medical consult evaluation may be needed preoperatively, depending on the patient's comorbidities, to optimize any underlying conditions and limit operative risk. Patients undergo bowel prep with a mechanical cleansing agent and oral antibiotics the day before surgery. In our practice, unless contraindicated, patients receive an epidural preoperatively as part of an enhanced recovery pathway. Antibiotics, thromboembolic prophylaxis, and in some cases stress-dose steroids are administered prior to induction of anesthesia.

Brooke Ileostomy

In 1952, Professor Bryan Brooke described his technique for everting an ileostomy in order to minimize skin excoriation [36, 37]. The Brooke ileostomy remains the preferred approach for patients who are not candidates for restoration of intestinal continuity in our practice.

When determining the placement of the ileostomy, the patient's abdomen should be assessed in the sitting and standing positions. The ideal location for the ileostomy is in

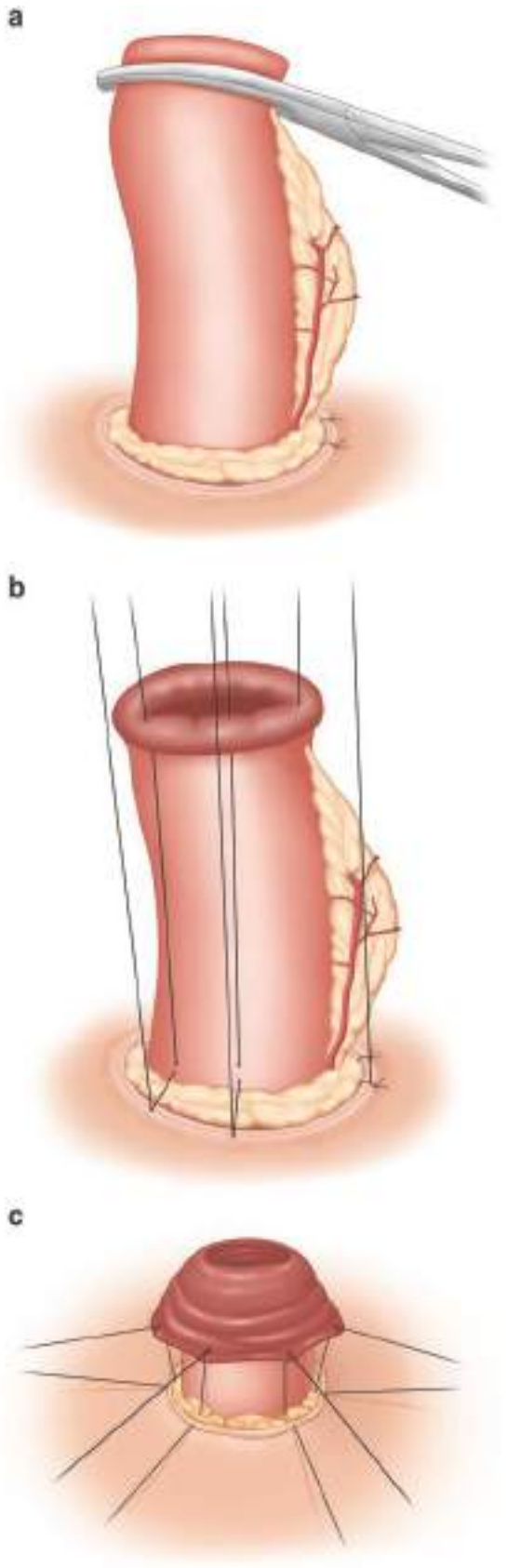


FIGURE 50-1. Construction of a Brooke Ileostomy. (**a**) The terminal ileum is extracted from the stoma site without tension on the mesentery. (**b**) Sutures are placed along the antimesenteric edge of the ileum and lateral to the mesentery allowing eversion of the bowel. (**c**) Everting sutures are tied and simple sutures are placed between the ileum and the dermis at the mucocutaneous junction.

a flat area over the right rectus muscle that is away from previous scars, deep abdominal folds or creases, and bony prominences. It is essential that a patient be seen by an enterostomal therapist to preoperatively mark the best site for the stoma [38].

Operative Details

A circular incision is made in the skin and carried down through the subcutaneous tissue until the anterior rectus sheath is encountered. The anterior rectus sheath is incised vertically and the rectus muscles are bluntly separated with handheld retractors. The posterior rectus sheath and peritoneum are then incised to create an opening that will accommodate two fingerbreadths. After ensuring no twisting of the bowel or mesentery, the terminal ileum is delivered through the opening (Fig. 50-1a). The ileostomy is matured with 3–0 chromic suture. A full thickness suture is placed at the open end of the ileum; a seromuscular bite of the bowel wall is then taken at the skin level and followed with a subcuticular bite through the dermis (Figure 50-1b). Four to five everting sutures are placed (Figure 50-1c), with particular care taken at the mesentery to avoid injury to the mesenteric vessels (a simple suture may be placed at this site). After placing the everting sutures, they are tied, and simple sutures are placed circumferentially between the cut edge of the ileum and the dermis to complete approximation of the mucocutaneous junction.

Operative Considerations

While obesity remains a relative contraindication to IPAA, management of obese patients with a stoma also presents significant challenges. Stoma-related complications occur in up to 36 % of patients [39], with obesity representing a key risk factor for stoma failure. Obese patients present technical difficulties caused primarily by mechanical factors: the foreshortened mesentery and the thick layer of the subcutaneous fat through which the intestine has to be placed. Stoma necrosis, retraction, parastomal herniation, and mucocutaneous separation are among the possible complications of a permanent end Brooke ileostomy, although not exclusively among the morbidly obese patients. In order for this group of patients to achieve the best possible long-term outcome, strict collaboration between the enterostomal therapist and the surgeon is critical. Revision of an ileostomy is often a very challenging operation in the obese patient; thus, proper placement, with appropriate preoperative evaluation for siting, is imperative. The impact of a poorly functioning ileostomy on patient's quality of life should not go

unnoticed, especially considering the fact that several of the UC patients are young with an active lifestyle.

Outcomes

To evaluate the Health-Related Quality Of Life (HRQOL) of patients who had a permanent Brooke ileostomy compared to the general population, Camilleri-Brennan et al. [40] conducted a mail survey using the quality of life questionnaire SF-36 version 2 (SF-36II) [41]. The authors evaluated the difference between patients and the general population for all dimensions and summary scores. The scores directly relating to physical well-being as well as the Physical Component Summary were similar between the two groups. Comparable results were also achieved for the energy and vitality dimension and pain scores. Scores in the mental health and role-emotional dimensions, as well as in the social functioning dimensions, and general health perceptions were analogous to that of the general population. This study suggested that despite the presence of a permanent ileostomy, HRQOL was very similar to that of the general population. The results clearly underscore the notion supported by other authors that a perceived negative impact of the ileostomy does not appear to affect HRQOL. Therefore, a permanent end ileostomy remains a viable option for UC patients requiring surgery and should always be discussed when counseling the patient regarding surgery.

Continent Ileostomy

There have been several modifications of the original description of the continent ileostomy popularized by Nils Kock in 1969 [42]. Creation of a continent ileostomy, or Kock pouch, requires an elaborate operation that involves the building of an ileal pouch with an internal valve to prevent and control the flow of enteric contents into the ostomy bag. With improvements in our understanding of inflammatory bowel disease and surgical technique, there are few patients today for whom the Kock pouch is an appropriate alternative to IPAA anastomosis following proctocolectomy. Specifically, this operation should be offered in specialized centers to patients with UC and a locally advanced low rectal cancer that will need adjuvant therapy postoperatively; patients who already have a Brooke ileostomy after proctocolectomy and wish to improve their quality of life; patients who are not candidates for an IPAA because of poor sphincter function; patients who prefer a continent ileostomy to an IPAA as a personal choice; and lastly, patients who have failed an IPAA but prefer a continence-preserving procedure to a Brooke ileostomy [43, 44]. Contraindications to this procedure include Crohn's disease, obesity, critically ill patients, and the psychologically unfit patients because of the inability to intubate. This procedure has also been performed in the pediatric population with satisfactory results [43–45].

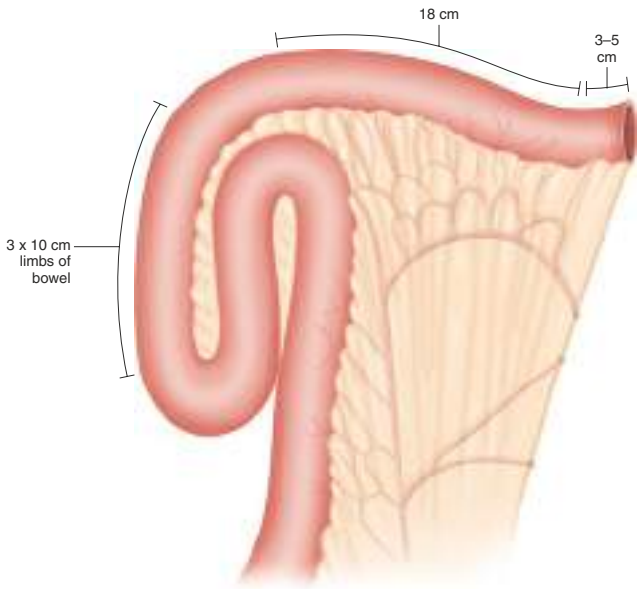


FIGURE 50-2. Construction of a Kock Pouch—about 50 cm of small bowel is used to create the Kock pouch. The distal 3–5 cm is used for the outlet, the middle 18 cm is used to construct the nipple valve, and the proximal 30 cm is utilized in creation of the pouch.

Operative Details

About 50 cm of small bowel is used to fashion a continent ileostomy (Kock pouch) (Figure 50-2). The outlet is constructed from the distal 3–5 cm of this segment, the nipple valve is created from the next 18 cm of bowel, and the remaining 30 cm is used for the pouch. Excising the peritoneum and mesentery on both sides of the arcade skeletonizes the mesenteric vessels of the small bowel used to build the nipple valve (Figure 50-3).

The pouch is generally created in an S-shape by folding the 30 cm length of small bowel into 10 cm limbs with one more cephalad to the other. A posterior row of sutures is placed between each limb and an enterotomy made along the S-shape (Figure 50-4). The incision will be antimesenteric along the middle limb and closer to the mesentery along the two outer limbs. A second posterior layer of sutures is created to re-approximate the cut edges (Figure 50-5). The nipple valve is then created with three passes of a GIA stapler without the knife (two along either side of the mesentery and one along the anterior aspect) (Figure 50-6). A two-layer closure of the anterior portion of the pouch is then performed. A circumferential row of interrupted sutures are placed between the outlet and the pouch to help maintain the position of the nipple valve (Figure 50-7).

To create the stoma aperture a small circular incision is made in the skin and carried through the subcutaneous tissue. A vertical incision is made in the fascia, the rectus muscle is retracted, and the peritoneum incised ensuring that the opening can accommodate two fingerbreadths. The outlet is brought

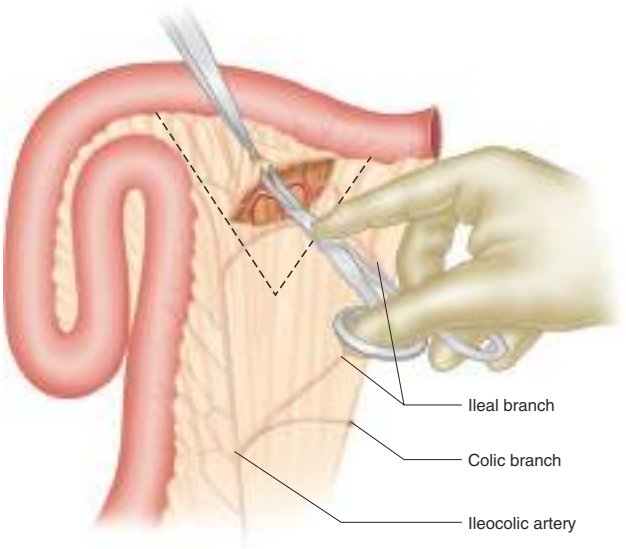


FIGURE 50-3. Construction of a Kock Pouch—the mesentery of the small bowel to be intussuscepted (marked by *dashed lines*) is skeletonized assisting formation of the nipple valve. The blood supply of this segment of bowel is identified with trans-illumination and the peritoneum and mesentery on either side of the vasculature is excised.

up to the opening and the pouch secured to the abdominal wall by placing sutures laterally and medially (Figure 50-8). The outlet is transected at a location that will enable the matured stoma to be flush with the skin. A curved Medina catheter is placed into the most dependent portion of the pouch and secured in place by suturing the rubber collar on the catheter to the skin (Figure 50-9).

Operative Considerations

The two main long-term problems with a continent ileostomy are malfunction of the valve and pouchitis. Malfunction of the valve causes incontinence and difficult intubation of the pouch and occurs in 11–20 % of patients [46–48]. When the continence mechanism fails, a traditional Kock pouch does not necessarily become a conventional ileostomy, but rather the "slipped valve" creates a functional obstruction requiring further surgery for revision or conversion to a standard Brooke ileostomy. Valve revision is successful in most patients. The incidence of pouchitis in Kock pouches is nearly identical to that after IPAA and management is similar.

Outcomes

Kock pouch procedures have recently fallen out of favor. The largest series were published in the late 1970s [46–48] and since the early 1980s fewer continent ileostomies have been performed as the great majority of appropriate patients choose to undergo an IPAA. However, recent data suggest

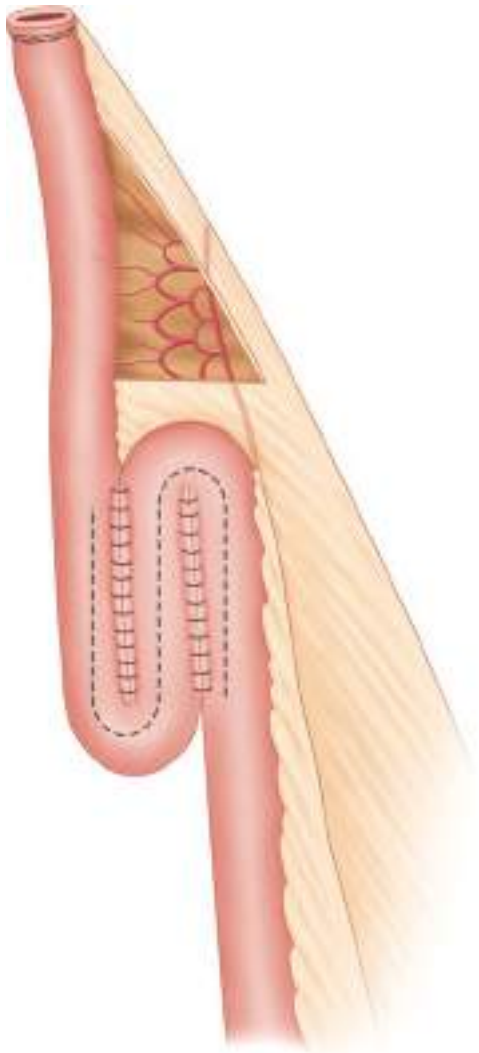


FIGURE 50-4. The S-shaped pouch is constructed by folding the proximal 30 cm of bowel into 3–10 cm limbs with sutures placed between the limbs. An enterotomy is made (*dotted line*) starting at the distal aspect.

that continent ileostomies in well-selected and properly motivated patients can be durable with long-term pouch survival rates approaching 80 % [49]. Overall long-term follow-up showed excellent results: between 70 and 89 % of patients have continence for gas and stool, and ultimately 95 % never had to wear an appliance [46–48].

Nessar et al. [50] reviewed the Cleveland Clinic continent ileostomy experience comparing HRQOL in continent ileostomy patients and those whose Kock pouch failed requiring removal and conversion to an end ileostomy. Results were evaluated using the continent ileostomy surgery follow-up questionnaire and the Cleveland Global Quality of Life (CGQL) scale. Patients with an end ileostomy were more than twice as likely to report social, work, and sexual restrictions and to require a higher antidiarrheal medication

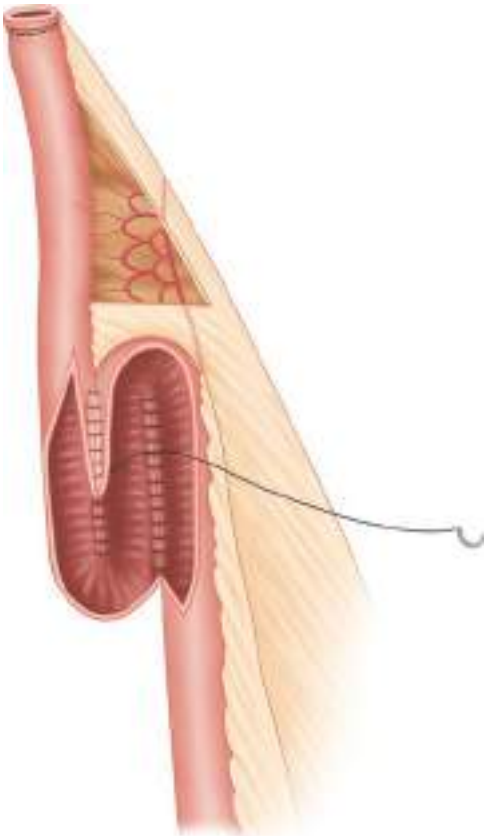


FIGURE 50-5. An inner posterior layer is created starting at the proximal end forming the pouch.

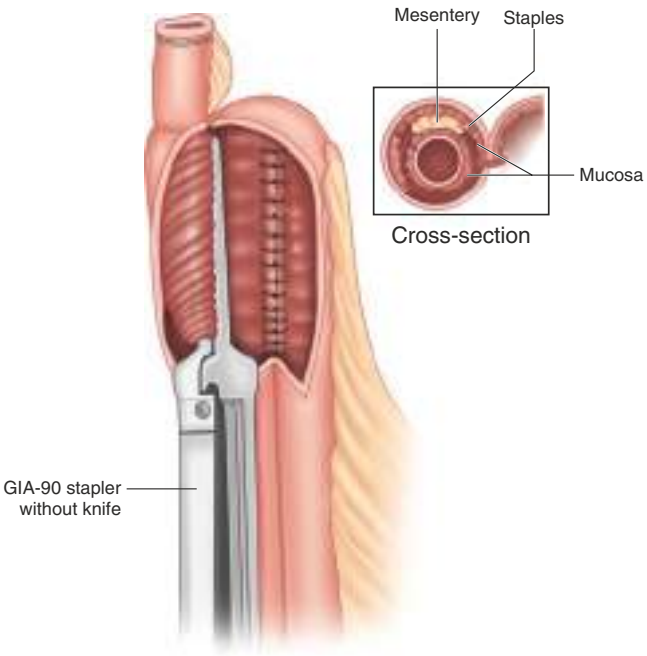


FIGURE 50-6. The nipple valve is created with three firings of a GIA 90 mm stapler without the knife.

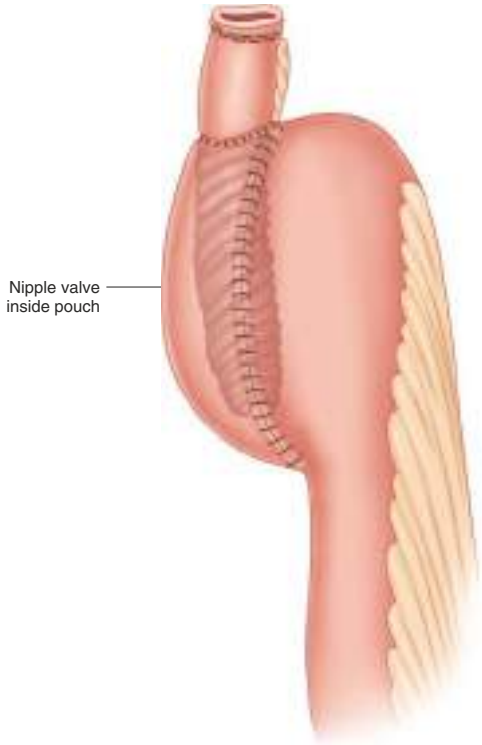


FIGURE 50-7. The anterior aspect of the valve is then completed with an inner and outer layer of sutures. To help maintain the nipple valve position a row of interrupted sutures is placed between the pouch and the outlet.

and fiber intake compared with patients with a continent ileostomy. Patients with a continent ileostomy reported having a better appetite and less abdominal pain than the end ileostomy group and rated a higher score for overall happiness. CGQL measurements were better on all scales as well as the summary scale in the continent ileostomy group. Kohler et al. compared quality of life between Brooke ileostomies, Kock pouches, and IPAA [51]. Patients with IPAAs had fewer restrictions in sports and sexual activities than those with Kock pouches, whereas those with Kock pouches had fewer restrictions in these activities but more restrictions in travel than those with Brooke ileostomies. In contrast, performance in the categories of social life, recreation, work, and family was similar between groups. They concluded that a well-functioning IPAA is superior to both Brooke ileostomies and Kock pouches in terms of overall quality of life.

Total Abdominal Colectomy with Ileorectal Anastomosis

Until the 1950s, total proctocolectomy with end ileostomy was the only available approach for UC patients failing medical management. In the 1940s reports of subtotal colectomy with

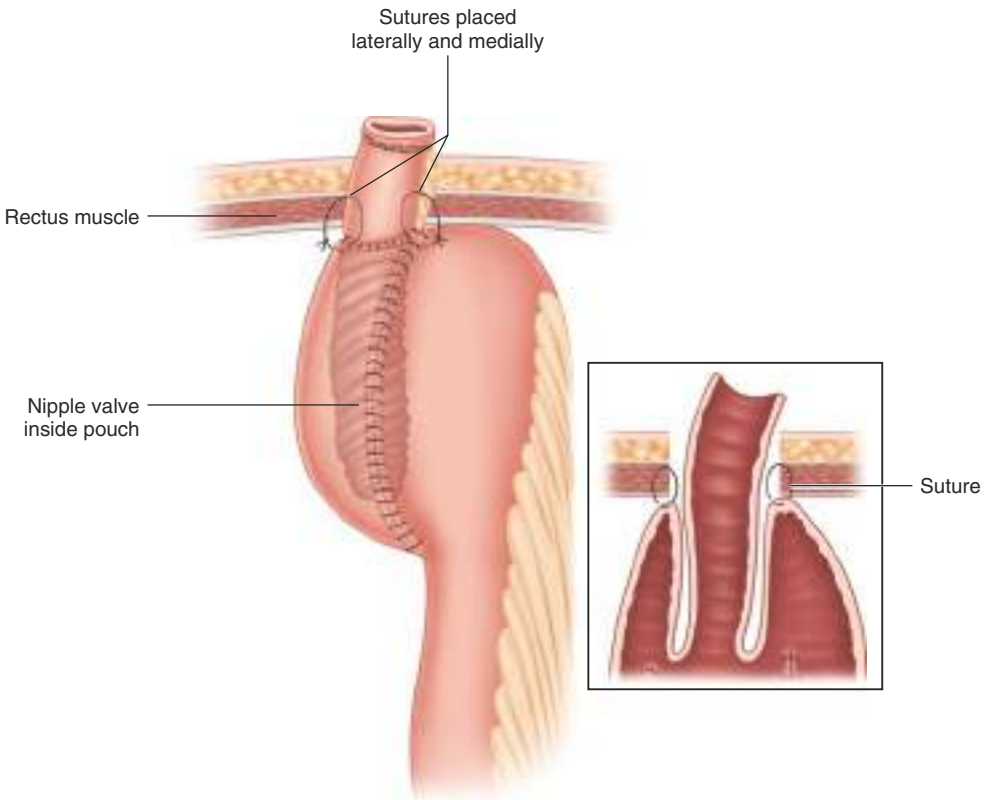


FIGURE 50-8. Sutures are then placed between the pouch outlet and the posterior sheath of the abdominal wall on the lateral and medial aspects.

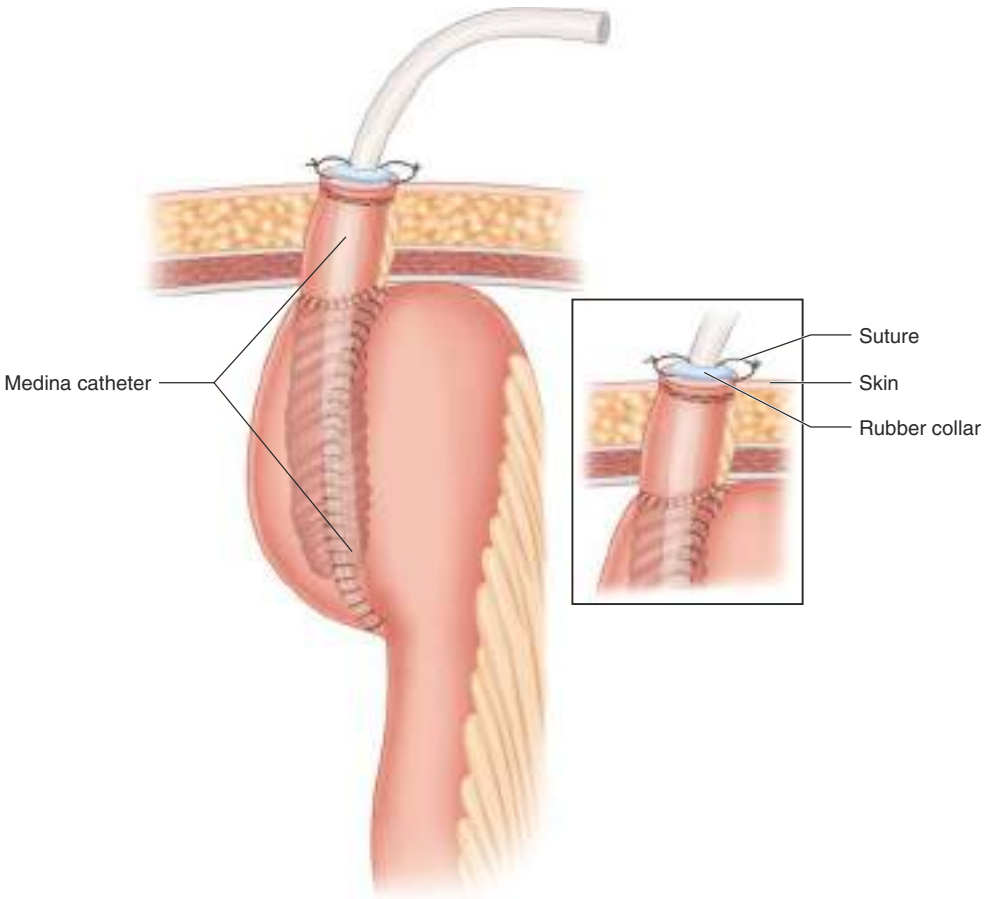


FIGURE 50-9. A Medina catheter is placed into the most dependent aspect of the pouch and secured to the skin.

ileorectal anastomosis (IRA) as an alternative to total proctocolectomy in selected patients were first published. Prior to the description of IPAA, this procedure quickly became a valid alternative to total proctocolectomy in highly selected patients with minimal rectal inflammation and adequate rectal compliance to avoid a permanent stoma [52, 53]. Advantages included lack of a permanent stoma, performance of a one-stage, less invasive operation, and avoiding pelvic dissection with its associated risk of sexual dysfunction [54].

In 1978, Parks et al. described the IPAA and Utsonomiya popularized it in the 1980s [55, 56]. Since then, IPAA has become the procedure of choice for patients affected by UC with excellent long-term functional results and a low risk of persistent cuff inflammation or neoplastic degeneration in the retained rectum [57, 58]. Consequently, many surgeons have abandoned IRA in favor of IPAA or total proctocolectomy in patients not candidates for IPAA. The pros and cons of the different surgical approaches are listed in Table 50-4 [17, 54, 59–61]. Patient selection is clearly critical in assuring long-term favorable outcomes in patients undergoing an IRA. Total abdominal colectomy with ileorectal anastomosis (TAC-IRA) is now generally reserved for patients with limited rectal involvement, good rectal compliance, and no dysplasia or cancer. Adequate rectal compliance and normal anal sphincter function are critical for good long-term results. This can be initially assessed by digital rectal examination, but is more accurately characterized by rigid/flexible proctoscopy and anal manometry. Patients with poor sphincter function, severe rectal disease, and a non-distensible rectum should not be offered an IRA. TAC-IRA may be done via a minimally invasive or open approach depending on the nature and severity of disease, previous surgical history, comorbidities, and surgeon experience.

Operative Details: Open Approach

The procedure is performed with the patient in the modified lithotomy position with the legs supported by stirrups, ensuring that all pressure points are appropriately padded. A vertical midline incision is made and the abdomen is explored with careful examination of the bowel for possible manifestations of Crohn's disease or the presence of malignancy.

The ascending colon and terminal ileum are fully mobilized by incising the lateral peritoneal reflection from the cecum up to the hepatic flexure. The right ureter and gonadal vessels and duodenum should be identified and separated from the mesentery to prevent inadvertent injury. The transverse colon is separated from its attachments to the stomach with or without preservation of the greater omentum. In our practice, the greater omentum is generally resected with the transverse colon (Figure 50-10). The lesser sac is entered and the omentum separated from the greater curvature of the stomach caudal to the gastroepiploic vessels. Dissection is carried to the splenic flexure exercising care to avoid splenic injury. Traction on the omental or colonic attachments to the splenic capsule may result in an avulsion injury and can often be avoided by dividing any omental attachments before applying traction. The dissection is then carried along the descending colon. Adhesions of the sigmoid colon to the abdominal and pelvic sidewall are divided and the lateral peritoneal reflection is incised. Care is taken to identify the left ureter and gonadal vessels to ensure their safety. Dissection is continued superiorly up to the splenic flexure, and with a combination of blunt and sharp dissection from the proximal and distal aspects, the splenic flexure is completely freed. At this point, full mobilization of the colon from the terminal ileum to the rectosigmoid junction has been accomplished.

The terminal ileum is transected with a GIA stapler and the mesentery of the colon is ligated and divided. If malignancy is not suspected, high ligation of the named vessels is not necessary and the mesentery can be divided close to the bowel wall. Larger vessels should be doubly ligated or divided with a vessel-sealing device. The inferior mesenteric artery is generally preserved in order to avoid injury to the hypogastric plexus and preserve adequate blood supply to the rectal stump. The rectosigmoid junction is divided at the level of the sacral promontory.

The ileorectal anastomosis can either be performed in an end-to-end or side-to-end fashion via a handsewn or stapled technique. We generally prefer to create a side-to-end ileorectal anastomosis. A flexible sigmoidoscopy is then performed to ensure that the anastomosis is patent, hemostatic, and healthy appearing, and an anastomotic leak test is conducted.

TABLE 50-4. Pros and cons in ulcerative colitis surgery

IRA	IPAA	TPC
+ Function	+ Low cancer risk	+ Cancer risk
+ One surgery	+/– Defecatory function	+ One surgery
+ Low risk of sexual/urinary dysfunction	– Risk of sexual/urinary dysfunction	– Permanent fecal diversion
– Recurrent disease	– Multiple surgeries	– Risk of sexual/urinary dysfunction
– Cancer risk	– Decreased fertility	– Decreased fertility

IRA ileorectal anastomosis, *IPAA* ileoanal pouch anal anastomosis, *TPC* total proctocolectomy

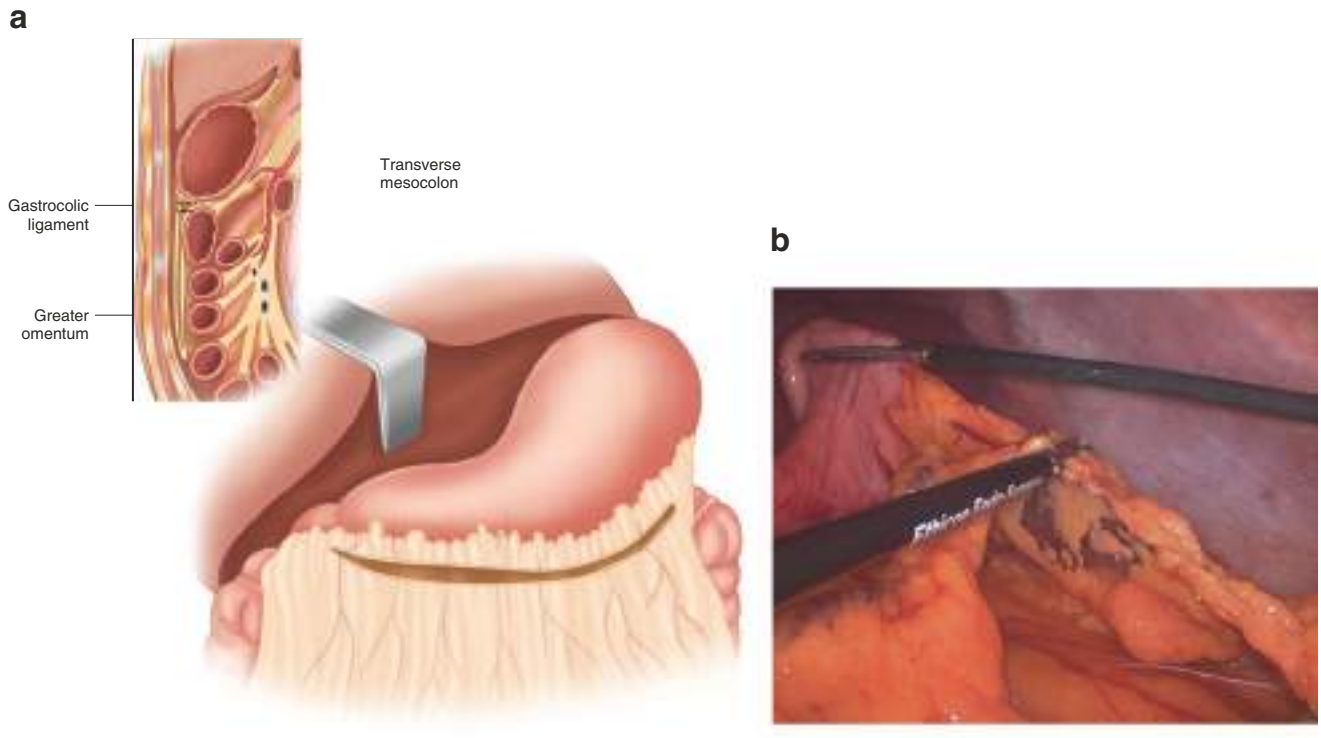


FIGURE 50-10. (**a** and **b**) The omentum is divided along the greater curvature of the stomach distal to the gastroepiploic arcade.

Operative Details: Laparoscopic Approach

The procedure is performed with the patient in the modified lithotomy position with the legs supported by stirrups and both arms tucked, ensuring that all pressure points are appropriately padded. An infraumbilical (supraumbilical for a hand-assisted procedure) port is placed via an open technique. The abdomen is explored with careful examination of the bowel for possible manifestations of Crohn's disease or the presence of malignancy and ability to perform the procedure laparoscopically is assessed. If a laparoscopic approach is feasible, then four additional trocars are placed in the right and left upper and lower quadrants for a straight laparoscopic procedure. If the surgeon elects to perform hand-assisted approach, two additional trocars in the bilateral lower quadrants and the hand-assisted port are placed via a Pfannenstiel incision about two fingerbreadths above the symphysis pubis.

The patient is then placed in the Trendelenburg position with the right side up. The cecum is retracted anterolaterally and the ileocolic artery and vein are identified (Figure 50-11). An incision is made just inferior to the vessels and a mesenteric window created. The duodenum should be visualized not only to avoid inadvertent injury but because it is an important landmark used to confirm correct identification of the ileocolic artery and vein. The vessels are then divided away from the origin if malignancy is not suspected. Mobilization continues superiorly, sweeping down the second portion of the duodenum and separating it from the posterior aspect of the transverse mesocolon (Figure 50-12). The dissection then continues laterally in the plane between the mesocolon and Gerota's fascia. The appendix is then retracted toward the splenic flexure and the lateral peritoneal reflection is divided from the cecum to the hepatic flexure until the site of medial mobilization is met (Figure 50-13). Care is taken to avoid injury to the duodenum.

Dissection continues with serial ligation and division of the transverse mesocolon and omentum caudal to the gastroepiploic arcade (Figure 50-14a, b). This mobilization may be aided by placing the patient in reverse Trendelenburg. In the presence of benign disease, the mesocolon can be ligated and divided close to the bowel wall with a vessel-sealing device. Through a combination of blunt and sharp dissection, the splenic flexure is mobilized ensuring no undue traction on the spleen (Figure 50-15a, b). The patient is placed with the left side up and the small bowel retracted toward the right side. The left mesocolon is serially ligated and divided and the left-sided peritoneal reflection is divided. The sigmoid colon is retracted medially and the lateral attachments of the sigmoid colon are incised taking care not to injure the left ureter or gonadal vessels. The sigmoidal branches are ligated and divided. Once the colon has been mobilized up to the rectosigmoid junction, it is extracted through a Pfannenstiel incision, the bowel is transected, and the anastomosis is created in the same way as the open approach.

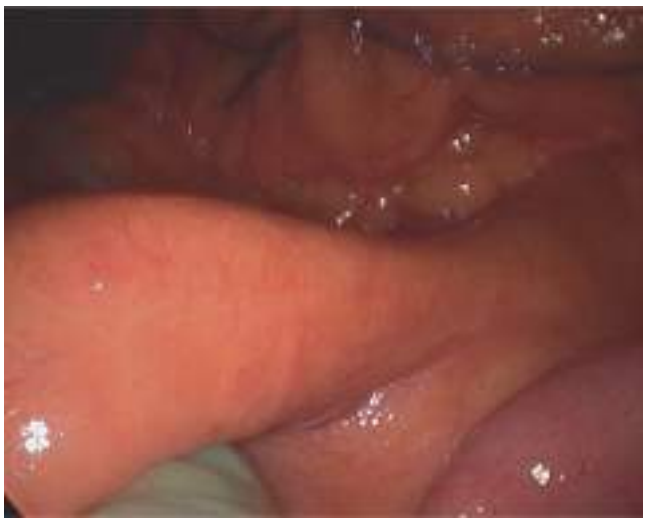


FIGURE 50-11. Identification of the ileocolic pedicle.

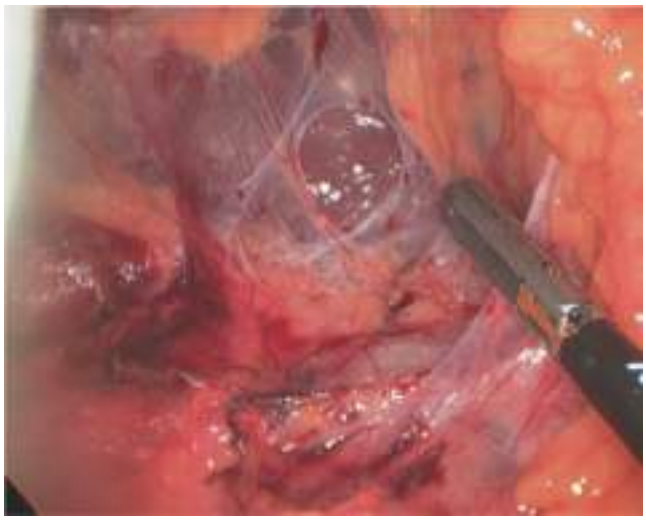


FIGURE 50-12. Medial to lateral dissection and creation of the mesenteric window.

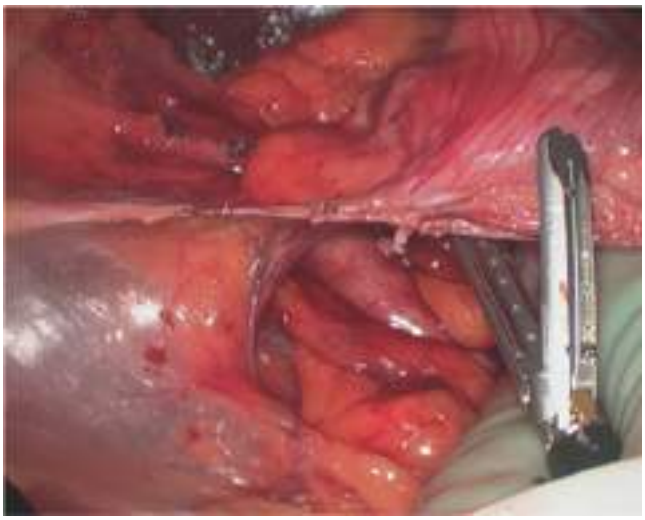


FIGURE 50-13. Division of the lateral attachments.

Outcomes

In UC, an IRA is a safe procedure with a reported overall morbidity between 8 and 28 %[60–63] including small bowel obstruction, anastomotic leak, abdominal abscess, pulmonary embolism, sepsis, rectal bleeding, wound infection, abdominal wall dehiscence, urinary tract infection, transient urinary retention, hematoma, and stoma complication. In addition IRA does not involve extensive pelvic dissection, unlike IPAA or total proctocolectomy, minimizing the risk of sexual and urinary dysfunction. Hence, higher fertility rates may be expected in IRA patients compared to IPAA although definitive studies providing evidence for better fertility rates in UC patients are lacking. Nonetheless, IRA should be considered and discussed with women in their reproductive age [64].

Disease recurrence in the rectal remnant in continuity is significant and these patients should be monitored and followed up endoscopically. The cumulative probability of having a functioning IRA at 5 years has been reported as high as 84 % [63, 65], 69 % at 10 years [62, 65], and between 46 and 69 % at 20 years [64]. In the Cleveland Clinic series comparing 22 IRA with 66 IPAA patients matched for age, gender, and follow-up time, the cumulative probability of having a functioning IRA at 5, 10, 15, and 20 years was 81, 74, 56, and 46 %, respectively, in accordance with previously published work [60]. Functional results are typically described in terms of number of bowel movements and incidence of soiling or urgency. The Cleveland series of 22 IRA patients reported six bowel movements per day (range 2–11), 5 % incidence of nighttime seepage, and 68 % mostly/sometimes grade of urgency [60]. Pastore et al. described a median number of six bowel movements per day (range 2–20), with median number of one nocturnal bowel movement (range 0–10) among 90 patients undergoing total abdominal colectomy and IRA. Three patients had more than eight daily stools with frequent soiling and urgency. At the time of follow-up, antidiarrheal medications were taken by 53.3 % of patients, whereas 31.3 % required low doses of systemic or topical steroids. More than 90 % of patients considered that their health status had improved after the operation. Quality of life was improved in 84 % [63].

The main indication for proctectomy is recurrent proctitis refractory to medical management [60, 62, 63, 65], followed by dysplasia or cancer, and the development of Crohn's disease. Options for these patients include IPAA, Brooke ileostomy, or a continent ileostomy (Kock pouch). IPAA can often be safely performed in the majority of these patients, thus preserving bowel continuity and avoiding permanent fecal diversion [60]. Among 86 patients undergoing IRA for UC, 46 (53 %) required completion proctectomy for refractory proctitis

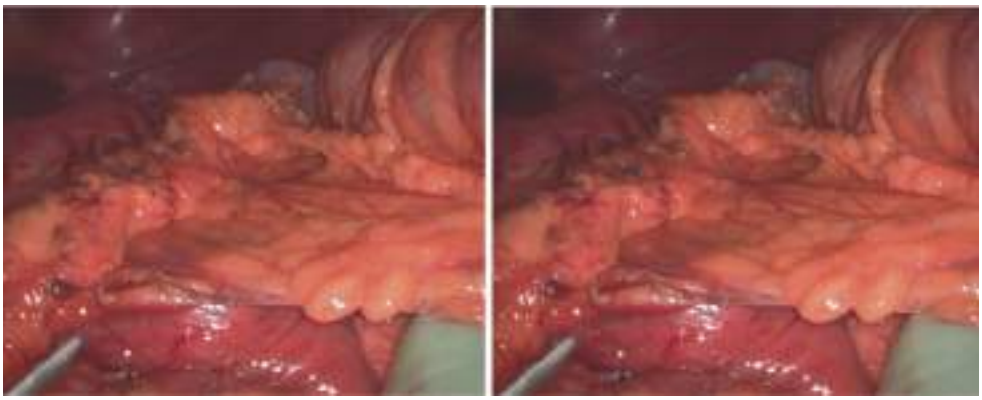


FIGURE 50-14. (**a** and **b**) Ligation and division of the transverse mesocolon and omentum caudal to the gastroepiploic arcade.

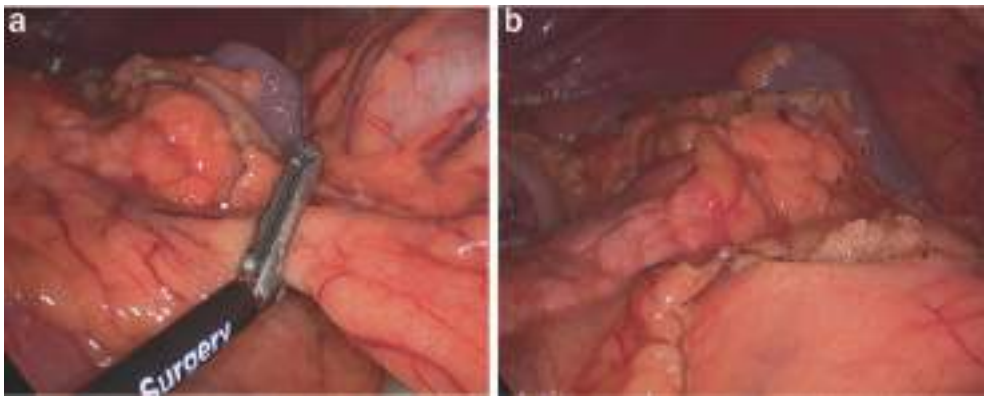


FIGURE 50-15. (**a** and **b**) Mobilization of the splenic flexure.

($n=24$), rectal dysplasia ($n=15$), and rectal cancer ($n=7$) at a median interval of 10 years (range 1–33) [60].

Endoscopic monitoring of the rectal remnant is essential given the high rate of disease recurrence, as well as the risk of dysplasia/cancer which increases with time. In the Cleveland Clinic series, the overall cumulative probability of rectal dysplasia in the retained rectum increases from 9 % at 10 years to 25 % at 20 years [60]. The overall incidence of rectal cancer after an IRA varies in the literature based on the length of follow-up, ranging from 0 to 8 %. In the Cleveland Clinic series, the incidence of cancer was 0, 2, 5, and 14 % at 5, 10, 15, and 20 years, respectively [60]. In the Scandinavian series, no cancer was reported at 13-year and 18-year follow-up, respectively [62, 65], thus emphasizing the importance of strict patient selection.

Most patients who develop rectal cancer in the retained rectum presented at an advanced stage (stages III–IV), suggesting the possibility of a more aggressive biology and making close surveillance imperative [60, 66]. Rectal biopsies every 6–12 months are advised following IRA in UC patients. If dysplasia is found, completion proctectomy is indicated. Patients with long-standing UC who are not able or willing to undergo surveillance should not be offered an IRA. It is also important to emphasize that colectomy with IRA should not be offered to patients with preexisting dysplasia or cancer due to the increased risk of further neoplastic degeneration [67]. However, patients with advanced metastatic disease may benefit from an IRA due to their short life expectancy and the palliative nature of their treatment.

Total Proctocolectomy with End Ileostomy

Proctocolectomy with Brooke ileostomy was the standard of care for the treatment of ulcerative colitis until the early 1980s when Utsonomiya popularized the IPAA [56]. While restorative proctocolectomy with IPAA with the intent of maintaining intestinal continuity is now the gold standard in the surgical management of UC, certain patients are not candidates for this procedure, typically due to patient or disease-related factors or personal preference (Table 50-5). Once these patients are referred to the surgeon with an indication for surgical intervention, they should be evaluated and offered a total proctocolectomy with a permanent ileostomy, or in certain circumstances an ileorectal anastomosis as discussed previously.

By removing all diseased epithelium, a proctocolectomy cures patient disease, eradicates the associated risk of malignancy, and eliminates the need for costly medications and time-consuming lifelong follow-up. The disadvantages of this operation include the presence of a permanent ileostomy, the potential for nerve injury during pelvic dissection, and

Table 50-5. Contraindication to IPAA

Absolute	Relative
Severe fecal incontinence	Severe morbid obesity
Locally advanced low rectal cancer involving the sphincters	Locally advanced low rectal cancer requiring neoadjuvant treatment
Perianal Crohn's disease	Crohn's disease
	Previous extensive small bowel resections
	Personal preference

IPAA—ileoanal pouch anal anastomosis

the risk of perineal wound healing problems. A proctocolectomy with an end ileostomy is indicated in patients who are not candidates for an IPAA (Table 50-5) or a Kock pouch. The operation may also be indicated if other medical problems make a more complex, longer operation too risky [68, 69]. Finally a total proctocolectomy should be considered in patients who desire a single operation for cure or whose work and other daily activities make an ostomy appliance easier to manage than frequent bowel movements.

There are no absolute contraindications to this procedure. However, in the emergent setting, it is advisable to stage the procedure with an initial abdominal colectomy. This strategy avoids the morbidity associated with rectal dissection, which can be potentially difficult and time-consuming in an unstable patient. This procedure can be performed through a laparotomy incision, single incision, hand or laparoscopic assisted, or totally laparoscopically as the authors have previously described [70]. There are no large studies comparing these approaches in this very selected group of patients. Intuitively, a totally laparoscopic approach should result in lower incidence of hernias, with the exclusion of parastomal hernias. As with an abdominal colectomy with ileorectal anastomosis, the choice of a minimally invasive or open approach is dependent on nature and severity of disease, previous surgical history, comorbidities, and surgeon experience.

Operative Details: Open Proctectomy

If the severity of disease or other patient factors necessitate a staged approach, the initial total abdominal colectomy proceeds as above, but rather than creating an ileorectal anastomosis, the rectal stump is left in situ and the terminal ileum is fashioned into an end ileostomy. The rectosigmoid is transected with a linear stapler at the sacral promontory (Figure 50-16). The staple line can be reinforced with interrupted Lembert sutures if there is increased concern for dehiscence, but this is not our common practice. A rectal tube is left in place for 5 days postoperatively to ensure adequate evacuation of rectal contents and decompression of the rectal stump. The proctectomy with or without ileal pouch can be performed several months later when the patient's overall health improves and they are no longer on medications.

Whether the rectal dissection is done at the same time as the colonic mobilization or as the second operation of a staged approach, the dissection begins with division of the terminal branches of the inferior mesenteric artery (the superior rectal arteries) and complete posterior mobilization of the rectum. Bilateral ureters and the sympathetic neural plexus, which lies directly posterior to the inferior mesenteric artery at the pelvic brim, are identified and swept free. The terminal branches of the inferior mesenteric artery and vein are ligated and divided at the level of the sacral promontory.

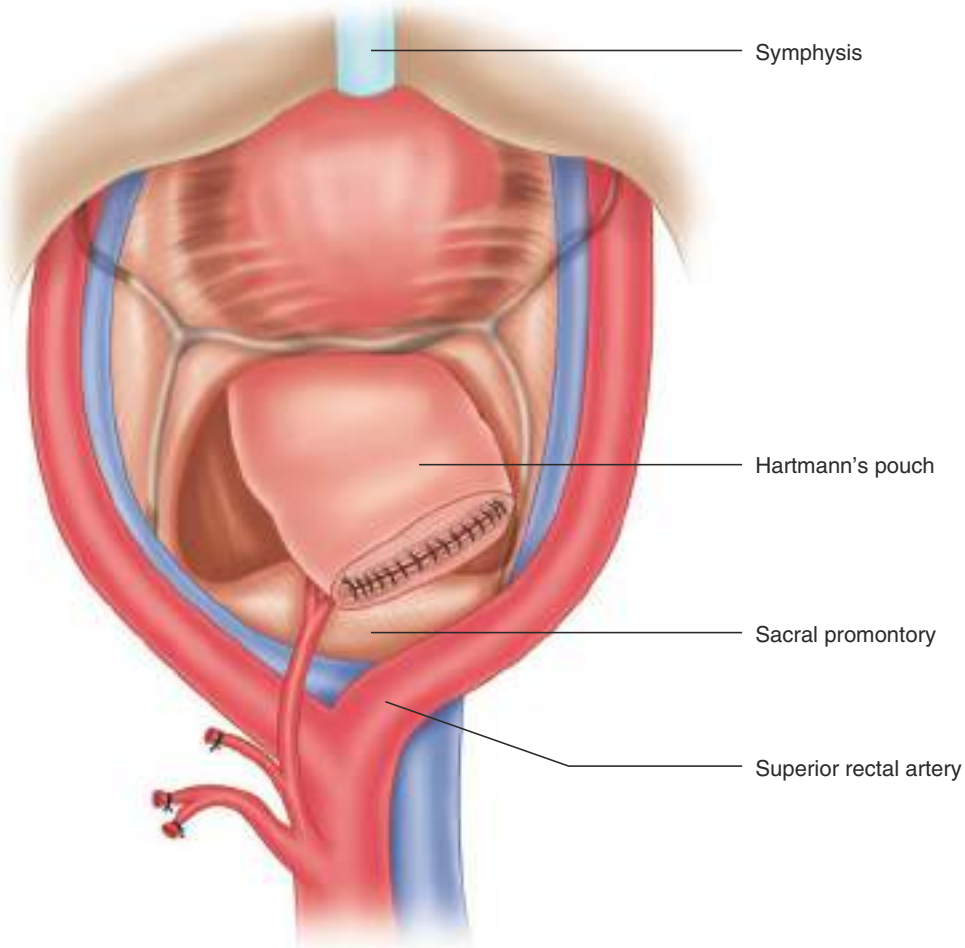
The parietal peritoneum is incised inferiorly and laterally to gain access to the presacral space between the fascia propria of the rectum and the presacral fascia. The rectum is retracted anteriorly and sharp dissection is carried out in the areolar tissue. Care must be taken to ensure that the presacral venous plexus remains covered to avoid bleeding that can often be difficult to stop and may be life-threatening. Dissection should be carried down in the posterior plane beyond the coccyx and Waldeyer's fascia is incised. The lateral rectal stalks are then divided as close to the rectal wall as possible to avoid injury to the pelvic plexus. Attention is then turned to anterior dissection in the rectovaginal or rectovesicular space posterior to Denonvilliers' fascia. At this point, the rectum should be circumferentially mobilized to the levator ani muscles. If the colectomy had not been done at a prior operation, the terminal ileum is transected at its junction with the cecum with a GIA stapler. Then the abdominal wound is closed, the ileostomy is created, and attention turned to the perineal dissection.

A pursestring suture is placed to close the anus at the level of the anal verge. A circular incision is made in the intersphincteric groove and carried through the subcutaneous tissue (Figure 50-17). The anococcygeal ligament is divided and the pelvic cavity is entered posteriorly. The incision is extended circumferentially mobilizing the entire distal rectum and anus. Care should be taken anteriorly to avoid injury to the vagina or prostate. The specimen is extracted through the perineal opening and the wound is then closed in layers (Figure 50-18).

Operative Details: Laparoscopic Proctectomy

As with the open approach, the rectal dissection begins with division of the terminal branch of the inferior mesenteric artery (the superior rectal artery). The rectal stump and distal sigmoid colon are retracted superiorly and anteriorly out of the pelvis exposing the inferior mesenteric artery (IMA). The peritoneum to the right of the superior rectal artery is

FIGURE 50-16. Distal transection at the level of the sacral promontory.



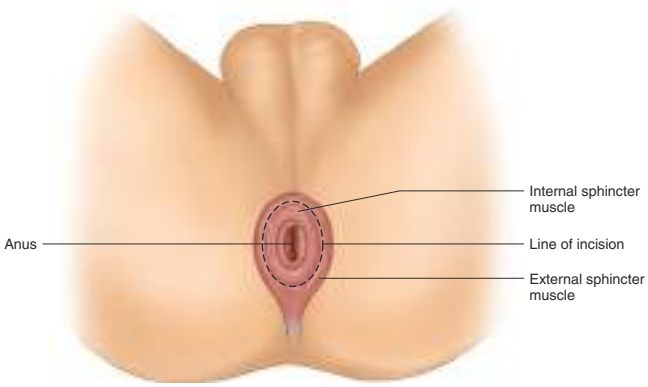


FIGURE 50-17. Perineal dissection—circular incision made along the intersphincteric groove.

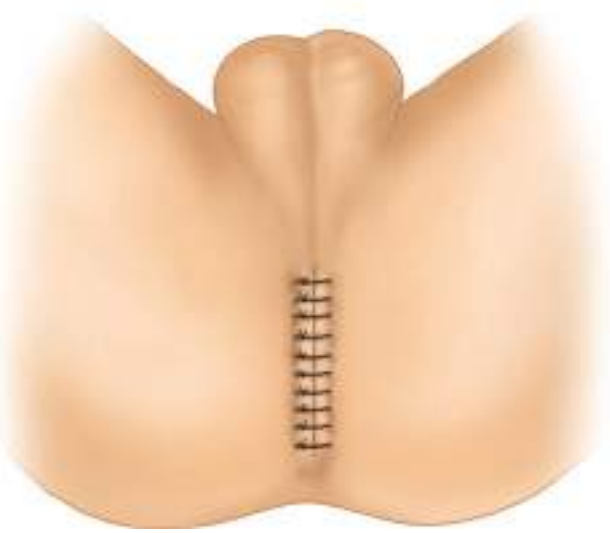


FIGURE 50-18. Closure of perineum.

incised starting at the sacral promontory and extending cephalad to the origin of the IMA. A mesenteric window is created allowing the visualization of the left ureter and gonadal vessels. The hypogastric nerves are swept posteriorly and the superior rectal artery is ligated and divided with a vessel-sealing device. The retrorectal space is entered and the rectum is completely mobilized circumferentially as above down to the pelvic floor. After ensuring no twisting of the bowel or mesentery, the cut edge of the ileum is brought out and the end ileostomy matured. The perineal dissection proceeds as above with the specimen brought out through the perineal incision.

Restorative Proctocolectomy with Ileal Pouch Anal Anastomosis

Before proceeding with an IPAA, fecal continence should be fully evaluated particularly in patients presenting preoperatively with impaired function. Multiparous women, particularly after multiple vaginal deliveries with episiotomies or lacerations, should be asked about their continence function. While it is important to note that continence significantly worsens in all patients during a flare, with multiple bloody and liquid bowel movements, the report of incontinence should be further discussed and investigated. A digital rectal examination performed by the operating surgeon often provides enough information to decide if evaluation by manometry and a rigid probe 3-D endoanal ultrasound should be entertained. Gearhart and colleagues [71] prospectively evaluated 42 women with anorectal manometry and endoanal ultrasound. All patients were continent at the time of evaluation. Endoanal ultrasound revealed significant sphincter defects in 19 patients, 4 of whom had involvement of both sphincters, as a result of an obstetric trauma. The findings of the endoanal ultrasound correlated with anal physiology studies which revealed significantly decreased resting pressures, squeeze pressures, and shorter anal canal length. All patients underwent an IPAA. The participants were surveyed postoperatively with the Cleveland Clinic Florida scale (Wexner score), Fecal Incontinence Severity Index (FISI), or Fecal Incontinence Quality of Life (FIQL) scale. The authors did not find a correlation between the size of the sphincter defect and postoperative incontinence. Almost all responders reported episodes of seepage. Three patients with sphincter defects (15.8 %) were dissatisfied with the functional outcome of the IPAA and said they would not undergo this procedure again. Finally 5 % of them underwent pouch excision. Given these outcomes among patients without reported preoperative incontinence, the existence of problems with defecation prior to surgery (incontinence, diabetic neuropathy, or other neurogenic disorders) should be considered a relative contraindication for IPAA.

Patients who present with very low rectal cancer requiring abdominoperineal resection for oncologic reasons obviously are not candidates for an IPAA. The standard oncologic principles for treatment of rectal cancer apply to rectal cancer in ulcerative colitis. Patients with stage II–III disease benefit from and should receive neoadjuvant chemoradiation therapy to decrease the risk of local recurrence and to increase the chances of achieving an R0 resection as previously shown by the Dutch and German rectal cancer trials [72, 73]. Neoadjuvant chemoradiation therapy does not represent an absolute contraindication to an IPAA for appropriate patients, but does clearly worsen long-term outcome. In a recent study from the Cleveland Clinic, pouch failure rate in rectal cancer patients was 42.9 % after radiation versus 17.6 % in patients who did not receive radiation [74]. A multidisciplinary approach to these patients is mandatory to balance oncologic principles, quality of life, and patient preference. Adjuvant radiation therapy should be avoided at all costs and it is typically not recommended or utilized [75, 76].

More than one-third (34.9 % or 78.6 million) of US adults are obese and the obesity epidemic has not spared the IBD population [77]. While studies from the Cleveland Clinic and other large volume centers have shown equivalent functional outcomes in obese patients undergoing IPAA [78], the authors consider morbid obesity a relative contraindication to immediate IPAA [79]. In a recent series from Washington University, obesity was associated with an increased risk of overall (80 % vs. 64 %, $p=0.03$) and pouch-related (61 % vs. 26 %, $p<0.01$) complications following IPAA [80]. In patients with an elective indication for surgery, performing an abdominal colectomy first as part of a staged approach has been proposed as a way for the patient to subsequently undergo weight reduction surgery before proceeding with the definitive restorative procedure. In the super obese (BMI>50) [81], this may never become an option given the time required for such a significant weight loss and therefore either permanent fecal diversion or abdominal colectomy with an ileorectal anastomosis should be considered. In order to avoid serious complications, increased hernia formation, and the need for multiple reoperations, with increased morbidity, mortality, and costs, meticulous preoperative evaluation using a strategic multidisciplinary team approach is mandatory. When safe to postpone surgery for a reasonable time, we have referred patients in our practice for weight reduction surgery in preparation for a procedure that could otherwise result in a permanent stoma. In these cases, laparoscopic gastric banding, or more recently a gastric sleeve procedure, has been performed given the need for these patients to maintain their entire intact small bowel for a successful IPAA. If the long-term use of corticosteroids is the primary reason for the increased BMI, they should undergo a staged procedure which allows them to discontinue corticosteroid therapy to facilitate weight loss. A goal of a BMI of ≤ 28 should be the target in mutual agreement with the patient

before proceeding for the IPAA in order to maximize the chances of a functional pouch and to avoid a permanent stoma.

Although advanced age was once considered a relative contraindication to IPAA, this has been reevaluated in the setting of optimized surgical and medical management and minimally invasive approaches [82, 83]. It is clear that IPAA can be safely offered to selected elderly UC patients who are strongly motivated and possess normal defecatory function. Their results seem to be stable over time and comparable to those of younger patients [83].

Operative Technique

If the patient is to undergo an RPC-IPAA, the resection of the colon and rectum is performed as described previously, but the rectum is divided with a TA stapler leaving a short rectal cuff. An ileal pouch can be created in the J, S, or W configuration (Figures 50-19 and 50-20), but the preference of the authors is the J-pouch construction.

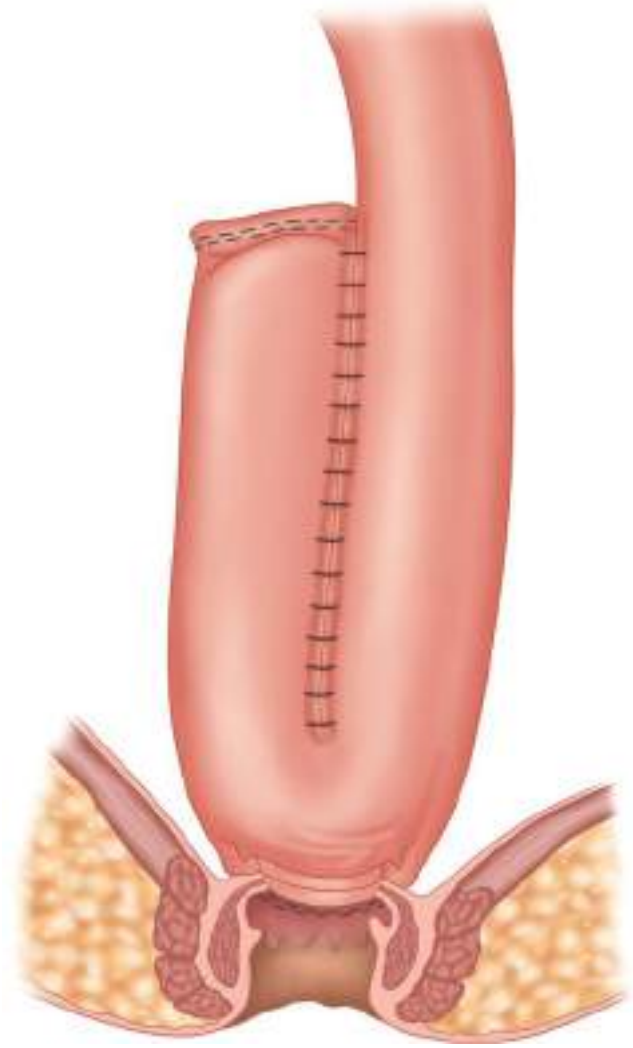


FIGURE 50-19. J-pouch configuration.

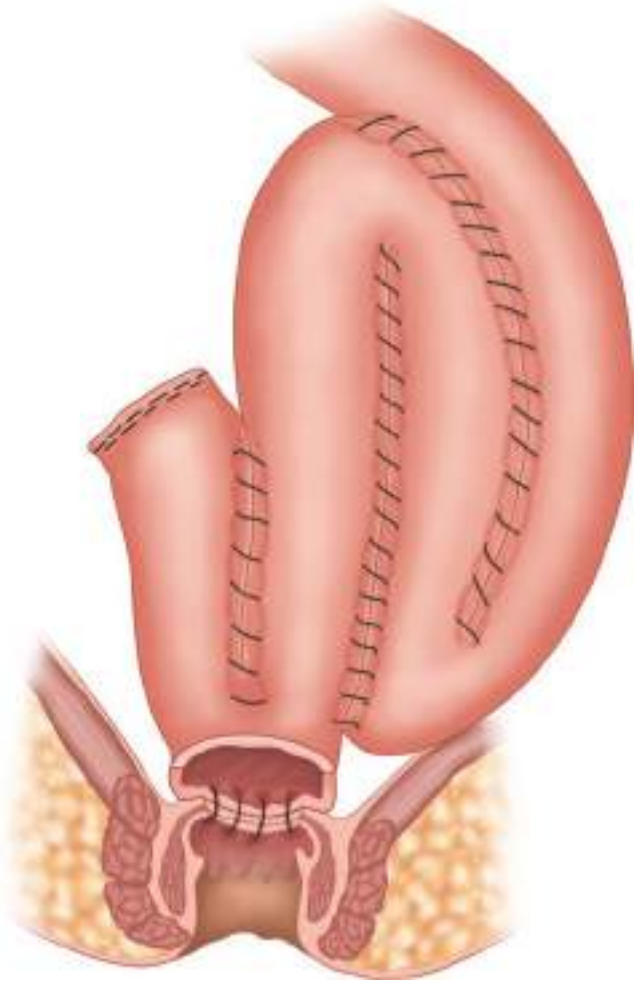


FIGURE 50-20. W-pouch configuration.

The length of the ileal J-pouch should be about 15–20 cm in length (Figure 50-21). The stapled end of the terminal ileum is oversewn with 4–0 silk Lembert sutures. After ensuring adequate blood supply to the terminal ileum, the apex of the pouch is chosen by bringing the ileum over the pubis and identifying the longest section of mesentery to enable a tension-free anastomosis. A stay suture is placed along the antimesenteric side of the apex. The two limbs are approximated and sutures are placed between the proximal and distal limbs at the ileomesenteric junction (Figure 50-22a, b). Corresponding longitudinal enterotomies are made on the proximal and distal limbs. Serial firings with a GIA stapler are used to create the pouch (Figure 50-23a, b) with care taken to ensure that the mesentery is not included in the staple line (Figure 50-24). The pouch is everted by gently applying Babcock clamps after each staple fire to aid in creating a common channel (Figure 50-25a, b). After the last firing (Figure 50-26a, b), the staple line is inspected for bleeding (Figure 50-27a, b) and the pouch reduced with gentle traction on the apical stay suture (Figure 50-28a, b, c). The anvil of an EEA stapler is brought out through the apex and secured in

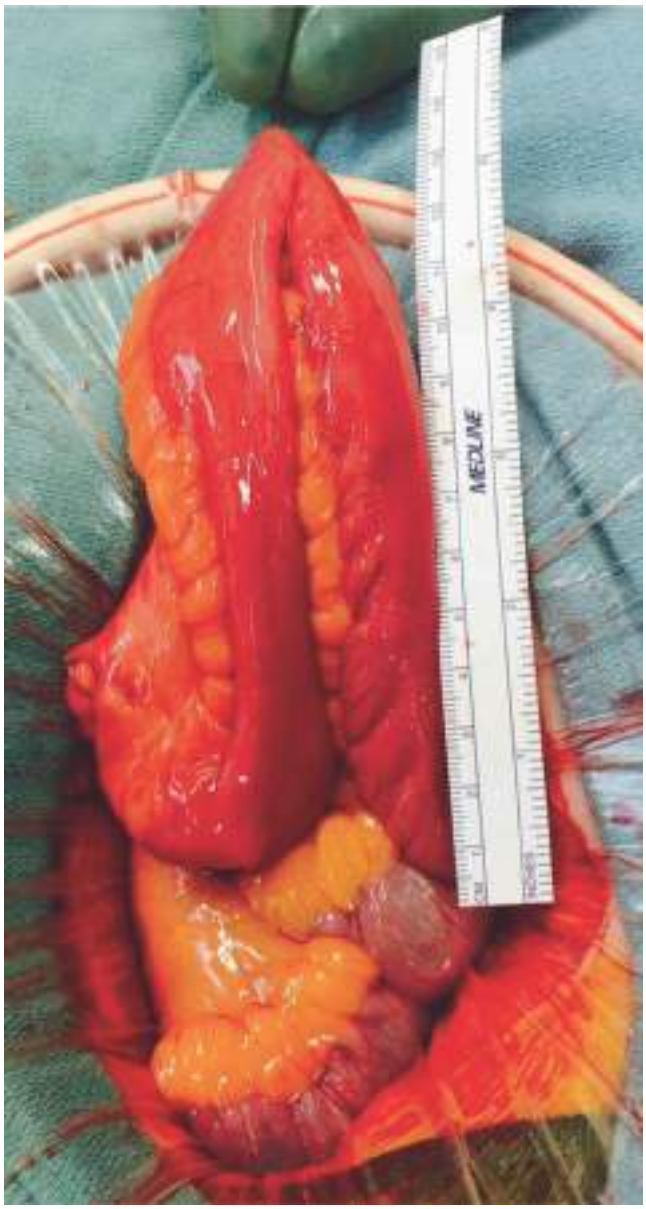


FIGURE 50-21. J-pouch should be 15–20 cm in length.

place with a pursestring suture (Figure 50-29). The common enterotomy is closed in two layers (Figure 50-30). The EEA stapler is inserted transanally and after ensuring no twisting of the bowel or mesentery the ileoanal anastomosis is created. A flexible sigmoidoscope is then inserted to inspect the staple lines and perform an anastomotic leak test. It is our practice to divert patients with a temporary loop ileostomy for 3 months.

Special Considerations

Pouch Configuration

The introduction of restorative proctocolectomy and IPAA into clinical practice has improved quality of life in the majority of UC patients seeking surgical intervention for disease management. There have been several modifications of the technique since the original description by Parks and Nicholls [55] and Utsunomiya and Iwama [56]. Parks' initial ileal reservoir was a triple loop S-pouch, with a 5 cm long exit conduit, which created problems with emptying [55]. Subsequently the limb was shortened to less than 2 cm with significant functional improvement [84]. Currently, other pouch designs in use include the double loop J-pouch [56] and the quadruple loop W-pouch [85, 86]. The lateral isoperistaltic H-pouch is now of historical interest only [87]. Each pouch design has its own advantages, and while the J configuration is most commonly used currently due to relative technical ease and speed of performance [88, 89], there is a role for the other two in very selected situations. The S-pouch with the long exit limb allows for further reach in tall male patients with short mesentery [90], while the W-pouch has a large capacity and better compliance [85]. When comparing the W-pouch with either the S- [90] or the J-pouch [86, 91, 92] in the so-called "maturation period"(immediately following ileostomy closure), the W-pouch group patients have significantly less frequent bowel movements compared to either group. However, two randomized prospective trials comparing the J-pouch to the W-pouch did not confirm those findings and the two configurations had the same functional results at 1 year of follow-up [93, 94]. We prefer a J-pouch for the vast majority of our patients because of the lower complication rate and the excellent functional results in our hands [88, 89].

Anastomosis

The second topic of major controversy is the type of the anastomosis and the fate of the anal transition zone (ATZ), the so-called stapled ileal pouch distal rectal anastomosis versus a handsewn ileal pouch anal canal anastomosis with mucosectomy. The potential advantages of preserving the ATZ include preservation of the highly specialized anoderm, therefore better function; decreased trauma to the sphincter mechanism, therefore better continence; less tension on the anastomosis, therefore fewer septic complications; ease of construction, therefore shorter operative times. The disadvantages include the theoretical risk of malignant degeneration of the rectal cuff mucosa. We will discuss the functional results and the risk of neoplastic degeneration separately.

The initial descriptions of IPAA included a mucosectomy to the dentate line [55, 56, 95]. The dilatation necessary for complete mucosectomy [96] or the eversion of anorectum used at that time to facilitate mucosal removal [97, 98] caused significant decrease in the maximum resting pressure [96] and increase of the threshold sensation, which correlated with an increased number of episodes of incontinence [97, 98]. Avoidance of extensive manipulation of the anal sphincter complex limits the degree of trauma. Furthermore, the ATZ retains some of the anoderm sensory capacity, which together with the rectoanal inhibitory reflex allows for the sampling of rectal contents resulting in improved continence, whereas mucosectomy results in loss of this

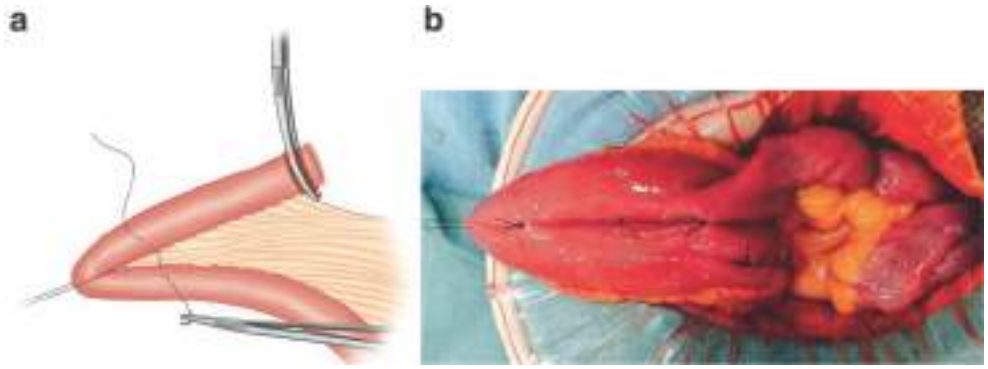


FIGURE 50-22. (**a** and **b**) A stay suture is placed along the antimesenteric aspect of the apex of the pouch. Additional sutures are placed between the two limbs of the J-pouch at the ileomesenteric junction.

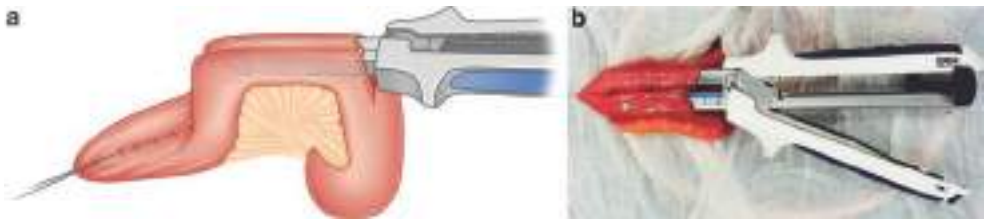


FIGURE 50-23. (**a** and **b**) Corresponding longitudinal enterotomies are created on the proximal and distal limbs of the pouch and the forks of a gastrointestinal stapler are gently inserted into each limb.

FIGURE 50-24. Care is taken to ensure that the mesentery of the ileum is not incorporated into the staple line.

sensation [99]. Several comparative long-term studied have reported better functional results for the stapled IPAA [100–104]. We compared patients with a mucosectomy with patients with intact ATZ and found that even in the presence of chronic inflammatory changes, patients with an intact ATZ have significantly better continence, defecatory function, satisfaction, and quality of life [57]. Gemlo et al. [100] evaluated 235 patients with a mean follow-up of 70 months and found that elimination of a mucosectomy dramatically reduced nocturnal major incontinence, nocturnal minor incontinence, daytime minor incontinence, and daytime pad use. Sagar et al. [104] studied anal physiological results in 20 patients up to 12 months after stapled IPAA. After an initial decrease, at 12 months, resting anal pressure was almost normal, the rectoanal inhibitory reflex was present in 19 patients, and sampling was observed in 17 patients. The compliance and capacity of the reservoir increased significantly. Ability to discriminate flatus from feces was associated with return of the rectoanal reflex and sampling. When the theoretical advantages of a stapled IPAA over a handsewn anastomosis with mucosectomy were evaluated in a prospective randomized fashion, no difference in functional results was noted [105–107]. However, these studies did not examine long-term function and conclusions are difficult to make based on this short follow-up and are limited by inadequate power to detect small differences. Surgeons in favor of stapled IPAA often point to a greater rate of anastomotic complications after mucosectomy and handsewn IPAA. Preserving a short rectal cuff lessens the tension on the anastomosis, supposedly reducing anastomotic complications. The Cleveland Clinic group evaluated 692 patients, 238 with handsewn IPAA and 454 with stapled IPAA. In the handsewn IPAA group, 25 patients (10.5 %) had 32 septic complications, and 24 required 89 reoperations. In seven patients, the pouch was excised. In the stapled IPAA group, 21 patients (4.6 %) had 23 septic complications, and 14 required 40 reparations. One patient needed pouch excision [108]. Again, when the complication rates were evaluated in a prospective randomized fashion, no difference was noted [105–107]. Beyond functional considerations, there are concerns regarding preservation of inflamed rectal mucosa

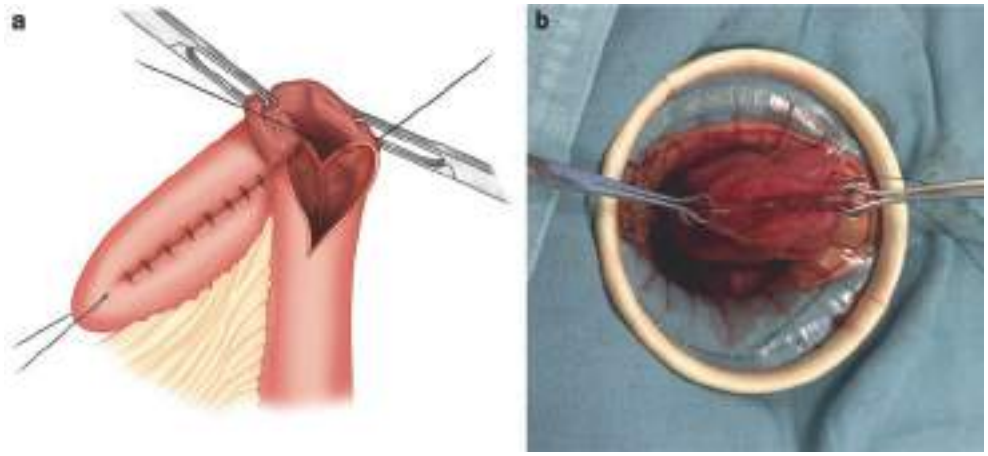


FIGURE 50-25. (**a** and **b**) The pouch is everted with the gentle application of Babcock clamps along the staple line until the intact apical septum is reached.

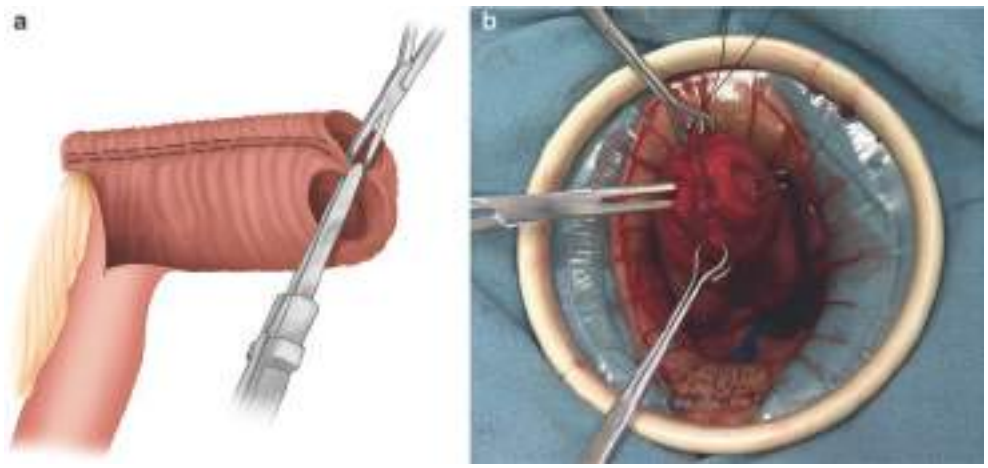


FIGURE 50-26. (**a** and **b**) Division of the most distal aspect of the septum is often assisted by gentle passage of a right angle clamp to guide the stapler.

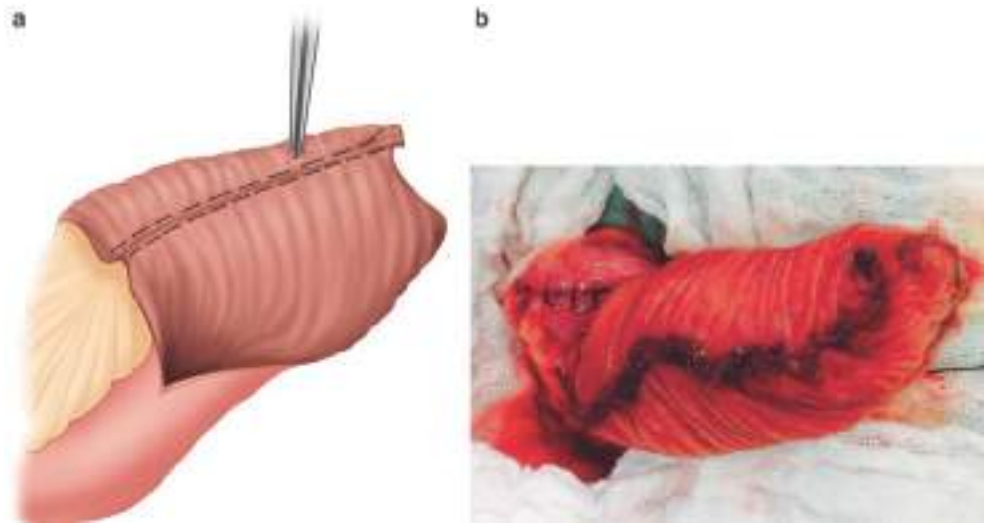


FIGURE 50-27. (**a** and **b**) Suture lines inspected to ensure hemostasis.

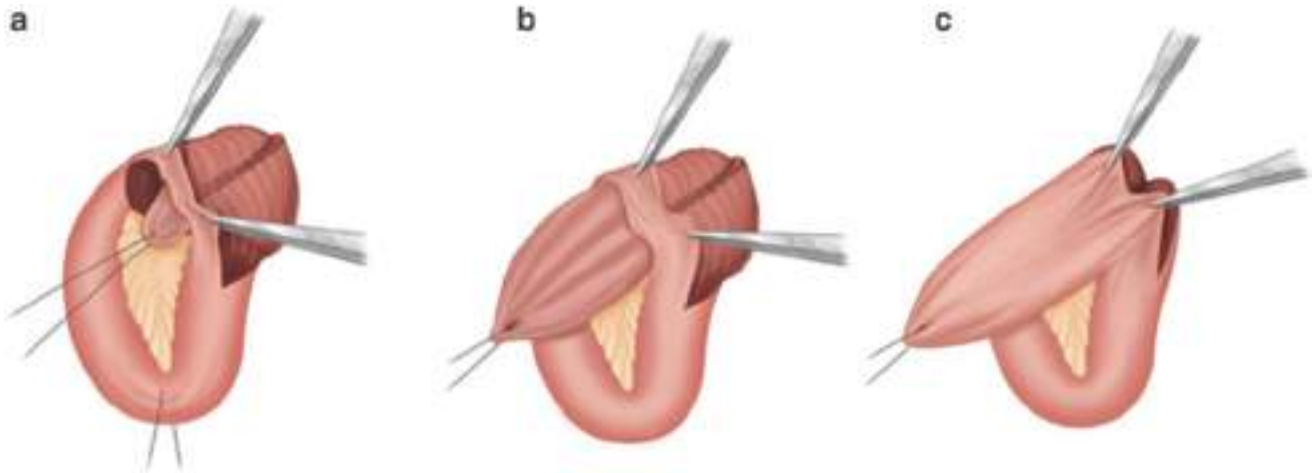


FIGURE 50-28. (**a–c**) By placing traction on the apical stay suture and countertraction on the edge of the enterotomy, the pouch is reduced.

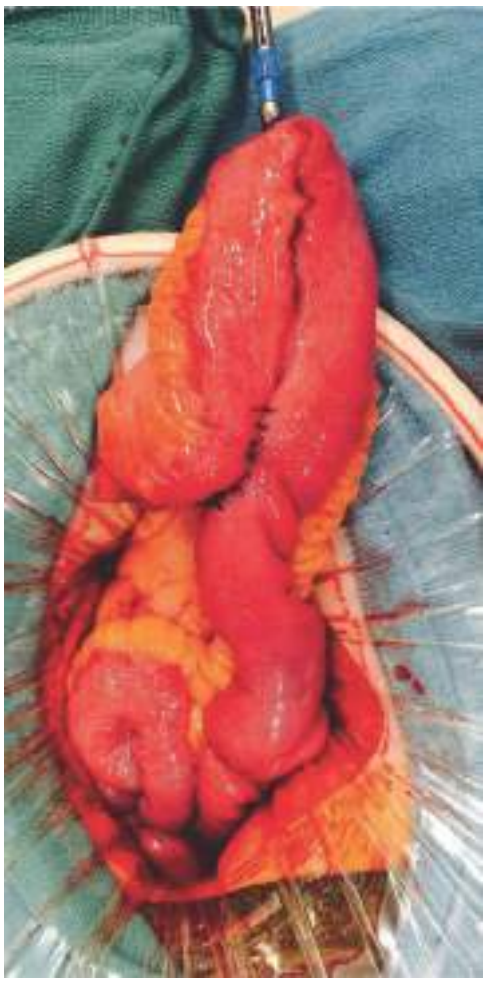


FIGURE 50-29. The anvil of an EEA stapler is brought out through the apex.

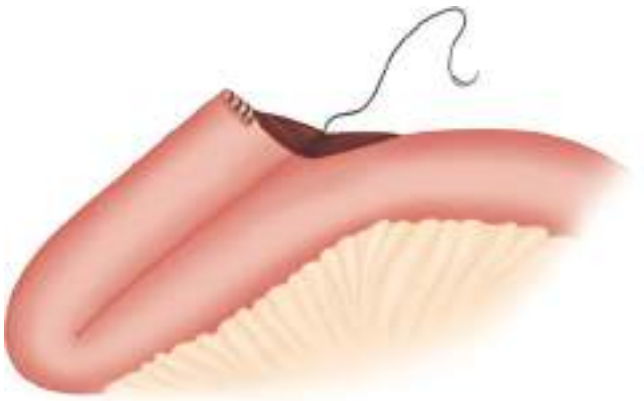


FIGURE 50-30. The common enterotomy is closed with a two-layer closure.

and associated persistent symptoms associated [109, 110]. The Cleveland Clinic group noticed that in their series symptomatic inflammation of the retained mucosa occurred in 14.7 % of patients; 4.1 % of patients had inflammation of the anal canal alone, and 10.6 % had pouchitis. Surgical intervention was required in 12.9 % of the total patients with isolated anal canal inflammation and 10.6 % of those with anal canal inflammation plus pouchitis [109, 110]. These patients are usually treated with topical steroids or 5-ASA. If medical management fails, a transanal mucosectomy with ileal pouch advancement is performed with excellent results [109]. When we looked at our stapled IPAA patients with chronic inflammatory changes, we found that their function was still superior to their mucosectomy counterparts, with minimal symptoms of cuffitis and no surgical interventions required at 36 months of follow-up [57, 58].

These outcomes may be explained by the shorter anal cuffs retained in patients undergoing laparoscopic operations.

Advocates of the mucosectomy argue that the entire diseased anorectal mucosa, including the ATZ, must be removed to eliminate the risk for future dysplasia and cancer. Anatomic studies have shown that actual microscopic extent of the ATZ is highly variable. Fenger [111], using Alcian blue staining, found that the mean span of the ATZ was 8.9 mm (range 0–20 mm), starting up to 6 mm below the dentate line. Thompson-Fawcett et al. [112] measured the ATZ by two techniques: whole-mount Alcian blue staining and a computer map of the histological findings based on longitudinal sections taken every 3 mm. They found that the Alcian blue technique overestimates the length of the ATZ, which usually commences just above the dentate line. The median length of the ATZ measured from computer maps of the histology was only 4.5 mm. Due to this variability, mucosectomy does not reliably remove the entire rectal mucosa [113]. Small islets of residual rectal mucosa have been identified in up to 14 % of patients and in 7 % it was located at the actual ileoanal anastomosis [113]. To determine the long-term risk of dysplasia and cancer in the retained mucosal cuff after stapled IPAA, the Cleveland Clinic group published their series of 210 patients with at least 5 years (median 77 months) of follow-up [114]. Dysplasia developed in seven patients (3.3 %) at a median of 11 months postoperatively. Patients with history of cancer or dysplasia in the colon or rectum were at a higher risk of developing dysplasia. Two patients, each with low-grade dysplasia detected on three separate occasions, underwent mucosectomy 29 and 38 months after detection of low-grade dysplasia, but no cancer was found. The five other patients with dysplasia on one or two occasions were treated expectantly and were dysplasia free for a median of 72 months. More importantly, preservation of ATZ did not lead to the development of cancer after 5–10 years of follow-up. The authors recommend long-term surveillance to monitor dysplasia, and if repeat biopsy confirms persistent dysplasia, mucosectomy with pouch advancement was advised [114]. When we looked at our experience with preservation of the ATZ in patients without dysplasia or cancer at the time of surgery, we found no evidence of subsequent dysplasia or cancer in 225 patients over a 36-month follow-up period. Our results suggest that in selected patients, i.e., without dysplasia or cancer, the preservation of the ATZ is safe [57, 58]. We have subsequently changed our surveillance protocol for patients with preserved ATZ from 1- to 3-year intervals [57, 58]. We believe that there is a role for both procedures in clinical practice. We preserve the ATZ in older patients with borderline sphincter function and in tall obese male patients to decrease tension on the anastomosis. Mucosectomy is otherwise advised in the presence of high-grade rectal dysplasia or cancer, in the pediatric population [115], and in patients with primary sclerosis cholangitis known to have a high risk of dysplasia and cancer [116].

Optimizing Reach

An anastomosis between the ileal pouch and anal canal performed under tension is associated with increased risk of dehiscence with severe short-term and long-term sequelae [117]. Described approaches for improving reach include leaving the pouch unattached in the pelvis, diverting the patient proximally, and returning at a later date for pouch anastomosis. Few studies have evaluated and compared the several reported techniques for lengthening the small bowel mesentery, including complete small bowel mobilization to the origin of its mesentery, ileocolic vessel ligation close to their origin from the superior mesenteric pedicle, and transverse mesenteric relaxing incisions [118]. These strategies facilitate a tension-free IPAA in most cases. In our practice, we have found that utilization of a staged approach is the best strategy to avoid finding ourselves in such a situation where the pouch does not reach the pelvic floor or the tension on the anastomosis is causing ischemia. By optimizing body weight, tissue characteristics, and general medical conditions, we have almost eliminated the need for mesenteric lengthening from our practice. For patients with an extremely short mesentery, an alternative strategy has been described by Goes et al. [119]. Multiple vascular ligations are performed between the right colon wall and the marginal vascular arcade, while the right branch of the middle colic artery is preserved and provides the blood supply to the ileal branch of the ileocolic artery. The right colic and ileocolic arteries at their origin and the superior mesenteric trunk at its distal third are divided. This technique is time-consuming and technically challenging and can lead to pouch ischemia, but it offers additional length in extreme situations.

Crohn's Disease

Ileal pouch surgery is contraindicated in patients with Crohn's colitis [120, 121]. Despite significant effort to correctly diagnose patients before surgery, some patients undergo surgery with a preoperative diagnosis of indeterminate colitis or ulcerative colitis and are found to have Crohn's disease on final pathological evaluation of the specimen. Sagar et al. [122] and Deustch et al. [123], in two separate unselected series, reported a pouch failure rate of 45 % at 10 years in patients with a preoperative diagnosis of mucosal ulcerative colitis who were subsequently proven to have Crohn's disease. In another series [124], only one of nine patients with preoperative clinical features suggestive of Crohn's disease had a functioning pouch, with complications consistently occurring within months of ileostomy closure. In contrast, 15 of 16 patients without preoperative features of Crohn's disease had maintained their pouch, generally with good results. These studies suggest that the pelvic pouch procedure should not be performed in patients with preoperative clinical features of Crohn's disease. However, it is possible that there is a subgroup of patients with Crohn's colitis who might be candidates for an ileal pouch procedure.

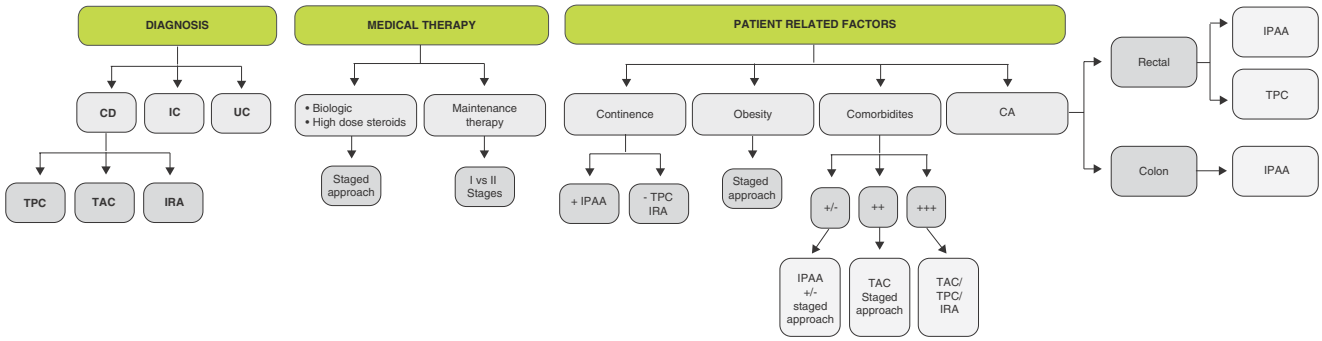


FIGURE 50-31. Algorithm showing the management of Ulcerative colitis. *CD* Crohn's disease, *IC* Indeterminate colitis, *UC* Ulcerative colitis, *TPC* Total proctocolectomy, *TAC* Total abdominal colectomy, *IRA* Ileo-rectal anastomosis, *IPAA* Ileal pouch anal anastomosis, *CA* Cancer.

Panis et al. [125] reported a series of 31 patients with Crohn's disease with no evidence of perineal or small bowel disease who were specifically selected for ileoanal pouch as an alternative to ileostomy. Of the 31 patients, only six (19 %) experienced specific complications 9 months to 6 years after surgery, and at the 5-year follow-up, there was no significant difference between patients with Crohn's disease and patients with ulcerative colitis in terms of stool frequency, continence, gas/stool discrimination, leak or need for protective pads, and sexual activity. In the future, more sophisticated diagnostic tests may allow selection of a subgroup of patients with Crohn's disease appropriate for ileal pouch procedures. At present, we do not offer IPAA in our practice to patients with preoperative clinical features of Crohn's disease.

The algorithm in Figure 50-31 shows the management of ulcerative colitis.

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51
Complications of the Ileal Pouch

Daniel L. Feingold and P. Ravi Kiran

Key Concepts

- Pelvic sepsis after pouch surgery is associated with worse function and risks pouch failure. However, prompt management of early postoperative septic complications can preserve pouch function and increase pouch retention rates.
- Technical challenges during pouch surgery include ensuring tension-free reach, preserving adequate blood flow to the pouch, and creating an appropriate diverting ileostomy.
- A three-stage approach is recommended for patients who are malnourished, have severe active colitis, or are under treatment with larger doses of steroids or immunosuppressive medications in order to reduce pouch-related complications.
- The potential diagnosis of Crohn's disease should be considered in any patient presenting with fistulizing disease after pouch surgery as this affects management and prognosis.
- Repeat ileal pouch-anal anastomosis using a revised pouch or a new pouch is a reasonable option for selected patients with pouch failure.
- Mucosectomy at the time of a pouch-anal anastomosis does not prevent future dysplasia or cancer as islands of rectal mucosa may persist.
- Women with ulcerative colitis who undergo total proctocolectomy have a higher rate of infertility than women treated non-operatively, although a laparoscopic approach may reduce this risk.

Introduction

Ileal pouch-anal anastomosis (IPAA) is the preferred method for restoring gastrointestinal tract continuity after total proctocolectomy. While the majority of patients recover uneventfully from this operation, a proportion of patients develop complications that are unique to this procedure and deserve specific consideration. Complications after pouch surgery can be grouped into septic versus non-septic-related complications (including mechanical issues); alternatively, IPAA complications can be conceptualized as intraoperative, early postoperative, and late postoperative (Table 51-1).

Pouch-related complications can significantly affect functional outcomes and patients' quality of life, require multiple corrective procedures, and result, ultimately, in pouch failure [1]. Understanding the possible pouch-related complications and consideration of these complications in the operating room during pouch creation can reduce the incidence of these adverse events. In the postoperative setting, it is important to promptly address complications to better preserve pouch function and to reduce the risk of pouch failure which may be defined as the need for construction of a permanent stoma with or without excision of the pouch [2].

Modifying risk factors and focusing on preoperative planning details can potentially reduce the incidence of complications after pouch surgery and hence facilitate pouch function and preservation. Preoperative risk factors associated with pouch failure include type of resection (performing a completion proctectomy rather than total proctocolectomy), type of anastomosis (hand-sewn rather than stapled), diagnosis of Crohn's disease, and comorbidities [3]. Modifying risk factors to minimize risk of pouch failure should include appropriate medical management leading up to pouch surgery, expeditious surgical management to avoid needing urgent total abdominal colectomy with subsequent completion proctectomy, and medical optimization of comorbidities. Body mass index greater than 30 is also associated with septic complications after IPAA and obese patients should be counseled appropriately in advance of pouch surgery [4]. In fact, it may be reasonable to perform an initial abdominal colectomy to allow control of disease and achieve weight loss prior to proctectomy and IPAA.

In an effort to minimize the complications after a pouch procedure, it is important to individualize the operative plan to each patient. Deciding whether or not to operate in stages is one such

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TABLE 51-1. Complications of the ileal pouch

Intraoperative	Problems with reach of the pouch
	Pouch ischemia
	Problems with stoma creation
	Problems with staplers and creating the anastomosis
Early postoperative	Anastomotic leak and pelvic sepsis
	Bleeding from the pouch
Late postoperative	Pouch-vaginal fistula
	Pouch-perineal fistula
	Pouch sinus
	Crohn's disease after pouch surgery
	Incontinence
	Outlet obstruction
	Pouchitis and cuffitis
	Pouch prolapse
	Leak from the tip of the "J"
	Dysplasia and cancer after pouch surgery
	Small bowel obstruction
	Sexual dysfunction
	Infertility

consideration that may impact the risk of complications. While well-nourished patients of average build with mild colitis who are not maintained on immunosuppressive medications may be candidates for single-stage procedures, this option is rarely utilized as a leak from an unprotected IPAA can have devastating complications including loss of the pouch. The vast majority of IPAA patients who do not undergo a three-stage procedure will undergo a two-stage procedure whereby the pouch is defunctionalized by a loop ileostomy (Figure 51-1). Patients who are malnourished, have severe active colitis, or are under treatment with larger doses of steroids or immunosuppressive agents are recommended to undergo a three-stage procedure in an effort to reduce the risk of complications. When the type of colitis based on colonoscopic biopsy is unclear preoperatively, an initial subtotal colectomy may help ascertain the diagnosis of Crohn's disease and determine the suitability of a pouch at the subsequent operation.

Another factor to consider when individualizing patient care in anticipation of an IPAA deals with the use of biologics. The findings of single-institution studies, confirmed by meta-analysis, demonstrate that patients with ulcerative colitis receiving infliximab, an antitumor necrosis factor-α antibody, are at particular risk for developing post-IPAA septic complications; a planned three-stage approach needs to be considered in this situation [5, 6]. This is especially true if the patient had experienced poor control of the disease despite aggressive medical management with these agents.

Another potential modifiable factor related to pouch complications deals with the use of radiotherapy prior to IPAA. Preoperative pelvic radiation in the setting of colitis-associated cancer is associated with an increased risk of subsequent pouch failure [7]. Oncologic benefits and anticipated pouch function should be carefully considered before proceeding with neoadjuvant radiotherapy in patients planning restorative proctocolectomy.

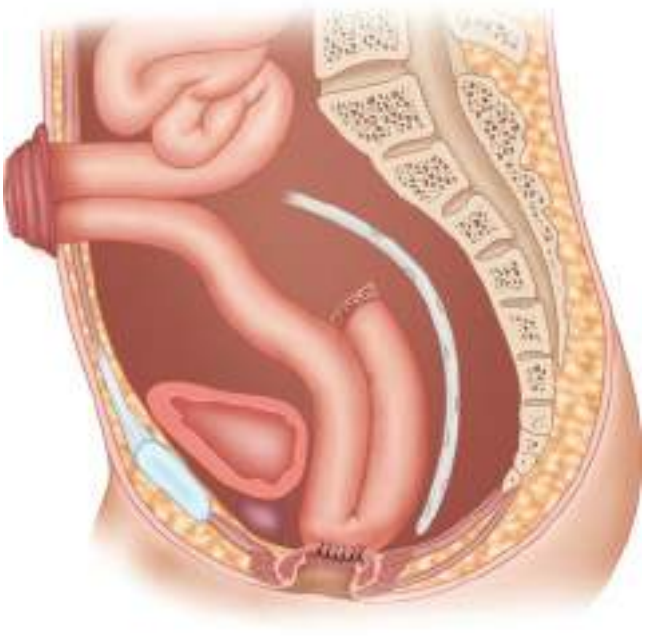

FIGURE 51-1. Ileal "J" pouch-anal anastomosis with defunctioning loop ileostomy.

Excessive weight gain (greater than 15 % increase) after ileostomy closure in patients with inflammatory bowel disease is also associated with pouch failure, though the underlying mechanism is not clear [8]. Counseling patients regarding appropriate weight control after restoring intestinal continuity may help improve pouch retention.

Intraoperative Complications

The two most common configurations currently used for IPAA are the "J" and "S" pouches which can be anastomosed via stapled or hand-sewn technique (Figure 51-2). While most primary ileoanal pouches are constructed in "J" fashion (20 cm long) and are stapled to the IPAA, the decisions to use one configuration over another and to staple or hand-sew are based on personal preference and unique patient factors [9]. The option of a planned mucosectomy with a hand-sewn IPAA is, in general, reserved for patients undergoing redo IPAA, with high-grade dysplasia or cancer involving the distal rectum, or those with familial adenomatous polyposis with polyps carpeting the distal rectum. In cases where a mucosectomy and hand-sewn IPAA are planned, an "S" configuration may fit through the pelvic floor anatomy better than a "J" pouch which can become distorted, especially in men with a long anal canal [10]. When creating the IPAA, it is critically important to avoid tension across the anastomosis, to maintain correct orientation of the pouch coming down to the low pelvis, to preserve the blood supply to the pouch and the residual anorectum, and to avoid incorporating nearby pelvic structures like the vagina, prostate, and seminal vesicles into the anastomosis.

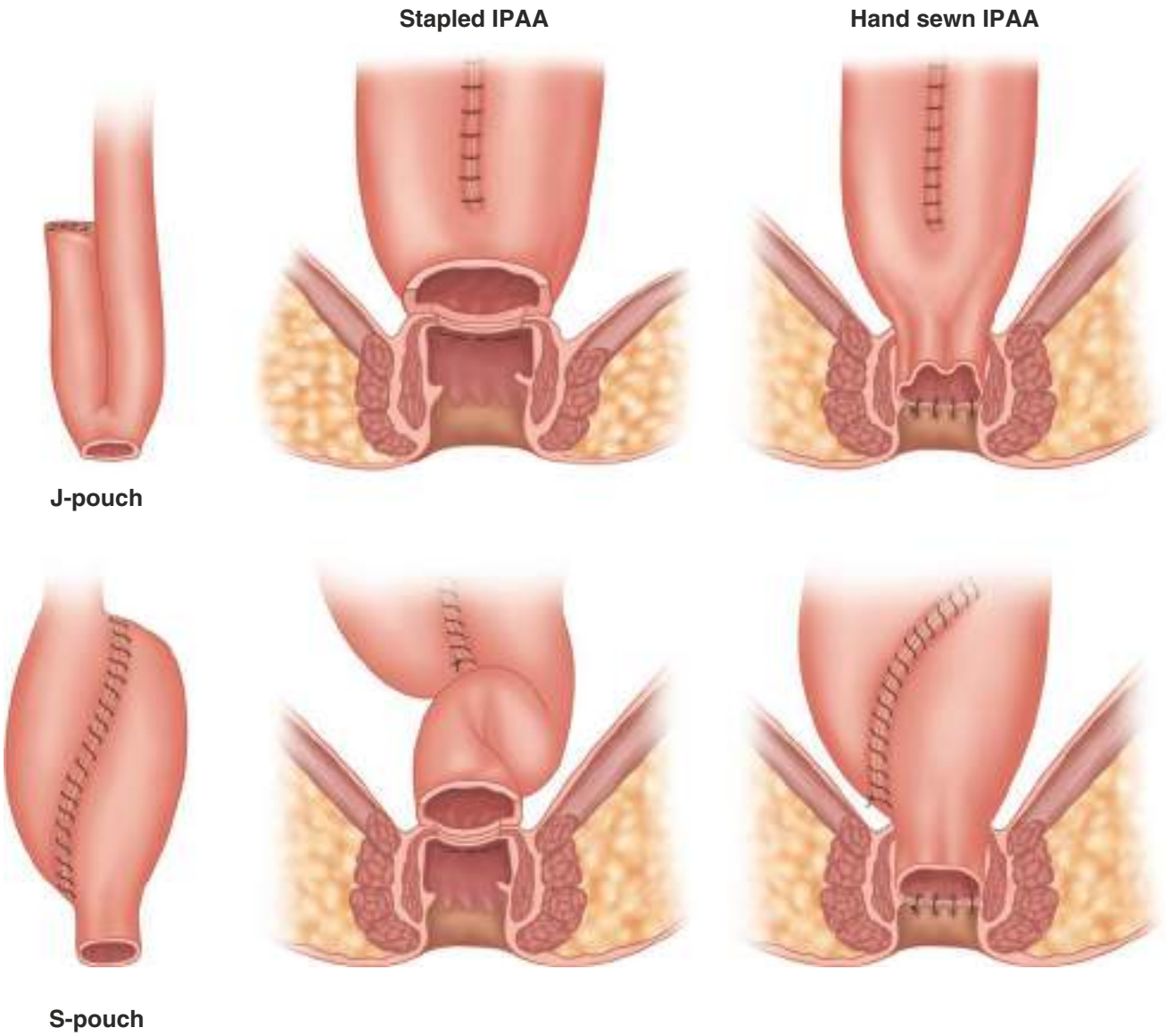

FIGURE 51-2. The "J" and "S" pouch configurations used in stapled and hand-sewn anal anastomoses.

Problems with Reach of the Pouch

Ensuring adequate reach of the pouch to the pelvic floor can be difficult and represents one of the more technically challenging aspects of a pouch procedure that can jeopardize the ability to create an IPAA and can directly impact the risk of postoperative complications. Tall patients, those with a high BMI, and patients with extensive previous abdominal or pelvic operations are particularly at risk for encountering a problem with reach. Weight loss in anticipation of surgery may be helpful. Maneuvers in the operating room that are routinely employed to facilitate reach include high ligation of the ileocolic vessels, complete release of the small bowel mesentery from the retroperitoneum, mobilization of the duodenum, and excision of the redundant mesenteric tissue lateral to the superior mesenteric vessels ("jib-sail"). Releasing incisions across the mesentery perpendicular to the small bowel mesenteric vessels supplying the pouch can also provide added reach (Figure 51-3). While sacrificing branches of the SMA or even the main trunk of the SMA may be required to improve reach, these maneuvers can compromise the blood flow to the pouch and are rarely required.

Difficulty with reach of the pouch can be anticipated before rectal transection by using a long Babcock forceps to simulate the reach of the most dependent part of the bowel to be used in the creation of the pouch and delivering this bowel down into the pelvis (Figure 51-4). Manual palpation through the anal canal helps determine the anticipated reach of the mobilized bowel. This exercise, best done prior to completing the proctectomy, can alert the surgeon that there may be a reach issue and the operation can be modified to increase the chance of a successful IPAA. In cases where reach remains a problem despite implementing the maneuvers described above, it may be helpful to orient the pouch coming down to the IPAA with

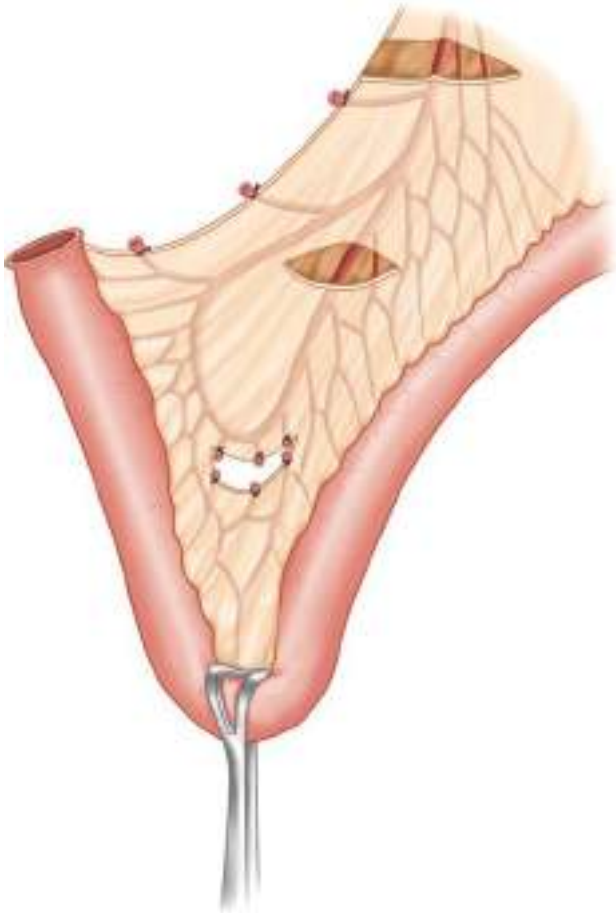

FIGURE 51-3. Lengthening of the ileal mesentery in anticipation of "J" pouch construction. The peritoneum is scored to provide additional reach. Selective ligation of the mesenteric arcade can also reduce tension; transillumination of the mesenteric fat can be helpful.

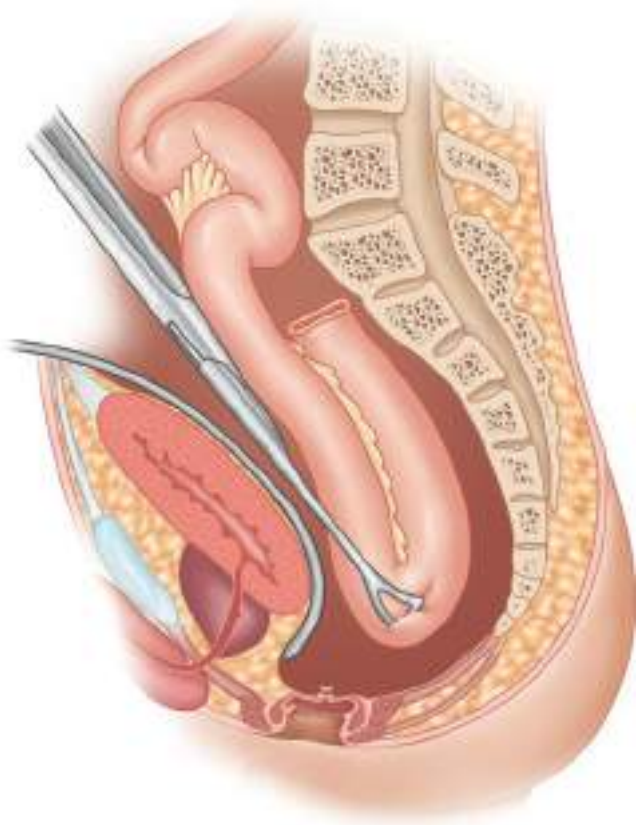

FIGURE 51-4. Simulating the reach of the "J" pouch to the level of the anastomosis.

its mesentery oriented anteriorly as this can release tension across the tissues. In certain circumstances, and where the pathology permits, the rectal stump may intentionally be left slightly longer in order to minimize tension at the IPAA. If a "J" pouch cannot reach appropriately, changing to an "S" configuration may be advisable as this adds approximately 2 cm of extra reach to the IPAA. In rare cases where a pouch is created and insufficient reach cannot be remedied, it is recommended to secure the closed pouch to the pelvis and create a defunctioning ileostomy; this maneuver may allow the pouch to lengthen over time in anticipation of repeat attempt at IPAA.

Pouch Ischemia

In an effort to provide reach, care should be taken to avoid overzealous skeletonization of vessels within the small bowel mesentery which can result in ischemia. The pouch blood supply can also be injured by direct trauma while scoring the mesentery or by creating a traction injury across the mesentery by creating an IPAA with excessive tension. Twisting the pouch around its mesentery as it is brought down to the IPAA can affect arterial inflow and venous outflow causing ischemia or bowel obstruction and should be avoided. Confirming correct orientation of the pouch by following the cut edge of the ileal mesentery from the mobilized duodenum to the IPAA can help prevent twisting of the pouch. Pouch ischemia requires pouch excision and an attempt at creating another pouch.

Problems with Stoma Creation

Creating a defunctioning loop ileostomy for an IPAA patient can be challenging especially in patients with difficult reach or a high BMI because the ileal mesentery is fixed at the root of the SMA and at the low pelvis and this can restrict the surgeon's ability to exteriorize the bowel. One possible option available to facilitate stoma creation and minimize tension across the IPAA is to defunctionalize using a more proximal segment of the bowel. Patients diverted in this fashion need to be monitored for high ostomy output. Anticipating diversion difficulties and discussing potential strategies to address these with the patient allows for setting more realistic expectations and highlights the importance of individualized operative planning requisite for pouch surgery. These strategies may include

mandating weight loss prior to surgery, trading off the ideal stoma location for one that is functionally better, and instituting a medical regimen early on to preempt high output stoma issues.

Problems with Staplers and Creating the Anastomosis

Once the pouch has been created and prior to bringing the pouch down to the pelvis, insufflating the opened, distal end of the pouch with an air-filled bulb syringe as a leak test will alert the surgeon to any structural issues that need to be addressed. Prior to firing the circular stapler, it is important to exclude nearby pelvic structures from being incorporated into the stapler mechanism. This requires a combination of careful assessment of the field through the abdomen and also a digital exam from below confirming the vagina is free. When performing a stapled IPAA, like any low pelvic anastomosis, mechanical circular staplers are prone to misfire; an on-table pouchoscopy after creating the IPAA is needed to check the integrity of the anastomosis and the health of the pouch [11]. Although a misfiring is disheartening, the situation is usually salvageable.

When a defect in the anastomosis is detected, adequate assistance to facilitate the necessary retraction and exposure allowing access to the field from the abdomen and the perineum is needed. The specific management in this situation depends on the location, size, and cause of the staple line defect. For a small dehiscence, a defunctioning stoma may be sufficient to allow healing. In this situation, attempt at suture closure through an abdominal or trans-anal approach should be considered. In the case of a major dehiscence due to stapler misfiring or possibly from a breach in the cuff staple line from inserting the circular stapler too far, the IPAA may have to be taken down and redone. In this situation, once the pouch is brought up from the pelvis, an assessment of the structure and reach of the pouch as well as of the length and condition of the anal canal is performed. In some situations it may be possible to place a purse string to close the remaining rectal cuff to allow repeat stapling, but typically a mucosectomy with hand-sewn IPAA will be required.

Early Postoperative Complications

Complications related to the anastomosis and pelvic sepsis can affect the long-term function of the pouch. Prompt diagnosis and management of these complications is required to preserve pouch function.

Anastomotic Leak and Pelvic Sepsis

Pelvic sepsis related to pouch surgery is loosely defined as an abdominopelvic or perianal infectious process detected by clinical, radiologic, or operative means within 3 months of IPAA creation or within 3 months of stoma reversal. Depending on the manifestations and severity of the infection, this can be a significant complication associated with worse functional outcomes, diminished quality of life, and, potentially, pouch failure [1].

An anastomotic disruption may be an isolated finding discovered incidentally on pre-stoma reversal evaluation or can present clinically with pelvic sepsis. While patients with a pelvic abscess usually exhibit the expected signs and symptoms of infection, some IPAA patients have a more indolent presentation with persistent ileus or fail to meet expected recovery milestones after the surgery. Patients with hemodynamic instability and peritonitis require operative exploration to evaluate the anatomy, washout the field, and effect drainage (Figure 51-5). Patients with less impressive clinical

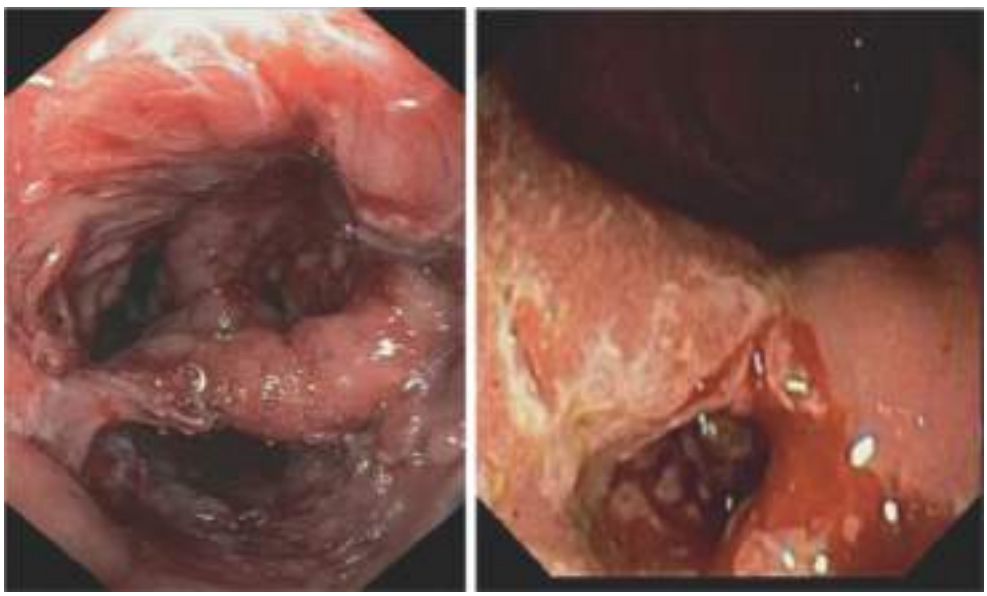

FIGURE 51-5. Pouchoscopy demonstrating IPAA dehiscences with posterior defects.

findings can undergo cross-sectional imaging to guide management. CT scan of the abdomen and pelvis with intravenous and water-soluble oral and trans-anal contrast is helpful to diagnose an abscess and an associated leak. In patients with an abscess amenable to percutaneous drainage, prompt drainage and broad-spectrum IV antibiotic administration may allow for control of the sepsis and may minimize the long-term consequences to the pouch.

Whether abscess drainage should be performed transanally or percutaneously is a matter of debate due to concerns over the development of an extra-sphincteric fistula related to percutaneous drainage. When a break in anastomotic integrity is demonstrated coexistent with an abscess, trans-anal drainage through the anastomosis is preferable; however, when the anastomosis is intact, percutaneous CT-guided drainage is preferable. This strategy allows prompt drainage of abscesses while minimizing the risk of an extra-sphincteric fistula.

Bleeding from the Pouch

This low-frequency complication can be further minimized by performing a dedicated inspection of the back row of staples along the mesentery of the small intestine after pouch construction and before IPAA creation and over-sewing any bleeding sites. Postoperative pouch bleeding may manifest as bleeding through the anus or up through the loop ileostomy. Pouchoscopy with cauterization, clip application, or epinephrine injection usually controls the bleeding. In patients with generalized oozing, instilling ice-cold saline with dilute epinephrine into the pouch facilitates hemostasis [12].

Late Postoperative Complications

Due to the defunctioning nature of the loop ileostomy, some pouch-related complications do not manifest clinically until after stoma reversal. Pre-stomal reversal pouch imaging with water-soluble contrast (done by fluoroscopy or CT scan) and flexible pouchoscopy are routinely performed but do not eliminate the occurrence of late complications.

Pouch-Vaginal Fistula

Pouch-vaginal fistula (PVF) is a potentially disabling complication that can cause significantly diminished quality of life. The overall risk of PVF ranges from 4 to 16 % with pouch failure occurring in as many of 30 % of these patients [13]. Common symptoms include discomfort, irritation, incontinence, and recurrent vaginal and urinary tract infection. In order to tailor the most effective treatment to each patient, the size, nature, and location of the fistula, the state of the perineum and sphincter mechanism, and the configuration, size, and health of the pouch need to be assessed. While exam under anesthesia is considered the gold standard study to evaluate PVF, imaging studies are relied on to provide additional information and include water-soluble pouchogram, vaginogram, and pelvic MRI (Figure 51-6). CT or MR enterography can be useful as well to delineate the anatomy above the pouch.

The potential diagnosis of underlying Crohn's disease should be considered in any patient presenting with fistulizing disease after IPAA ostensibly performed for ulcerative colitis as this affects PVF management and prognosis. In practice, differentiating septic complications from Crohn's disease is difficult especially when pathognomonic clinical and histopathological features of Crohn's disease are absent. In general, PVF occurring in a colitis patient within 1 year of stoma reversal is likely due to a septic complication of the IPAA while fistulas presenting beyond the first year should raise the specter of Crohn's disease [14]. A thorough review of the history and medical records pertaining to the IPAA surgery and the postoperative course may provide insight into the potential etiology of the PVF and review of the pathology from the pouch surgery and even from preoperative biopsies may prove helpful.

The recommended treatment for a patient with PVF depends on the severity of the symptoms and their effect on the patient's quality of life and on the specific anatomic and pathologic details that are elucidated on a case-by-case basis. Examination under anesthesia allows for assessment of the fistula tract and the associated tissues. Active inflammation with induration of the tract and surrounding tissues may respond to drainage and

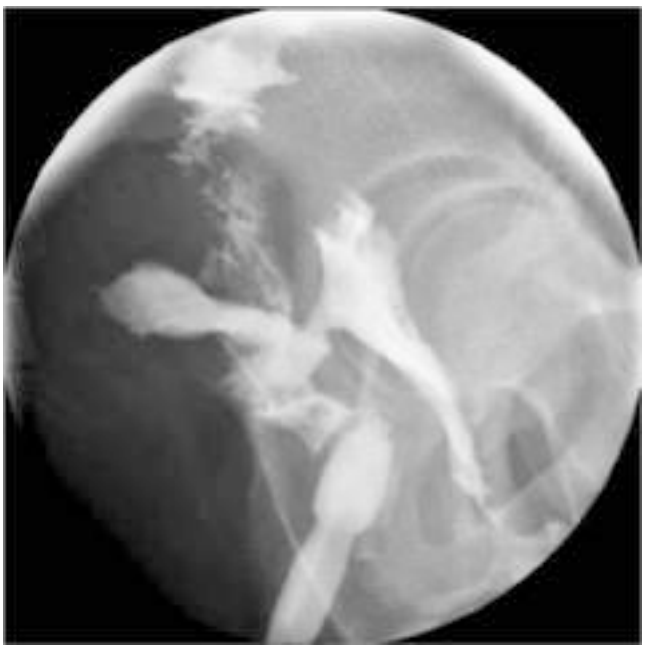

FIGURE 51-6. Gastrografin enema demonstrating a pouch-vaginal fistula with contrast filling both structures.

seton placement which may restore the elasticity and tensile strength of the tissues to be used in future definitive repair of the PVF. Medical treatment with antibiotics, anti-inflammatories, and Crohn's disease medications may be required to reduce inflammation in anticipation of a repair procedure. Although there is a risk of ultimate pouch failure for patients with PVF, up to 85 % of these fistulas can heal using a variety of surgical approaches in combination with medical optimization [13].

Treatment Options for PVF

Advancement Flap Repair

This is a local repair that may be considered in patients with a low, simple PVF without excessive inflammation. Prone jackknife positioning with general anesthesia provides the best exposure to the field. Placing four quadrant effacement sutures or using a Lone Star™ retractor (Cooper Surgical Inc., Trumbull, CT) further improves exposure. Using appropriately sized Hill-Ferguson retractors in both the vagina and anal canal allows for visualization of the fistula so that a fistula probe can be passed to identify the actual tract. In the absence of smoldering infection and if the tissues are supple and healthy, consideration may be given to creating a flap for repair.

The fistula opening in the pouch is circumscribed and, after the infiltration of 0.25 % Bupivacaine with epinephrine, a U-shaped broad-based flap is raised, mobilizing mucosa and submucosa with the fistula opening at the apex of the flap. The fistula tract is dissected within the pouch-vaginal septum and is excised and the resulting defect is approximated using #2-0 Vicryl suture. The flap is secured to the pouch-anal mucosa with sutures incorporating the adjoined sphincter mechanism ensuring a tension-free repair. If the defect on the vaginal aspect is small, it may be left alone. However, when large, the edges of the defect are freshened and the defect is approximated with interrupted absorbable sutures. Patients are kept on strict bedrest for 24 h and the bladder catheter is removed after 48 h.

The success of an advancement flap in the setting of PVF is influenced by the underlying etiology of the fistula, the quality of the tissues involving the fistula, and technical considerations at the time of the repair. Flap ischemia, bleeding under the flap, and tension across the flap risk failure of this procedure are to be avoided. Patients with a failed advancement flap may be candidates for a redo flap procedure provided any residual local sepsis or ongoing inflammation is addressed and the tissues allow for a redo flap [15, 16].

Trans-vaginal Repair

This can occasionally be attempted when poor access, as with a mild stenosis of the IPAA, impedes repair via the pouch. A vaginal advancement flap repair is performed using similar principles as described above.

Fibrin Glue, Fistula Plug, Biologic Mesh Repair, and Gracilis Muscle Interposition

These perineal procedures have been described for the management of PVF and, given the variable success rates associated with these procedures, will not be reviewed in further detail [17–19].

Perineal Pouch Advancement

This can be performed through a perineal approach. The anterior half of the IPAA is disconnected from the anal canal and the pouch is mobilized down from the vagina and is reapproximated to the anal canal after freshening and repairing the tissue surrounding the defect in the rectovaginal septum. If the defect on the vaginal aspect is large, the edges are freshened and the tissue is approximated with interrupted absorbable sutures. The degree of mobilization obtainable through this technique is often limited given the constraints of operating trans-anally.

Redo IPAA

Redo IPAA is the definitive treatment option for patients with PVF who have failed prior attempts at repair and desire restoration of the continuity of the intestine. Patients with an otherwise healthy perineum, adequate sphincter mechanism, and a low suspicion of having Crohn's disease may be considered for a redo IPAA.

Redo IPAA is performed via a combined abdominoperineal approach so that the pouch can be disconnected from the prior anastomosis. These operations are usually technically challenging and preoperative planning should consider the placement of ureteral stents to avoid ureteric injury. After pouch-anal disconnection, the fistula is excised and debrided to prepare the pouch for repeat IPAA if the existing pouch is salvageable. The pouch may be augmented or refashioned, as required, based on intraoperative evaluation of the health and capacity of the pouch. The length of remaining small intestine and anticipated challenges with reach influence whether or not the pouch is revised or excised and created anew. If the status of the pouch is not sufficient, a neoileal pouch may be required. Once the pouch is prepared and the vaginal defect is repaired, mucosectomy and repeat IPAA are completed in hand-sewn fashion followed by a protecting loop ileostomy. If the greater omentum is available and can be mobilized to reach the low pelvis, an omental pedicle flap is used as an interposition between the pouch and the vagina to potentially reduce recurrent fistulization.

Redo pouch surgery is a reasonable option for selected patients with pouch failure due to a variety of conditions besides PVF including anastomotic leak, pelvic abscess, fistula, stricture, and pouch dysfunction from other causes [20–26]. While these salvage procedures are associated with acceptable

functional outcomes and quality of life, these outcomes are typically inferior to the results experienced with successful primary IPAA [27, 28]. Sphincter injury due to repeat operative trauma, mucosectomy with hand-sewn anastomosis, shortened length of remaining small intestine, and decreased compliance of a revised pouch may each contribute to worse functional outcomes after redo pouch surgery. The decision to proceed with redo IPAA requires consideration of anticipated function as well as the individual patient's conviction regarding the importance of long-term stoma avoidance.

Proximal Diversion

A defunctioning ileostomy is often considered as a temporizing measure to control symptoms and improve the quality of the tissues in anticipation of a local PVF repair or may be performed concomitantly with the repair. In certain cases pouch excision with permanent, conventional end ileostomy creation may be recommended; alternatively, conversion of the pouch to a continent ileostomy may be considered in select, highly motivated patients. The "K" pouch procedure is complex and risks additional complications due to the technical challenges inherent in creating the nipple valve mechanism and the continent ileostomy reservoir. Patients who undergo the procedure are, however, extremely satisfied with the operation [29]. Patients with pouch failure who are not candidates for another restorative procedure are generally recommended to undergo pouch excision as leaving the pouch in situ can cause long-term problems with seepage, anal pain, and overall decreased quality of life [30].

Pouch-Perineal Fistula

This is another potential septic complication after pouch surgery that may arise due to tracking of infection or may be due to undiagnosed Crohn's disease. The evaluation, management, and surgical options for pouch-perineal fistula are similar to those for pouch-vaginal fistula. Figure 51-7 illustrates the steps for an advancement flap repair for this kind of fistula.

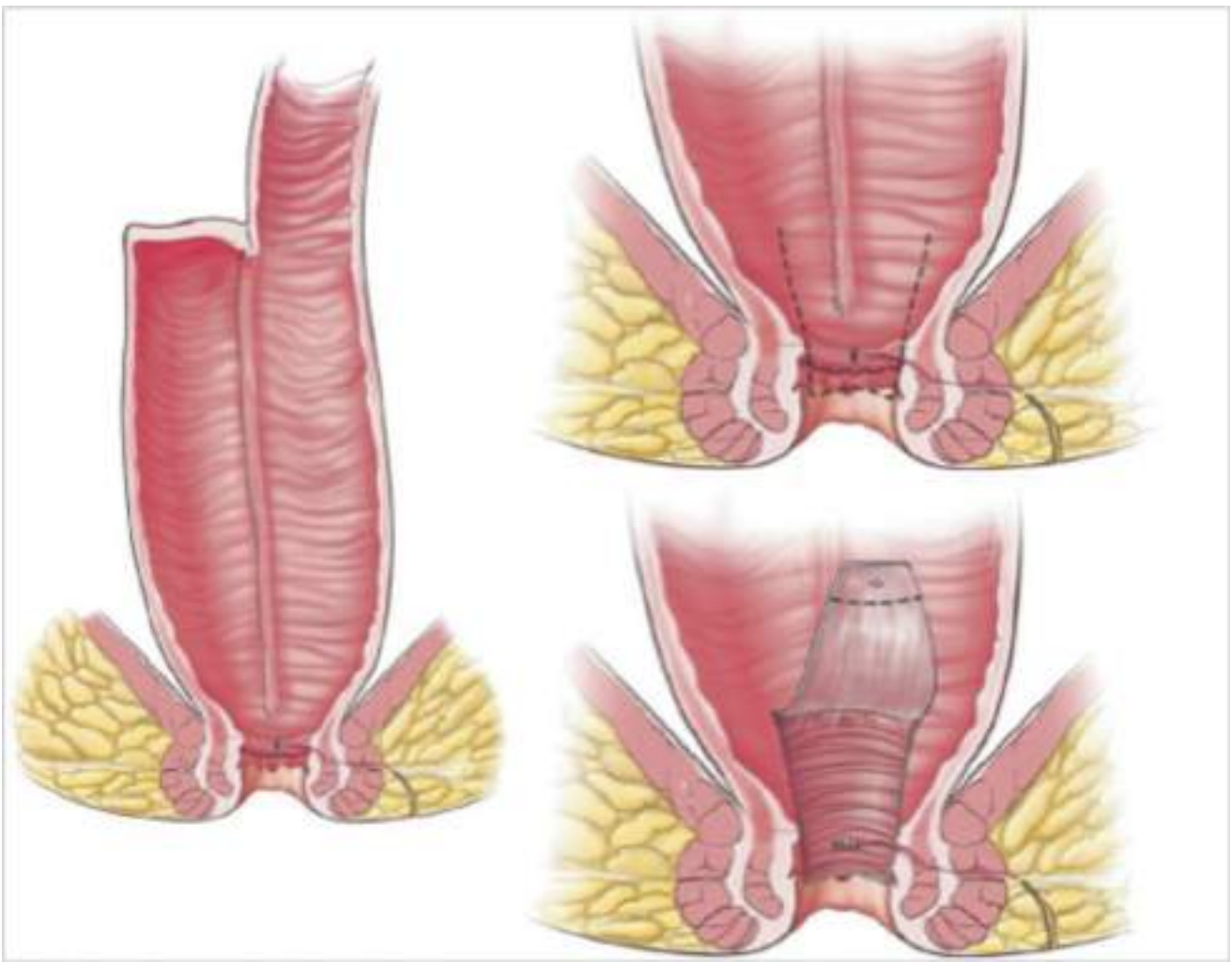

FIGURE 51-7. Technique for advancement flap repair of a pouch-perineal fistula.

Pouch Sinus

A pouch sinus, generally considered an anastomotic leak confined to a blind-ending tract, occurs in 2–8 % of patients after IPAA [31–34]. While these tracts may be asymptomatic and incidentally discovered, some patients present with symptoms ranging from minor inflammation to pelvic sepsis, pain, pouch dysfunction, and pouch failure. In terms of treatment, debridement, unroofing, fibrin glue injection, pouch revision, and redo pouch have all been described with variable rates of healing. Symptomatic presentation is a significant predictor for low healing rates and is associated with a high risk of pouch failure. Management is individualized to each patient and depends on the presenting symptoms, size, and location of the sinus as well as other factors such as whether or not the patient is diverted. Observation is recommended over intervention, when permitted by clinical circumstances, as these sinuses can resolve spontaneously.

Sinuses detected incidentally in patients without an ostomy are usually best left alone. Patients with a sinus detected incidentally on routine evaluation before stoma reversal are usually recommended to delay reversal for a few months until repeat evaluation demonstrates the sinus has healed (Figure 51-8). Patients with a symptomatic sinus or a non-resolving tract may be managed by trans-anal debridement with drainage, unroofing of the sinus, or glue injection. Proceeding with ileostomy reversal may be considered in selected asymptomatic patients with a persistent small tract who have failed attempts at resolving the sinus. Symptomatic patients who fail local attempts to resolve their sinus may go on to require diversion, pouch revision, or redo pouch surgery.

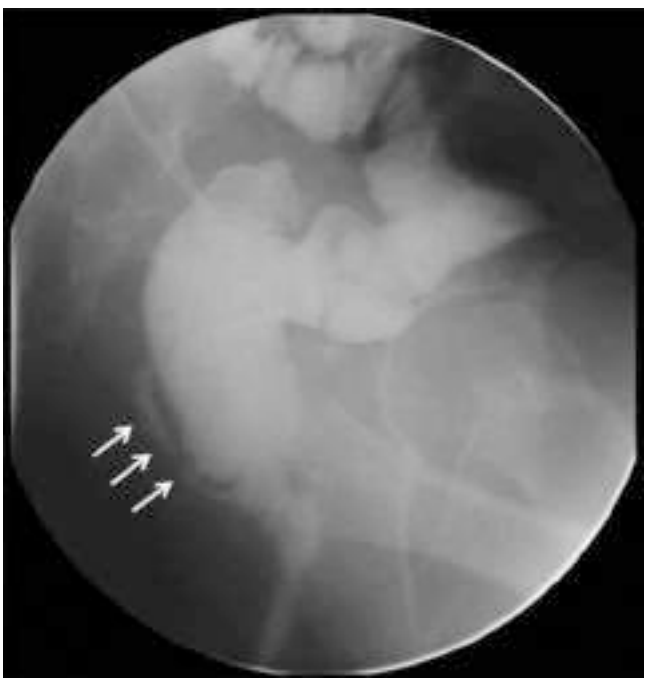

FIGURE 51-8. Gastrografin pouchogram demonstrating a posterior sinus (at *arrows*).

Crohn's Disease After Pouch Surgery

In general, patients with Crohn's disease are not considered good candidates for IPAA because of the high rates of pouch complications, including failure, in this group of patients [35–37]. However, even with a histologic diagnosis of Crohn's colitis, a highly select subset of patients with disease entirely confined to the colon and rectum and in whom the small intestine and anoperineum are spared may be candidates for an IPAA provided patients are thoroughly counseled regarding the higher risks of long-term pouch loss [36].

Pouch patients with presumptive ulcerative colitis or indeterminate colitis may, after developing complications, ultimately be diagnosed with Crohn's disease. The diagnosis of Crohn's disease after pouch surgery is usually based on the presence of perianal fistulas unrelated to the surgery, non-necrotizing granulomas on histopathology, or inflammation and ulceration in the afferent limb or in the small intestine on endoscopy in the absence of nonsteroidal anti-inflammatory use [38]. Confirming the diagnosis of Crohn's disease after pouch surgery can be challenging. In the early postoperative period after restorative proctocolectomy, septic complications related to the pouch may manifest with findings similar to Crohn's disease as reviewed earlier in this chapter. In terms of long-term effects after pouch surgery, Crohn's disease may interfere with pouch function by affecting the body, afferent limb, or anastomosis of the pouch, the perineum, or the proximal small intestine.

Management depends on the disease manifestations (inflammatory, fibrostenosing, fistulizing) and the resulting symptoms. Pouch-related complications in the setting of Crohn's disease are more difficult to resolve compared with complications in patients without Crohn's disease and have a higher rate, ultimately, of pouch failure [3, 39]. Treatment relies on a combination of conventional medical therapy for Crohn's disease and surgical intervention tailored to the specific complication at hand. Endoscopic balloon dilation may be used for isolated short-segment strictures reserving surgery for stricturing disease not amenable or responsive to through-the-scope interventions. Bowel-preserving stricturoplasty, a cornerstone of Crohn's disease management, if appropriate, is preferred over bowel resection in these cases. In the presence of localized disease at these sites, stricturoplasty of the pouch-anal anastomosis, pouch body, and small bowel proximal to the pouch with or without a defunctioning

ileostomy may help control symptoms and salvage the pouch. Perianal disease may be managed with drainage and medical therapy in anticipation of future surgical intervention. Extensive or refractory Crohn's disease may require diversion and possible pouch excision.

Incontinence

Functional issues after undergoing IPAA can significantly impact quality of life. Patients may present with varying degrees of urgency, seepage, pad dependence, nocturnal leakage, and incontinence [9, 40]. Patients over 50 years of age at the time of IPAA have higher rates of postoperative incontinence and this dysfunction can become more pronounced with longer post-IPAA follow-up [41]. Control issues may be due to pouch abnormalities like pouchitis, cuffitis, presacral sinus, or a chronic presacral cavity related to an anastomotic leak. Another contributing factor can be weakness of the sphincter mechanism that may have preexisted the IPAA or may be postsurgical in nature from mucosectomy or other operative trauma [42]. Evaluation of the pouch, anal canal, and sphincter mechanism can usually elucidate the etiology of these symptoms and treatment is tailored to the underlying problem.

Outlet Obstruction

Problems with pouch evacuation may be due to a mechanical or anatomic cause like IPAA stricture, pouch prolapse, or kinking of the outflow of the pouch which can occur in patients with an "S" pouch with a long efferent limb (Figure 51-9). A functional pouch evacuation disorder can be due to paradoxical, non-relaxation of the puborectalis muscle which can present similar to chronic post-IPAA bowel obstruction [43]. Treatment of IPAA outlet dysfunction depends on the underlying cause of the symptoms. Biofeedback with pelvic floor retraining may be helpful for some patients without a mechanical cause of the symptoms. Enemas and intermittent self-intubation to vent or to irrigate the pouch may be useful for patients with obstruction from either anatomic or functional causes.

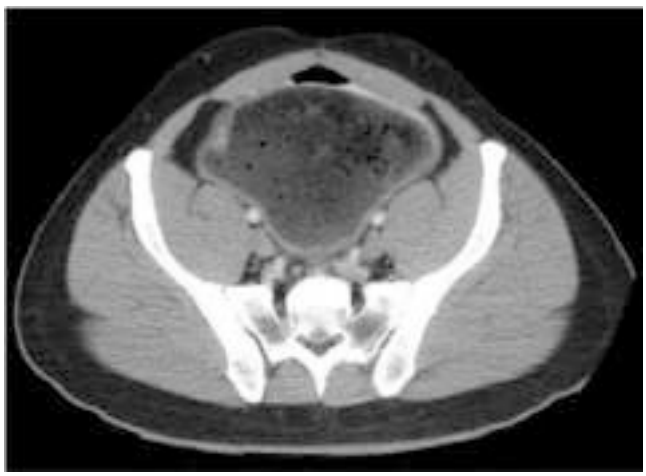

FIGURE 51-9. CT scan of a patient with outlet obstruction of an "S" pouch due to kinking of the outflow tract. The pouch is distended with fecalized material.

Pouchitis and Cuffitis

Pouchitis and cuffitis are distinct post-IPAA entities that have similar presentations and treatment options. These conditions relate to poorly understood, nonspecific inflammation of the pouch or of the retained rectal columnar mucosa above the anal transition zone that causes bleeding, cramping abdominal pain, anal discharge, tenesmus, urgency, and increased frequency. Pouchitis is the most common complication requiring medical treatment after IPAA and occurs much more commonly in pouch patients with ulcerative colitis as compared with pouch patients with polyposis [35]. An estimated 40 % of ulcerative colitis patients develop pouchitis after IPAA and some patients develop a chronic pouchitis condition [2, 44]. Patients are diagnosed by pouchoscopy and biopsy (Figures 51-10 and 51-11).

Treatment for pouchitis and cuffitis is primary medical and often includes antibiotics, probiotics, anti-inflammatories, and steroids that can be administered orally or trans-anally. Patients who exhaust medical therapy and remain symptomatic may benefit from a diverting ileostomy, pouch excision, and possible redo pouch surgery. Small focal areas of cuff inflammation may be addressed with ablation. Recalcitrant cuffitis may be treated with mucosectomy and pouch advancement or may require redo IPAA if the cuffitis is due to a longer segment of retained rectum at the time of the original IPAA.

Pouch Prolapse

This is a rare complication occurring in less than 1 % of patients after IPAA [45]. Patients have been reported to present with mucosal prolapse or full-thickness prolapse. Diagnosis is usually based on symptoms and physical examination and initial treatment relies on dietary manipulation, bulking agents, and avoidance of straining. Biofeedback may be useful, as well. Patients with symptomatic mucosal prolapse may undergo definitive treatment with excision of the redundant mucosa. Patients with full-thickness prolapse may require an abdominal approach with fixation of the pouch to the sacrum [46]. Volvulus of the pouch is extremely rare and will not be discussed in detail.

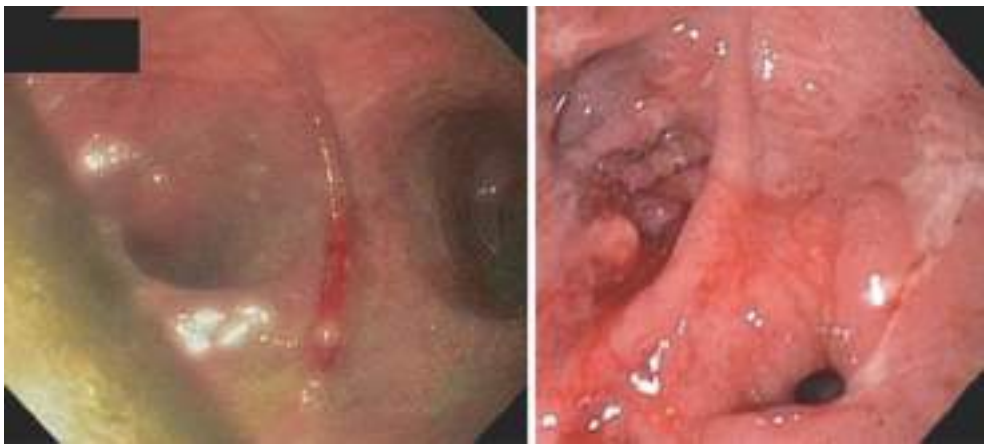

FIGURE 51-10. Pouchitis on flexible pouchoscopy. On the *left*, notice the erythematous mucosa and the watery consistency of the pouch contents. Patients can also have friable, ulcerated, or edematous mucosa as seen on the *right*. These findings can mimic and may be difficult to differentiate from Crohn's disease of the pouch.

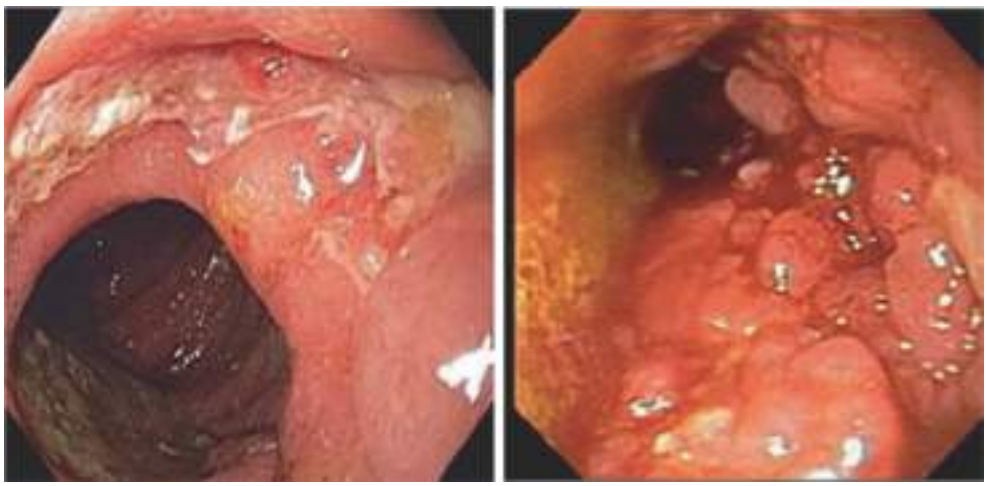

FIGURE 51-11. Cuffitis on flexible pouchoscopy. The inflammatory changes are limited to the rectal mucosal remnant and can be severe.

Leak from the Tip of the "J"

Leak from the tip of the "J" is less common than anastomotic leak after IPAA and occurs in less than 1 % of pouch patients [47] (Figure 51-12). Since the tip of the "J" is formed by the terminal portion of the small intestine, care must be taken to ensure adequacy of blood supply to the segment when this is stapled. Over-sewing of the staple line is also prudent. Patients present with variable and often nonspecific symptoms of abdominal pain, fever, and changes in pouch output and some patients develop an abscess or fistula. These leaks can be difficult to discover on routine pre-stoma reversal evaluation and may not become symptomatic until after the ileostomy is taken down. The indolent course associated with this particular pouch complication may explain why some patients are not diagnosed until the time of reoperation. Salvage surgery may involve suture repair of the pouch or excision of the tip of the "J" (Figure 51-13).

Dysplasia and Cancer After Pouch Surgery

Dysplasia and cancer can develop in the ileal pouch, in retained rectal mucosa, or in the anal transition zone after IPAA and has been reported to occur in patients with ulcerative colitis and familial adenomatous polyposis. Mucosectomy at the time of IPAA does not prevent future dysplasia as islands of rectal mucosa may persist even after "complete" mucosectomy at the time of IPAA [48]. The development of dysplasia or neoplasia within the pouch of ulcerative colitis patients is extremely rare such that routine surveillance of the pouch is not warranted [49]. Ulcerative colitis patients, whether stapled or hand-sewn after mucosectomy, should be counseled about the future risk of malignant degeneration in or near the anal transition zone and can be offered periodic surveillance. Prior colorectal dysplasia or cancer and chronic pouchitis are risk factors for developing

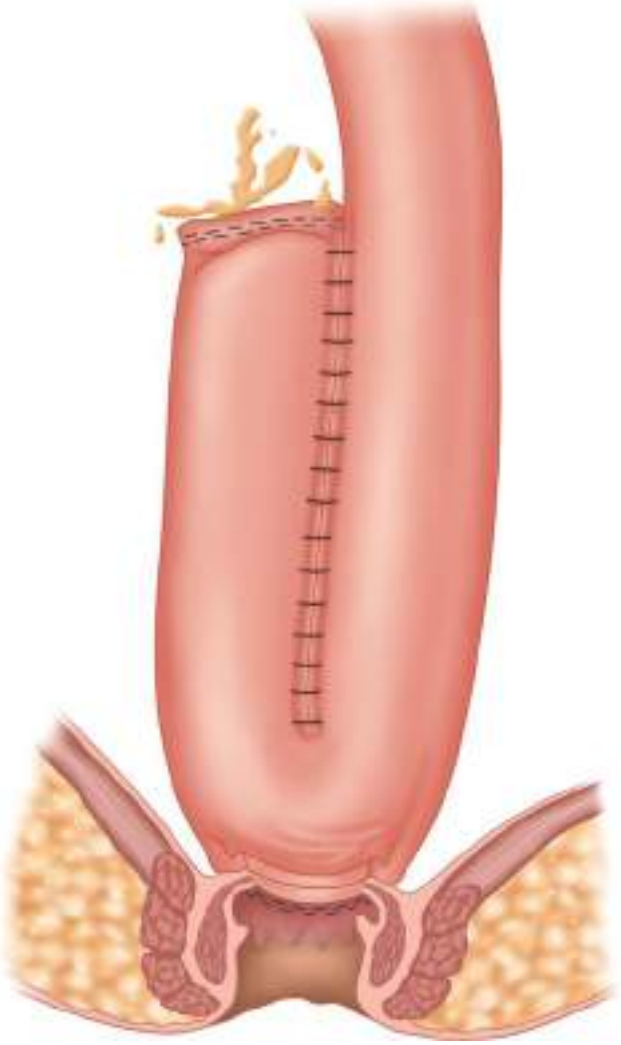

FIGURE 51-12. Leak from the tip of the "J".

pouch neoplasia; these patients may benefit from a more targeted pouch surveillance program [50]. Pouch patients with familial adenomatous polyposis are at risk for developing future polyps or cancer and should undergo annual surveillance with pouchoscopy and biopsies [51]. Pouch patients with focal dysplasia are recommended to undergo ablation or excision and surveillance. Patients with cancer will most likely require radical surgery with pouch excision.

Small Bowel Obstruction

SBO is one of the most common long-term complications after IPAA occurring in as many as 25 % of patients [2, 52]. Obstruction above the level of the pouch, most commonly due to adhesions, may also be due to volvulus, internal hernia, or stenosis at the site of stoma reversal. Laparoscopy, generally thought to reduce the formation of adhesions as compared with open surgery, has not been shown to reduce the long-term incidence of SBO in pouch patients [53, 54]. Adhesion barriers have been studied in the setting of pouch surgery but are not used routinely in practice [55]. Adhesive SBO in pouch patients is treated in the same fashion as SBO after other abdominal operations with bowel rest, decompression, and exploration with adhesiolysis, if necessary. The rate of requiring adhesiolysis appears to be higher in patients with SBO after pouch surgery compared with patients who have had other types of abdominal surgery.

Sexual Dysfunction

Historically underappreciated and underreported, sexual dysfunction after total proctocolectomy with IPAA may affect up to 20 % or more of patients [56, 57]. Men may

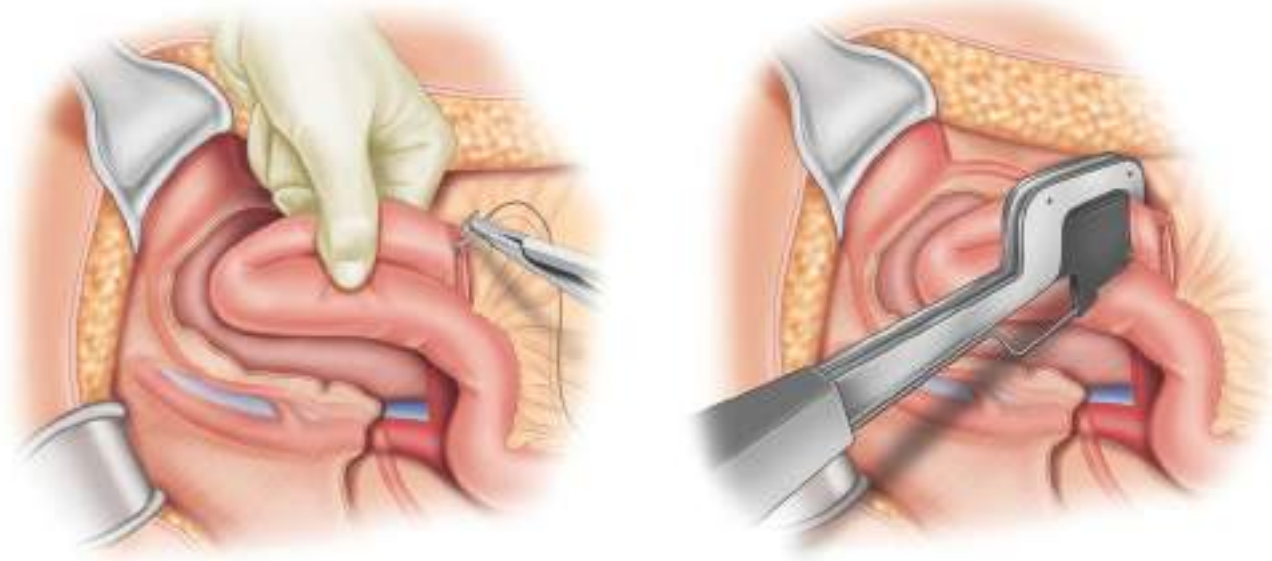

FIGURE 51-13. Leak from the tip of the "J" treated with suture repair or excision.

develop erectile dysfunction and retrograde ejaculation and women can experience alterations in sexual desire, arousal, and satisfaction and can suffer from dyspareunia [58]. The etiology of sexual dysfunction after IPAA is multifactorial and may involve nerve injury, altered pelvic anatomy, issues related to body image, presence of an ileostomy, and pouch dysfunction. In a large retrospective review of sexual function after IPAA, including 762 men and 692 women, 56 % of patients reported no change in function, 25 % reported having improved function, and 19 % had worse function postoperatively [41]. The seemingly paradoxical improvement in function may be attributed to improved quality of life experienced by patients after pouch surgery.

Hypogastric nerve injury during pelvic dissection should be avoided in order to reduce the incidence of sexual dysfunction. Performing close rectal dissection rather than total mesorectal excision has been studied and does not appear to improve preservation of sexual function [59]. Similarly, laparoscopic pouch surgery, as compared with open surgery, does not influence the risk of sexual dysfunction [60, 61].

Infertility

Women with ulcerative colitis have decreased fertility rates after total proctocolectomy compared with women who are managed non-operatively. A meta-analysis estimated that these patients have a threefold increased risk of infertility [62]. The differences in fecundity are thought to be due to adhesions and occlusive scarring of the fallopian tubes resulting from the pelvic dissection [58]. The higher rate of fertility described after laparoscopic pouch surgery compared with open procedures is thought to be due to decreased pelvic adhesions in this setting [63, 64]. Women contemplating pouch surgery should be counseled appropriately regarding the risk of future infertility and the possible impact of the laparoscopic approach.

Conclusion

While the ileal pouch remains a common operation, unfortunately pouch-related complications may occur and can impact quality of life, require multiple repeat interventions, and result in poor function or even loss of the pouch. Modifying patients' risk factors and considering the range of pouch-specific complications before, during, and after pouch surgery can potentially reduce the risk of these adverse events. Any healthcare provider managing these patients should have a thorough understanding of the potential complications and things to watch for in order to maximize quality outcomes for these patients.

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Infectious Colitides

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Key Concepts

- Common bacterial colitides are often the result of food-borne pathogens from undercooked meat or contaminated vegetables.
- Parasites are an important pathogen in the differential diagnosis of diarrhea and colitis, especially in patients who have traveled abroad.
- Cytomegalovirus can cause a life-threatening colitis usually in the setting of decreased immune status such as HIV or inflammatory bowel disease.
- Travelers to low-income parts of the world frequently have the misfortune of developing acute diarrhea, caused by various forms of *Escherichia coli* in over 50 % of cases.
- Diarrhea in the setting of HIV or immunosuppression for transplantation requires an extensive workup for bacteria, viruses, and protozoa.

Infectious colitis is a worldwide cause of morbidity and mortality. Estimates suggest that 2–4 billion episodes of infectious diarrhea occur in developing countries annually [1], and around 48 million Americans were afflicted with food-borne illness in 2012 [2]. Bacteria, parasites, viruses, or fungi may cause infectious colitides.

Pseudomembranous colitis, caused by the *Clostridium difficile* toxin, has become an increasingly more common cause of infectious colitis and should be included in the differential diagnosis for any patient presenting with an acute diarrheal illness. This entity is fully discussed in Chap. 53.

Bacterial Colitides

Campylobacter

Campylobacter typically produces diarrhea and fever. The stool may be bloody, and infection may be accompanied by abdominal pain. *Campylobacter* results in up to 14 % of cases worldwide, with *Campylobacter jejuni* the usual culprit. Transmission is commonly through contaminated poultry, but many animals can be infected. A recent report described an outbreak of campylobacter enteritis following a mud bike race, thought to be from ingestion of contaminated mud [3].

Infection of the terminal ileum and cecum can mimic acute appendicitis. Most illnesses last less than 7 days, but up to 16 % of patients may harbor the organism for 2–10 weeks. Complications of infection can include hemorrhage, toxic megacolon, pancreatitis, Reiter syndrome, and Guillain–Barre' syndrome [4].

Stool samples with fecal leucocytes and blood support the diagnosis of infectious colitis, but diagnosis of *Campylobacter* is made by culture of the bacteria. Colonoscopy may demonstrate segmental edema, loss of vascular pattern, and patchy erythema of the mucosa. These findings are nonspecific and may be difficult to differentiate from that of other colonic mucosal diseases [5].

The majority of patients do not require treatment, as the disease is self-limiting. Fluoroquinolone antibiotics, which are also active against *Shigella* and other common enteric organisms, can be used empirically. However, resistance to fluoroquinolones is becoming a major problem, with Smith et al. [6] showing an increase in resistance from 1.3 to 10.2 % between 1992 and 1998. In some countries, resistance has been found in up to 80 % of isolates [7]. Azithromycin has been shown to be effective when fluoroquinolone resistance is an issue, while Erythromycin is a third-line choice.

Salmonella

Salmonella can cause both typhoid and non-typhoid illnesses. The non-typhoid version causes self-limited diarrhea. *Salmonella typhi* and *Salmonella paratyphi* cause typhoid fever, while *Salmonella enteritidis* and *Salmonella typhimurium* are the most common serotypes in the United States.

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The major route of transmission is by the "5 Fs": flies, food, fingers, feces, and fomites [4]. Contaminated meat and poultry are the main sources of infection, but imported jalapeno, peanut butter, mangoes, live animals (turtles), smoked salmon, and sesame paste have all been implicated in major outbreaks [8].

Infections with non-typhoidal *Salmonella* present with nausea, vomiting, abdominal cramps, and diarrhea. Symptoms may occur between 8 and 48 h after ingestion of contaminated food. Illness can last up to 3 weeks and bacteremia may occur in up to 10 % of patients. Typhoid fever can manifest with high fever, delirium, abdominal pain, splenomegaly, and skin rash. Typhoid fever occurs when organisms penetrate the small bowel wall and enter the lymphatics and ultimately the bloodstream [4].

Diagnosis is established by identification of the organism with blood culture or cultures from the stool. Endoscopic findings in non-typhoidal *Salmonella* infection may include hyperemia, mucosal friability, aphthous erosions, or deep ulcers with segmental involvement. Typhoid disease may show punched-out ulcers with slightly raised margins, with the most commonly affected areas being the terminal ileum and right colon. In Lee's report of seven patients, the left colon was spared in all cases [9].

Antibiotics are traditionally reserved for patients where bacteremic disease is suspected or would place the patient at marked risk. These are patients who are febrile or toxic, young (3 or less) or elderly (65 or older). Patients with sickle cell disease, inflammatory bowel disease, or acquired immune deficiency syndrome (AIDS) or patients on steroids or hemodialysis should be considered for antibiotic treatment. When indicated, fluoroquinolones are the treatment of choice [10]. For patients with typhoid fever, azithromycin should be used both in developing countries and in travelers returning to industrialized countries [11].

Shigella

Shigellosis is most commonly a disease of children under 5 years of age but can affect all age groups. It is the third most common enteric infection in the United States, but is uncommon in Europe [8]. *Shigella sonnei* accounts for more the two-thirds of cases in the United States and is typically spread through contaminated food or water, or person-to-person contact. In developed countries, *Shigella* is seen most frequently in day care centers, in nursery schools, and in male homosexuals [8].

Diarrhea is initially watery without blood, but tenesmus and bloody stools develop 3–5 days after onset. Bacteremia is uncommon, but perforation, megacolon, hemolytic-uremic syndrome, and severe dehydration may occur. Children typically have mild infections, which may last up to 3 days. Adults have more prolonged courses, with severe cases lasting 3–4 weeks.

Symptoms include lower abdominal pain, rectal pain, and diarrhea. Stool cultures are needed for diagnosis, and stool typically contains red and white blood cells. Colonoscopy shows nonspecific erythema, edema, and loss of vascular pattern. In a study of 33 patients with shigellosis, Speelman [12] found continuous inflammation, more prominent distally, mimicking that of inflammatory bowel disease. Luminal exudate and star-shaped ulcerations may also be seen [13].

Antibiotic treatment is always indicated for *Shigella* infections. Resistance to tetracyclines, co-trimoxazole, and ampicillin was 45 % or higher in a study of 191 isolates by Pons et al. in 2010. Resistance to ciprofloxacin and azithromycin remained well under 5 % [14]. Although fluoroquinolone resistance is slowly becoming an issue, treatment may be with either ciprofloxacin 750 mg daily for 3 days or azithromycin 500 mg daily for 3 days [10].

Escherichia coli

Escherichia coli is one of the most populous of the normal intestinal flora. Five groups of *E. coli* cause enteric infections: enteropathogenic *E. coli* (EPEC), enterotoxigenic *E. coli* (ETEC), enteroadherent *E. coli* (EAEC), enteroinvasive *E. coli* (EIEC), and enterohemorrhagic *E. coli* (EHEC) [4].

EPEC is associated with diarrhea in infants and nursery outbreaks, while EAEC can cause persistent childhood diarrhea. ETEC and EAEC (mainly children) are two of the leading causes of traveler's diarrhea, especially in Latin America and the Caribbean [15], while EIEC is an endemic cause of dysentery in South America and Eastern Europe and has been a rare cause of food-borne outbreaks in the United States [8].

EHEC causes hemorrhagic colitis with bloody or mucoid diarrhea and is a common cause of infectious colitis in Western countries, including the United States. *E. coli* O157:H7, a subtype of EHEC, was first identified in 1982, from outbreaks in Michigan and Oregon. It is an important cause of acute bacterial colitis, especially from undercooked ground beef [16]. Although less common than *Salmonella* or *Campylobacter*, *E. coli* O157:H7 shows a higher hospitalization and fatality rate [17]. Most cases start with non-bloody diarrhea and resolve spontaneously. Some patients will progress to bloody diarrhea, and 5–10 % of these can progress to the life-threatening hemorrhagic-uremic syndrome or thrombocytopenic purpura [18].

Non-O157 strains have recently emerged as an important cause of infection worldwide. Outbreaks in the United States between 2011 and 2013 from frozen food products and sprouts have been associated with serotypes O121, O145, and O26. One of the largest outbreaks occurred in Germany in the summer of 2011. Investigations implicated an organic sprout farm near Hamburg. Over 20 % of affected patients developed hemolytic uremic syndrome from the toxin-producing serotype O104:H4 [19].

Many hospital laboratories are routinely testing for *E. coli* O157:H7 on stool culture, but it should be requested in any patient with bloody diarrhea. PCR assays are in various degrees of development [20]. Colonoscopy findings show shallow ulcerations, marked edema, and longitudinal ulcer-like lesions throughout the colon. Inflammation tends to predominate on the right side of the colon [21].

Clinical data do not support the use of antibiotics for hemorrhagic *E. coli* infection. In fact, some studies show that antibiotics and anti-motility agents may cause increased production of toxin and increase the risk of hemolytic uremic syndrome. Rifaximin 200 mg three times a day for 3 days may be used for EAEC, as well as fluoroquinolones or azithromycin [10]. Attempts to develop a vaccine against *Escherichia coli* for traveler's diarrhea have not proven successful [22].

Yersinia

Yersinia can occur from handling of contaminated animals or animal products, or ingestion of contaminated food or water (most commonly undercooked pork or contaminated milk). Typical symptoms are fever, diarrhea, and abdominal pain, lasting up to 3 weeks. The infection may cause mesenteric adenitis or ileitis, mimicking Crohn's disease. Extraintestinal symptoms, such as migratory arthritis, Reiter's syndrome, and erythema nodosum, may occur.

Radiographic and endoscopic findings also may be indistinguishable from Crohn's disease with erosions and ulcerations on the right side of the colon [23]. Laboratory isolation is difficult, while hemagglutination is an indirect test with titers in the 1:128 range suggestive of infection. The disease is usually self-limited, but in prolonged cases or patients with extraintestinal manifestations, aminoglycosides, trimethoprim-sulfamethoxazole (TMP-SMX), doxycycline, and fluoroquinolones have all been used successfully [4].

Vibrio

Vibrio can cause either a cholera or noncholera illness. Infections are usually associated with consumption of raw or undercooked shellfish. The Cholera and Other Vibrio Illness Surveillance (COVIS) system reported 7700 cases in the United States over a 15-year period ending in 2010, with the highest incidence in the gulf coast states of Alabama, Florida, Louisiana, and Texas [24]. Most patients with gastroenteritis reported having eaten raw oysters in the week before their illness.

Patients with *Vibrio parahaemolyticus* infection typically present with diarrhea and abdominal cramps. About half have fever and vomiting. Stool testing does not typically test for *Vibrio* species, but may be specially requested, especially when illness develops within 48 h of ingesting raw or undercooked shellfish. Most patients don't require treatment, but tetracycline, fluoroquinolones, aminoglycosides, and third-generation cephalosporins are usually effective [25].

Vibrio cholera and invasive *Vibrio* infections can cause profuse watery diarrhea, vomiting, and muscle cramps. Stool volumes may reach a liter per hour, and this can lead to shock and death within hours without treatment. *Vibrio cholerae* O1 and *Vibrio cholerae* O139 are major sources of cholera outbreaks. An estimated 2.8 million cases occur annually in endemic countries (mostly Asia and Africa) with 87,000 cases in non-endemic countries [26].

Raw or undercooked shellfish again is the most common cause, and most cases in the United States come from foreign travel or Gulf Coast shellfish. Treatment of cholera includes aggressive fluid replacement. Ciprofloxacin (1 g orally for one dose) or doxycycline (300 mg orally for one dose) is the antibiotic of choice. Vaccines for overseas travelers have not proven to be effective and are not available in the United States [27, 28]. Vaccines for endemic populations have demonstrated some potential, but fail to meet all the requirements of the World Health Organization [29].

Other Bacterial Colitides

Tuberculosis is prevalent in the developing world. Mycobacterium tuberculosis is primary to the lungs and may be carried to the intestinal tract from swallowed sputum. Patients may present with abdominal pain, weight loss, anorexia, and fever. Because of its predilection for the ileocecal regions, findings frequently mimic Crohn's disease or appendicitis. Cultures are difficult, and a positive skin test is not diagnostic [4]. Endoscopic biopsies of ulcers may be helpful [30].

Classic radiologic signs include a contracted terminal ileum with a wide ileocecal valve (Fleischner sign) and a narrow ileum opening into a contracted cecum (Sterlin's sign) [31]. Medical management is complicated and is beyond the scope of this discussion. Surgery is indicated for complications, most commonly obstruction or perforation.

Aeromonas causes diarrhea, most commonly in the tropics. Persistent diarrhea, usually lasting longer than 2 weeks, is common. The bacteria may be cultured, but a specific request to the lab may be needed. The disease is usually self-limited. Treatment, in prolonged cases or immunocompromised hosts, is typically with a fluoroquinolone or azithromycin [32].

Bacteroides fragilis is part of the normal colonic flora, but a subclass that secretes a toxin has been recognized as a cause of acute diarrhea in endemic regions. *Arcobacter* is considered an emerging food-borne pathogen. A study of isolates from patients with acute diarrhea acquired in Mexico, Guatemala, and India showed 8 % of specimens with *Arcobacter* and 7 % with *Bacteroides* [33].

Listeria monocytogenes is a rare cause of gastroenteritis, most commonly presenting as diarrhea in an immunocompromised patient. The largest listeriosis outbreak in the

Table 52-1. Treatment of bacterial colitides

Campylobacter	Azithromycin 500 mg daily for 3 days or erythromycin 500 mg four times daily for 3–5 days
Salmonella	Mild illness—none. Possible bacteremic disease—levofloxacin 500 mg (or other fluoroquinolone) daily for seven (immunocompetent) or 14 days (immunocompromised)
Shigella	Ciprofloxacin 750 mg (or other fluoroquinolone) daily for 3 days or azithromycin 500 mg daily for 3 days
EHEC (*E. coli*)	None
EAEC (*E. coli*)	Rifaximin 200 mg three times daily for 3 days
Other *E. coli*	Same as *Shigella*
Yersinia	Same as *Shigella*
Vibrio	Same as *Shigella*
Tuberculosis	Usual TB treatment
Aeromonas	Same as *Shigella*
Traveler's diarrhea	Same as *Shigella*

With permission from DuPont HL. Approach to the patient with infectious colitis. Curr Opin Gastroenterol. 2012;28:39–46 [10]

United States occurred in 2011 from contaminated cantaloupes, causing 147 illnesses and 33 deaths [34]. Symptoms include diarrhea, nausea, and vomiting, often with fever. Listeria should be considered a cause of food-borne outbreaks of febrile diarrhea when routine cultures fail to identify a source [35]. Disease is usually self-limited, and antibiotic treatment is not indicated, but ampicillin or TMP-SMX may be used in higher risk patients [36].

Chlamydia trachomatis is a common cause of proctitis in homosexual males or women practicing anoreceptive intercourse. It may present with bloody diarrhea, mucopurulent anal discharge, tenesmus, and anal pain. Rectal examination may show extreme tenderness, and sigmoidoscopy may show typical findings of proctitis. The bowel may become fibrotic with progressive disease.

Culture for chlamydia can be obtained from stool or rectal swab. Nucleic acid amplification tests (NAAT) are currently considered the gold standard for testing. Azithromycin (1.0 g orally single dose) and doxycycline (100 mg orally twice daily for 7 days) are highly effective for treatment, with treatment of all sex partners indicated, as well [37].

Neisseria gonorrhoeae is a common sexually transmitted disease that can cause proctitis, especially in homosexual males. Symptoms start about a week after exposure and may include mucus discharge, rectal bleeding, and diarrhea. Diagnosis is made by rectal swab on chocolate agar (Thayer-Martin). Single-dose ceftriaxone 125 mg IM cures nearly 100 % of uncomplicated disease, while fluoroquinolones are an acceptable alternative [38].

See Table 52-1 for a summary of treatment for bacterial colitides [10].

Parasitic Colitides

Entamoeba

Amebiasis is caused by the protozoan parasite *Entamoeba histolytica*. It is prevalent in the tropical areas of Central and South America, Africa, and India. Most cases of amebiasis in the United States are from immigrants or travelers returning from an endemic area. 2970 cases of amebiasis in the United States were reported to the Centers for Disease Control and Prevention (CDC) in 1993 [39]. Infection occurs from ingestion of fecally contaminated food or water or by oral/anal sexual contact.

Disease presentation can include asymptomatic colonization, diarrhea and dysentery, or liver or brain abscess. The majority of patients who ingest cysts from *E. histolytica* remain asymptomatic. A typical incubation period is 2–4 weeks followed by gradual onset of abdominal pain and bloody diarrhea. In rare cases (<0.5 %), this can lead to fulminant colitis, toxic megacolon, or extraintestinal abscess.

Diagnosis can be made by stool microscopy, antigen detection, PCR, serology, and endoscopy. Colonoscopy is preferred over sigmoidoscopy because colitis can be limited to the right side. Bowel preparation should be avoided because it will decrease the detection of the parasites. The mucosa of the colon may have friability, may show classic flask-shaped ulcerations, and may be indistinguishable from inflammatory bowel disease. Microscopic analysis of aspirate from the base of the ulcers or biopsy of the ulcer edges can show the cysts and prove to be diagnostic for amebiasis.

Treatment of intestinal amebiasis is metronidazole 750 mg PO tid for 10 days [40, 41] (Table 52-2). Intravenous antibiotics are reserved for severe cases or those resistant to oral therapy. Surgery can be necessary in cases of perforation, peritonitis, and abdominal catastrophe.

Anisakis

Anisakidosis is primarily caused by *Anisakis simplex* and *Pseudoterranova decipiens*. The majority of the cases in the world (>90 %) occur in Japan [42]. The first case in North America was described in 1975 and involved the cecum [43]. Infection typically results from the consumption of raw or undercooked fish during which larvae can attach themselves to mucosa of the stomach (most common), small bowel, or colon. Incidence has been increasing as foods like sushi, sashimi, ceviche, and anchovies gain popularity [44, 45].

TABLE 52-2. Summary of parasitic colitis treatment

Diagnosis	Pathogen	Treatment
Amebiasis	*Entamoeba histolytica*	Metronidazole 750 mg three times daily for 10 days
Anisakidosis	*Anisakis simplex Pseudoterranova decipiens*	Albendazole 400–800 mg for 6–21 days
Ascariasis	*Ascaris lumbricoides*	Mebendazole 100 mg twice daily for 3 days Albendazole 400 mg single dose
Strongyloidiasis	*Strongyloides stercoralis*	Ivermectin at 200 μg/kg/day for 2 days Albendazole 400 mg twice a day for 7 days[a] Thiabendazole at 50 mg/kg daily for 2 days[a]
Trichuriasis	*Trichuris trichiura*	Mebendazole 100 mg twice daily for 3 days Albendazole 400 mg daily for 3 days
Enterobiasis	*Enterobius vermicularis*	Mebendazole 100 mg single dose or Albendazole 400 mg single dose
Cryptosporidiosis	Cryptosporidium	Nitazoxanide
Balantidiasis	*Balantidium coli*	Tetracycline 500 mg four times a day
Giardiasis	*Giardia lamblia*	Metronidazole 250 mg three times a day for 7 days Tinidazole 2 g as a single dose
Schistosomiasis	*S. haematobium* *S. Mansoni* *S. Japonicum*	Praziquantel 40 mg/kg single dose
Tapeworm	*Taenia solium* (pork) *Taenia saginata* (beef) *Diphyllobothrium latum* *Hymenolepis nana* *Dipylidium caninum*	Praziquantel 5–10 mg/kg single dose Niclosamide 2 g single dose
Chagas	*Trypanasoma cruzi*	Benznidazole Nifurtimox

[a]Denotes second-line treatment

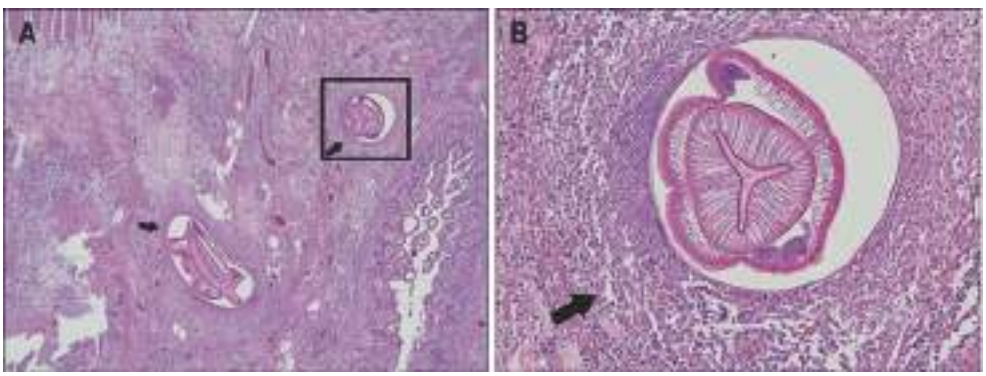

FIGURE 52-1. Histopathologic findings show the severe infiltration of inflammation and edema in all layers of the intestinal wall with a submucosal eosinophilic granuloma around larvae (*arrows*), which were findings of anisakiasis (**a**) (H&E X40), and magnification view of square showed eosinophilic granuloma around anisakiasis larva (**b**) (H&E X200). Kang DB, Oh JT, Park WC, Lee JK. Small bowel obstruction caused by acute invasive enteric anisakiasis. Korean J Gastroenterol. 2010;56:192–5 [114].

The majority of patients with anisakidosis present with gastric involvement; only about 4 % of cases present in either the small bowel or colon. Intestinal anisakidosis presents with vague complaints such as lower abdominal pain, fever, diarrhea, nausea, and vomiting [46]. After consumption, the larvae burrow into the intestinal mucosa and cause an intense hypersensitivity reaction with formation of granulomas and infiltration of eosinophils (Figure 52-1). Symptoms can mimic appendicitis, Crohn's ileitis, diverticulitis, gastroenteritis, or other causes of an acute abdomen. In rare cases, the infection can require surgery due to perforation, intussusception, small bowel obstruction, or pneumoperitoneum.

Diagnosis of intestinal anisakidosis is very challenging and almost never made preoperatively. A history of ingestion of raw fish can be a useful clue. If the diagnosis is made prior to any surgical intervention, then albendazole 400–800 mg orally for 6–21 days is effective (Table 52-2) [47].

Ascaris

Ascariasis is caused by the intestinal nematode *Ascaris lumbricoides*. It is prevalent in areas of the world with warm and humid climates such as China, India, southeast Asia, Africa, Latin America, and the Caribbean [48]. There are more than one billion people infected with the parasite worldwide.

The life cycle begins with ingestion of eggs. The larvae then hatch in the small intestine and migrate into the venous circulation where they break into the lung spaces. From there they ascend into the trachea and are swallowed back into the intestine, where they can grow into adults and create more eggs. As adults, the nematodes can live in the intestine for 1–2 years and produce up to 200,000 eggs per day. The eggs can live in the environment for years, which contributes to the high infection rate.

Most patients with ascariasis are asymptomatic. As the larvae migrate through the lungs, patients may complain of pneumonia-like symptoms. The larvae can also produce an allergic reaction with an urticarial rash. Most patients with intestinal ascariasis are children, because the lumen of the bowel is narrower, allowing for easier obstruction. A common site of obstruction is at the ileocecal valve. Large quantities of the worms can lead to formation of a mass that can intertwine and cause obstruction, volvulus, intussusception, or perforation [49].

The diagnosis of ascariasis is made by stool microscopy. The eggs have a characteristic appearance and are easily identifiable. During the larval pulmonary stage, eosinophilia in the bloodstream can be seen. Retrograde contrast studies may show obstruction or curvilinear densities as the parasite may ingest some of the barium. Treatment is very effective with cure rates as high as 90 % [50]. Mebendazole 100 mg twice daily for 3 days or albendazole 400 mg as a single dose are common therapeutic regimens (Table 52-2). Obstructed patients with no peritoneal signs can be managed conservatively with hydration and nasogastric tube decompression. Surgery is reserved for complicated cases of obstruction and perforation. During laparotomy, the ball of worms can be simply milked into the colon provided there is no perforation or bowel ischemia.

Strongyloides

Strongyloidiasis is caused by *Strongyloides stercoralis*, another intestinal nematode. The disease is most prevalent in the tropical climates of the world, as well as the Appalachian region of the United States. Larvae of *Strongyloides* are shed in the feces and then penetrate another host through the skin. Like the *Ascaris*, they travel to the lungs and then are swallowed into the intestine. They lodge in the intestinal wall and produce offspring. *S. stercoralis* is unique in that its entire life cycle can occur within the host and result in autoinfection.

Hyperinfection can also occur in conditions of immune suppression and results in large numbers of worms traveling through the lungs and intestines. Disease usually presents in two phases: acute and chronic. The acute phase is hallmarked by skin abnormalities from larvae penetration otherwise known as larva currens. Vague pulmonary and abdominal complaints may infrequently be seen as the worms migrate through. Chronic infection is a result of autoinfection, which can lead to epigastric abdominal pain and diarrhea [51, 52].

Strongyloidiasis can sometimes present with a pancolitis and can be confused with ulcerative colitis. Endoscopic features may include yellowish-white nodules, erythema, and loss of vascular pattern [53]. Detecting larvae in the stool makes the diagnosis of strongyloidiasis; however, multiple tests may be necessary. Other options include duodenal biopsy, enzyme-linked immunosorbent assay (ELISA) testing, or bronchial washings.

All patients with *S. stercoralis* should be treated because of the risk of autoinfection. The first-line option for treatment is ivermectin at 200 μg/kg/day for 2 days. Other options are albendazole 400 mg twice a day for 7 days and thiabendazole at 50 mg/kg daily for 2 days [54] (Table 52-2).

Trichuris

Trichuriasis is caused by *Trichuris trichiura*, also known as the whipworm. There are an estimated 600–800 million infected individuals worldwide, primarily in humid and tropical regions of the world [55]. Infection occurs by ingestion of contaminated soil/food. The larvae live in the cecum and colon and can shed up to 20,000 eggs per day. Like the roundworm, most infected with the whipworm are asymptomatic. As the wormload in the cecum and colon increases, symptoms such as diarrhea, tenesmus, and hematochezia can occur. Stools can be watery and will have a characteristic odor.

Trichuriasis can cause rectal prolapse and the worms can be visualized on the rectal mucosa (Figure 52-2). Blood loss can lead to anemia and, for unclear reasons, growth retardation. Diagnosis is made by identifying the barrel-shaped eggs in the stool or by visualizing the worms on the colonic or rectal wall during endoscopy. Treatment is either mebendazole 100 mg twice daily for three days or albendazole 400 mg daily for three days [56] (Table 52-2). Surgery is reserved for cases of rectal prolapse.

Enterobius

Enterobiasis is caused by the pinworm *Enterobius vermicularis*. Unlike other nematodes where infections occur primarily in tropical regions with poor sanitation, enterobiasis is prevalent in all parts of the world including urban areas of the United States and Europe. Children are the most commonly affected group [57].

Infection occurs by ingestion of eggs. Adult pinworms live in the cecum for as long as 13 weeks. About four weeks after ingestion, female pinworms migrate to the perianal skin and

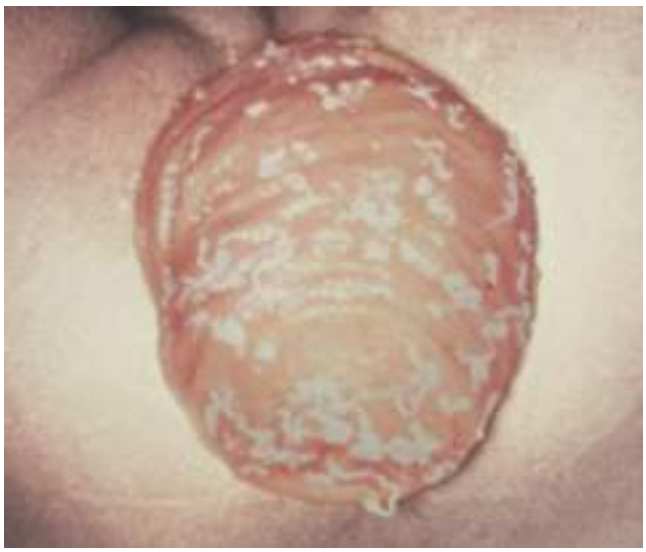

FIGURE 52-2. Whipworm and rectal prolapse. Prolapsed rectum from whipworms [114]. Available from http://phil.cdc.gov/Phil/details.asp.

FIGURE 52-3. Eggs of *Enterobius vermicularis* on wet mount [115]. Available from http://www.cdc.gov/dpdx/enterobiasis/gallery.html#eggs.

can lay up to 11,000 eggs. The larvae quickly mature and can cause an intense pruritis ani. The intense scratching facilitates fecal–oral transmission to classmates and family members.

Enterobiasis rarely causes significant abdominal or intestinal complaints. The most common clinical feature is perianal irritation. In young girls it is a well-known cause of vulvovaginitis. Other symptoms can include teeth grinding, enuresis, urinary tract infection, and insomnia. Diagnosis is typically made by the scotch tape test. This entails taking a strip of clear tape and pressing it against the buttocks. The tape is then transferred to a slide where the eggs can be seen under a microscope. The eggs have a characteristic appearance (Figure 52-3).

Treatment can be with either mebendazole or albendazole. Mebendazole can be given as a single 100 mg dose and is often repeated 2–4 weeks later. Albendazole is given as a single 400 mg dose for adults and 100 mg for children less than two, which is then repeated seven days later (Table 52-2). Usually the entire family is treated empirically.

Cryptosporidium

Cryptosporidiosis is caused by *Cryptosporidium*, an intracellular protozoan. The first human case was described in 1976 [58]. In the 1980s, it became a common cause of debilitating diarrhea in AIDS patients. The diarrhea caused by *Cryptosporidium* is usually seen in one of the four settings: childhood diarrhea in developing areas, travelers' diarrhea, debilitating diarrhea in immunocompromised patients, or waterborne outbreaks in developed areas in the immunocompetent host.

The parasite is ingested in contaminated food or water. The oocysts then excyst within the small bowel lumen, where they can multiply, and then shed via the stool. *Cryptosporidium* oocysts are highly infectious and require only a few to cause infection. They are also extremely small, which allows them to avoid being filtered by conventional water filters. They are resistant to chlorination and can spread with person-to-person contact [59]. Only heating, freezing, or ozonation can destroy the oocysts.

Disease presentation is hallmarked by explosive watery diarrhea and may be associated with abdominal pain, fever, nausea, and vomiting. In immunocompetent hosts, the disease is usually self-limited. Immunocompromised patients have a more protracted course which can be debilitating and sometimes life-threatening. In this patient population, the most common site of extraintestinal infection is the biliary tree, which can cause acalculous cholecystitis or sclerosing cholangitis.

Diagnosis is made by identifying oocysts in stool or in bodily fluids via microscopy, PCR, ELISA, or loop-mediated isothermal amplification (LAMP) [60]. The test may need to be repeated three times to detect the infection. Treatment in immunocompetent patients is primarily supportive (hydration, nutrition, and anti-motility agents), as the disease is self-limited. There is no drug or antimicrobial that has been shown to be effective in controlling cryptosporidiosis. Nitazoxanide is the only Food and Drug Administration [5]-approved medication and may shorten the clinical course of the disease (Table 52-2). In AIDS patients, the most effective form of therapy is the institution of highly active antiretroviral therapy (HAART) [61, 62].

Cholecystectomy may be useful in cases of acalculous cholecystitis and endoscopic retrograde cholangiopancreatography (ERCP) may help in cases of sclerosing cholangitis. Prevention is key with strict handwashing and treatment of affected water and food supplies. Research is currently under way in the development of a vaccine against *Cryptosporidium* [63].

Balantidium

Balantidiasis is caused by *Balantidium coli*, the largest and only ciliated protozoan that infects humans. Pigs serve as the main reservoir for human infection and transmission occurs through ingestion of contaminated food or water. Balantidiasis is endemic in Southeast Asia, South America, and the Western Pacific islands.

Once the parasite is ingested, the cysts embed in the colon causing ulceration and inflammation. This can result in asymptomatic infection, non-bloody diarrhea, or severe bloody diarrhea. Severe diarrhea can result in large volume loss, peritonitis, and even death. Visualizing trophozoites in a stool sample can make the diagnosis. The parasite can also be seen on biopsy specimens of ulcers taken during endoscopy. Treatment with tetracycline 500 mg four times a day is usually effective (Table 52-2). Metronidazole and doxycycline are also effective. Surgery is rarely necessary.

Giardia

Giardiasis is caused by *Giardia lamblia* and is one of the most common parasitic infections in the United States. It can occur in almost any country and most climates. There are three methods of transmission: waterborne, food-borne, and direct fecal–oral. Waterborne transmission occurs when feces contaminate water sources. Infection can occur from drinking from mountain lakes or streams, or when fecal matter from children contaminates recreational water, like swimming pools. Uncooked foods such as salads and cold meat are the most common food sources [64].

Direct fecal–oral is common amongst children at day care centers as well as anal–oral encounters in males who have sex with males. After ingestion, *Giardia* excysts in the stomach to produce trophozoites (Figure 52-4). These attach to the small bowel mucosa and can cause villous blunting and crypt hypertrophy. Diarrhea usually begins 1–2 weeks after infection. Patients tend to have greasy stools with a foul odor and often have other accompanying symptoms such as abdominal cramps, nausea, anorexia, weight loss, vomiting, and fever. Many patients are either asymptomatic or have a benign course. Chronic cases especially in children can lead to malabsorption and growth retardation.

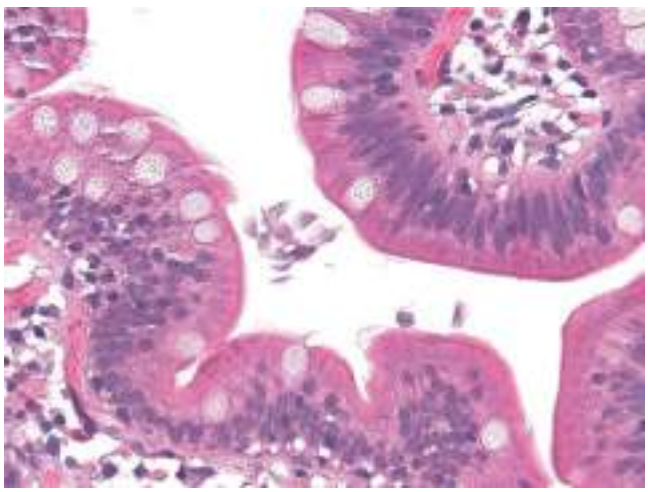

FIGURE 52-4. Duodenal giardiasis. Pale pink organisms are identified in the lumen. No architectural distortion or inflammation is seen. (Courtesy of Jeanette R. Burgess, MD).

Stool ova and parasite examination can easily make the diagnosis. There are a variety of commercial tests available that employ ELISA or immunofluorescence. Endoscopy to obtain small bowel or duodenal biopsy is sometimes used when stool assays are inconclusive. The mainstay of treatment is the nitroimidazole class of drugs. Metronidazole 250 mg three times a day for seven days is the most common regimen, though not FDA approved [65] (Table 52-2). Tinidazole 2 g as a single dose is better tolerated. Alternative medicines include albendazole, nitazoxanide, paromomycin, quinacrine, and furazolidone.

Schistosomiasis

Schistosomiasis is primarily caused by three species of trematodes: *S. haematobium*, *S. mansoni*, and *S. japonicum*. It is one of the most prevalent helminthic infections worldwide. Most infections occur in the tropics, such as South America, Africa, Middle East, Asia, and the Philippines [66, 67].

Eggs of this parasite are shed in the urine and stool of humans. Snails then serve as the intermediate host, where they metamorphose into mobile cercariae in the water. These cercariae attach and penetrate the skin, which can lead to cercarial dermatitis. They migrate to heart and lungs over the next week, travel to the liver, continue to mature, and travel to their final destination. *S. haematobium* settles in and around the bladder; *S. mansoni* and *S. japanocium* settle in the mesenteric vasculature of the small and large bowel. Eggs that are deposited in the body cause a tremendous immune response, which leads to destruction of that host organ.

Depending on the organ that is damaged, schistosomiasis can lead to dermatitis, Katayama fever, obstructive uropathy, bladder cancer, intestinal fistulas and strictures, hepatosplenic disease, pulmonary hypertension, glomerulonephritis, and neural and spinal cord pathology. Intestinal schistosomiasis can cause abdominal symptoms like pain and diarrhea and can lead to more complicated issues such as fistulas, ulcers, and polyposis. In rare cases, perforation or obstruction can occur, necessitating the need for surgical intervention.

Diagnosis is typically made by identification of eggs in the stool by microscopy. Serologic assays, radiographs, and endoscopy can also assist in making the diagnosis. Colonoscopy may show erosions and petechial and superficial ulcerations, and tissue biopsy can identify the eggs in the colonic mucosa. The mainstay of treatment is a praziquantel given as a single dose of 40 mg/kg (Table 52-2). Cure rates in excess of 85 % have been described.

Tapeworms

Tapeworms are cestodes or parasitic flatworms. They all have different life histories but typically live in the intestines of the species they infect. The most common tapeworms to infect humans are *Taenia solium* (pork), *Taenia saginata* (beef), *Diphyllobothrium latum*, *Hymenolepis nana*, and *Dipylidium caninum*. Most carriers of taenia are asymptomatic.

Patients with *T. saginata* may feel the motile proglottids passing through the anus. Remarkably, they can grow as long as 55 ft (Figure 52-5). Symptomatic patients complain of vague abdominal pain and cramps, nausea, vomiting, anorexia, and weight loss. Ingesting the eggs of *T. solium* can result in cysticercosis and cause a variety of neurological issues. Diagnosis is made by analyzing the parasite using microscopy or by using ELISA or PCR technology.

Infection with *D. latum* results from eating raw fish. Chronic infection can lead to megaloblastic anemia because the broad tapeworm attaches in the ileum. The worms can sometimes obstruct small ducts and cause cholangitis, pancreatitis, or appendicitis. H. nana has no intermediate host and usually infects humans by ingestion of eggs in areas of poor hygiene. Infection with *D. caninum* occurs when children ingest fleas or lice of pets.

The treatment for all the tapeworms is a single dose of praziquantel 5–10 mg/kg or niclosamide 2 g [68] (Table 52-2). A bowel preparation may be recommended a few hours after treatment to help purge remaining proglottids.

Trypanosoma

Trypanosomiasis (Chagas disease) is caused by *Trypanosoma cruzi*, a flagellate protozoan parasite. It is endemic in Mexico, Latin America, and South America. A triatomine vector known as the reduviid bug infects humans.

There are two clinical manifestations of Chagas disease: acute and chronic. The acute stage follows parasite entry through the skin. Many patients are asymptomatic, but some may show vague signs like malaise, fever, peripheral edema, periorbital edema, hepatosplenomegaly, and lymphadenopathy. After the acute stage, the body enters an indeterminate stage where many stay asymptomatic for life. 10–30 % of patients develop symptomatic chronic Chagas disease, which can lead to cardiomyopathy and megadisease, namely megaesophagus and megacolon [69, 70].

For unclear reasons, the parasite causes destruction of neurons in the lining of the gastrointestinal tract, which leads to dilatation and dysfunction. The sigmoid colon is the most affected segment. Patients usually complain of constipation and abdominal pain from distention. Volvulus and bowel ischemia necessitating surgery can occur in severe cases. Treatment for megacolon is primarily conservative with high fiber diet, laxative, and enemas. Fecalomas requiring disimpaction can be common. All patients with acute and chronic Chagas should be treated medically. The two drugs available are benznidazole and nifurtimox (Table 52-2). Both have significant side effect profiles with gastrointestinal and central nervous system (CNS) toxicities.

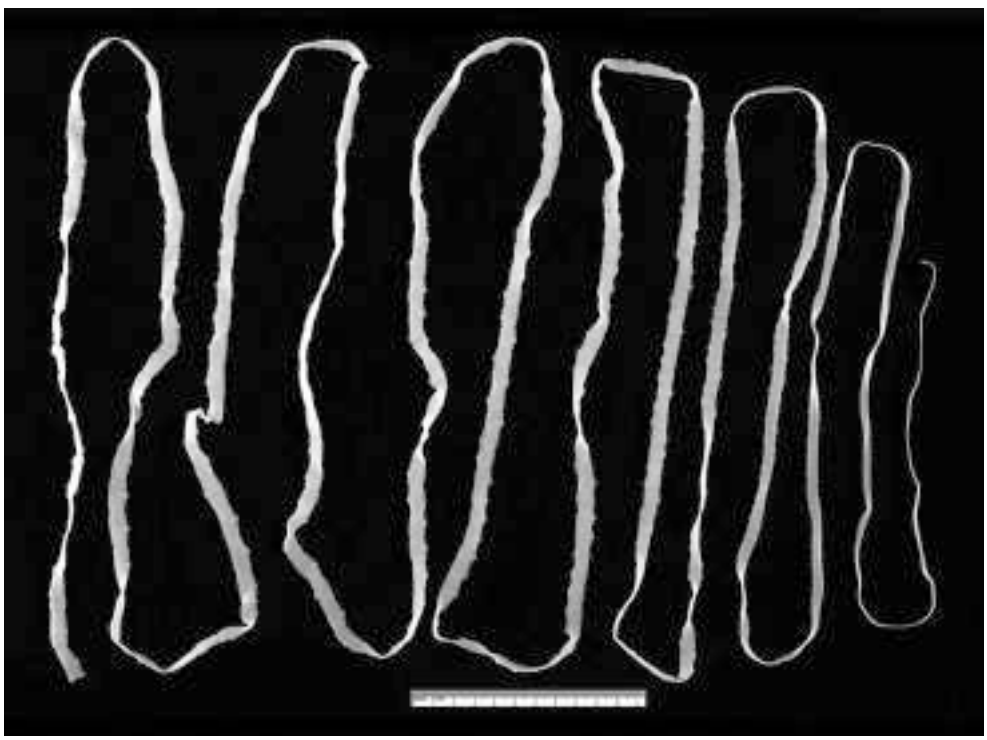

FIGURE 52-5. *Taenia saginata* adult worm measures approximately 4 m in length. These worms may grow to over 50 ft [116]. Available from http://phil.cdc.gov/Phil/details.asp.

Viral Colitides

Cytomegalovirus

Cytomegalovirus (CMV) is a DNA virus and member of the herpes virus family. Prevalence of the virus is quite high with rates approaching 60–70 % in US cities and close to 100 % in various parts of Africa [71]. Most immunocompetent patients with CMV are asymptomatic, whereas immunodeficient hosts can suffer from life-threatening illness.

Similar to other viruses in the herpes family, once primary infection occurs the virus will enter a latent/dormant state. It can be challenging to differentiate between reactivation of latent infection versus primary infection. In immunocompromised patients, CMV can cause devastating illness to organ systems such as the lungs, liver, brain, gastrointestinal (GI) tract, heart, and even skin. Colitis related to CMV is most common in patients with AIDS or inflammatory bowel disease.

Patients can present with ulcers and inflammation in the esophagus and throughout the colon, which can lead to pain, diarrhea, and fever. Severe CMV colitis can cause perforation and gangrene requiring urgent surgical intervention. Diagnosis of CMV is typically made by biopsy of infected tissue. Cells with CMV have "owl's eye" inclusion bodies, which are pathognomonic (Figure 52-6).

Flexible endoscopy is also very useful and can show friability, erythema, and heaped-up tissue resembling a mass (Figure 52-7). PCR assays are available to assist with diagnosis. CMV plays a special role in the ulcerative colitis (UC) patient. Cytomegalovirus reactivation is common in patients with severe colitis, with a reported prevalence of 4.5–16.6 %, and as high as 25 % in patients requiring colectomy for severe colitis [72]. CMV is also a cause of treatment failure in patients with UC. There are four main drugs used in the treatment of CMV: ganciclovir, foscarnet, valacyclovir, and cidofovir.

Other Viruses

Herpes simplex virus (HSV) is also a DNA virus and member of the herpes virus family. There are two main strains, HSV-1 and HSV-2. The prevalence of HSV-2 may be as high as 20 % in the United States and can approach nearly 50 % in countries in South America and Africa.

HSV-2 is the main cause of recurrent genital infections and proctitis. Patients with proctitis can present with anal pain, bloody discharge, tenesmus, bleeding, sacral paresthesias, and difficulty urinating. The majority of the cases of proctitis are in patients who have rectal intercourse [73]. The disease is usually limited to the distal 10 cm of the rectum. Endoscopic features include ulceration and necrosis. Culturing open sores or rectal aspirate can typically make the diagnosis. PCR tests and serum testing for antibodies can also aid in identifying HSV.

There is no cure for herpes, but outbreaks can be controlled with acyclovir 400 mg three times a day for 7–10 days.

Other viruses can cause colitis, but they are usually found in immunocompromised or AIDS patients. Adenovirus can cause a colitis that closely resembles CMV colitis [74]. Other colitis-forming viral pathogens in AIDS patients include human herpesvirus type 6, astrovirus, picobirnavirus, calicivirus, Norwalk, and rotavirus [75].

The 2014 West African outbreak of Ebola has led to a few Americans contracting the disease. Ebola virus is spread by contact with infected bodily fluids from other humans or primates. Within a few days to a few weeks, patients will develop fever, sore throat, muscle aches, and headaches, which is then followed by rash, vomiting, and severe diarrhea. The diarrhea is often voluminous and can lead to hypotension and shock. It is unclear as to whether bacterial toxins or invasion of mucosa causes the diarrhea. Treatment of Ebola is primarily supportive. Antidiarrheal agents may be

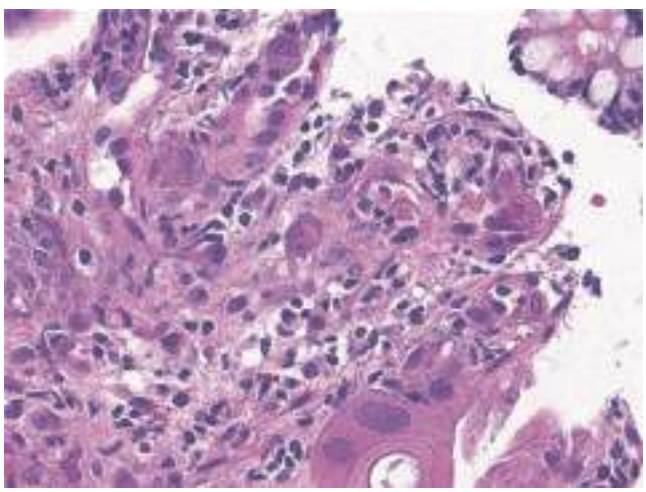

FIGURE 52-6. Cytomegalovirus colitis. Infected cells are enlarged with eosinophilic intranuclear and intracytoplasmic inclusions. (Courtesy of Jeanette R. Burgess, MD).

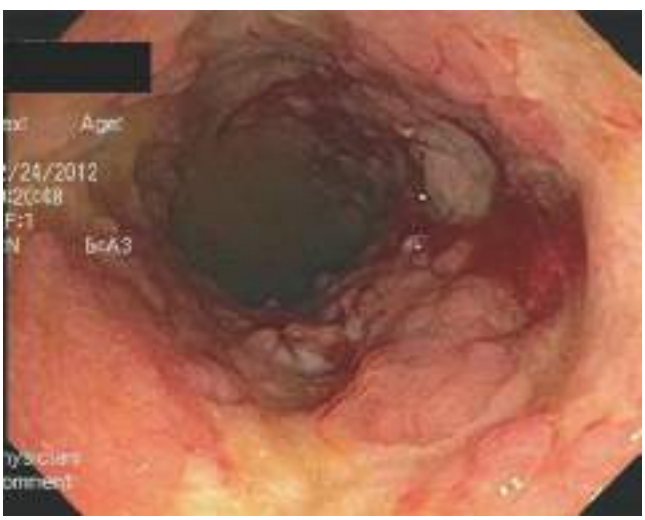

FIGURE 52-7. Endoscopic appearance of CMV colitis in the descending colon.

used, especially in cases with massive GI loss, but close monitoring for distention and other adverse events is mandatory [76].

Fungal Colitides

Histoplasma

Histoplasmosis, caused by *Histoplasma capsulatum*, is endemic in the Ohio and Mississippi river valleys. Though it is most commonly known for causing a pulmonary infection, *Histoplasma* can lead to progressive disseminated histoplasmosis (PDH) causing life-threatening illness in many organ systems, especially in immunocompromised hosts. Gastrointestinal involvement is most common in subacute PDH. Ulcerations of the small and large bowel are present in many cases with the terminal ileum and cecum being the most frequently involved areas. Severe cases may have deep ulcerations with pseudopolyps, which may appear similar to adenocarcinoma or inflammatory bowel disease [77, 78].

Diagnosis is made by tissue culture or tissue histology showing granulomas and yeast within the mucosa. Surgery is reserved for cases of perforation, obstruction, or failure to respond to medical therapy. In many occasions, the diagnosis is not even known preoperatively. The mainstay of medical treatment is intravenous amphotericin B. Itraconazole may be used in mild cases or when amphotericin is not tolerated.

Candida

The *Candida* species are thin-walled yeasts that grow by budding. They are found worldwide and have become a significant cost burden to hospitals and patients. The yeast typically is not pathogenic in patients unless immune systems are diminished. Nearly every organ system in the body can be affected by candidiasis. Candidal infections of the colon are uncommon as only a handful of case series and case reports have been published in the literature [79]. *Candida albicans* is the most common organism. Patients are often very ill with diffuse abdominal pain and diarrhea. Flexible endoscopy may show white curd-like plaques on the mucosa. Visualizing the budding yeast and hyphae with culture or biopsy makes the diagnosis. Treatment depends on the severity of the disease. Fluconazole at varying doses and varying lengths is commonly used. Surgery is reserved in cases of perforation or peritonitis. Mortality is high in this patient population because of the concomitant immunosuppression.

Other Fungi

Aspergillosis, caused by the mold *Aspergillus*, is another fungal infection primarily in the immunocompromised patient [80]. Though the most common clinical manifestation is pulmonary, gastrointestinal-invasive aspergillosis is possible in disseminated cases. These patients present with fever, abdominal pain, tenderness, and bleeding. Bowel resection is required in cases of ischemia and bowel perforation. Demonstration of characteristic hyphae from biopsy specimens or from culture makes the diagnosis. Treatment is with voriconazole and a second-line agent is amphotericin B.

Cryptococcosis, caused by *Cryptococcus neoformans* and *Cryptococcus gattii*, primarily affects the lung and the central nervous system. Risk factors for infection are disease states that cause immunosuppression, such as AIDS, transplantation, steroid use, cancer, and sarcoidosis. Cryptococcus can however affect any organ system in the body. Within the gastrointestinal tract, it can cause colitis and occasional spontaneous perforation. Nodules and ulcers in the stomach and small intestine, which can resemble Crohn's disease, are other manifestations of disseminated Cryptococcus [81]. Diagnosis is made by microscopy of biopsy specimens or culture of bodily fluids. Treatment in severe cases is intravenous amphotericin B.

Special Situations

Traveler's Diarrhea

Travelers to low-income parts of the world frequently have the misfortune of developing acute diarrhea. Disease is characterized by three or more unformed stools in 24 h associated with other gastrointestinal issues, such as abdominal cramping, tenesmus, nausea, vomiting, fever, or urgency of bowel movement.

Incidence of diarrhea has been shown to inversely correlate to the income level of the country visited [82]. Overall rates have declined in the last two decades, but rates remain over 20 % in parts of South Asia and West/Central Africa [83]. Cruise ship passengers and staff are at risk for outbreaks of norovirus, which may be difficult to contain once started.

The average duration of untreated traveler's diarrhea is 4–5 days, with average incapacitation of less than a day. Most travelers are able to continue their activity unaltered [84]. More than 10 % will present with diarrhea after returning home [85]. Traveler's diarrhea is caused by various forms of *Escherichia coli* in more than 50 % of cases. *Campylobacter*, *Shigella*, and *Salmonella* are the other frequent bacterial etiologies [15] (Table 52-3). Parasites tend to cause more prolonged diarrhea, with *Giardia lamblia* and *Entamoeba histolytica* the most common [86].

Campylobacter or *Salmonella* infection may increase the risk of developing inflammatory bowel disease [87], while a number of infectious agents have also been implicated in the development of postinfectious irritable bowel syndrome [88]. Many organisms can cause diarrhea, but bloody diarrhea is typically the result of *Shigella*, *Salmonella*, *E. coli* 0157, *Campylobacter*, and *Entamoeba histolytica* [86].

Table 52-3. Regional differences in etiology of Traveler's diarrhea

Organism	Latin America and Caribbean (%)	Africa (%)	South Asia (%)	Southeast Asia (%)
ETEC	35–70	25–35	15–25	5–15
EAEC	25–35	0–35	15–25	n/a
Campylobacter	1–7	5–25	15–25	25–35
Salmonella	0–15	5–15	<5	5–15
Shigella	5–30	5–15	5–15	<5
Norovirus	15–25	15–25	5–15	<5
Rotavirus	15–25	5–15	5–15	<5
Giardia	<5	<5	5–15	5–15

Data compiled from compilation from: Steffen R, Hill DR, DuPont HL. Traveler's diarrhea a clinical review. JAMA. 2015;313(1):71–80 [83] and Montes M, DuPont HL. Infectious diseases. 2nd ed. Philadelphia: Mosby Elsevier; 2004. Chapter 43, Enteritis, enterocolitis and infectious diarrhea syndromes; p. 477–90 [110]

Laboratory investigation is indicated when the diarrhea is severe, bloody, or prolonged. This should include stool culture and microscopy looking for parasites. Antigen testing is indicated if *Giardia*, *Cryptosporidium*, or *Entamoeba* are suspected. Blood cultures may be useful in the septicemic patient [89].

Prophylactic bismuth subsalicylate has been shown to reduce diarrhea rate by 65 % when given four times daily but due to its salicylate component should be used with caution in patients at risk for bleeding [90]. Rifaximin, which is an antibiotic that is poorly absorbed from the intestinal tract, significantly reduced the incidence of traveler's diarrhea in a meta-analysis of over 500 patients [91]. The use of probiotics has not been shown to be beneficial [83].

Systemic antibiotics reduce the incidence of traveler's diarrhea by more than 90 %, with fluoroquinolones most frequently used. Concerns about adverse reactions and bacterial resistance make antibiotic prophylaxis controversial, and prophylaxis is not currently recommended for most travelers. High-risk patients may benefit from prophylaxis and include patients with a history of stroke, insulin-dependent diabetes mellitus, chronic renal failure, and inflammatory bowel disease as well as patients with ileostomies or colostomies [83].

Self-treatment in the event of illness should include oral hydration, treatment with loperamide, and a 1–3 day course of a fluoroquinolone. In countries with known antibiotic resistance, azithromycin may be substituted [92].

Infections in Inflammatory Bowel Disease

Infectious complications are a major concern in patients with inflammatory bowel disease (IBD). Numerous pathogens can play a role in enteric infections, including *Clostridium difficile*, *Salmonella*, *Shigella*, *Campylobacter*, *Escherichia coli*, cytomegalovirus, and *Entamoeba histolytica*.

Mylonaki et al. found that about 10 % of relapses were caused by infections, with more than half of those attributed to *Clostridium difficile* [93]. Another report found that up to 20 % of patients with IBD flare-ups had positive stool ELISA testing for *Clostridium difficile* [94]. This mirrors the increased incidence found in numerous studies of overall *Clostridium difficile* infection (CDI). These infections increase risk of hospitalization as well as colectomy in patients with inflammatory bowel disease [95].

Clostridium difficile in IBD may be atypical, with bloody stools and younger patient age. CDI should be considered in the absence of diarrhea in patients with constitutional symptoms and leukocytosis. Small bowel disease (CDI) may occur after colectomy in IBD patients [96].

Medications used to treat inflammatory bowel disease are all associated with infections. Purine antimetabolites predispose to infections by some of the herpes viruses, with cytomegalovirus a major cause of colitis. Immunosuppression with corticosteroids increases the risk of Candidal infections, which can affect the bowels. TNF antagonists increase risk of granulomatous infections, such as extrapulmonary tuberculosis [97].

CMV infection is very prevalent in patients with inflammatory disease, with numbers as high as 33 %. Many of these patients are "innocent bystanders," and the diagnosis of active CMV disease can be challenging. CMV colitis can clearly complicate IBD colitis and should strongly be considered in steroid-resistant cases [98].

Several bacterial agents have also been postulated as infectious causes of inflammatory bowel disease. These include *Mycobacterium avium paratuberculosis*, non-pylori Helicobacter, *Escherichia coli* (EIEC), and *Campylobacter concisus* [99].

Diarrhea and HIV

The human immunodeficiency virus (HIV) targets CD4+ T-lymphocytes, a major player in the immune defense system in the human body. A large concentration of CD4+ cells are found on the gut mucosal lining, so it is no surprise that infection with HIV can cause a plethora of gastrointestinal complaints [100].

Nearly all patients infected with HIV develop some sort of gastrointestinal complication [101]. Colitis can produce symptoms such as abdominal pain, tenesmus, and urgency.

TABLE 52-4. Pathogens causing enterocolitis in HIV patients

Bacteria
Campylobacter jejuni
Salmonella
Shigella flexneri
Aeromonas hydrophila
Plesiomonas shigelloides
Yersinia enterocolitica
Vibrio
Mycobacterium avium complex
Escherichia coli (enterotoxigenic, enteroadherent)
Bacterial overgrowth
Clostridium difficile
Parasites
Cryptosporidium parvum
Microsporidia
Cystoisospora belli
Entamoeba histolytica
Giardia lamblia
Cyclospora cayetanensis
Viruses
Cytomegalovirus
Adenovirus
Calicivirus
Astrovirus
Picobirnavirus
Human immunodeficiency virus
Fungi
Histoplasma capsulatum

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The list of pathogens that can cause colitis is extensive and includes bacteria, viruses, and parasites (Table 52-4). Though opportunistic infections are the most common cause of diarrhea, many noninfectious etiologies exist as well.

Workup of diarrhea in an HIV-infected patient begins with assessment of the disease itself: i.e., CD4 count and HIV viral load. Other tests include stool microscopy for ova, cysts, and parasites, bacterial culture, *Clostridium difficile* toxin, and PCR testing for parasites and viruses. Colonoscopy allows for visualization and biopsy of the colonic and terminal ileum mucosa for histologic analysis and CMV PCR. Not all cases require flexible endoscopy, but in culture-negative patients, endoscopy can help make the diagnosis in 50 % of cases [102, 103].

Cross-sectional imaging, such as CT scan, antegrade barium studies, and tuberculosis testing are other options when no diagnosis has been made. An algorithm for evaluating patients with HIV-associated diarrhea is shown in Figure 52-8.

Like diarrhea from other causes, treatment is initially geared at resuscitation and rehydration. Pathogen-specific treatment should be initiated as soon as identification is made. Antiretroviral therapy (ART) will drastically reduce viral load allowing for CD4 count to rise. ART assists in the resolution of opportunistic infections and decreases future chance of infection [104]. Anti-motility agents such as loperamide and diphenoxylate can help curtail symptoms in cases where workup has been negative and ART has been unsuccessful. Octreotide may be used in refractory cases of HIV enteropathy with limited benefit [105].

Diarrhea and Solid Organ Transplantation

Due to the high levels of immunosuppression needed to prevent graft rejection, solid organ transplantation patients are also at higher risk for infectious gastrointestinal complications. Estimates of diarrhea in this population range from 22 to 52 % [106, 107]. Infectious etiologies are the most common cause of diarrhea in solid organ transplant patients, whereas graft versus host disease (GVHD) is the most common cause of diarrhea in stem cell transplant patients.

Cytomegalovirus (CMV) and *Clostridium difficile* are the two most common culprits [108]. Workup typically starts with stool culture, *Clostridium difficile* toxin assay, and blood CMV viral load. Colonoscopy can be useful as a second-line test. Other tests include fecal leukocytes, ova and parasites, isospora and cyclospora assays, *Cryptosporidium* antigen screen, and norovirus PCR.

Echenique et al. reported their experience of 422 admissions for diarrhea over an 18-month period. The majority of the cases had no identifiable etiology and were self-limited. *Clostridium difficile*, norovirus, and cytomegalovirus were the most common identified agents. Other bacterial and parasitic causes were very rare [109]. Treatment of the diarrhea is geared to the identified agent. Modifications of immunosuppression dosages and regimens may be required.

Evaluation of Patient with Infectious Diarrhea

Evaluation of the patient with acute diarrhea should include a careful history of possible exposures (family members, foods) and travel history. Stool culture is probably not indicated in patients who are not hospitalized and who have mild to moderate diarrhea. Patients with severe diarrhea, persistent diarrhea, weight loss, extremes of age, or immunodeficiency issues should have more thorough testing.

Microscopic evaluation of fecal smears can be easily accomplished. Polymorphonuclear leukocytes may suggest an invasive or inflammatory pathogen, while mononuclear leukocytes may be seen with typhoid fever or amebic dysentery. Many organisms produce fecal leukocytes, so a positive test is an indication for stool cultures and empiric antibiotic treatment.

Parasitic evaluation is indicated for patients with diarrhea lasting longer than 2 weeks, as well as patients in a day care setting, male homosexuals, or HIV-infected patients (Figure 52-8). Special stains are indicated in immunocompromised patients, looking for cryptosporidia or microsporidia. ELISA evaluation can directly detect *Isospora*, *Giardia*, *Cryptosporidium*, and *Entamoeba* [110].

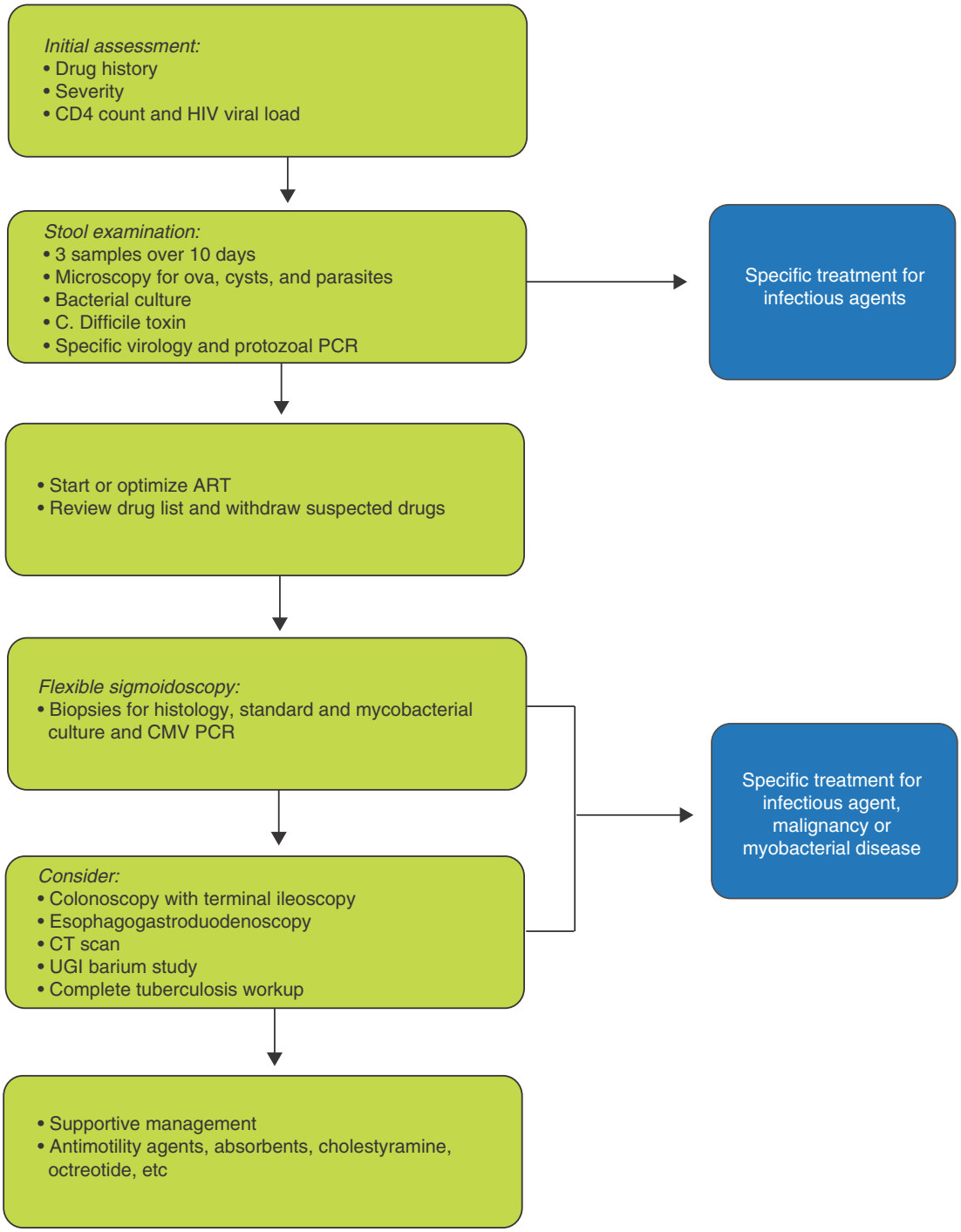

FIGURE 52-8. Algorithm showing the management approach to the HIV patient with diarrhea. With permission from Feasey NA, Healey P, Gordon MA. Review article: the aetiology, investigation and management of diarrhoea in the HIV-positive patient. Alimt Pharm There. 2011; 34(6): 587–603 [100]. © John Wiley and Sons.

Salmonella, *Shigella*, and *Campylobacter* are the most frequently discovered pathogens on stool culture, especially in patients with bloody diarrhea [111]. *Vibrio* testing should be done with a history of travel to coastal areas or a history of seafood ingestion. Special agars may be needed to isolate *E. coli* O157:H7. The laboratory may need to be notified to culture if unusual agents, such as *Yersinia* or *Aeromonas*, should be considered. *Clostridium difficile* testing should be done in patients with a history of prior antibiotic use.

Proctosigmoidoscopy is useful in patients with bloody diarrhea, prior antibiotic use, history of anal manipulation, or an immunocompromised status. Higher risk patients may also benefit from colonoscopy or gastroduodenoscopy with biopsies, looking for CMV inclusions, fungi, or acid-fast bacilli. Viral cultures may also be useful in these patients. Endoscopy can help to exclude other causes of noninfectious diarrhea, such as inflammatory bowel disease or ischemic colitis [112].

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Clostridium difficile Infection

David B. Stewart Sr.

Key Concepts

- The incidence and severity of *C. difficile* infection is increasing worldwide.
- Testing for *C. difficile* infection has transitioned to the more sensitive nucleic acid amplification tests (NAATs).
- Exposure to healthcare facilities, prior antibiotic therapy, and proton pump inhibitor use are common risk factors for infection.
- The preponderance of studies suggests that infection with ribotype 027 is associated with worse disease outcomes.
- The mainstay of CDI therapy is resuscitation and treatment with metronidazole and/or vancomycin.
- Fecal microbiota transplant is a promising emerging therapy.
- Surgery can be avoided in most patients but should be considered in cases of continued clinical deterioration despite maximal medical therapy.

Introduction

During the previous 20 years, *Clostridium difficile* infection (CDI) has transitioned from being a relatively uncommon diarrheal illness principally limited to patients rendered immunocompromised from cancer treatment or HIV to a billion dollar per year hospital-acquired infection with a diverse at-risk patient spectrum. Since this epidemiological shift has placed every inpatient at higher relative risk for developing CDI, and considering the potential for this infection to reach a severity requiring surgical intervention as a last resort, a knowledge of *Clostridium difficile* is important for the general and colorectal surgeon. This chapter reviews the epidemiological changes that have surrounded CDI during the previous two decades, as well as touching upon the key microbiological features of this bacterium that promote CDI and which account for its symptoms. A review of the clinical science directing the proper use of antibiotics against *C. difficile* is provided, as is a discussion of surgical treatment options as well as fecal microbiota transplantats (FMT) as an emerging alternative to conventional medical and surgical therapies.

Epidemiology

Rising Incidence and Increasing Severity

During the previous two decades, and particularly within the previous 15 years, there has been a population level increase in the incidence of CDI both in the United States and in Western Europe [1–3]. Due to greater government funding in European countries, a larger volume of epidemiologic studies and those with the greatest detail related to prevalent strains (ribotypes) of *C. difficile* [4] have come from Europe. The trends observed in those regions, however, mirror changes in CDI observed in the United States, and this parity between these regional studies provides a similar conclusion when the data is summarized. *C. difficile* is the predominant form of antibiotic-associated diarrheal illnesses in acute care facilities, and it is reliably estimated to be the causal microbe in at least 15–25 % of such cases [5]. During the previous century, a precipitous increase in the incidence of CDI has been documented; in a study from Quebec evaluating patients from 1991 to 2003, Pepin and colleagues [6] documented a population-level increase of CDI approaching fivefold, while those defined as elderly (≥65 years of age) experienced an approximately eightfold increase in CDI incidence. In the United States, the most recent data from the Agency for Healthcare Research and Quality reported [7] that in 2009 there were 336,600 hospitalizations which involved CDI either as a primary or a secondary diagnosis, a number comprising 1 % of all hospitalizations in the United States during that year. Likewise, the Centers for Disease Control (CDC) reported that between 1993 and 2009, hospital stays effected by CDI increased fourfold, while rates for persons ≥65 years of age increased by 200 % [8, 9]. Similar trends of increasing

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incidence have been reported [10] in European countries such as France and Belgium, especially during periods of so-called outbreaks, with patients of advanced age being disproportionately affected. The impact of this rising incidence on healthcare costs translates into an over 3 billion dollar annual burden to the US healthcare system, when costs from inpatient and outpatient treatments are both included. [11] While there is a consensus that studies such as these have documented a veridical shift in disease prevalence, recent data from the CDC has documented stability in the incidence of CDI in the United States from 2010 to 2011 [9, 12]. Though this data encompasses a very short time period in epidemiological terms, it is useful in so far as it allows for standardization of disease incidence on the basis of the type of *C. difficile* testing being used. This is a subtle but important factor, since many hospitals transitioned their method of CDI testing from enzyme immunoassay (EIA) platforms to the more sensitive nucleic acid amplification tests (NAATs). This change in testing protocol could, arguably, have artificially increased the reported incidence of CDI apart from an actual change in disease incidence. The effect exerted by the type of CDI testing on reported incidences has been described elsewhere [13], though as more hospitals in the US have adopted NAAT testing protocols, the effect of testing platforms on future reports of CDI incidence will likely be lessened.

Of even greater concern than a rising incidence of CDI, however, were reports from multiple regions of an increase in severity associated with this infection. In 2005, there were several published reports of epidemical outbreaks of *Clostridium difficile* associated with two previously underreported observations: higher mortality rates overall, and higher mortality among patients not previously considered to be at risk for CDI, let alone fulminant forms of this disease. Loo and colleagues [14] described the results of a prospective study conducted at 12 hospitals in Quebec in an effort to accurately describe the incidence and risk factors for CDI. After reviewing the care of 1703 CDI patients, the incidence of CDI was estimated to be 22.5 per 1000 hospital admissions. The 30-day mortality attributable to CDI was calculated to be a robust 6.9 %, and the use of quinolone and cephalosporin antibiotics was associated with development of the infection. This study provided details on specific isolates using pulsed field gel electrophoresis (PFGE) and other molecular techniques in order to identify the presence or absence of toxin genes as well as toxin regulatory genes. Warny *et al*. extended these findings, [15] with an analysis of *C. difficile* isolates from 124 separate patients from Quebec and other Canadian regions, the United States, and the United Kingdom. Using standard PFGE and restriction fragment length polymorphism fingerprinting, the predominant strain in the Warny study was confirmed to be what is now referred to as ribotype 027. Both the Warny and Loo studies demonstrated *C. difficile* ribotype 027 was not only associated with the production of both toxins A and B, as well as a third toxin now referred to as binary toxin, but that it was also associated with >15 times the volume of toxin A and B production than the other ribotypes evaluated. In the Loo study, identification of one of several forms of gene deletions occurring at a putative toxin inhibitory gene was also described as a potential causal factor for increased toxin production. These two studies produced some of the first data that provided clinically relevant information regarding the incidence of CDI at the institutional and regional level, helping to establish a relationship between antibiotic use and CDI, and providing a plausible explanation for outbreaks based upon genetic characteristics clustered within one potentially epidemical ribotype of *C. difficile*.

Two additional studies from the same time period further emphasized the relationship between CDI and fluoroquinolone antibiotics. In a retrospective case–control study from Pittsburgh, Muto *et al*. [16] described the results of an institutional outbreak where, during a 2-year period, there were 253 cases of CDI associated with admission to a healthcare facility, of which 26 required emergent colectomy and 18 died of disease-related complications. Odds of CDI were associated with clindamycin (OR = 4.8), ceftriaxone (OR = 5.4), and levofloxacin (OR = 2.0), with each of these agents serving as independent risk factors. There was a particularly strong association between the use of fluoroquinolones and outbreaks of CDI, and one of the two clonal lines associated with such outbreaks was suspicious for ribotype 027. Similarly, McDonald and colleagues [17] reviewed 187 clinical *C. difficile* isolates obtained from eight US healthcare facilities located in the Northeast, the Southeast, and the West, performing PFGE, toxinotyping, and restriction endonuclease analysis (REA), as well as using PCR to evaluate the presence of toxin genes and their regulatory genes, all in an effort to characterize the predominant clonal line of *C. difficile*. When comparing newer isolates to a historical tissue bank of earlier *C. difficile* isolates, a significant increase in the incidence of ribotype 027 was observed, as was a more frequent occurrence of resistance to certain quinolone antibiotics. Further, the frequent presence of the genes for toxins A and B and binary toxin, and a predilection for large deletions in genes (such as *tcdC*) whose function may include suppression of toxin production, provided evidence of the emergence of a type of *C. difficile* with molecular characteristics which would explain its frequent associations with epidemical forms of severe CDI.

To summarize, there is evidence from North America and Western Europe that the incidence of CDI has increased during the previous century and that this increase in incidence accelerated during the previous two decades. Though simultaneous improvements in the rapidity and sensitivity of *C. difficile* testing contributed to changes in incidence due to greater detection rates, this alone does not discount descriptions of a legitimate increase in disease frequency. The emergence of at least one ribotype of *C. difficile* (ribotype 027) during outbreaks of severe disease provides further evidence of a change in CDI in healthcare facilities, and certain genetic

characteristics of this ribotype suggest that this strain of bacterium may have certain selective advantages toward epidemical forms of the infection.

Clinical Risk Factors for CDI

The literature is replete with long lists of clinical factors identified as being frequently associated with the development of CDI. In many cases, these risk factors are not causally related to CDI in an independent manner, and in most cases the one commonality which they share is frequent contact with acute or chronic healthcare facilities.

A distinction must first be made between healthcare facility-acquired CDI, and the rarer form of the disease, community-acquired CDI (CA-CDI). A generally accepted definition for CA-CDI centers on an onset of disease at least 12 weeks after any personal contact with a healthcare facility [18]. While this is a reasonable definition, it does leave open the possibility that a patient labeled as having CA-CDI may have contracted *C. difficile* while in contact with a facility, and for various reasons, they developed symptoms of the illness in a latent fashion. Therefore, what should be called a case of truly community-acquired CDI would be a distinct entity, and a rarer one, compared to the more common healthcare facility acquired, community-onset CDI. Since CA-CDI is an uncommon manifestation of CDI, and since CDI is not a reportable disease in the United States and other countries, the limited surveillance and incidence data obscure an accurate measurement of the incidence of CA-CDI. The CDC [19] published data in 2005 suggesting that in the United States the incidence of CA-CDI was 7.7 cases per 100,000 persons annually. In this report, approximately 35 % of patients had not received antibiotics within 40 days of developing symptoms of CDI. In a more recent study from 2014, Collins *et al.* [20] reviewed a 5 % random sample of Medicare beneficiaries, totaling more than 860,000 subjects. This study estimated that the incidence of CA-CDI was only 0.18 % of the study population, with approximately 57 % of the CA-CDI cohort having received oral antibiotics within 90 days of the onset of symptoms. In this study, 14 % of CA-CDI patients required an ICU admission, while only 1 % required surgery due to CDI. In-hospital mortality was surprisingly high at 9 %. While it is possible that an at-risk person could contract *C. difficile* from the environment (soil, water, food or animals) [21–23], a study by Chitnis and colleagues [24] reported that of 984 patients with CA-CDI, only 35.9 % did not receive antecedent antibiotics and only 18 % had no contact with healthcare facilities. Those patients with no preceding contact with healthcare facilities who developed CA-CDI had exposure either to infants younger than 1 year of age (thus, children who had been in previous contact with a healthcare facility) or exposure to household members with CDI. The data currently available suggests that CA-CDI is probably not a disease with a distinct pathophysiology as compared to healthcare-acquired, healthcare-onset CDI. This is an important point considering that many of the described community-acquired cases developed in persons with some direct contact with healthcare centers, with contact with patients who themselves had recently used antibiotics, and in scenarios involving contact with individuals who harbored these two risk factors. The development of CDI in a person without recent contact with a facility, a hospital patient or a CDI patient, and all without antecedent antibiotic use, is likely a very uncommon phenomenon.

For the remainder of the chapter, unless otherwise specified, CDI will refer to healthcare facility-acquired, healthcare facility-onset CDI.

Advanced Age

Advanced age is one of the most frequently cited risk factors for CDI [25–27]. While it is possible that elderly individuals may have changes to their gut microbiome, or to their gut immunity, that predispose them to develop CDI, the current evidence indicates that age primarily serves as a risk factor by its association with many other risk factors which themselves are more directly responsible for the development of CDI.

Contact with a Healthcare Facility

Both acute care and long-term care settings pose a risk for CDI due to higher populations of at-risk persons, with the convergence of other additional risk factors. The risk posed by residence in a care facility may increase in magnitude [28] with longer durations of stay in such settings. Since the primary mode of disease transmission in care settings is person to person through a fecal–oral transmission route, it is not surprising that with increased potential exposure to the organism, the estimated prevalence of asymptomatic colonization of adult patients admitted to an acute care setting ranges from 7 to 26 % [29] and may be as high as 5–7 % among elderly subjects in subacute or long-term care facilities [30]. Considering that these studies are older, it is likely that these percentages would be higher if these studies were repeated in the present day, especially if such studies included patients cared for during outbreaks of selectively advantaged types of *C. difficile*.

Use of Antibiotics and Their Effect on the Microbiome

The most important, and the most modifiable, of all risk factors for CDI revolve around the use of antibiotics. The manner in which antibiotics effect the development of CDI, however, is much more complex than previously recognized.

There is ample evidence that antibiotics, of any class, increase the risk of CDI and that this risk increases with the number of agents and with their length of use. In one of the best studies to date to describe the risk relationship between non-*difficile* directed antibiotics and CDI, Stevens and colleagues [31] performed a 1-year retrospective study of 7792 patients, of whom 241 developed CDI. There were both dose-dependent relationships, as well as cumulative dose associations, between the use of antibiotics and the development of CDI; the number of antibiotics, and the number of days of their use, also increased the risk of CDI. When using the cohort with one non-*difficile* directed antibiotic as a reference group, the use of five such agents was associated with a hazards ratio for the development of CDI of 9.6. The use of fluoroquinolones was noted to be an independent risk factor for CDI in this study, an observation which has been described elsewhere [32].

Particular antibiotics may increase the risk of CDI to a greater degree than other agents. Whether this is due more to the effect of the antibiotics on commensal flora, or the effect of these antibiotics on *C. difficile* itself, or perhaps a combination of the two, is uncertain. In a recent systematic review, Slimings and Riley [33] reviewed 13 case–control studies as well as one cohort study. Of the antibiotic classes analyzed, second-, third-, and fourth-generation cephalosporins (OR = 2.23–3.2), clindamycin (OR = 2.8), and fluoroquinolones (OR = 1.6) were associated with higher odds of developing CDI. Though this review was limited due to the heterogeneity of the individual studies meta-analyzed, it provides an updated estimate of the relative risk accrued by classes of antibiotic agents.

One of the emerging concepts in digestive disease states is that the human gut contains myriad host-associated microbial communities which vary not only between different regions of the alimentary tract, but which vary depending on the health and disease states of their human host. Though the causal mechanisms are not well understood, in part due to the high degree of statistical "noise" inherent to most microbiome studies, changes in gut microbial communities may not only reflect a host disease state, but rather, these gut microbial changes may actually *direct* host disease states. Host-associated microbial communities maintain a degree of integrity within the larger environment of the microbiome, and they are able through unknown means to influence, or "communicate with," other microbial communities within the same human host. These microbial communities include more than simply bacteria, although it is the bacterial component of the microbiome that has received the most attention, and it may be this component, more than any other, which in a normal state confers resistance to bacterial pathogens such as *C. difficile* [34]. Specifically how the microbiome confers resistance to CDI is not understood at the individual bacterial level, because the current data is largely descriptive and inferential rather than establishing causal relationships. However, several broad concepts have been repeatedly observed and are worth noting. The primary difference between healthy and unhealthy gut environments is a matter of microbial population density and diversity. Based upon 16S rRNA sequencing, high microbial counts (greater than 10^{12} bacteria/gram of feces) with a high degree of bacterial species diversity, and with the possible predominance of two or more particular phyla (such as those including *Firmicutes*, *Bacteroides*, and *Acinetobacter*) are factors associated with a relative resistance to CDI [35–37]. Rather than there being one or only several combinations of bacteria which help to prevent CDI, most studies have identified *Bacteroides* spp., *Bifidobacteriae*, and *Lachnospiraceae* with other combinations of microbes as being the most effective at preventing colonization with *C. difficile* [35, 38]. This suggests that the issue of maintaining gut health is one of bacterial diversity in great enough numbers, with a lesser emphasis on particular combinations of taxa. While antibiotics do, in fact, reduce microbiota diversity and density through their indiscriminate killing of bacteria, their effect on the development of CDI may be even more important through the mediatory effect of bile salts in the gut. For example, in vitro studies have demonstrated differential effects on *C. difficile* spores by conjugated and deconjugated forms of cholate and chenodeoxycholate, with the latter inhibiting spore germination at ten-fold lower concentrations than the former [39, 40]. Under healthy conditions, therefore, chenodeoxycholate suppresses *C. difficile* growth arising from vegetative forms of the bacterium. It is also known that cholate and chenodeoxycholate are metabolized into the secondary bile acids deoxycholate and lithocholate, respectively. Deoxycholate stimulates *C. difficile* germination, while lithocholate inhibits this process; interestingly, deoxycholate is also lethal to vegetative forms of *C. difficile*. Studies in rodents have demonstrated that antibiotics change the proportion of bile salts present in the colon, increasing cholate concentrations, which may result in greater germination of *C. difficile* spores, with a concomitant decrease in deoxycholate and its inhibition on *C. difficile* growth. This effect from antibiotics may be more important than the provincial concepts that these drugs decrease competition for nutrients and quorum-based inhibitions in colony growth, though no doubt these are also mechanisms by which antibiotics promote CDI.

Perioperative Prophylactic Antibiotics and Mechanical Bowel Preparations

In keeping with the previous discussion regarding alterations in background bacterial populations and the development of CDI, questions have been raised regarding whether perioperative prophylactic antibiotics and/or a mechanical bowel preparation increase the risk of CDI. Since these two measures are often used together, if each were to represent an

independent risk for CDI, then their combination may pose even greater odds of developing the infection. Despite the controversy among surgeons regarding the need for bowel preparations prior to elective colorectal surgery, there is fairly convincing evidence that mechanical bowel preparations do not significantly elevate the risk of CDI. In a retrospective review of data from multiple hospitals in the state of Michigan, Morris and colleagues [41] reviewed the care of 2263 colectomy patients, of whom 1685 received a mechanical bowel preparation. A mere 54 patients within the study population developed CDI, and neither the use of a bowel preparation nor the use of preoperative oral antibiotics were associated with CDI. In a more recent study, Kim *et al*. [42] reviewed the same statewide database as Morris and colleagues, using propensity score matching to compare 957 paired cases of patients undergoing colectomy who either did or did not receive an oral laxative with oral preoperative antibiotics. Those who received a bowel preparation were actually found to have a lower incidence of CDI, though the absolute magnitude of this difference was small (0.5 % versus 1.8 %; $p=0.01$).

The effect that prophylactic parenteral antibiotics have on the incidence of CDI is much more difficult to study precisely, in large part due to the admixture of patients who are undergoing their first surgery and who have had limited preoperative contact with healthcare facilities, who are then compared alongside those patients with previous surgeries and relatively recent hospitalizations. It is this latter group of patients who are more at risk for developing CDI even after a single dose of prophylactic antibiotics due to their status as an asymptomatic carrier. The incidence of asymptomatic carriage decreases during the life of healthy subjects from 40 to 60 % in the neonatal period to as low as 2–4 % in healthy adults who are not frequently in contact with hospitals [43]. The rates of asymptomatic carriage are also higher in particular disease groups, such as those with inflammatory bowel disease (see below). No studies to date have properly segregated patients by disease category and history of exposure to healthcare facilities in order to provide a credible estimate of risk. In a study from 2002 which analyzed 157 CDI patients, Morris [44] and colleagues noted that 9.5 % of all CDI patients received prophylactic perioperative antibiotics as the only discernible risk factor; this study was small, with relatively few CDI patients for the 6-year time frame encompassing patient inclusion, and therefore further studies would be required to gauge the scope of the problem. What is clear is that, though infrequent, a single dose of antibiotics can potentially lead to CDI, and even more rarely, to life-threatening forms [45] of CDI. While this is not sufficient grounds alone to forego prophylactic antibiotics prior to abdominal surgery, given the clear benefit they provide in other areas of surgical outcomes, these observations underscore the need to de-escalate and discontinue antibiotics as soon as possible.

Immunocompromised States

There is a clear association between a compromise to the immune system, whether from HIV or from cancer, and the development of CDI. Studies have not precisely distinguished the association between immunosuppression causing CDI directly and immunosuppression requiring hospital care and thus leading to the convergence of other risk factors, such that immunosuppression is only circumstantially associated with CDI. The actual state of affairs probably incorporates both of these aspects. In a recent study by Gebo, [46] the relative risk for HIV patients developing CDI was twice that previously described, with an estimated 8.3 cases per 1000 patient years. Based on a multivariate analysis, a CD4 count of ≤50 cells/μL was an independent risk factor for developing CDI, with an adjusted odds ratio of 27.6. The absence of normal cellular immunity is also a likely role in patients with cancer who develop CDI, being especially common among those with hematologic malignancies [47] who require bone marrow transplantation.

Inflammatory Bowel Disease (IBD)

CDI is associated with both ulcerative colitis (UC) and Crohn's disease (CD); [48] there is no consensus as to whether one phenotype of IBD is more likely to promote CDI. Though the current data on IBD patients is heavily skewed toward those patients seeking medical care due to an exacerbation of their disease, the most recent population level and institutional studies estimate that the incidence of CDI in this group of IBD subjects ranges [48, 49] from 6 to 20 %. IBD populations may harbor an innate immune dysregulation, [50] which may lead to a chronic dysbiosis; [51] this, in concert with their more frequent need for hospitalizations and antibiotics, as well as the frequent use of immunosuppressive medications as medical therapy for IBD, produces a merging of host and environmental factors promoting CDI in IBD patients. With respect to IBD medical therapy, the data demonstrating risk for CDI is somewhat limited. At least one study [52] from 2009 reviewed 10,662 IBD patients, estimating that the use of infliximab was not associated with higher odds of CDI; corticosteroids, however, were associated with a threefold increased relative risk of CDI. There is also limited evidence [53] that the combination of *difficile*-directed antibiotics in the setting of ongoing immunomodulator therapy is associated with poorer outcomes (such as higher odds of death or colectomy within 3 months of admission) though the risk for developing CDI imposed by immunomodulators is unclear.

The development of CDI in the setting of a flare of IBD symptoms is associated with a higher rate of surgery, with one study estimating a sixfold [54] higher increase toward needing intestinal surgery. The incidence of recurrent CDI

is also higher in IBD patients, [55] and mortality rates for CDI in IBD patients may be higher than for CDI patients alone [56].

Proton Pump Inhibitors

The use of proton pump inhibitors (PPIs) is extremely common among hospitalized patients; their actual need probably falls far below their actual use, and it may be the case that these drugs are ordered almost by habit, especially since they are mistakenly viewed as being relatively harmless. The release [57] of a statement by the Food and Drug Administration warning of the association between PPIs and CDI has promoted a reevaluation of the proper role of acid-suppressing medications among inpatients, especially among those patients who are not experiencing reflux symptoms, and for those patients who are not critically ill but who are being given PPI therapy for "prophylaxis" or other more questionable indications. The means by which PPIs promote CDI is usually suggested to involve a fecal–oral route of transmission, with the concept being that an alkalinized stomach might allow for a greater number of ingested *C. difficile* (both active and spore forms) to survive the gastric environment, reaching the colon in a viable state to then go on to create an infection if other factors are also present. It should be noted that while this model has a certain conceptual appeal, it is far from established beyond reasonable doubt, especially when considering that gastric acid does not reliably eradicate *C. difficile* spores. PPIs (and H2 blockers) may have other mechanisms by which they promote CDI. One recent in vitro study [58] by Stewart and colleagues demonstrated that omeprazole actually stimulated the expression of *C. difficile* toxin genes and that this effect was present in both basic and acidic ambient conditions. In addition to a direct effect on *C. difficile*, PPIs may affect the other bacterial members [59] of the microbial community by decreasing diversity, with one recent study suggesting that these drugs reversibly decrease operational taxonomic unit counts for up to 1 month after exposure. There may also be off-target effects of PPIs on colonocytes themselves; Hegarty and colleagues [60] performed in vitro testing using PPIs and T84 cells (a human colon cancer line); PPIs resulted in alterations to gene expression in colonocytes associated with changes involving cell-to-cell junctions, toxin susceptibility and bile acid transport.

Though the majority of individual studies show an association between PPIs and CDI, the number of meta-analyses is far smaller, and these systematic reviews have provided contradictory evidence in favor of [61], as well as against [62], such an association. The weight of the current evidence lies in favor of PPIs placing patients at risk for CDI, though the issue is far from settled, and the degree of influence independently exerted by PPIs may be small.

Hospital Environmental Factors

Hand hygiene is effective at preventing the transmission of *C. difficile* (both spores and active bacteria) in acute and subacute care settings; [63, 64] there is a preponderance of evidence that soap and water is better at removing spores from hands than alcohol-based cleansers [65]. Isolation techniques for patients with CDI, [66] including dedicated toilets and terminal cleaning programs, [67] can decrease institutional CDI rates.

Microbiological Considerations for *Clostridium difficile*

Pathogenicity Locus Genes

Clostridium difficile is a variably motile, Gram-positive, obligate anaerobe which derives its latter name from "difficulties" isolating this organism in culture in previous eras. With modern anaerobic techniques, culturing *C. difficile* is no longer a significant challenge. That portion of *C. difficile*'s genome most responsible for human disease is referred to as the Pathogenicity locus (PaLoc) [68], which is most commonly a 19.6 kb island of genes (Figure 53-1) that encodes for toxins A (*tcdA*) and B (*tcdB*). Some ribotypes of *C. difficile* also produce another toxin referred to as binary toxin, whose genes (*CDT*) and their regulators are located outside the PaLoc.

The three most commonly discussed regulatory genes within the PaLoc are *tcdR*, *tcdC*, and *tcdD*. *tcdC* is important for the clinician to be familiar with since it is occasionally cited as a risk factor for severe forms of disease, being frequently found in a variant form in *C. difficile* associated with outbreaks. The *tcdR* gene produces proteins which are structurally and functionally similar to bacterial sigma factors, [69] a large family of RNA polymerase transcriptional factors which are vital both for transcription of *tcdA* and *tcdB* as well as for promoting the transcription of *tcdR* itself [68–71]. Ambient factors are known to increase the expression of *tcdR*, such as antibiotics, nutrient and carbon sources, pH and temperature changes, [71] and *tcdR* in turn increases the transcription of the entire PaLoc except for *tcdC*. This inverse pattern of gene transcription was one of the first suggestions that perhaps *tcdC* had a putative negative regulatory function [71]. It is now known that the protein produced by *tcdC* is a membrane-bound acidic protein [72] which in its active form exists as a homodimer. In vitro studies have demonstrated that the product of *tcdC* prevents the product of *tcdR* from directing RNA polymerase to the promoter for *tcdA*, sequestering *tcdR* products in a manner similar to anti-sigma factors studied in other bacteria.

Reports of outbreaks associated with *tcdC* variants have been published, with the suggestion that a truncated *tcdC* protein product may not effectively inhibit *tcdA* transcrip-

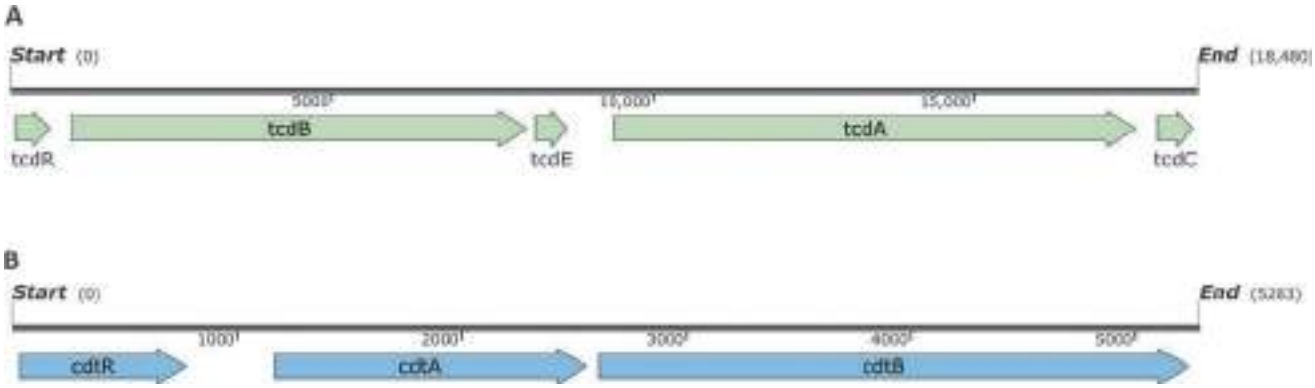

FIGURE 53-1. Schematic demonstrating the regulatory and toxin genes of the Pathogenicity locus (*upper portion*) and the binary toxin genes (*lower portion*).

tion, potentially leading to a larger volume [15] of toxin production. Studies collecting clinical isolates of patients with CDI for the purpose of studying this issue are few. In an analysis of 69 CDI patients whose dominant *C. difficile* was genetically characterized, Stewart *et al*. [74] determined that the presence of binary toxin and a *tcdC* truncation (18 or 36 base pair deletion) was associated with a higher incidence of recurrent CDI (OR = 5.3). In a follow-up study also focused on recurrent CDI, the same group observed [75] that two particular single nucleotide polymorphisms of the *tcdC* gene strongly predicted recurrent CDI. While *tcdC* variants may potentiate the risk of recurrence, there are other studies which have questioned whether *tcdC* has any clinical impact on CDI, especially with respect to severity of disease. Goldenberg and colleagues [76] failed to observe an association between binary toxin and *tcdC*, and disease severity, by reviewing over 200 *C. difficile* isolates. It should be noted that only 8 % of these isolates were ribotype 027, despite a high prevalence of *tcdC* truncations. Additional data calling into question the clinical relevance of *tcdC* for disease severity comes from Nigel Minton, [77] whose lab used an eloquent allele exchange system to introduce the loss of, and the subsequent restoration of, *tcdC* function in CD630, a well-characterized reference strain. This study was particularly valuable in that it demonstrated that the presence of a functional *tcdC* product did not affect volume of toxin production.

Toxin Nomenclature and Physiology

Toxins A and B are considered part of the Large Clostridial Toxin (LCT) family. These toxins are 308 kDa and 269 kDa, respectively, hence their designation as "large." Though there are studies which have attempted to weigh the relative contribution of these two toxins toward injury of colonocytes, especially given the rare occurrence of tcdA(−)/tcdB(+) ribotypes, [78] studies using isogenic strains [79] producing either toxin A or B were shown to be capable of causing life-threateningly severe CDI in rodents, while simultaneously using a gene knockout approach to demonstrate cytopathy in vitro and symptoms of disease in vivo. As described in an excellent review, toxins A and B have a multi-modular domain structure (ABCD model), [80] where A represents the biologically active N-terminus, B represents the C-terminal binding domain, C represents a cysteine protease domain, and D is a hydrophobic domain. The mechanism by which LCTs are taken up by cellular targets includes a receptor specific binding of the B domain which facilitates receptor-mediated endocytosis; a decrease in the pH of the resultant endosome promotes pore formation with translocation of a portion of the toxin across the endosomal membrane and into the cytoplasm of the cell. The D domain, being hydrophobic, is instrumental in forming these endosomal pores and in promoting membrane translocation of the toxin. The C domain then promotes autoproteolysis which allows the A domain to be released into the cytosol. The end effect of toxins A and B is mediated through targeted Rho GTPases (Rho, Ras, and CDC42), which are involved in cytoskeletal organization. These toxins perform monoglucosylation of these GTPases, resulting in cytoskeletal disruption and eventual cell death [81, 82].

The binary toxin (*CDT*) is not as prevalent as toxins A and B. *CDT* is part of a different family of toxins, having an ADP-ribosyltransferase function (the ADPRT family) [83]. The prevalence of this toxin is estimated to be 15 %, [84] although there is clearly a higher incidence of this toxin among ribotype 027 isolates. *CDT* is made up of two independently transcribed components, *CDTa*, which is the enzymatic component, and *CDTb*, the transporter element [78, 85]. In vitro studies using Caco-2 cells have demonstrated that *CDT* has a unique characteristic in promoting its adherence to, and entry into, target cells. The target cell is induced by *CDT* to produce multiple microtubular protrusions which

increase the apical membrane surface area five-fold, which helps with both toxin and bacterial adherence [86]. The downstream effect of the toxin on cellular targets is similar to that observed with toxins A and B; ADP-ribosylation blocks polymerization of G-actin to F-actin, leading to a disruption of actin equilibrium, with resultant cytoskeletal disruption leading to cell death.

While the binary toxin may not be present in the majority of clinically encountered ribotypes, the vast majority of clinically relevant types of *C. difficile* will produce toxins A and B. Deletions of *tcdA* are more common than *tcdB*, though both of these variants are uncommon in clinical practice [87, 88].

Association Between Bacterial "Type" and Disease Severity

Some of the earliest reports [15–17] of outbreaks of severe CDI which also included data on molecular typing pointed to a particular strain of *C. difficile* as the culprit of these severe instances of disease. This strain has been variably referred to as NAP-1, REA BI, and toxinotype III, though more recently these competing monikers have been replaced with reference to this organism as ribotype 027. The preponderance of studies suggest that this ribotype is associated with worse disease outcomes, though ribotype 027 designation does not appear to be an independent, stand-alone factor which is sufficient or necessary for severe disease, as there are examples of ribotype 027 not associated with adverse outcomes, [75] and since there are other ribotypes which can also be associated with severe disease [97]. This point is important to remember in reviewing the literature, as many clinical studies which have implicated ribotype 027 as an "epidemical strain" may not have adequately controlled for other factors which could account for adverse disease outcomes in the form of elevated recurrence rates, need for ICU care, need for colectomy or death. In a study focusing on patients with severe forms of CDI, Walk and colleagues [98] reviewed 34 cases of severe disease identified from a larger cohort of 310 CDI cases. Based on an initial and unadjusted univariate analysis, multiple covariates, including ribotype, were associated with severe CDI. However, after controlling for other potentially confounding factors, only a subject's white blood cell count and albumin were associated with the development of severe CDI; ribotype 027, as well as ribotype 078 (discussed below), was not associated with disease severity.

There are plausible molecular mechanisms which might, in the right clinical setting, account for greater odds of severe or recurrent disease associated with ribotype 027, which speaks to the evolutionary fitness of this strain of *C. difficile* but which does not require that ribotype designation be a principal determinant of disease outcome. First, there is evidence that 027 may be selectively advantaged to become the predominant type of *C. difficile* in health care facilities. In a small study [99] comparing patients being admitted to a single US hospital either from home or from a long-term care facility, ribotype 027 was found to be much more prevalent in long term care facility residents than were other strains of the bacteria. Patients with 027 were found to have higher six month mortality rates, though the ability for the authors to control for confounding factors was limited due to the small study sample size and due to population heterogeneity. In a review of a Canadian provincial database on patients in an acute care setting, Labbe [100] and colleagues analyzed both ribotype and clinical outcomes in both epidemical and non-epidemical periods of CDI. Ribotype 027 was associated with higher CDI-related mortality in this study, and the data suggested that antibiotic use for non-*difficile* infections was strongly associated with a shift toward a predominance of ribotype 027 within the CDI population, a change which frequently preceded outbreaks and which suggested a causal relationship between 027 and those outbreaks.

Secondly, 027 may be advantaged in terms of its efficiency in forming spores. *C. difficile* is an obligate anaerobe, and primarily in an effort to survive the aerobic environment outside the gut, the organism is capable of developing endospores, which are physiologically dormant and non-reproductive bacterial structures. Due to their metabolic quiescence, spores are resistant to antibiotics, and in the case of *C. difficile*, these spores are resistant to alcohol based hand sanitizers as well [65]. There are several genes which regulate sporulation in *C. difficile*, though a key regulator, and the most frequently studied, is *Spo0A* (Stage 0, sporulation protein A). This gene product may have a role in activating spore formation during periods of limited nutritional resources [101]. There are studies which have suggested that 027 is more transmissible due to a greater frequency of sporulation, and that perhaps the spores produced by 027 are more resistant to adverse environmental factors [102]. However, as pointed out in a review by Smits, [103] there are a number of studies calling this observation into question [104].

It has been proposed that ribotype 027 may have an advantage in toxin production compared to other ribotypes. This difference has been described both in terms of volume of toxin production [105] as well as in harboring genes not only for toxins A and B but also for binary toxin [106]. Other studies have suggested increased resistance of 027 toward *difficile*-directed antibiotics. [107] As with the other potential virulence features for 027, these observations have not been unanimously reported.

A judicious summary of the literature on 027 would be as follows. The bulk of research on *C. difficile* is *in vitro*, which while potentially valuable, does introduce a degree of artificiality to those research findings. *C. difficile* is a living organism which responds to its environment in the same manner that any other organism does. *In vitro* study or manipulation of *C. difficile* usually involves creating an ideal environment for bacterial growth and survival, and usually in complete

isolation to other bacteria, not to mention to the exclusion of other important components of the gut microbiome such as viruses. Described another way, the ambient environment of *C. difficile* research is a nested and synthetic one, frequently far removed from anything analogous to the human gut in either a healthy or a diseased state. It would be unreasonable to expect that observations of bacterial behavior in a lab environment would be directly reproducible to the situation in the human gut without important qualifications. In fact, the rationale behind the study of a gut microbiome lends to the opposite framework to that of an atomistic study of microorganisms one at a time, the latter being much more akin to the majority of *in vitro* research today. It is this difference between a laboratory culture and a living microbial community which may help to account for the disparity between those studies which found ribotype, toxin genes or some other bacterial factor as being predictive of bacterial behavior, and those studies which could not repeat these observations. Ribotype 027 definitely carries the genetic machinery which one would think is necessary for virulence, in the form of a well-preserved PaLoc, and with a higher prevalence of the binary toxin gene. What may be more important, however, than well-conserved toxin genes is the propensity of 027, like many other bacteria, to be lysogenous, which is to harbor bacteriophage genetic material in the form of a prophage. This viral genetic material is incorporated into the bacterial genome and carried along as a (largely) silent passenger. The prophage genetic material is replicated in a linear fashion with the *C. difficile* genome, which is a significant metabolic demand on the bacterium to maintain replication fidelity in the process of copying viral genetic material in addition to its own. This situation creates a strong deletional bias among bacteria to shed unnecessary physiological debts, which includes pressure in favor of losing any components of prophage DNA which do not offer some advantage to *C. difficile*. There are studies which have described a diverse number of phages which have contributed to lysogeny in *C. difficile*, [108] and studies have demonstrated that lysogeny can result in a greater volume of toxin production in 027 strains [109]. The process of lysogeny may account for recent comparative genomic studies [110] which have noted that epidemical forms of 027 have, on average, 234 additional genes compared to reference strain CD630, and that up to five ribotype-unique genetic regions were noted, including a previously unreported phage island. From all of this, a circumstantial case can be made that 027 is itself a heterogeneous subset of *C. difficile*, containing variants some of which are more, and some of which are less, selectively advantaged to produce outbreaks and severe forms of disease. This heterogeneity cannot be explained by the PaLoc, but rather it is related to the horizontal transmission of mobile genetic elements (such as phages, and transposons, the latter of which will not be discussed in this chapter due to space limitations). Those forms of "epidemical 027" have collected a critical mass of integrative genetic elements to create outbreaks of disease, and it is the interaction between *C. difficile* and its gut environment that can allow for outbreaks to develop through lateral gene flow, leading to the subsequent transmission of these epidemical, genetically enhanced *C. difficile* strains between human hosts in the hospital setting.

There are also other ribotypes which like 027 demonstrate facility at causing outbreaks. Briefly, one such ribotype is 078, which may represent an important zoonotic [111] link for CDI in humans. Ribotype 078 harbors *CDT* in addition to *tcdA* and *tcdB*, and it has been associated with greater severity of disease than other non-027 ribotypes [75, 97]. Interestingly, 078 is also capable of lysogeny, [112] though comparative genomics studies for this ribotype are currently lacking.

Diagnosis of *C. difficile* Infection

Clinical Presentation

CDI is a toxin-mediated disease whose hallmark is diarrhea. There are instances of asymptomatic carriage as referenced earlier in this chapter, though this is not generally a feature of a healthy subject, and in virtually every case described in the literature, carriage occurs among patients and healthcare workers, those who have frequent and prolonged exposure to areas where *C. difficile* is endemic. Patients who maintain a carriage state without symptoms of CDI are those who have the ability to develop an antibody to toxins A and B [113]. Studies on carriage status have demonstrated that an asymptomatic colonized state is more likely to develop in patients with greater concentrations of antibodies to toxin A compared to those who have symptoms of CDI; [114] higher titers of this antibody have also been associated with lower rates of recurrent CDI, [115] as have antibodies to toxin B [116].

For the majority of patients, if there is no diarrhea, there is no CDI. The one notable, albeit rare, exception would be those patients who have such life-threatening colitis from CDI that they have a paralytic colon, though in these instances the totality of clinical findings would strongly suggest a diagnosis of CDI such that the absence of diarrhea would not mislead the astute clinician. Other signs and symptoms (such as tachycardia, abdominal distention, abdominal pain/peritonitis, and hypotension) are variably associated with CDI depending on its severity. CT scan findings can include bowel wall thickening, pericolic fat stranding, megacolon, and ascites as the most common radiographic markers of severe infection (Figures. 53-2 and 53-3). Though segmental colitis with CDI is possible, in most cases, either a left-sided colitis with or without proctitis, or in more severe cases a pan-colitis, will be observed. Pneumoperitoneum and portal venous gas are uncommon radiographic features. Plain films and ultrasounds have little, if any, utility in diagnosing or managing this infection.

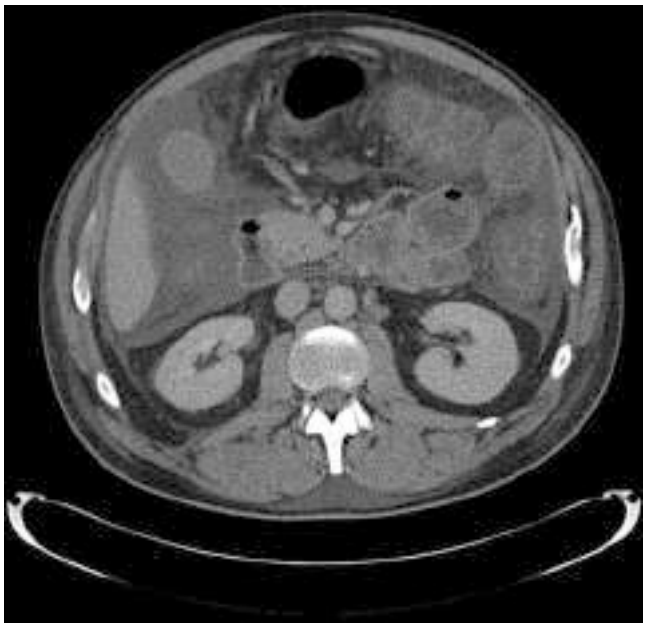

FIGURE 53-2. CT findings in a patient with severe, complicated CDI. Note the presence of ascites and the mural thickening of the left colon.

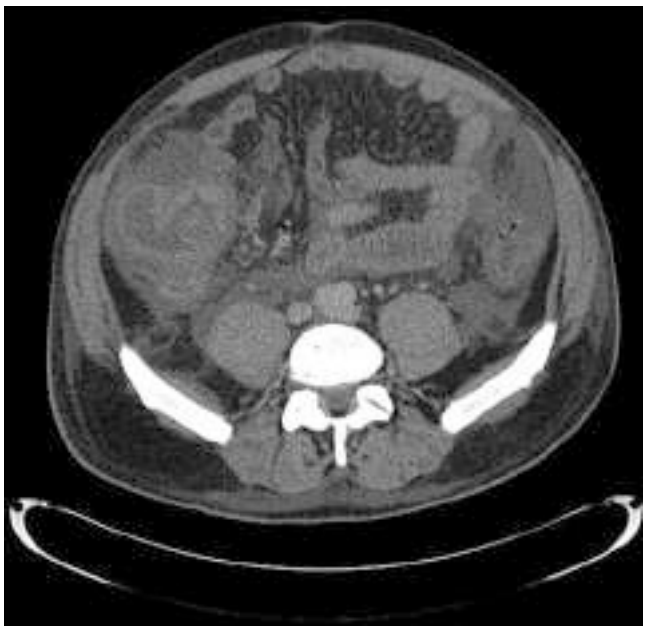

FIGURE 53-3. Severe, complicated CDI with characteristic cecal thickening. Colonic wall thickening to this degree is typical of fulminant CDI.

Laboratory Diagnosis

Historically, the diagnostic tests of choice for CDI involved either a tissue culture cytotoxicity neutralization assay (CNA) or toxigenic culture [117]. CNA involves stool cultures incubated with normal serum while a second sample of stool is incubated with antitoxin. With these aliquots exposed to cellular cultures, morphological changes consistent with the effects of toxins A and B are searched for during a 48-h period. The absence of cytopathy with both aliquots was considered a negative study, while cytopathy only observed in the sample without antitoxin was considered positive for CDI. These tests were often repeated with dilution for confirmation. Clearly, this form of testing is slow and labor intensive, and though it is a test with high specificity, its sensitivity was less than toxigenic culture, which itself is laborious [118].

With the later development of antibodies to toxins A and B, immunologic centered tests were developed. These initial tests were plagued by inaccuracies induced by the presence of antibodies to glutamate dehydrogenase (GDH), a cell wall antigen [118, 119]. A more specific form of immunologic testing was made available by the subsequent development of enzyme immunoassay tests, (EIA) and development of EIA testing against toxins A and B produced testing with >80 % sensitivity and >90 % specificity [120]. Further advances demonstrated that GDH provided a >98 % negative predictive value, while positive tests required confirmation through some other method [118].

At the present time, many hospitals have transitioned to one of several forms of nucleic acid amplification testing (NAATs). This group of tests use real-time PCR, loop-mediated amplification (LMAP), or helicase-dependent amplification techniques [118] to detect highly conserved sequences of the toxin A or B gene. NAATs are more sensitive than toxigenic culture and GDH-based approaches, and NAATs have increasingly become a standard, and stand-alone, test for CDI [11]. Although there are recommendations by some to use GDH as an initial screening test, with either EIA or NAAT for confirmation as part of a two-step process toward diagnosis, PCR-based NAATs are sufficiently sensitive and specific to serve as an adequate single step toward diagnosing toxigenic *C. difficile*. Routine retesting with NAATs to confirm eradication of the infection is not recommended as part of routine clinical practice, since NAATs are quite sensitive, and since *C. difficile* DNA may linger within stool for as long as 30 days after resolution of infection, leading to a false-positive test [121].

Clinical Severity Scores

There are several clinical severity guidelines which have been published, with the 2010 Infectious Disease Society of America/Society for Hospital Epidemiology in America (IDSA/SHEA) [18] and the 2013 American College of Gastroenterology [11] guidelines being those most commonly used in the United States. The IDSA guidelines define mild or moderate CDI as being associated with a white blood cell count (WBC) <15,000 cells/μL and a serum creatinine <1.5 times the patient's premorbid level. Severe CDI is then

defined as disease exceeding these two indices, while "severe, complicated" disease is CDI accompanied by such factors as hypotension, ileus, or megacolon. The ACG guidelines share certain similarities with the IDSA/SHEA schema, defining mild CDI as diarrhea without other abnormalities, and with severe CDI including those patients with either a WBC ≥ 15,000 cells/μL or a serum albumin of <3 g/dL. Moderate CDI then would range between mild and severe disease, while complicated CDI is defined in this system as anyone requiring ICU admission, a temperature ≥ 38.5°C, ileus, significant abdominal distention, altered mental status, a WBC either >35,000 or <2000 cells/μL, a serum lactate >2.2 mmol/L, or any evidence of organ dysfunction. An excellent comparison of these different systems as well as others used more frequently in Europe is provided by Katzman [122].

Two of the potential advantages of using a severity scale such as these are avoiding ambiguity in describing the severity of a patient's CDI between healthcare providers, while providing a consistent and empirical basis for choosing antibiotic therapy by reference to a scoring system that standardizes both disease definitions and their treatment. These systems, however, are quite limited for use by the surgeon, since most CDI patients treated by surgeons will be approached in consultation, and these patients are a selected subgroup of CDI patients who are not the principal focus of these scoring systems, systems largely devised by non-surgeons who primarily treat a different CDI cohort. Virtually all of the patients treated by surgeons will fall into the severe or severe, complicated categories of disease, yet most of these patients will not require surgery, which limits the discriminatory power of these systems in terms of choosing between medical and surgical therapy. The antibiotics recommended on the basis of these systems in many cases do not make sense given the proposed severity of the infection (i.e., the option of providing oral vancomycin for patients in the severe, complicated category who may be in septic shock or who may have an ileus). Further, the clinical markers of severity may be sensitive, insofar as those who are severely ill will be captured by these systems, though they are hardly helpful in guiding the decision to perform a colectomy, and this represents a significant knowledge gap in clinical research on CDI. Serum creatinine elevations as a marker of CDI severity, for example, may not be discriminatory, especially with respect to choosing surgical intervention, as in the case of a patient who is under-resuscitated but able to be resuscitated with appropriate medical care. Yet clinical indices such as serum creatinine are often referred to as indicators for surgery, without qualification, in the literature. Extreme values of WBCs should also be interpreted with caution by the surgeon. Neutropenic patients, especially those being treated for hematologic malignancies, may be at increased risk for CDI while simultaneously being protected from the most severe forms of the infection, both being a result of their neutropenia since functional leukocytes may be required for *C. difficile* toxins to exert their full and deleterious effect on colonocytes [123]. The more common aberrant WBC finding in CDI is an extreme leukocytosis, with counts of 50,000 cells/μL or higher being fairly common. However, there are aspects of this infection which make it unique compared to other diseases surgeons encounter. An exaggerated leukocytosis may be driven by both toxigenic [78] and non-toxigenic factors, [124] and these phenomena may not be directly related to the severity of colitis. An excellent description of bacteria–host interactions apart from the effect of toxins (an understudied aspect of CDI) was recently published by Jafari and colleagues, [124] who used human gastrointestinal mucosa studied in an ex vivo model to demonstrate increases in pro-inflammatory cytokines, such as IL-8, in response to the bacteria. This development may promote neutrophil migration to the gut, enhancing the cytopathy induced by toxins. Of even greater interest was the observation of bone marrow-derived dendritic cell activation which occurred apart from *C. difficile* toxins. IL-1β was also increased in a toxin-independent manner, and there were other cytokine changes which were felt to have a significant effect on T-cell responses to the infection. Though the purpose of this paper was not to investigate peripheral WBC counts in CDI, the information provided may help to partially explain the clinical observation that this infection can promote very elevated WBC counts, counts which are sometimes far more abnormal than the overall status of the patient. Though treatment will be discussed below, serum creatinine and lactate levels may indeed reflect disease severity, assuming there has been no delay in diagnosis and institution of treatment for the patient to otherwise account for these findings. However, without confirmation of maximal medical therapy having been delivered, these indices should probably not serve as justification for surgery, at least not as standalone indices. Neutropenia and significant leukocytosis require further study in terms of how they both reflect severity of CDI and the need for surgery, and this will probably be influenced both by characteristics of the predominant *C. difficile* type causing the infection and the genetics of the human host with respect to their cytokine response to infection. Therefore, the surgeon's interpretation of the significance of a WBC of 70,000 cells/μL, for example, should probably be adjusted from how this would be interpreted in other diseases such as diverticulitis or colitis from inflammatory bowel disease where, unlike CDI, such a finding would virtually always mandate emergent surgery.

Antibiotic Therapy for CDI

Metronidazole and Vancomycin

Excellent reviews of antibiotics either previously used for CDI or which lack enough scientific data to support their routine recommendation can be found by Venugopal [125]

and Wilcox [126]. In clinical practice, there are primarily two agents used for treating CDI, those being metronidazole and vancomycin.

Oral metronidazole preceded oral vancomycin as first-line treatment beginning in the mid-1990s due to concerns that overuse of vancomycin may select for resistant strains of bacteria such as *Enterococcus* [127]. Not only is metronidazole able to be provided in a parenteral route for CDI, but its cost is far lower than oral vancomycin. The data comparing metronidazole to vancomycin has evolved since initial studies on this topic, allowing for greater certainty regarding the proper use of these two agents. Prior to 2007, there were several [128, 129] small and underpowered studies which were not placebo controlled, and some of which did not adequately stratify patients based on severity of disease. These earlier studies suggested that metronidazole had similar rates of efficacy and recurrence compared to vancomycin, not to mention a significant cost savings in favor of metronidazole. In 2007, Zar and colleagues [130] published the first prospective, randomized, double-blinded, placebo-controlled trial comparing metronidazole and vancomycin, while also stratifying for CDI severity. In this study, patients were grouped into mild and severe disease categories, and although the severity scale used for this study was somewhat *ad hoc*, it was nonetheless based on factors known to be associated with disease severity. This study demonstrated that for mild CDI, rates of clinical cure were not significantly different between metronidazole and vancomycin, though for severe CDI, vancomycin was associated with higher rates of cure (97 % vs. 76 %; $p=0.02$). Though there have been abstracts and presentations of data at meetings, which have provided further support to these observations, the Zar study was very important for guiding current recommendations that metronidazole is the appropriate first-line agent for non-recurrent, mild-to-moderate CDI, a decision which balances efficacy, cost, and the potential risks of emerging resistant bacterial strains. Unlike vancomycin, metronidazole is effective by a parenteral route. The dosage should be 500 mg three times daily for 10–14 days. Longer lengths of treatment are not supported by evidence. Failure to demonstrate a response to metronidazole therapy within the first 5–7 days of treating mild-to-moderate CDI, or a deterioration to severe CDI, should prompt a change to vancomycin [11]. There is no evidence to support oral vancomycin combined with oral metronidazole, especially for milder forms of CDI.

For severe CDI, as defined by IDSA/SHEA criteria, [18] ideal treatment would involve oral vancomycin dosed at 125 mg four times daily for 10–14 days. There is a tendency for clinicians to increase this dosage, though there is little evidence to support such a practice given very high fecal concentrations [125, 131] of vancomycin at 125 mg dosing. For severe, complicated CDI, recommendations are for oral vancomycin (if tolerated) at 500 mg four times daily, though the clinician will often be required to instead use vancomycin enemas due to factors such as an ileus. The addition of parenteral metronidazole at 500 mg every 8 h is also recommended by IDSA/SHEA; though it provides little drawback, the evidence of "double therapy" in patients with CDI of this severity has been understudied, and so this recommendation does not carry the weight of evidence to support it as dogma. The use of vancomycin enemas has lower level support in its favor for fulminant cases of CDI; this evidence is from small and underpowered studies, [132] and the available data certainly would not support the use of intracolonic vancomycin for CDI of lesser severities. With the use of vancomycin, the clinician should remember that the use of cholestyramine is contraindicated due to its ability to bind to vancomycin.

For recurrent CDI, recommendations are to repeat a course of treatment using the same agent from the preceding course. Second recurrences are generally approached with vancomycin given in pulsed or tapered forms, for which there are several approaches aimed at eradicating vegetative forms of the bacterium. It should be mentioned that more recent data suggests that vancomycin should be used both for first recurrences [133] and potentially for all first CDI episodes in patients with inflammatory bowel disease, [134] given reports of higher success rates in both circumstances.

Fidaxomicin

Fidaxomicin is a macrocyclic compound [135] which exhibits its antibacterial activity through inhibition of bacterial sigma subunits which serve as transcription factors, thus preventing the expression of key bacterial genes. This agent has a more limited spectrum of activity than many other antimicrobials, with in vitro studies demonstrating resistance to fidaxomicin in certain *Bacteroides*, *Enterococcus*, and *Staphylococcus* species [136]. In 2011, the first Phase III study was published, [137] evaluating 629 patients, the majority of whom were treated per protocol. In this study, clinical rates of cure were non-inferior in the fidaxomicin group compared to the vancomycin treatment arm (92.1 % versus 89.8 %, respectively), while a significantly lower recurrence rate was observed in those treated with fidaxomicin in both the intention to treat and the per protocol groups. The group with lower recurrence rates was those *without* the potentially epidemical NAP1 strain. The results of this important study were limited by its inclusion of patients who received metronidazole, vancomycin or both as soon as 24 h prior to enrollment, which could clearly have affected the study results. The study also excluded patients with hypotension, fever or a leukocytosis greater than 30,000 cells/μL, and the study's approach to defining severity of disease was somewhat at variance with established guidelines in the literature, all of which makes the application of these results to the typical "surgical CDI" patient of less relevance. Further, this study did not provide evidence of equal efficacy with

vancomycin with potentially more virulent strains, such as ribotype 027.

There are a number of in vitro and in vivo observations suggesting a potential advantage to the use of fidaxomicin compared to vancomycin. There may be a longer post-antibiotic effect [138] compared to vancomycin, both in terms of the parent compound (10 h vs. 5.5 h) and also when comparing a metabolite of fidaxomicin to vancomycin. In a manuscript by Mullane and colleagues, [139] one of the first descriptions of the worsened cure rates in CDI patients receiving concomitant antibiotics for non-*difficile* infections was provided. The use of concomitant antibiotics was associated with lower cure rates (84 % vs. 92 %; $p<0.001$) and a significantly longer time to resolution of diarrhea (97 h versus 54 h; $p<0.001$). In this study, the use of fidaxomicin in the setting of concomitant antibiotics was associated with a higher cure rate than in those patients treated with vancomycin (90 % versus 74 %; $p=0.04$), with a lower rate of recurrent CDI (16.9 % versus 12.2 %; $p=0.04$). There is limited though intriguing in vitro evidence that fidaxomicin and its principal metabolite, OP-1118, reduce the expression of key *PaLoc* genes involved with toxin production (*tcdR*, *tcdA*, *tcdB*) in reference strains as well as in 027 isolates [140]. Though a considerable degree of further study would be needed on this topic, this observation, if confirmed, would indicate that fidaxomicin may not only target *C. difficile*, but may induce a change to its transcriptome favoring a reduction in the toxins that mediate the infection. A recent meta-analysis [141] of the limited body of literature on fidaxomicin concluded that while clinical cure rates were quite similar between fidaxomicin and vancomycin (OR = 1.17), relapse rates and sustained cure rates were improved in those treated with fidaxomicin. Interestingly, these results were sustained in both severe and non-severe CDI. There is also emerging evidence [142] that given fewer relapse rates, the use of fidaxomicin is cost-effective in severe cases of CDI and in those who have experienced their first relapse, as compared to costs associated with vancomycin. Additional studies will be needed to define the role of fidaxomicin among inpatients with CDI, especially those with severe disease and among those who develop CDI in the setting of hospital outbreaks. Fidaxomicin is dosed at 200 mg twice daily for 10 days for mild-to-moderate CDI, and this route would obviously be unavailable to those with fulminant colitis. Whether this drug can be delivered by retention enemas, in the manner of vancomycin, is also unknown. Currently, due to the higher cost of the drug, and considering reports of emerging *C. difficile* strains with a variant form of RNA polymerase B who have elevated MICs to this drug, [11] fidaxomicin should not be prescribed cavalierly as the third routine option for inpatients with CDI alongside metronidazole and vancomycin. Its role among the CDI patients that surgeons typically treat is unclear, as most of the studies on this drug are aimed at a different CDI population.

Surgery for CDI

The incidence of patients with CDI who require surgery is estimated to be as high as 10 % [143–145] although this would certainly be the upper limit, with the actual number likely being closer to 5 % or fewer (Figures. 53-4, 53-5, and 53-6). There are numerous papers, all with a retrospective methodology, which have documented the high mortality rates associated with severe, complicated CDI, and which have attempted to identify clinical indices associated with mortality. Several of these works have extrapolated from this data several possible markers for the need

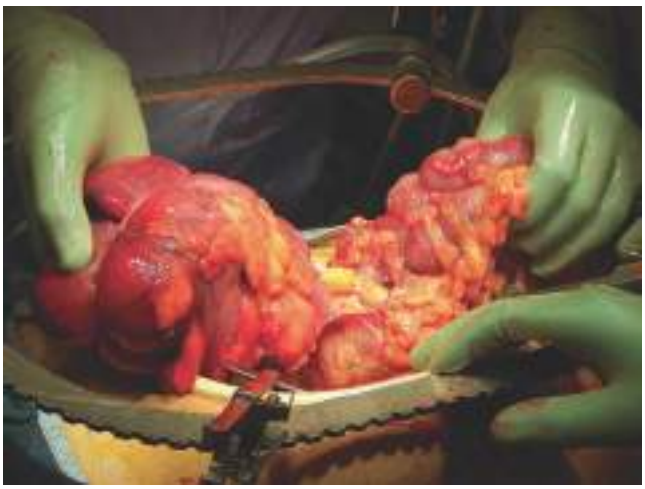

FIGURE 53-4. Patient with fulminant CDI with a dilated and thickened colon, with telangiectasias and serositis indicative of severe, transmural inflammation mediated by *C. difficile* toxins.

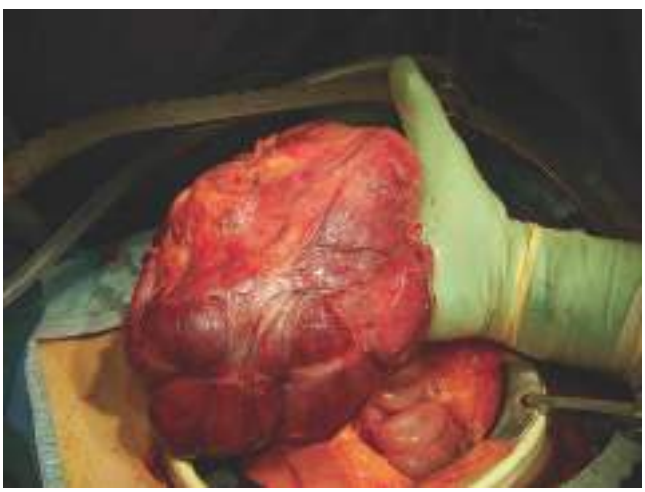

FIGURE 53-5. Non-confluent regions of transmural ischemia observed in a patient with fulminant CDI. The combination of bacterial toxins as well as septic shock can produce nonviable large intestine.

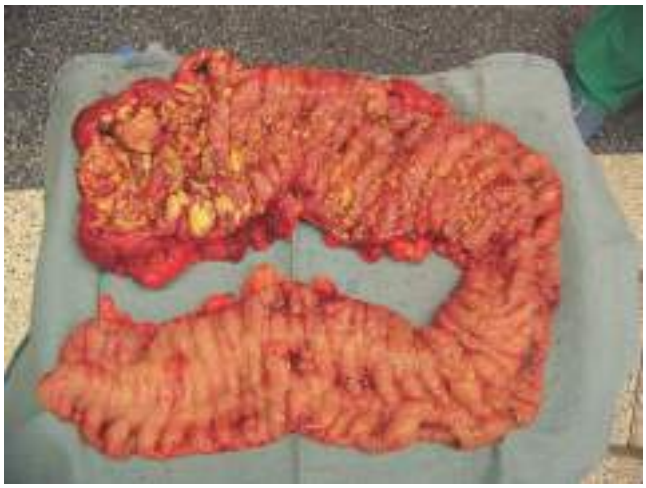

FIGURE 53-6. Gross findings of mucosal thickening, inflammation, and pseudopolyps, consistent with severe CDI.

for colectomy. In 2001, Dallal and colleagues [144] reviewed an approximately 11-year experience at a single referral center. The incidence of CDI for the final year included for analysis was 1.2 %; the highest incidence of "life-threatening" CDI reached a zenith of 3.2 %. Out of 2334 hospitalized patients, 44 required a colectomy with a postoperative mortality rate of 57 %; 20 others were reported as dying as a direct result of CDI. An antecedent and recent surgery and previous lung transplantation were associated with development of CDI, while lung transplantation was associated with severe CDI. In 2008, Byrn *et al.* [146] reviewed the medical records of 73 CDI colectomy patients at a single hospital spanning an 11-year period. This surgical subgroup comprised only 1.3 % of the institution's CDI population, with an inpatient mortality rate of 34 %. Findings of organ dysfunction such as the need for intubation, the need for vasopressors, and mental status changes were identified as predictors of mortality, as was an elevated and/or prolonged elevation of arterial lactate levels. Similar findings were also reported by Hall and colleagues [147] who described the outcomes of 36 colectomy patients identified from 3237 consecutive CDI patients. A total of 64 % of the colectomy patients survived to be discharged; the need for intubation prior to surgery and the need for vasopressors were identified as significantly increasing odds of inpatient mortality.

There are two systematic reviews evaluating the survival benefit of total colectomy for fulminant forms of CDI, though they approach the issue from slightly different perspectives. Bhangu and colleagues [148] meta-analyzed 31 studies in order to compare survivors and non-survivors following colectomy for CDI; this review included patients who underwent partial colectomy in addition to those who underwent total colectomy. Among the study population, total colectomy comprised 89 % of the surgeries performed. In addition to a strong association between postoperative mortality and preoperative findings of septic shock as well as other manifestations of organ failure such as acute renal failure and the need for intubation, partial colectomies were associated with an approximately 16 % need for reoperation to resect additional colon. The conclusion of this study was that total colectomy with an end ileostomy, as opposed to lesser colon resections, is the preferred surgery for fulminant CDI failing medical therapy. The authors provided the caveat that perhaps, in highly selected patients, partial colectomies may have a role. In a second review by Stewart and colleagues, [149] a meta-analysis of 510 patients was performed in order to evaluate whether total colectomy performed in the setting of failing medical therapy provided any measurable survival benefit. Pooled odds ratios of mortality were lower in the total colectomy cohort (OR = 0.70); those undergoing partial colectomy were not included in this review.

More recently, an alternative surgical intervention was proposed by Neal and colleagues, [143] where instead of performing a partial or total colectomy with an end ileostomy, patients deemed to need surgery for fulminant CDI underwent the construction of a loop ileostomy, with intraoperative lavage of the colon with eight liters of PEG via the stoma, followed by postoperative lavage of the colon via the ileostomy using intraluminal vancomycin, and with the addition of parenteral metronidazole, both for 10 days following surgery. These patients ($n = 42$) were compared to a historical control group of CDI patients who had undergone colectomy with an end ileostomy. The two surgical groups were similar in terms of their preoperative APACHE scores and their preoperative clinical indices such as WBC, serum albumin, need for vasopressors or mechanical ventilation, and immunosuppression. The treatment group experienced a significantly lower mortality rate (19 % versus 50 %), and, as an added benefit, in 83 % of patients the ileostomy was able to be constructed laparoscopically. Interestingly, one patient underwent a laparoscopic total colectomy (based on the wording of the manuscript, it would appear during the same anesthetic as the ileostomy construction), while two patients required a return to the operating room for a total colectomy (one due to recurrent vasopressor requirements, and the other due to abdominal compartment syndrome).

Based on the totality of clinical data currently available, the proportion of patients requiring surgical intervention for fulminant forms of CDI appears far smaller than the proportion of patients who develop fulminant forms of this infection. Given this, surgery should be viewed as an intervention which, while potentially life-saving, will be required in only a small minority of patients. It is also important to remember that the majority of publications studying the issue of surgery for CDI approach the subject through a retrospective analysis of outcomes among patients who were selected for

surgery; these studies attempted to identify clinical indices associated with mortality or the need for surgery, though the study methods are limitations in this effort given the bias introduced by a primarily, or in some cases exclusively, surgical cohort. What is perhaps most important to recognize, however, is that surgery should be reserved for patients who have failed maximal medical therapy, and defining when adequate medical therapy has been reached is a topic which has not been systematically studied. Certainly, adequate medical therapy would include goal-directed resuscitation achieved in a timely fashion, the de-escalation of non-*difficile* directed antibiotics, and the appropriate use of *difficile*-directed antibiotics, even if the latter are instituted prior to the results of confirmatory stool tests being available. In clinical practice, it is clear that this is not frequently the scenario which unfolds and that the surgeon is often consulted on a critically ill CDI patient who may not have received timely and/or appropriately directed care. Surgery may then be required to salvage such patients, though it is not always clear if the need for surgery in this scenario was inevitable, being due to a virulent strain of bacteria, or whether the patient's complicated sepsis is a sequela of an undertreated infection.

Additional studies are needed in several areas. The current severity scales discussed earlier will be unhelpful for the majority of patients surgeons are asked to evaluate, since virtually all of these patients will have severe or severe, complicated CDI, and yet the published literature suggests that only a small fraction of such patients will truly require exigent surgery. Identifying those indices which best predict the unavoidable need for surgery, if such clinical markers exist, will be important, and a careful reevaluating of the currently cited markers for surgery (such as WBC—see above discussion [124]) will be necessary to avoid overly aggressive surgical intervention. This will be especially important in the case of ileostomy and colonic lavage, which is admittedly less invasive and better tolerated than colectomy, but which might result in surgeons inappropriately lowering the threshold to perform surgery, in an effort to prevent an adverse disease outcome which would not have occurred had appropriate medical therapy been continued. It seems prudent to recommend that surgeons be involved early in the course of severe or severe, complicated CDI, at least as consultants, and perhaps as the primary caregivers if aggressive resuscitation is not being provided to patients with fulminant forms of disease. While stand-alone factors such as leukocytosis may serve as general indicators of disease severity, the decision to surgically intervene in the disease will more reliably be made by an evaluation of the trend of the patient's state in the setting of goal-directed resuscitation (which will often significantly lower WBC and improve renal function) with appropriate antibiotics. At this time, the decision to use ileostomy and colonic lavage should be part of a research protocol, since it is not at all clear which ribotypes of *C. difficile* will respond to diversion and lavage, and since the sickest CDI patients may not tolerate the use of PEG and intracolonic lavage in a compromised hemodynamic state.

Fecal Microbiota Transplant

Fecal microbiota transplant (FMT) involves the use of donor stool which has been screened for a litany of infectious agents and is then applied to patients with CDI either via a nasogastric/nasoduodenal tube or, more commonly, by lower endoscopy. Its mechanism of action involves increasing the bacterial population diversity and density, reestablishing healthy microbial communities which were eradicated through the use of antibiotics. Studies have shown that FMT creates a population shift in 16S rRNA surveys, shifts which closely approximate the taxa present in the stool of the FMT donor [150]. These changes in host-associated microbial communities have been observed, in the absence of antibiotics, to persist for up to 1 year after FMT [151, 152]. FMT is known to help break the cycle of multiple recurrences of CDI which have been treated with straight and pulsed/tapered regimens of vancomycin, but what is an emerging concept is the use of FMT for fulminant CDI (both case reports [153–155] and unpublished personally communicated case series). Surgeons should be involved with the on-protocol use of FMT for patients traditionally evaluated as potentially requiring surgery.

Conclusion

C. difficile infection has evolved to be a potential threat for virtually any inpatient, acting as an opportunistic pathogen in response to microbiota changes induced by the use of antibiotics. Though the antibiotics available to treat CDI are still limited, newer agents such as fidaxomicin show a measure of promise. Surgeons have a key role in treating this infection, as it is a potentially life-threatening form of colitis which in a minority of cases requires surgery. Timely and aggressive medical care including fluid resuscitation and proper antibiotic stewardship are the cornerstones of good practice, and surgeons can be helpful in ensuring that CDI patients receive this, even in their role as a consultant. The proper role of surgery requires refinement, beginning with additional studies in less biased study populations to further identify which clinical markers indicate the irreversible failure of medical therapy and the need for surgery. Which surgery should be used (total colectomy versus ileostomy and colonic lavage) is unclear and will require correlating surgical outcomes with often neglected microbiological data in a prospective and multicenter fashion, as different ribotypes may respond differently to these surgeries. Lastly, there is seminal data that FMT may provide a salvage therapy for fulminant forms of CDI, and surgeons should be involved in studying this issue as an alternative to both antibiotics and surgery.

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54
Radiation, Microscopic, Ischemic Colitis

Isabelle Raîche and Husein Moloo

Key Concepts

- Microscopic colitis is likely an underappreciated diagnosis. Although there is no "cure," the quality of life for a patient can be improved significantly with treatment which is typically medical and rarely surgical.
- Budesonide is the only evidence-based treatment for microscopic colitis
- Radiation colitis and proctitis spans a time course that ranges from acute to chronic which require different management strategies. Patients can present with problems even after 30 years of being asymptomatic.
- Colorectal cancer risk is increased with pelvic radiation and patients should be screened 5 years after completion of therapy.
- Surgical treatment for radiation proctitis/colitis should be individualized and based on the clinical context of the patient as morbidity and mortality rates are high postoperatively.
- Ischemic colitis represents the most common cause of gastrointestinal ischemia. The clinical picture has a wide spectrum ranging from mild cases with minimal mucosal ischemia to severe cases associated with transmural necrosis. Management and investigations need to be tailored depending on the clinical scenario encountered and patients require close vigilance by the surgeon.

Radiation Colitis

Introduction

An understanding of radiation injury to the colon and anorectal area is important for a coloproctologist. It is estimated that approximately 50 % of treatment protocols for cancer involve the use of radiation [1]. With malignancies such as anal cancer increasing, and a higher number of cancer survivors, the colorectal surgeon will continue to encounter post-radiation problems. The areas covered in this section consist of (1) pathogenesis, (2) prevention, (3) presentation, and (4) treatment. An important aspect to keep in mind while reading this section is the lack of high-quality evidence; an attempt has been made to provide the reader with recommendations based on the best evidence available.

Pathogenesis of Radiation Injury

The two main forms of radiation delivery are external beam radiation therapy (EBRT) and brachytherapy [2]. External beam is what we encounter most and is delivered via linear accelerators which produce high-energy X-rays. The planning is typically done in three dimensions with CT (computed tomography) images. Gray (Gy) is the standard unit to indicate the amount of absorbed radiation. Fractionation refers to giving the total dose over multiple sessions—for example, 50 Gray of radiation could be given over 25 sessions with 2 Gy per session. Fractionation is done to minimize collateral tissue damage while maximizing tumor destruction. Conformal radiation refers to the use of metal plates (multileaf collimators) to bend the X-rays in order to target the tumor and minimize radiation to normal tissue.

Brachytherapy refers to placement of the radiation source inside the body—i.e., beads or pellets.

Radiation damage has been described through the "target cell" theory. This theory focused on the epithelium of the bowel and explained acute effects through the damage done to this layer which is rapidly proliferating. The delayed effects were explained by damage of other target cells such as endothelial cells or fibroblasts as their turnover is slower compared to intestinal epithelium. The main addition to this thinking is that other tissues/cells are part of the injury process [3]. Therefore, alterations to the gut microflora, immune system, microvasculature, and immune system are all thought to play a role in the symptoms induced by radiation [3].

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When radiation is used in the treatment of abdominal or pelvic malignancies, the colon and rectum are sometimes included in the field of radiation. As a result, injury can occur. As with other treatments, there are patient and "radiation" factors that can influence outcomes.

Patient factors include Body Mass Index (BMI) with a higher BMI being protective. Smoking is a significant factor for worsening radiation-associated bowel complications [4], yet another reason to offer these patients a smoking cessation program. Additionally, previous surgery (fixing pieces of bowel in place—likely more relevant for small bowel injury), inflammatory bowel disease, diabetes, vascular and collagen vascular disease [3, 5, 6], and genetic predisposition are all predisposing factors [2].

The most important radiation factor is the dose. Other factors that play a role are the length of bowel radiated, fractionation, and use of chemotherapy [3].

Radiation effects can be considered acute or chronic. Acute symptomatology refers to those that occur during the actual treatment to 6 months after treatment is completed. Chronic radiation symptoms can continue on from the acute phase or after an asymptomatic period. Radiation symptoms can occur for up to 30 years after being latent; most patients will typically present with chronic changes 8–12 months after finishing their treatment [3, 7].

Prevention

The first question then is can anything be done to prevent acute changes especially because there appears to be a higher rate of chronic problems in patients who experience severe acute proctitis. The absence of acute symptoms does not preclude chronic changes and symptoms from occurring [7–9]. This process of severe acute injury leading to chronic changes is termed the "consequential" late effect [9, 10]. Prevention can be divided into those related to radiation delivery and those that are not.

The main goal with radiation delivery is to minimize damage to normal tissues surrounding the tumor. Conformal radiation therapy is one of the main methods of doing this. The 3D planning performed using CT and computer technology results in a higher dose of radiation delivery with less normal tissue being affected. Intensity-modulated radiation therapy (IMRT) is a technology whereby different intensities of radiation can be given (high and low) within the planned field. The neoplastic tissue is clearly identified as well as the normal tissue around it [11]. This modality has led to significant decrease in radiation toxicity and reduction in intestinal radiation during prostate cancer treatment even when compared to 3D planning/simulation [12]. In prostate cancer patients, acute and late radiation toxicity has also been reduced with the use of IMRT [13, 14]. In a study in prostate cancer, stereotactic radiation therapy has been found to cause lower rates of acute toxicity [14].

Brachytherapy, as mentioned previously, is when the source of radiation is implanted into the neoplasm (interstitial brachytherapy) or in a cavity which is close to the neoplasm (intracavitary brachytherapy). It can be used alone or with external beam radiation therapy and the goal again is to reduce normal tissue injury and is sometimes a good option for patients with inflammatory bowel disease [15, 16].

Proton beam radiation is an area where more research with respect to gastrointestinal toxicity is needed, but theoretically and with other tumors such as hepatocellular cancer the data looks promising [17]. The theory behind photon beams is that it "stops" in the target tissue and therefore collateral damage should be less.

With respect to non-radiation delivery factors, patient positioning has been found to be an effective way of reducing radiation to rectal wall, small bowel, and bladder—i.e., prone, Trendelenburg [18]. Other strategies employ bladder distension, abdominal wall compression, and determining position based on pretreatment contrast studies [11, 19].

The Multinational association of Supportive Care for Cancer and International Society of Oral Oncology has recently written a good paper to guide clinical practice with respect to Gastrointestinal Mucositis secondary to radiation injury [20]. Intravenous amifostine and sulfasalazine orally have been recommended as preventative measures for radiation proctitis and enteropathy. The panel also "suggested" that probiotics containing Lactobacillus could be used to prevent diarrhea in patients being treated with radiation for a pelvic malignancy. It was also specifically recommended based on the best available evidence that 5-ASA and related agents such as mesalazine not be used to prevent diarrhea in patients receiving radiation for a pelvic neoplasm. They also recommended against using misoprostol suppositories to prevent acute proctitis from radiation.

There are also operative maneuvers such as omental slings and tissue expanders that can be used to avoid radiation damage if it is planned post-resection.

Acute Radiation Colitis and Proctitis

Radiation damages the mitotic activity that is occurring at the base of crypts, where stem cells. Reside therefore the cells that migrate to line the bowel are damaged leading to a suboptimal mucosal surface and mucosal inflammation [21]. This can lead to diarrhea because of the impaired absorption. The barrier to bacteria is also affected because of this process and bacteremia can result [8]. Motility is also affected through the creation of Giant Migrating Complexes and this goes back to normal after treatment is complete; during treatment it is thought this alteration contributes to the diarrhea and cramping experienced by patients; diarrhea is the most common acute symptoms experienced by patients [22]. Other acute symptoms include nausea, tenesmus, fatigue, and abdominal pain [3]. Nearly all patients (50–75 %) expe-

rience symptoms in the acute period, but luckily these symptoms are usually self-limited. Consequently, treatment is usually supportive. Diarrhea, for example, can usually be controlled by antidiarrheal medications such as loperamide. Dietary modifications can sometimes help such as a lactose-free diet or one low in fat. Diarrhea that is severe can sometimes necessitate admission to hospital for intravenous hydration or parenteral nutrition. If first-line antidiarrheals such as loperamide are not effective, octreotide can be used to slow diarrhea [23]. Suppositories with steroids can also be used. Butyrate enemas have been shown to help in the acute proctitis setting with the thought that supplying colonocytes with this short chain fatty acid nutrition will help resolve damage that has occurred [24]. With respect to nausea, antiemetics are usually effective. Nausea is usually an earlier symptom seen in the first week of radiation treatment versus diarrhea and abdominal pain are typically seen 2–3 weeks into treatment [3].

Chronic Radiation Colitis and Proctitis

Chronic symptoms and complications from radiation can range in severity but can be debilitating and significantly affect the quality of life of an individual. The Radiation Therapy Oncology Group (RTOG) and the European Organization for Treatment and Research of Cancer (EORTC) have devised a grading for late effects of radiation with grades of 0–5. Zero represents the effect of radiation that created no change compared to baseline and five is the effects that led to death (Table 54-1) [25].

There is not a lot written specifically about radiation colitis. There are articles written regarding non-rectal radiation-induced injury. Based on these reports some predictions can be made regarding colitis. The most common symptom is likely diarrhea. Patients can also present with more severe symptoms such as obstruction or perforation. Determining specific complication rates regarding radiation colitis specifically is difficult because studies that describe theses usually include small intestine pathology as well [26].

The symptoms of chronic radiation proctitis are outlined well in Table 54-1. The pathophysiology of these complications is related to ischemic injury. The main pathology relates to fibrosis, atrophy, and vascular damage. Fibrosis which plays a prominent role in radiation injury is thought to occur because of the reaction of fibroblasts to cytokines, growth factors, and chemokines [2]. Atrophy results from the killing of cells and in concert with the other changes lead to malabsorption and strictures. The vascular damage from radiation can lead to dilation of small blood vessels—this is manifested as telangiectasias[2]. There can also be constriction of arterioles which leads to ischemia and in more severe cases necrosis; the fibrosis that occurs and which can progress over time can worsen the resultant ischemic injury [2, 3, 8]. The small vessel disease described is what distinguishes chronic from acute radiation changes.

Diagnosis

With an understanding of pathology, it is easier to understand chronic complications. Bleeding for example can be seen because of telangiectasias or ulcerations from ischemia. Malabsorption leading to diarrhea can be seen because of the atrophy of the mucosal lining or strictures leading to bacterial overgrowth. As mentioned earlier, radiation can also impact the nerves associated with gastrointestinal function and therefore accelerated small and large bowel motility can result [23]. With worsening ischemic strictures can occur leading to obstruction. With full thickness necrosis of the bowel wall, fistulas or free perforation can result. Surgery is complicated by the fact that anastomotic leak rates are higher when irradiated (with poorer blood supply) bowel is used [25].

Diagnosis is usually done with endoscopy and the features seen correspond to the pathological changes—telangiectasias, atrophy, and friable tissue. Biopsies, if necessary, can rule out processes such as inflammatory bowel disease, ischemic colitis, or drug-induced injuries. One should be cautious about taking biopsies in the radiated rectum as these have been implicated in a higher rate of fistula formation [27]. Histologic features of radiation therapy vary with the interval between completion of radiation treatment and onset of symptoms. Acute radiation injury (within 2–3 days after treatment) is characterized by surface epithelial damage, nuclear atypia with bizarre mitoses, attenuation and loss of crypts epithelium, increased apoptosis, and increased eosinophils with eosinophilic crypt abscesses. In the chronic phase of radiation injury, superimposed episodes of ischemia or the presence of mucosal or submucosal fibrosis can mimic primary acute or chronic ischemic colitis. The distinctive features of chronic

Table 54-1. Late radiation effects on small/large intestine

Grade	Symptoms
0	None
1	Mild diarrhea, mild cramping, bowel movement 5 times per day; slight rectal discharge or bleeding
2	Moderate diarrhea and colic; bowel movement >5 times per day; excessive rectal mucus and intermittent rectal bleeding
3	Obstruction or bleeding, requiring surgery
4	Necrosis/Perforation, Fistula
5	Death

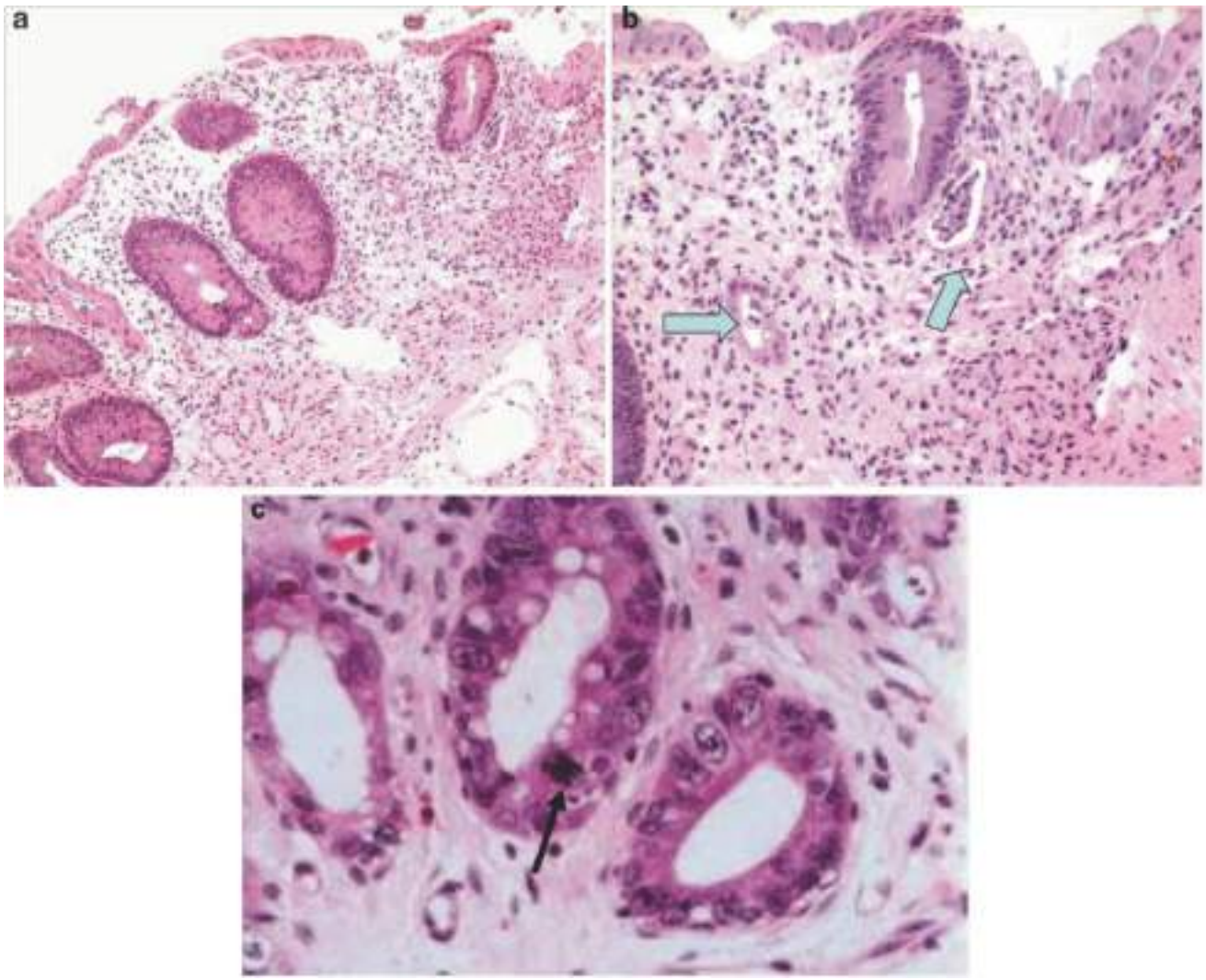

FIGURE 54-1. Radiation induced colitis. Colonic mucosa shows crypt distortion, crypt abscesses (*thick arrows*) and crypt atrophy, similar with inflammatory bowel disease. The crypt epithelium shows marked mucin depletion, regenerative nuclei and mitotic figures (*thin arrow*). Bizarre stromal fibroblasts and endothelial cells may be seen in lamina propria. Vascular injury may be also seen (not shown). Hematoxylin and eosin, ×100, ×200, ×4000. Reproduced with permission from Celia Marginean MD.

radiation injury include dilated, thickened, and hyalinized blood vessels, reactive or bizarre-shaped endothelial cells, fibroblasts and myofibroblasts, and foamy cells within the arteries (obliterative arteritis) [8] (Figure 54-1).

Management

Treatment of chronic radiation injury to the colon and rectum can be divided into medical, endoscopic, or surgical.

Medications

Medical treatment consists of topical versus systemic treatment. The main delivery method of topical treatment is via enema per rectum. Sucralfate enemas have been endorsed through the MASCC guidelines for the treatment of chronic radiation injury in patients who are having rectal bleeding [20, 28, 29]. There is one trial that showed oral sucralfate was beneficial in helping with diarrhea [30]; however, in their examination of the evidence, the MASCC recently suggested that oral sucralfate not be used [20].

5-ASA enemas have had mixed results and there is no clear evidence on whether it is beneficial for the treatment of chronic radiation proctitis or sigmoiditis and has been found to be harmful in some [31–33]. In the trial cited in the previous paragraph, it would seem that sucralfate is likely a more efficacious agent compared to 5-ASA [28]. Short chain fatty acid enemas still require further research prior to being able to recommend them as a treatment in chronic radiation proctitis [34]. Steroid enemas have also not been found to be consistently effective in the treatment of radiation proctitis [11, 23].

There is one trial that divided 60 patients into either a group that had betamethasone enemas, mesalamine orally, and metronidazole orally or a group that did not include oral metronidazole. In this trial it was found that bleeding and ulceration were lower in the group with metronidazole even up to 1 year [35]

A topical treatment that has been shown to be effective in dealing with bleeding from chronic radiation proctitis is topical formalin therapy. The theory behind this is that the formalin is used to chemically cauterize the telangiectasias and ulcers that are bleeding. The two main methods of delivery are via irrigation of formalin or direct application of a formalin soaked gauze onto the mucosa usually via a rigid proctoscope—the concentration typically used is 4 % although there are papers that have utilized 10 % solutions [8, 36, 37]. After either method it is recommended that a washout of the formaldehyde is done. It should also be noted that multiple applications may be required to achieve high efficacy rates of around 80 % (and sometimes higher); those with severe proctitis or taking an antiplatelet agent may require more applications [36–38]. For example, in one study the average number of applications of direct application with a cotton swab via a proctoscope was 3.5 with 1.5 more applications for patients taking aspirin or with severe proctitis [37]. Another important aspect of this treatment is to avoid contact with the anoderm as formalin can be irritating to this area. The irrigation or direct contact is done during an application until it can be visualized that cauterization has occurred of the affected rectal mucosa. For irrigation with formalin, it can be done in small aliquots ranging from 20–50 cc up to a total volume of 400–500 cc [38, 39]. It is important to be cognizant of the potential complications which includes anal or pelvic pain, stricture, rectal wall necrosis, and fistula formation [36, 39]. Finally, there may be a higher complication rate in patients who have received radiation for anal cancer [40].

Other medical treatments include use of vitamins—one study of 20 patients with chronic radiation proctitis looked at vitamin E and C use and whether a variety of symptoms improved. There was significant reduction in bleeding, diarrhea, and urgency, but it is important to note that the authors felt that a proper randomized controlled trial was required to see if these vitamins have actual benefit [41]. Loperamide was also examined with a small randomized controlled trial with a total of 36 patients and was found to decrease diarrhea and transit time and increase bile acid absorption [42]. Hyperbaric oxygen therapy has reasonable evidence to support its use for radiation proctitis [43, 44]; this recommendation (support for its use) is one of the changes that has been made in the most recent MASCC guidelines [20].

Endoscopy

Endoscopic therapy plays a role not only in the diagnosis of radiation injury to the bowel but can be used for treatment of it.

With respect to bleeding, argon plasma coagulation (APC) likely plays the biggest role and for many would be the treatment of choice prior to using formalin. It is a safe and effective therapy with bleeding cessation in 80–90 % of cases. Its advantage is also related to the fact that it coagulates to a reliable superficial depth. As with formalin instillation, it can require multiple treatments. Not only has there been found to be a reduction in bleeding, but bowel function has improved as well. There are no randomized controlled trials examining this particular technology, but based on multiple retrospective studies it appears to be safe and efficacious [45–47]. One has to be careful to avoid the dentate line because it can cause pain. Complications are rare and typically consist of rectal pain and cramping.

In one randomized trial comparing APC to formalin there was no difference in outcomes and both were found to be very effective in stopping bleeding (94 % APC and 100 % Formalin) [48]. In another randomized controlled trial with approximately 60 patients in each group, it was found that the addition of oral sucralfate to APC did not make a difference to the success rate of APC [49]. Historically, Nd:YAG laser therapy was used endoscopically, but with APC this is rarely used at present. In previous studies, it was found to be safe with rare complications of stricture, ulcers, fistula, and mucus discharge [50]. Another endoscopic technology that may find a wider application in the future is radiofrequency ablation as it can target a larger area and theoretically may have a lower stricture rate [51]. It is also important to remember that individuals who receive abdominopelvic radiation are at a higher risk of developing colorectal cancer. If there is not a reason to screen those patients earlier, they should definitely get surveillance done at 5 years post-completion of therapy.

Surgery

Surgical treatment is required for patients whose symptoms cannot be managed with medical or endoscopic therapy and also for complications such as perforations, fistulas, or strictures/obstruction. For both patients and surgeons, surgery is not something to be taken lightly. Individualized management plans are likely required depending on the context of the patient and discussion with at least one colleague or at a multidisciplinary setting regarding the management is recommended. Luckily, only 10 % of patients require an operative intervention for colorectal complications post-radiation [52]. In any type of bowel resection, one needs to be aware that anastomotic leak rates are high when putting two pieces of radiated bowel together and is lower if only one of the pieces is irradiated [53].

Pelvic fistulas can be one of the difficult problems that surgeons can encounter post-radiation. Similar management principles can be employed as with other types of fistulas—i.e., management of any ongoing sepsis and trying to optimize the situation for healing (knowing of course that with irradiated tissue fistulas are more difficult to repair) through measures such as nutritional optimization. With many of these patients whether it is a rectovaginal or rectourethral fistula, diversion will likely be necessary. Surgery will then

depend on factors such as how high the fistula is. Is it amenable to a perineal or abdominal approach and how will well-vascularized tissue be incorporated. The repair can therefore involve a flap reconstruction for a low rectovaginal fistula (i.e., gracilis or Martius) or a coloanal anastomosis with interposition of well-vascularized tissues such as omentum if it is a higher fistula. In the most severe cases, proctectomy or pelvic exenteration type procedures may be required.

Diversion may be helpful in non-fistula cases as well. Studies have shown that a colostomy or ileostomy may resolve symptoms of pain, tenesmus, sepsis, incontinence, and obstruction and improve quality of life to the point where further surgical intervention may not be needed [52, 54]. Because dissection can be difficult in an irradiated pelvis, transverse and descending colostomies were found to be safer than a sigmoid colostomy [52]. Diversion does not always help with bleeding, but there has been at least one retrospective study that has shown improvement in bleeding with a stoma [55].

Overall, on a 30-year retrospective review (looking at colorectal surgery for radiation injuries), the approach—resection versus diversion versus bypass—did not lead to a difference in success. It is not surprising, considering that it was a retrospective review where the surgeons picked an operative approach based on what was most reasonable [54]. The promising finding was that 70 % of patients had symptomatic relief. Of the different indications fistula repair had the lowest success rate (55 %) compared to stricture (78 %), hemorrhage (64 %), and perforation (100 %). It is sobering to note that the morbidity rate was 65 % with a mortality rate of 7 % [54]. The conclusion of this 30 years review is that treatment plans should be highly individualized and this lesson is likely the one that the surgeon should remember when dealing with these patients.

Microscopic Colitis

Introduction

First described in 1976, microscopic colitis (MC) is an inflammatory colitis and a relatively common cause of non-bloody diarrhea [56, 57]. Two main types of MC have been described: collagenous colitis and lymphocytic colitis [58]. Although considered to be a milder disorder when compared to other inflammatory bowel diseases such as ulcerative colitis and Crohn's disease [58], MC can have a significant impact on patients' quality of life [59, 60].

Epidemiology

The incidence of microscopic colitis is increasing [61–63]. In 2001, the estimate prevalence in the United States was 103 cases/100,000 persons [63]. It has been found in all age groups; however, it is more common in the older population and believed to be present in 10–30 % of patients older than 70 investigated for chronic diarrhea and presenting with a normal colonoscopy [58, 61, 62]. Collagenous colitis is more common in women, while lymphocytic colitis is equally distributed between genders [63, 64]. Relative incidence of collagenous vs. lymphocytic colitis varies between series; in a recent report, it was estimated that the prevalence of collagenous colitis was 39.3 per 100,000 persons vs. 63.7 for lymphocytic colitis [62, 63].

Etiology and Risk Factors

The cause of MC remains unknown; it is hypothesized to be multifactorial [65].

Genetics

A limited number of Familial cases of MC have been reported [62]. It is interesting to note that members of the same family can develop either collagenous or lymphocytic colitis [66]. An association has been found with HLA-DQ2 and TNF2 allele carriage and microscopic colitis suggesting a possible association with the pathogenesis of coeliac disease [67, 68]. On the other hand, NOD2/CARD15 gene, known to be linked to Crohn's disease susceptibility, was not found to be more frequent in MC patients compared to healthy controls [69]. MMP-9, another marker of inflammatory bowel disease, has been found more frequent in MC patients, but MMP 1 and 7 were not found to be associated with MC [70].

Infection

Stool cultures are negative in most patients with MC. However, onset after infection with *Yersinia enterocolitica*, *Clostridium difficile*, and *Campylobacter jejuni* has been described [58].

Smoking

In case–control study, smoking has been associated with an increased risk of MC (OR 2.12) [71]. In a retrospective review of 184 patients, smokers tended to develop symptoms earlier in their life: in one study the mean age at onset of diarrhea was 50.4 years old vs. 65.5 in the nonsmoking group. In the same study, smoking habits were not associated with increased risks of relapse [72].

Medications

Evidence regarding the association between MC and medications is equivocal. Some studies suggest a link between MC and nonsteroidal anti-inflammatory drugs (NSAIDS),

HMG-CoA reductase inhibitors (statins), proton pump inhibitors (PPI), and selective serotonin reuptake inhibitors (SSRI), while others did not find a similar association [64, 73]. Some classes of drugs potentially linked to MC such as NSAIDS and PPI are known to cause watery diarrhea as a common side effect confounding the potential causal relationship. Because they can exacerbate symptoms of a preexisting MC, further investigations may be prompted and lead to an MC diagnosis [74].

Autoimmunity

In a recent survey of 116 patients with MC, 30.4 % had an autoimmune condition [75]. Some diseases have a particularly strong association: celiac disease and thyroid disease. Other conditions that have been linked to MC include diabetes mellitus, arthritis, alopecia, psoriasis, and Sjögren's syndrome [75]. In contrast to Crohn's and ulcerative colitis, no association has been found with autoimmune liver conditions [58].

Clinical Manifestations

Clinical Presentation

Chronic, non-bloody, watery diarrhea is the hallmark of this disease [62]. It can occasionally lead to fecal incontinence, especially in the elderly. In a retrospective cohort study, fecal incontinence was present in 25 % of patients [76]. Watery diarrhea, even during flare-ups, rarely leads to dehydration [65]. Bile salt malabsorption can make diarrhea worse and therefore cholestyramine is sometimes used for treating these patients [77].

Weight loss is also common, being found in 41–46 % of patients [64, 76]. Abdominal pain is more common in MC patients compared to controls. Interestingly, patients considered to be in remission also have more abdominal pain compared to healthy control [65]. Fatigue is another frequent complaint of patients with MC, present in 50–60 % of patients; it is unclear if it is due to nocturnal diarrhea preventing rest or to the disease itself [58, 65].

Lymphocytic and collagenous colitis cannot be differentiated based on clinical presentation [62]. Interestingly, the pathologic abnormalities found in MC have been found in asymptomatic and constipated patients [65].

Complications

MC rarely leads to complications [62]. Cases of spontaneous perforation have been reported, but it is more common for perforation to occur as a result of a colonoscopy [78, 79]. "Fractured colon" associated with linear ulceration developing during colonoscopy has been described in collagenous colitis [80]. Collagenous deposition on the wall of colon is thought to render the wall less pliable and more likely to "fracture" during colonoscopy [81].

MC has not been found to be associated with an increased risk of colorectal cancer in a retrospective analysis of 547 MC cases [82]. A recent case–control study of 647 patients with MC followed for an average of 4.63 years found that MC was associated with a lower risk of colon cancer or adenomatous polyps [83].

Diagnosis

Histopathology is the mainstay of the diagnosis of MC. Because of the nonspecific clinical presentation the differential diagnosis is wide and includes inflammatory bowel disease, infectious colitis, medication-induced changes, celiac disease, bile salt malabsorption, lactose malabsorption, and irritable bowel disease [62, 84].

Colonoscopy with two or more biopsies in each of areas of the ascending, transverse, descending, and sigmoid colon respectively is the exam of choice to diagnosis MC. Biopsies should be sent separately [85]. The pathologic findings tend to be patchy involvement occurring anywhere in the colon; however, the disease is classically more severe in the right colon [84, 86]. Up to 30 % of rectal biopsies are normal in patients with MC, underscoring the need to obtain biopsies throughout the colon. MC was originally described in patients with a normal endoscopic exam and most patients with MC do have a normal exam. However, endoscopic abnormalities have been described in a small number. In a recent literature review of 42 articles (total number of patients included not mentioned), 88 patients with abnormal colonoscopy and a diagnosis of collagenous colitis were found. The most frequent findings were mucosal nodularity, alteration of the vascular pattern, and mucosal defects [87].

Pathologic findings of collagenous colitis include preserved crypt architecture and expanded lamina propria by a mixed inflammatory infiltrate, including plasma cells, eosinophils, and occasional neutrophils, mostly on the superficial portion underneath the surface epithelium. The crypt epithelium shows regenerative nuclear changes. Focally the subepithelial collagen layer is thickened, which is the main diagnosis feature, has a lacy appearance, and incorporates inflammatory cells and small capillaries. The surface epithelium shows markedly increased intraepithelial lymphocytes and focally may be detached from the mucosa. The pathologic findings of lymphocytic colitis include preserved crypt architecture and expanded lamina propria by numerous plasma cells, lymphocytes, and eosinophils. The surface and crypt epithelium are diffusely infiltrated by numerous T lymphocytes (diagnostic if >20 IELs per 100 epithelial cells), which by immunohistochemistry express CD3 and CD8 and lack CD4. The crypt epithelium shows hyperchromatic, regenerative nuclei (Figures 54-2 and 54-3).

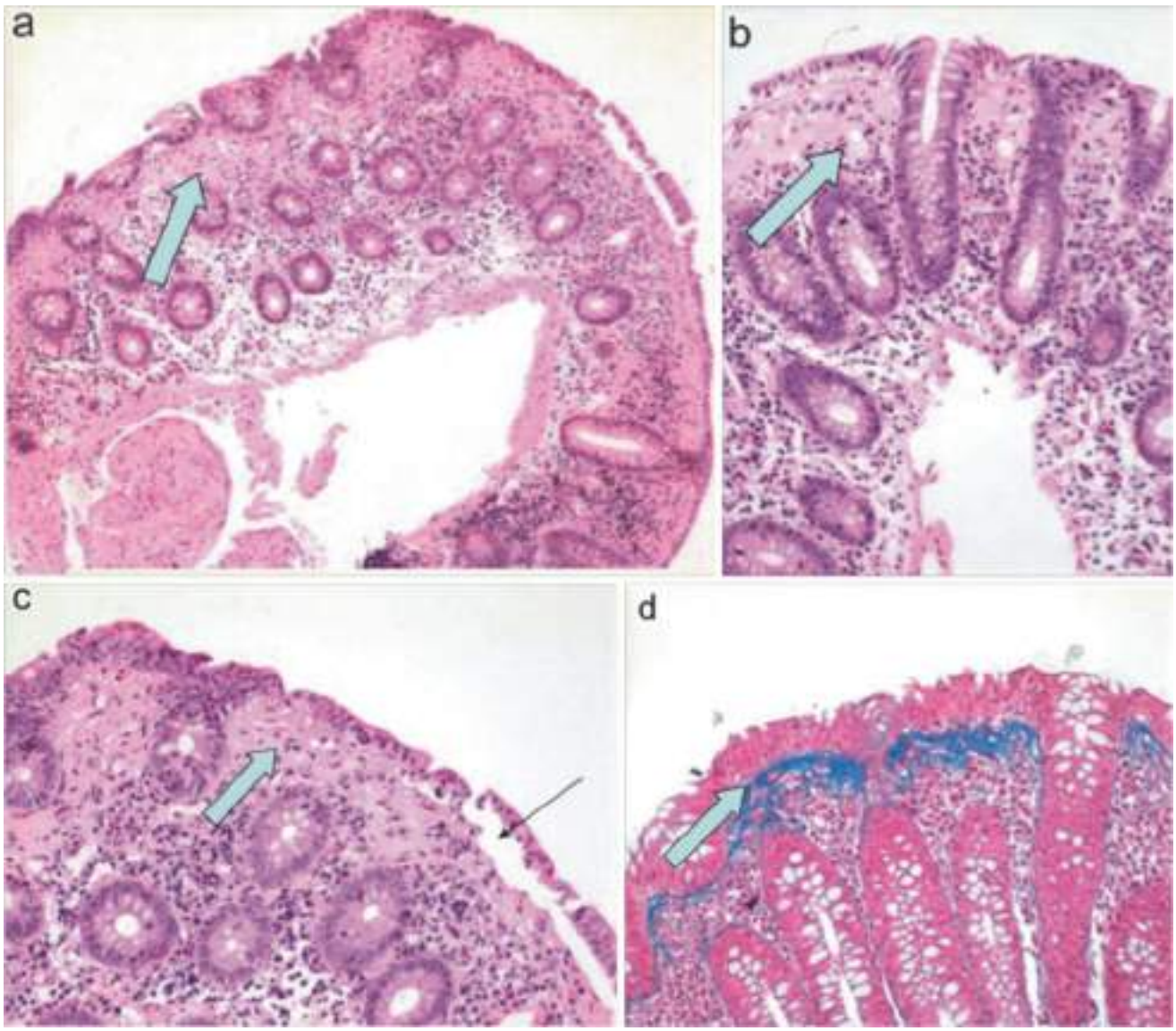

FIGURE 54-2. Collagenous colitis. (**a**) Colonic mucosa shows preserved crypt architecture. The lamina propria is expanded by a mixed inflammatory infiltrate, including abundant plasma cells admixed with eosinophils and occasional neutrophils, mostly on the superficial portion underneath the surface epithelium. The crypt epithelium shows regenerative nuclear changes. On several areas, the epithelial collagen layer is moderately thickened. Focally, the collagen band has a lacy appearance and incorporates inflammatory cells and small capillaries. The surface epithelium shows markedly increased intraepithelial lymphocytes and focally is detached (split) from the mucosa. Hematoxylin and eosin, ×100. (**b**) Thick subepithelial collagen layer, incorporating microcapillaries and inflammatory cells (*thick arrows*). Hematoxylin and eosin, ×200. (**c**) Thick subepithelial collagen layer, incorporating microcapillaries and inflammatory cells, with splitting of the surface epithelium (*thin arrow*). Hematoxylin and eosin, ×200. (**d**) Thick subepithelial collagen layer (*blue*), incorporating microcapillaries and inflammatory cells. Masson trichrome stain, ×200. Reproduced with permission from Celia Marginean MD.

Figure 54-4 presents an algorithm to illustrate pathologic diagnosis of MC. The term incomplete MC is used when a patient has pathological alterations not meeting the criteria for MC [85, 89]. A study conducted to assess observer variability in the diagnosis of MC found a high intra-observer and interobserver reliability for assessment of samples containing normal colon, inflammatory bowel disease samples, and MC samples. The reliability assessment for differentiating collagenous and lymphocytic colitis was lower but still good (κ=0.64–0.70 for types of MC vs. κ=0.84–0.86 for diagnosis of MC) [89].

Laboratory analysis usually shows nonspecific abnormalities such as mildly elevated inflammation markers. Fecal calprotectin and lactoferrin are not consistently elevated (in contrast to inflammatory bowel disease), limiting their use in the diagnosis of MC [90]. Research to identify reliable

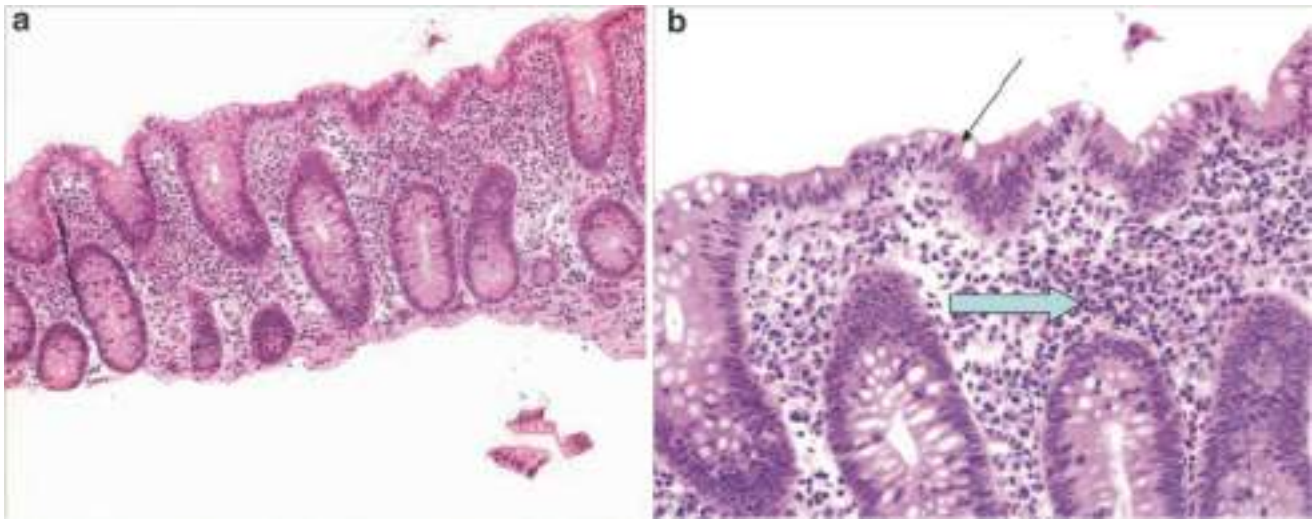

FIGURE 54-3. Lymphocytic colitis. (**a**, **b**) The colon shows preserved crypt architecture. The lamina propria is markedly expanded by numerous plasma cells, lymphocytes, and eosinophils (*thick arrow*). The surface and the crypt epithelium are diffusely infiltrated by numerous lymphocytes (*thin arrow*). The surface and crypt epithelium shows hyperchromatic, regenerative nuclei. Hematoxylin and eosin, ×40, ×100, ×200. Reproduced with permission from Celia Marginean MD.

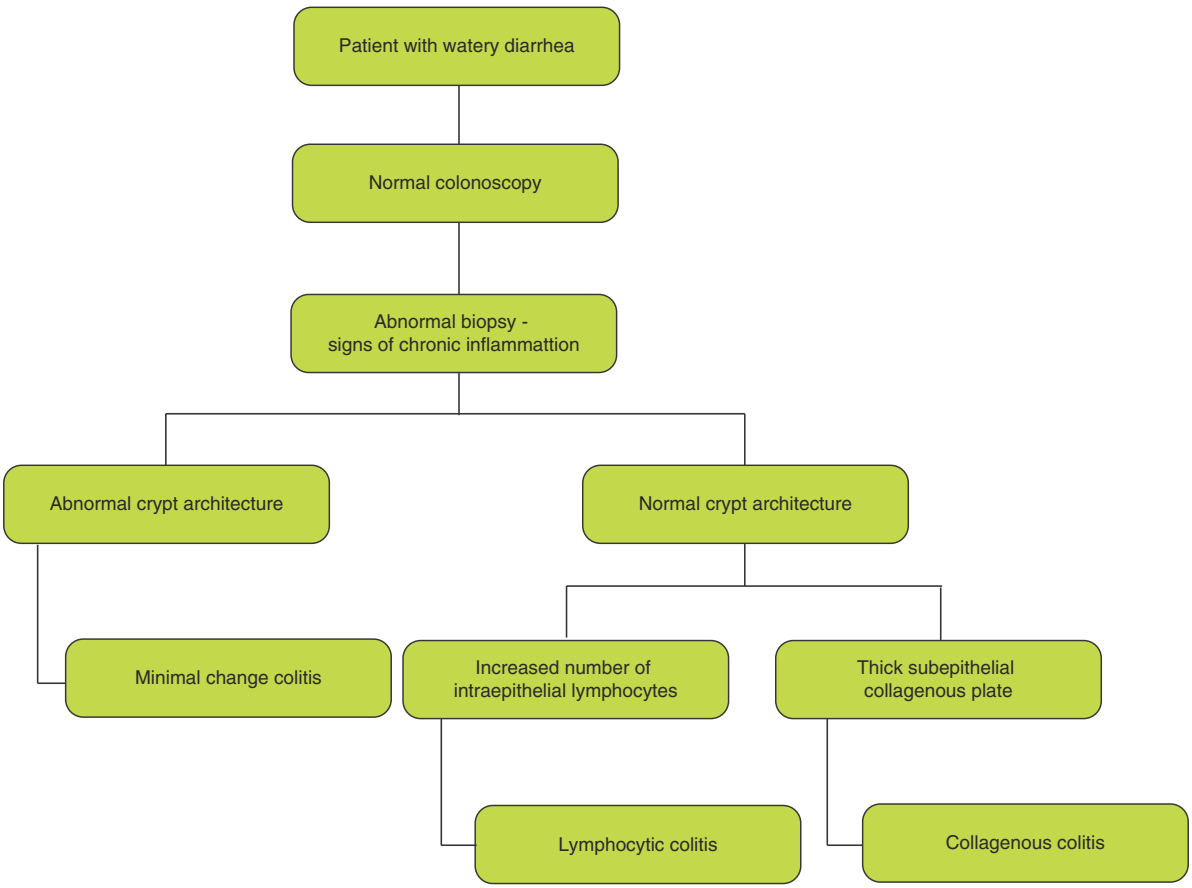

FIGURE 54-4. Algorithm for pathological diagnosis. Adapted from Warren, Edwards & Travis, 2002 [86].

biomarkers is ongoing [58, 65]. Imaging is typically normal and does not have a role in the diagnosis of MC [58].

Management

There is no curative treatment for MC. The goal of the treatment is to control the symptoms. In 2009, after conducting multiple surveys, Hjortswang et al. published criteria to define clinical remission based on the impact of the symptoms on patient quality of life. According to their work, patient with a mean of <3 stools per day and a mean of <1 watery stool per day should be considered in remission [91]. The role of pathologic response in recurrence rate and quality of life is not known currently [62]. Patients should be advised to stop smoking and dietary factors (dairy product, alcohol, caffeine) should be controlled. Long-term remission has been documented in 63–80 % of patients depending on the series [77]. The treatment and frequency of treatment course varies and the main options will now be discussed:

Budesonide

In a meta-analysis of nine randomized controlled trials, budesonide was shown superior to placebo to induce clinical and pathological response. However, the recurrence rate with treatment cessation was high [92]. Two Cochrane reviews have been published on the treatment of collagenous colitis and lymphocytic colitis [93]. When budesonide therapy was continued for 6 months after clinical remission, it was shown to prolong the disease-free interval from 45 to 207 days with 83 % of patients maintaining response vs. 28 % in the placebo group [94]. Increased stool frequency (>5 per day) and symptom duration longer than 12 months have been identified as factors associated with shorter duration of remission [95].

Prednisolone

The role of prednisolone in the treatment of MC is limited. It is associated with more side effects than budesonide [58]. In a recent meta-analysis, it was not shown to be superior to placebo [92].

Cholestyramine and Loperamide

Antidiarrheals are often recommended as the first line of treatment. They seem to have the most benefit in patients with mild symptoms. They are unlikely to induce a pathologic response and the long-term efficacy has not been proven. Patients with MC not responding to budesonide or recurring symptoms after multiple cycles of treatment should be tested for bile salt malabsorption; affected patients could benefit from cholestyramine [58, 62, 65].

Aminosalicylates

The evidence supporting the use of aminosalicylates in MC is limited. In a three-arm randomized controlled trial comparing budesonide, placebo, and mesalamine, there was no statistically significant difference between placebo and mesalamine at 8 weeks in terms of clinical remission [96]. A previous trial comparing mesalazine alone and mesalazine with cholestyramine for 6 months reported a remission rate >85 % in both groups, with a 13 % relapse rate in the remission group at 2 years. There was no placebo arm in this study [97].

Immunosuppressive and Anti-TNF Medications

This class of medication is generally reserved for patients refractory to other types of medical management because of their potential side effects. The role of azathioprine and mercaptopurine in budesonide refractory MC was studied through a retrospective review of 46 patients. Overall, thiopurines achieved remission in 41 % of patients; side effects included elevated liver enzymes and nausea/vomiting [98]. The evidence supporting the use of methotrexate in budesonide refractory MC is conflicting with one study reporting a clinical response in 16 of 19 patients and another study showing no improvement in nine patients [99, 100, 102]. Small series (less than ten patients) refractory to standard medical management report symptom improvement with the use of anti-TNF medication [103–104]. Larger studies are needed to better define the role of immunosuppressants in MC.

Bismuth Subsalicylate

Bismuth subsalicylate has been widely used, but there is limited evidence to support its use. A recent Cochrane review found only one partially published trial on bismuth subsalicylate including nine patients [105]. It was found to induce remission in 100 % of patients at a dose of 262 mg, eight tablets divided into three doses for 8 weeks [84]. The same authors published a 13-patient series with a response rate of 85 % and a 7 months remission in 69 % of patients [106]. Interestingly, bismuth subsalicylate has been found to be useful in treating chronic intractable diarrhea in up to 74 % of patients in a 31-patient case series [107].

Other Medications

Many other medications have been used to treat MC. *Boswellia serrata* extract and probiotics were not associated with a statistically significant response to treatment [94]. Antibiotics such as metronidazole and erythromycin have been used, but their effects have not been formally studied [65].

Surgery

Surgery has a limited role in the treatment of MC. Loop ileostomy, subtotal colectomy, and proctocolectomy with J-Pouch have been described to treat severe intractable disease [108, 109]. Indications for surgery are ill defined and likely to be less frequent as our understanding of the optimal medical regimen improves [58, 62, 65].

Ischemic Colitis

Introduction

The term ischemic colitis was coined by Martson and published for the first time in 1966 [110]. Colon gangrene had been recognized since the late 1800, but the physiopathology of the disease had remained unsolved until the mid-twentieth century [113]. Ischemic colitis (IC) can be defined as "the condition that results when blood flow to the colon is reduced to a level insufficient to maintain cellular metabolic function" [111]. It is a fairly common disease usually self-limited. Affected patients are often frail which explain the relatively high rate of mortality associated with this disease [112].

Anatomy and Physiology

Branches from the superior mesenteric artery and the inferior mesenteric artery supply the colon. Splanchnic vessels are amongst the most reactive in the body, with blood flow varying from 10 to 35 % of cardiac output depending on physiologic or pathologic conditions [112]. This characteristic partially explains the high frequency of a low flow state in the colon. Two watershed regions have been described in the colon where ischemia is most likely: the splenic flexure (area of Griffith) and the recto-sigmoid junction (Sudeck's point) [113]. This is superimposed on the fact that the colon receives the least amount of blood flow in the gastrointestinal tract as measured by blood flow to 100 g of tissue [113].

Epidemiology and Risk Factors

The incidence of IC varies between 4.5 and 44 cases per 100,000 person-years. It is the most frequent site of gastrointestinal ischemia [113]. It is more common in females and in patients over the age of 65 [114]. It is recognized as a disease affecting older, comorbid patients. Chronic obstructive pulmonary disease, thrombophilia, history of irritable bowel disease, constipation, diabetes, renal failure, hypertension, extreme exercise, myocardial infarction, and history of vascular disease have been identified as risks factors [111, 114, 115]. Multiple drugs are known to increase the risks of developing colonic ischemia—a literature review published in 2007 documented drug classes having been linked with development of ischemic colitis [116] (Table 54-2).

Table 54-2. Pharmacologic agents in order of evidence strength [111, 116]

Moderate evidence (further research would like have an impact on authors' confidence in the estimate effect)	Constipation-inducing medications Immunosuppressive agents Illicit drugs
Low evidence (further research is expected to have an important impact on authors' confidence in the estimate effect)	Antibiotics Appetite suppressants Chemotherapeutic agents Decongestants Diuretics Ergot alkaloids Hormones Laxatives Psychotropic medications
Very low evidence (estimate effect is uncertain)	Digitalis Satins Nonsteroidal anti-inflammatory agents Serotonin agonists/antagonists Vasopressor

There is a classic association between ischemic colitis and AAA repair. A review of 89,967 patients undergoing AAA repair showed a global incidence of ischemia of 2.2 %. The type of repair performed correlated with the incidence of IC. Almost 9 % of ruptured AAA repair were complicated by IC in contrast to 1.9 % of open elective procedures and 0.5 % of endovascular repairs [117]. Following all types of AAA repair, IC was associated with a mortality of 37.8 % vs. 6.7 % for the patients without this complication.

With ischemic colitis being so frequent after ruptured AAA, it has been suggested by some that routine sigmoidoscopy could be beneficial in this patient population. In a prospective trial of 161 patients only one-third of patients found to have IC on routine endoscopy developed symptoms [118]. Importantly, routine use of colonoscopy has not been shown to improve patient outcomes and therefore is not recommended [111, 119].

The first manifestation of ischemia in a postoperative patient is often rectal bleeding, generally happening in the first 48 h after surgery. These patients should be investigated with endoscopy [115]. In patients requiring surgery, anastomosis should be avoided to minimize the risk of graft contamination [120].

Pathophysiology

Mechanisms of ischemic colitis can be divided into non-occlusive arterial ischemia, embolic or thrombotic arterial occlusion, and mesenteric vein thrombosis. The mucosa is the first layer of the bowel to show ischemic changes, after which if there is a progression all layers of the bowel wall can be involved. Because it is furthest from the mesentery, the antimesenteric part of the bowel is affected first [111]. Transient mucosal damage can be seen after 20 min to 1 h of insufficient blood flow with transmural changes occurring after 8–16 h [121, 122].

Non-occlusive Ischemia

Non-occlusive ischemia is responsible for 95 % of IC cases [120]. Non-occlusive ischemia can be idiopathic without identifiable cause or may be secondary to a medical or surgical condition diminishing colonic blood flow [111]. Colorectal vascular anatomy explains why IC happens on the left side of the colon in >75 % of cases but affects the rectum in only 5 % of patients [116, 117]. When the ascending colon is diseased, the cecum is the most frequently affected colonic segment [112]. Colonic injury and the systemic response to IC are due to both the hypoxic state and reperfusion injury [115]. Most of the evidence presented in the chapter is based on the management of this type of IC.

Arterial Thrombosis and Emboli Related Ischemia

An embolic source of ischemia is a less frequent cause of colonic ischemia. It is often seen with concomitant small bowel ischemia and the distribution is less likely to follow the zones of watershed area. In a case–control study on 60 patients with segmental non-transmural ischemia, patients with IC were 2.5 times more likely to have a cardiac source of embolism than control patients with similar comorbidities and medications but without IC. Thirty-two percent of patients were placed on anticoagulation and 25 % on antiarrhythmic therapy after cardiac work-up including transthoracic echocardiogram, electrocardiogram, and rhythmic Holter monitoring [112, 123].

Venous Thrombosis

Venous thrombosis is more frequently related with small bowel ischemia; and it is the rarest cause of IC [113]. It tends to affect the ascending colon more frequently than the descending. The management of this entity is usually nonoperative : systemic anticoagulation and occasional catheter-directed thrombolysis are typically used to improve the situation.

A new entity, mesenteric phlebosclerotic colitis, has been described in 2003. Its etiology is still unknown. Patients present with abdominal pain, mesenteric venostasis, and fibrotic and calcified veins. The optimal management of this condition remains to be defined, so far it has been mostly surgical for severe cases [114].

Clinical Presentation

Abdominal pain and rectal bleeding are the most frequent symptoms associated with acute IC [125]. Nine to twenty-four percent of lower GI bleeds are caused by ischemic colitis [111]. In a review of 401 IC cases, 5 % required a blood transfusion [125]. Abdominal pain is usually combined with an urgent desire to defecate [115]. Other symptoms include nausea, vomiting, abdominal distension, diarrhea, dizziness, and syncope [125]. Right-sided colitis is less likely to be associated with rectal bleeding and this diagnosis should be kept in mind in patients with isolated right-sided abdominal pain [111].

IC can evolve from an acute reversible colopathy (70 %) into different clinical patterns including gangrene (10 %), chronic colitis (18 %), and fulminant colitis (2 %) [126, 127]. Strictures form in 3.3–9.4 % of patient—they are asymptomatic in the majority of cases [111].

Diagnosis

Laboratory Studies

Results from laboratory studies are often nonspecific. Increased white blood count and acidosis are associated with infarction. There is no reliable marker of ischemia. Increased lactate, LDH, CPK, or amylase can sometimes indicate tissue damage [120].

Stool culture should be sent in patients with uncertain diagnosis. *Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*, *E. coli* O157:H7, and parasites can cause a similar clinical picture. *C. difficile* should be considered even though it is usually not associated with bloody diarrhea [119]. *Klebsiella oxytoca* has been found in patients with right-sided hemorrhagic colitis mimicking ischemic colitis. It has been found more commonly in patients exposed to penicillin derivatives [128, 129].

Imaging

Plain films and contrast enema

In IC, plain abdominal films can be normal or show nonspecific findings of distention and ileus. Free air can be seen with perforation. Classic findings of bowel ischemia (i.e., thumbprinting and pneumatosis) are present in 21–30 % of plain films in patients with IC [111, 120]. Contrast enemas have a limited use in the acute phase as they may make ischemia worse by increasing intraluminal pressure. Contrast studies can be used after the acute process has resolved to assess stricture formation [115].

Abdominal CT scan

CT scans are frequently performed in the Emergency Room to evaluate patients with abdominal pain; CT scan with intravenous contrast is currently the imaging modality of choice to assess IC [111]. The accuracy of CT scan in determining bowel ischemia varies between 74 and 79 % depending on the study protocol and the experience of the radiologist [130]. In a recent review of CT imaging at different clinical phases during ischemia, 100 % of patients presenting in the acute phase had a radiologic abnormality, most frequently pericolonic fluid and free fluid, change in bowel wall densities, and

bowel wall thickening [131]. Pneumatosis was present in <5 % of patient in acute phase. The clinical significance of pneumatosis and portal venous gas is becoming controversial. It used to represent a definite sign of bowel wall necrosis and was associated with a dismal prognosis. However, recent reports have suggested that pneumatosis and portal venous gas can be associated with different conditions. Lassandro et al. described 25 other conditions presenting with pneumatosis [132]. In their review, pneumatosis and portal venous gas were a sign of transmural necrosis in 62–92 % [132]. When portal venous gas and pneumatosis were found in combination with bowel necrosis, the mortality rate was 71 % [132]. CT angiography has not been found to increase diagnostic accuracy in the acute setting [133]. It can be used to rule out superior mesenteric occlusion if clinically suspected; inferior mesenteric occlusion is of limited clinical significance as it is found in 10 % of asymptomatic patients older than 60 years old [111].

Endoscopy

Colonoscopy can be used to confirm the diagnosis of ischemic colitis and to exclude other etiologies for colitis. It should not be performed in patients with findings of peritonitis or known perforation. Findings indicating ischemia at the time of endoscopy include erythema (84 % of cases), edema (70 %), friability (43 %), superficial ulceration (57 %), deep ulceration (22 %), stenosis (8 %), and intraluminal blood (8 %) [117]. Disproportionate involvement of the antimesenteric side with occasional single linear antimesenteric ulcer and segmental involvement are also signs of IC. Hemorrhagic nodules can be seen if the ischemia reaches the submucosa. In severe and transmural ischemia, the bowel wall may be gray, green, or black [115]. It is difficult to evaluate the severity of the disease with endoscopy. In 2011, Beppu et al. presented a case series of 106 patients and compared their clinical course based on endoscopy findings. Patients with longitudinal and circumferential ulcers stayed in the hospital longer than patients with only redness and erosion [134]. Endoscopic findings should be integrated into the complete clinical context when making decisions regarding whether surgical or medical management should be undertaken [111]. If severe ischemia is suspected a biopsy should not be taken as the risk of perforation would be high. The endoscopy should be aborted when an ischemic segment is reached [111].

The features of acute ischemic colitis include preserved architecture of the colonic crypts, necrosis of the superficial portion of the crypts, sparing the deep portion of the crypts (with or without ghost of crypts), mucin depletion, and reactive changes in the residual crypt epithelium, which may mimic dysplasia. The lamina propria is hypocellular, with very rare or completely absent acute inflammatory cells (neutrophils), and shows hyalinization. Sloughed necrotic mucosa may produce a microscopic appearance of a pseudomembrane which is composed of fibrin admixed with numerous neutrophils and mucin. Numerous small intravascular hyaline thrombi are seen in small mucosal capillaries (Figure 54-5). Montoro et al. noted that those findings were more commonly observed in the first 48 h [124]. In more chronic presentation, mucosal atrophy and area of granulation tissue may be found as well as fibrosis in area of stricture [110].

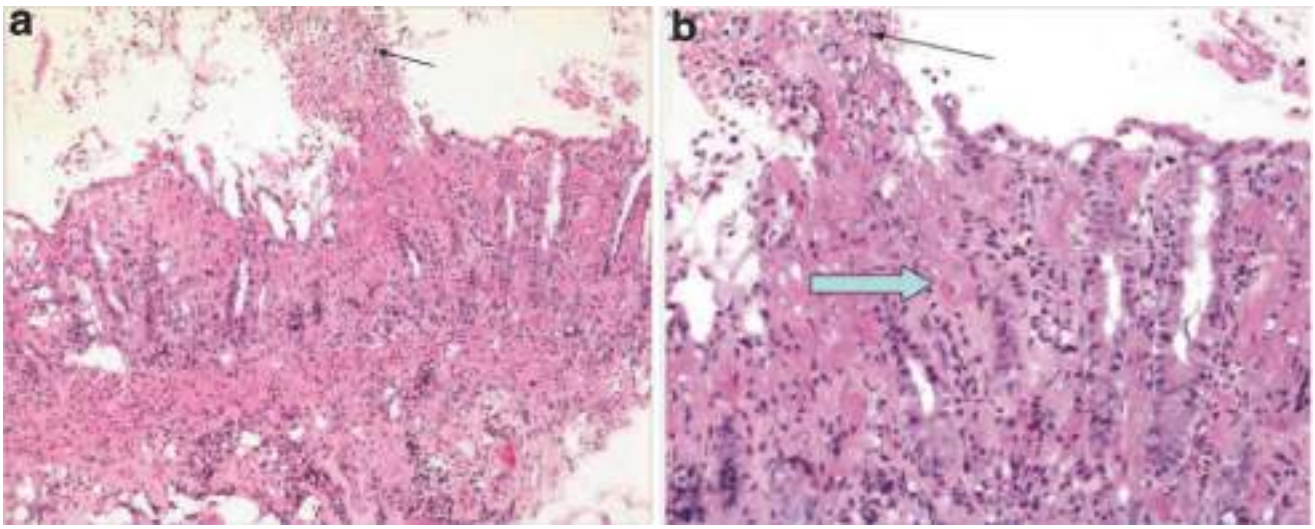

FIGURE 54-5. Ischemic colitis. (**a**) Colonic mucosa shows necrosis of the superficial portion of the crypts, sparing the deep portion of the crypts. The lamina propria is hypocellular and shows hyalinization (dense, eosinophilic color). Hematoxylin and eosin, ×100. (**b**) Sloughed necrotic mucosa may produce a microscopic appearance of a pseudomembrane erupting from a crypt, composed of fibrin admixed with numerous neutrophils and mucin (*arrows*). Numerous hyaline thrombi are seen in small vessels (*thick arrow*). Hematoxylin and eosin, ×200. Reproduced with permission from Celia Marginean MD.

Arteriography

Arteriography has a limited use in diagnosis of IC since it is usually an arteriolar disease. It can be used to exclude small bowel ischemia and large vessels occlusion. In the elderly and comorbid population usually presenting with IC, arteriography should be used cautiously, balancing the benefits of the information gained from the exam with the potential risks of a contrast load [115].

Ultrasound

Criteria suggestive of colonic ischemia include bowel wall thickening, altered pericolonic fat, and absence of Doppler flow with a thickened bowel wall. In a study of 62 patients with IC, the sensitivity of ultrasound was 93.5 %. Repeated exams showed improvement in patients successfully treated conservatively and no improvement in patients with transmural necrosis [135]. Ultrasound has its usual limitations—user dependent and limited by body habitus and the presence of bowel gas [116].

Management

There is limited empirical evidence to guide management of ischemic colitis [136]. Guidelines and recommendations are based on case series and expert consensus.

General Principles

Many patients with IC have a self-limited disease and would improve without specific intervention [111]. Treatment is usually supportive and includes the maintenance of hydration. Patients with an ileus may benefit from nasogastric tube decompression. Medications should be reviewed and those promoting splanchnic vasoconstriction should be stopped if possible and cardiac output should be optimized. Steroids should not be used to treat IC unless it is the consequence of a vasculitis [111].

Improvement should be seen in 1–2 days with complete clinical resolution in 1–2 weeks. Absence of improvement may suggest development of chronic ischemia or progression towards transmural ischemia.

If an endoscopy is performed in the acute phase, bowel preparation is contraindicated [115]. After complete resolution of the initial episode, patients should undergo a colonoscopy to ensure compete healing and assess for possible stricture [118]. Asymptomatic strictures can be observed; symptomatic strictures can be managed through surgical resection or endoscopic dilatation. Since no evidence supports the use of dilatation specifically for ischemic stricture, its use should be reserved for patients with too much comorbidity to undergo surgery [111]. The potential benefits of stent insertion in benign stricture remain to be defined [137]. In a retrospective study, balloon dilatation was associated with longer patency time than self-expandable stent and a lower rate of complications [138].

Antibiotics

Broad-spectrum antibiotics are recommended considering that the loss of mucosal integrity caused by ischemia can lead to bacterial translocation. However, there is no empirical evidence to support their use [111]. The use of antibiotics is based on older studies describing diminished bowel damage with antibiotics during an ischemic event [111]. Some studies conducted in animals documented bacterial translocation from bowel to mesentery and liver and also support the use of antimicrobials [120, 121].

The choice of antibiotic is based on expert opinions. Considering the possibility of translocation associated with bowel ischemia, the ACG guidelines recommend broad-spectrum antibiotics, and animal studies support the use of metronidazole [111].

Antithrombotic

Anticoagulation is not routinely recommended for patients with ischemic colitis secondary to microvascular pathology or low flow states. If bowel ischemia is due to venous thrombosis or arterial thromboembolic events, anticoagulation is indicated. Patients should be investigated for thrombophilia if no other risk factors are found on history. Antiplatelet agents are not generally recommended [120].

Surgical Management

Surgical indications include peritonitis, sepsis, radiologic evidence of perforation, suspicion of transmural ischemia on endoscopy, absence of improvement or deterioration under medical management (persistent sepsis or protein losing colopathy), and stricture causing obstruction [111, 115].

In the acute setting anastomosis creation is controversial especially on the left side. Huguier et al. published a series of 31 patients undergoing surgery for ischemic colitis: 17 had a primary anastomosis with a 11.7 % leak rate; the factors leading to primary anastomosis or stoma were not described [139].

Prognosis

Overall mortality rates vary from 4 to 12 % depending on the study [111]. In a recent literature review, 19.3 % required surgical intervention [140]. IC necessitating surgery is associated with higher mortality: 39 % in surgically treated patients vs. 6 % in medically managed patients [140].

The recurrence rate is difficult to compare amongst different patient cohorts because of the many factors involved in the development of the disease and its treatment. A retrospective review of 401 patients with IC found a recurrence

rate of 10 % at 5 years [125] and, not surprisingly, has been shown to increase with time [111]. Factors commonly associated with poor prognosis include right-sided colitis, male gender, peritonitis on presentation, absence of rectal bleeding, and concomitant renal dysfunction [140]. In a recent effort to establish a "prognostic scoring model" for IC, Chung et al. [141] reviewed 153 cases of IC. They identified ulceration on endoscopy, tachycardia, and shock in the first 24 h of presentation as the strongest predictor of poor outcomes defined as death, need for resection, and improvement delayed for more than 2 weeks [141].

Conclusion

There is no doubt that the term and conditions that encompass colitis span a varying spectrum of pathologies. Medical providers who care for these patients must have a thorough understanding of the medical, interventional, and surgical approaches to the diagnosis and treatment in order to optimize outcomes for this complex group of colonic pathologies.

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55
Intestinal Stomas

Michael F. McGee and Peter A. Cataldo

Key Concepts

- Preoperative stoma site marking and patient education improve stoma-related clinical outcomes, patient quality of life, and experience, while decreasing healthcare resource utilization.
- The finished stoma should protrude from the skin which improves appliance sealing and decreases complications.
- Optimal care for patients undergoing ostomy surgery includes preoperative and postoperative care by an ostomy nurse specialist, such as a WOCN-certified nurse.
- Early stoma-related complications such as leakage, peristomal dermatitis, and dehydration can often be remedied with stoma care and education.
- Loop ileostomy is preferred over transverse loop colostomy for temporary fecal diversion in most circumstances.
- Stapled and hand-sutured techniques are both acceptable for loop ileostomy closure.
- Asymptomatic parastomal hernias do not mandate repair, while mild symptoms may benefit from appliance modifications or stomal support belt. Suitable-risk patients with significant parastomal hernia symptoms may be candidates for repair.

Introduction

Stomas are employed as temporary or permanent means of fecal diversion in the management of a variety of gastrointestinal, neurologic, and genitourinary conditions. Approximately 120,000 stomas are created annually in North America, with an estimated prevalence of 450,000–800,000 ostomates [1]. Stomas can be fashioned in an "end" or "loop" configuration depending on surgical strategy and perioperative conditions and are classified by the location of exteriorized bowel (e.g., colostomy, ileostomy, jejunostomy).

Intestinal stoma creation, often relegated as a minor component of a larger operation, will significantly impact the patient and his or her support system. Stoma-related complications are common, but even absent complications, patient dissatisfaction with stoma appearance, and body image can negatively impact quality of life. Societal stigmas, ignorance, and misunderstandings can further complicate care. Conscientious surgical stewardship and collaborative nursing care can decrease complications and improve quality of life for ostomates. As such, mastery of preparing, creating, caring for, and reversing stomas are a hallmark of the colorectal surgeon's armamentarium.

Colostomy

Configuration

Creation of an end colostomy may be indicated in several benign and malignant diseases for permanent or temporary enteric drainage (Figure 55-1a). Low rectal cancer, recurrent anal cancer, severe anorectal Crohn's disease, or severe radiation proctitis may require a permanent end colostomy. An end colostomy may be used emergently for severe sigmoid diverticulitis (i.e., Hartmann's procedure) and as a means of trauma-related damage control. An end colostomy may be required in patients who are not candidates for restorative procedures that establish continuity with the anus or rectum such as those with fecal incontinence, severe neurologic impairment, old age, prohibitive medical comorbidities, and prior resection of the anal sphincter complex. Although sphincter-preserving operations increasingly garner attention, the end colostomy remains a relevant and sometimes necessary entity.

A loop colostomy can be used to divert fecal flow proximal to a tenuous anastomosis or problematic distal bowel on a temporary or permanent basis (Figure 55-1b). The redundant, non-peritonealized nature of the sigmoid and transverse colon make each suitable for a loop colostomy, although high outputs and prolapse may hinder transverse colostomies. The dual lumen nature of the loop colostomy

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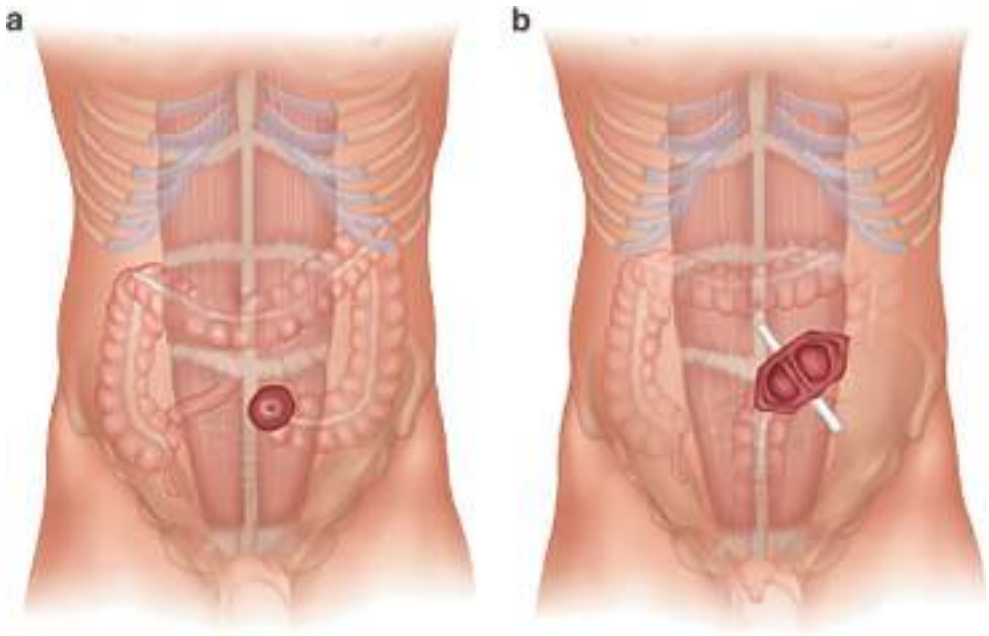

FIGURE 55-1. (**a**) End descending colostomy. (**b**) Loop sigmoid colostomy.

allows proximal diversion with retrograde venting of the distal segment, rendering the loop colostomy an excellent option for palliative diversion of obstructing lesions of the distal bowel. The loop colostomy may be used to temporarily protect colorectal or coloanal anastomoses. The loop colostomy may also be used to temporarily divert stool and facilitate staged repair for pelvic sepsis, rectal trauma, non-healing sacral decubitus ulcers, and anorectal fistulizing processes. Rarely, an iatrogenic or penetrating-trauma perforation of the colon can be mobilized and exteriorized as a loop colostomy, with the injury incorporated as the stoma orifice. Although a transverse loop colostomy is a relatively simple stoma to create, it is often poorly tolerated by patients due to its large size, cephalad location on the abdominal wall, and frequent stoma-related complications. In most instances, a loop ileostomy provides better short-term and long-term outcomes. Since both proximal and distal bowel conduits are accessed easily through the stoma trephine, loop stomas can often be closed easily through a peristomal dissection without laparotomy. Although loop stomas can usually be reversed easily, they may be employed on a permanent basis if needed and may be useful in the setting of unclear prognoses.

Physiology

Colostomy function is dependent upon the level of diversion. The colon receives approximately 1500–2000 mL of liquid stool from the small bowel daily, of which it reabsorbs approximately 90 % of water (1350 mL) and excretes 100–150 mL of water within solid waste [2, 3]. The majority of colonic fluid and electrolyte reabsorption occurs in the right colon. Distal colostomies arising from the sigmoid or left colon tend to produce more solid stool than proximal stomas fashioned from the transverse or ascending colon. Transverse colostomies may be more prone to fluid and electrolyte imbalances akin to small bowel stomas.

Similar to the wide range in bowel movement frequency and consistency seen across individuals, colostomies function variably. Since colonic transit time varies between 24 and 150 h [2], distal colostomies may function periodically as solid stool is propelled through the colon, whereas gas tends to pass more continuously. The episodic nature of stool passage through distal colostomies can lend itself to specialized colostomy irrigation techniques which may enable patients to control stool passage or occasionally avoid a stoma appliance altogether [4]. Proximal colostomies with liquid stool tend to function more continuously akin to small bowel stomas and are not well suited for stoma irrigation techniques.

Small Bowel Stomas

Configuration

Like colostomies, small bowel stomas (e.g., ileostomy, jejunostomy) can be used for permanent or temporary enteric drainage. A permanent end ileostomy (Figure 55-2a) is commonly used following a total proctocolectomy for Crohn's disease, whereas a temporary end ileostomy may be used following a total abdominal colectomy for ulcerative colitis for an eventual ileal-pouch anal anastomosis. Patients with hereditary cancer syndromes (e.g., familial adenomatous polyposis, hereditary non-polyposis colon cancer) who are poor candidates for restorative procedures may be offered a permanent end ileostomy. Repetitive bowel resections, which

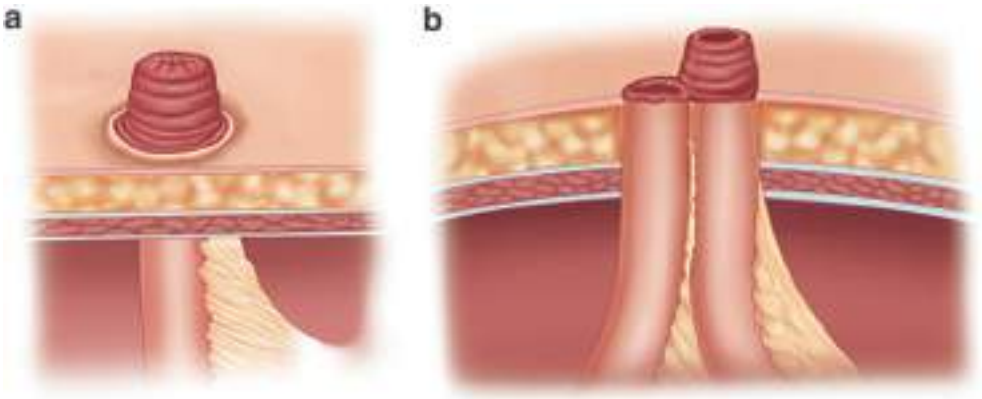

FIGURE 55-2. (**a**) End ileostomy. (**b**) Loop ileostomy.

may be seen occasionally in Crohn's disease, may require creation of a jejunostomy since no ileum may remain from prior resections. Akin to a colostomy, a temporary small bowel end stoma may be created in a damage control situation when anastomosis creation is inadvisable due to contamination, hemodynamic instability, poor tissue quality, or preoperative patient factors including nutritional status and immunosuppression.

Like a loop colostomy, a loop small bowel stoma (Figure 55-2b) is a helpful adjunct commonly utilized as temporary means of fecal diversion, although a well-constructed loop stoma can be permanent if needed. The small bowel caliber, robust vascularity, and distance from the distal colon and rectum make loop ileostomy a favorable choice for temporary diversion by many surgeons. Liquid ileostomy output can rarely lead to pouching problems, dehydration, electrolyte imbalance, and renal failure. A comparison of temporary diverting loop ileostomy and colostomy is debated later in this chapter.

Physiology

Since small bowel stomas bypass colonic sodium and water reabsorption, they may render patients with variable, but occasionally profound, fluid and electrolyte imbalances. Small bowel length is highly variable ranging from 275 to 850 cm [5] with a mean in situ length of approximately 500 cm [6] which receives from 9 to 10 L of fluid daily from proximal gastrointestinal sources. The majority of small intestinal nutritional absorption occurs within the first 150 of intestine, as nearly 6 L of fluid is reabsorbed from the jejunum while only 2.5 L is reabsorbed in the ileum [2]. Normal end ileostomy outputs can be highly variable ranging from 200 to 1200 mL daily with a composition listed in Table 55-1. As a result, stomas created more proximally in the small bowel (e.g., jejunostomy) bypass absorptive intestinal surface area and may cause nutritional, electrolyte, and fluid imbalance. Since fat-soluble nutrients are absorbed in the terminal ileum, proximal fecal diversion (greater than 100 cm proximal to the ileocecal valve) can render a patient with steatorrhea and vitamin B12 deficiency. Even creation of a new terminal end ileostomy that preserves the total length of small bowel may be transiently prone to high outputs due to diversion of the ileocecal valve and colon. Management of high ileostomy outputs is detailed later in the chapter.

TABLE 55-1. Composition of normal ileostomy effluent

	Daily excretion	Range	Concentration	Range
Wet weight	500 g	200–600 g		
Dry weight	38 g	24–48 g		
Water content			92 %	88–94 %
pH			6.3	6.1–6.5
Sodium	55 mEq	30–80 mEq	115 mEq/L	100–130 mEq/L
Potassium	4 mEq	3–6 mEq	8 mEq/L	5–11 mEq/L
Chloride	20 mEq	15–30 mEq	45 mEq/L	15–40 mEq/L
Calcium	18 mEq	15–40 mEq	25 mEq/L	10–64 mEq/L
Magnesium	8 mEq	7–9 mEq	15 mEq/L	10–28 mEq/L
Phosphorus	150 mEq	122–202 mEq		
Nitrogen	1 g	0.6–2.4 g		
Fat	2.2 g	1.5–3.8 g		

Adapted from Rombeau, "Physiologic and Metabolic Effects of Intestinal Stomas" [2]

Preoperative Considerations for the Ostomate

As with most aspects of surgery, conscientious preoperative preparation is essential and can profoundly impact the patient. Preoperative stoma site marking and patient education improve stoma-related clinical outcomes and patient quality of life and experience, while decreasing healthcare resource utilization. Although many medical centers provide robust complementary ancillary resources to assist the ostomate and surgeon, the surgeon is ultimately responsible for perioperative care and should be competent in preoperative stoma preparation.

Stoma Site Marking

Routine preoperative identification of potential stoma sites is a crucial skill for the colorectal surgeon and is recommended by ASCRS and the Wound, Ostomy, and Continence Nurses Society whenever stoma creation is a possibility [7, 8]. Preoperative stoma site marking decreases postoperative complications [9, 10] and improves stoma-specific quality of life, overall patient quality of life, confidence, and independence compared to non-marked patients and may decrease stoma care costs [11]. Creating any intestinal stoma, whether permanent or temporary, in a properly chosen location is the most important predictor of an ostomate's quality of life following stoma construction.

The ideal stoma site is based on individualized assessment of the patient with respect to body habitus, contours, scars, bony prominences, and the umbilicus assessed in the standing, sitting, and laying positions. Special consideration to the patient's lifestyle, occupation, impairments, and preferences should be sought in conjunction with the patient. The "stoma triangle" (Figure 55-3a) is bounded by the anterior superior iliac spine, the pubic tubercle, and the umbilicus and has

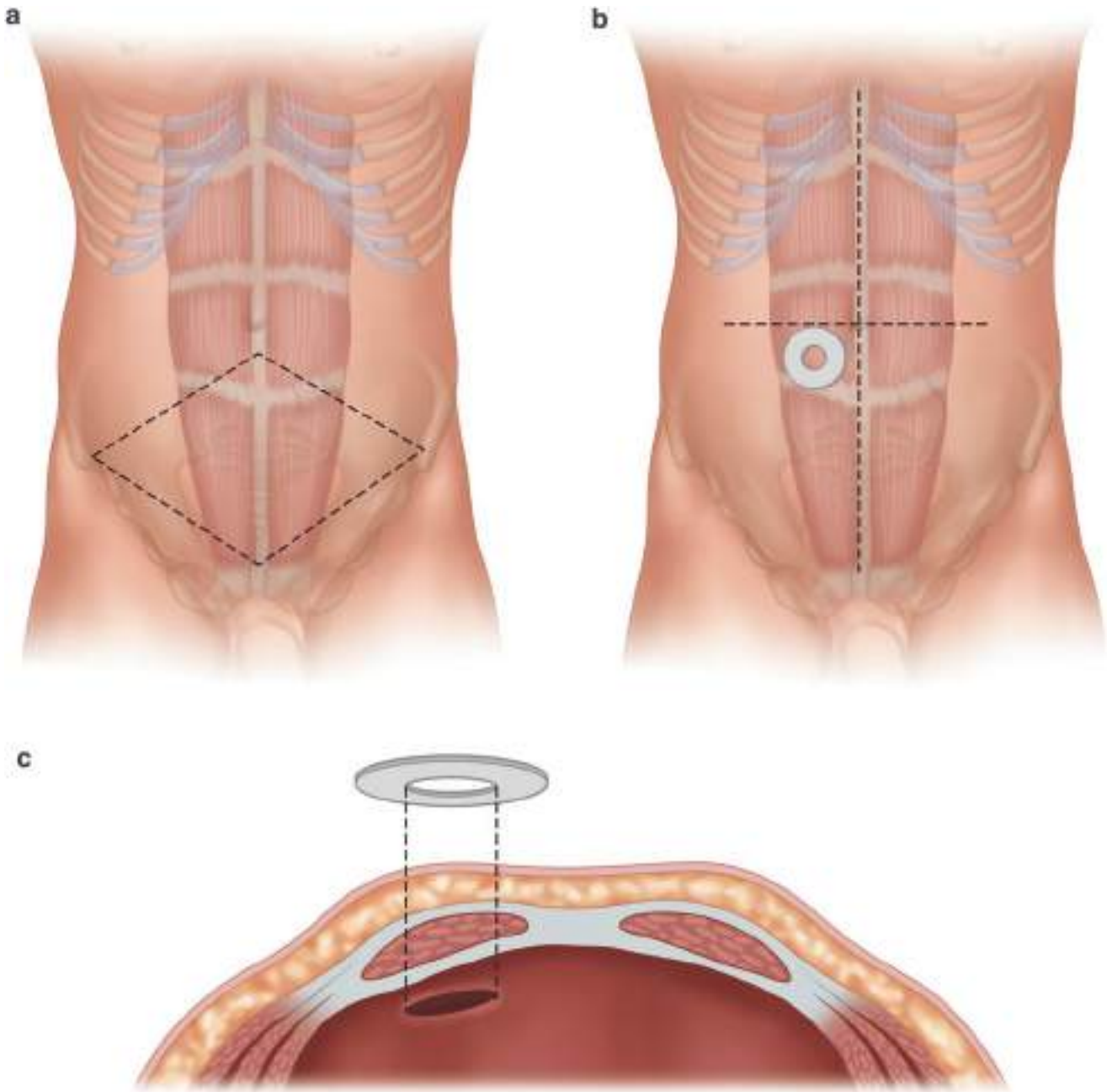

FIGURE 55-3. (**a**) The "stoma triangle." (**b**) Intersection of the infraumbilical fat pad and rectus sheath, marked by a stoma siting ring. (**c**) Cross-sectional view of the stoma trephine path and stoma siting ring, fashioned perpendicular to the abdominal wall without veering medially or laterally.

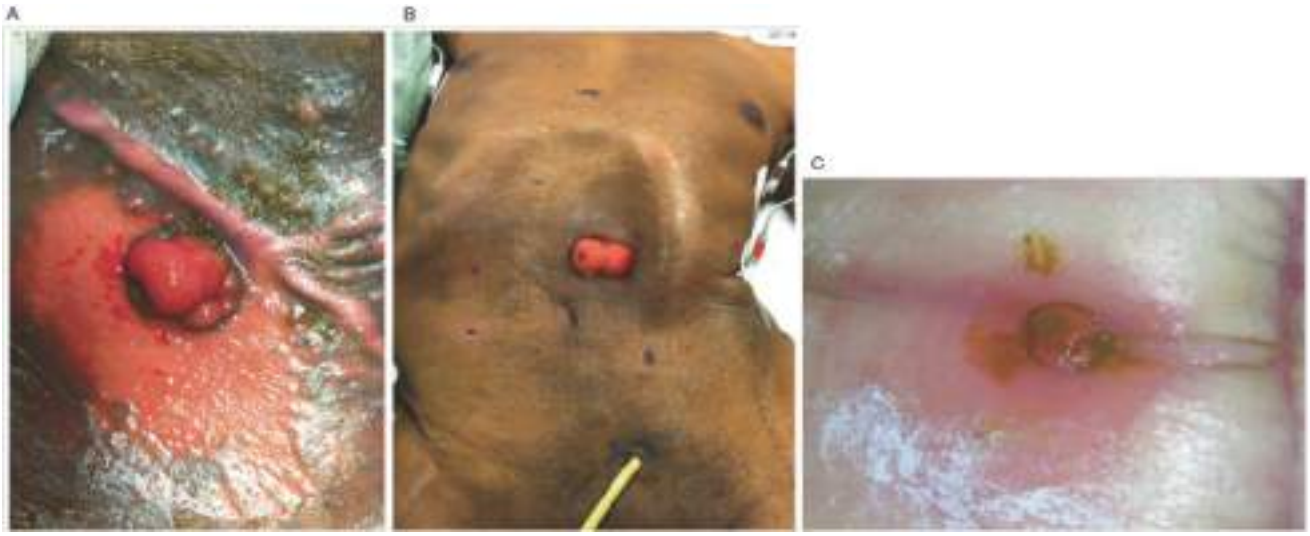

FIGURE 55-4. (**a**) A loop ileostomy created too close to an incision which interfered with stoma appliance sealing, resulting in leaks and marked skin excoriation (photo credit: Michael McGee). (**b**) A transverse loop colostomy created too close to the costal margin, causing frequent appliance dislodgement (photo credit: Michael McGee). (**c**) Stomas created in a skin fold, which may not be realized until the patient is sitting or bending over [photo credit: Wound, Ostomy, and Continence Nurses Society (http://www.wocn.org/page/ImageLibrary)].

been used by some groups to initially direct the surgeon to a preliminary area suitable for stomas [12]. The stoma site is at the geometric center of the triangle within the rectus sheath. Alternatively, the surgeon may identify the intersection of the infra-umbilical fat pat summit and the rectus sheath as a preliminary stoma site (Figure 55-3b, c) [13]. All efforts should be made to keep the stoma within the rectus sheath, as this is argued to decrease risk of parastomal herniation, although meta-analyses failed to show an effect in stoma location [14, 15].

After preliminary selection of a site, the surrounding peristomal skin must be carefully inspected ensuring the site avoids scars, folds, creases, and the umbilicus that may hinder stoma appliance application and cause leakage (Figure 55-4a). Ideally, the site should have a 2-in. perimeter of clear, intact skin to adequately seal with a stoma appliance, and a commercially available stoma-siting disk may help with siting (Figure 55-3c). The costal margin, anterior superior iliac spine, and pubic symphysis should be avoided since these bony prominences may dislodge the stoma appliance (Figure 55-4b). Skin folds and creases are not typically appreciated until the patient is sitting, so the correct site should be reconfirmed once the patient is sitting (Figure 55-4c). While the patient is sitting, it is equally important that the patient has a clear sight line to the stoma site. Patients with a large pannus may require moving the site superiorly along the rectus to a supra-umbilical sight ensuring sight lines to the intended area. Moreover, an obese pannus may be thinner superiorly compared to inferiorly, easing stoma trephine creation. Lastly, the patient should be assessed while standing to confirm that the intended site avoids the pants waistline, pendulous breasts, or hernias. While standing, attention to the patient's posture, contractures, and stoma site location while bending should be assessed. Finally, reviewing potential stoma sites with the preoperative patient confirms suitable sites for both patient and practitioner.

Stoma sites should be marked with an indelible marker or tattooed with a fine gauge needle (26 gauge) and India ink [13]. Stoma sites can be marked several days in advance and protected with an occlusive transparent dressing to protect the ink from washing away. Multiple potential stoma sites can be identified, marked, and ranked in order of preference affording the surgeon options should intra-operative findings require alternate stoma locations. Rarely, two stomas may be required for urinary and fecal drainage (e.g., for pelvic exenteration) and each stoma site should be created on opposite sides and at different levels whereby avoiding interference in case a stoma belt is needed. Since preoperative stoma site markings may wipe away with antiseptic skin preparations, the surgeon may find it helpful to etch a small epidermal scratch mark at each site with an 18-gauge needle following anesthesia induction to mark the site for the duration of the operation.

Preoperative Stoma Education

The mainstay of stoma education traditionally occurs in the postoperative period; however, emerging evidence suggests that preoperative stoma education may be equally important. Several factors may hinder postoperative stoma education. Pain, medications, and psychological stress may diminish

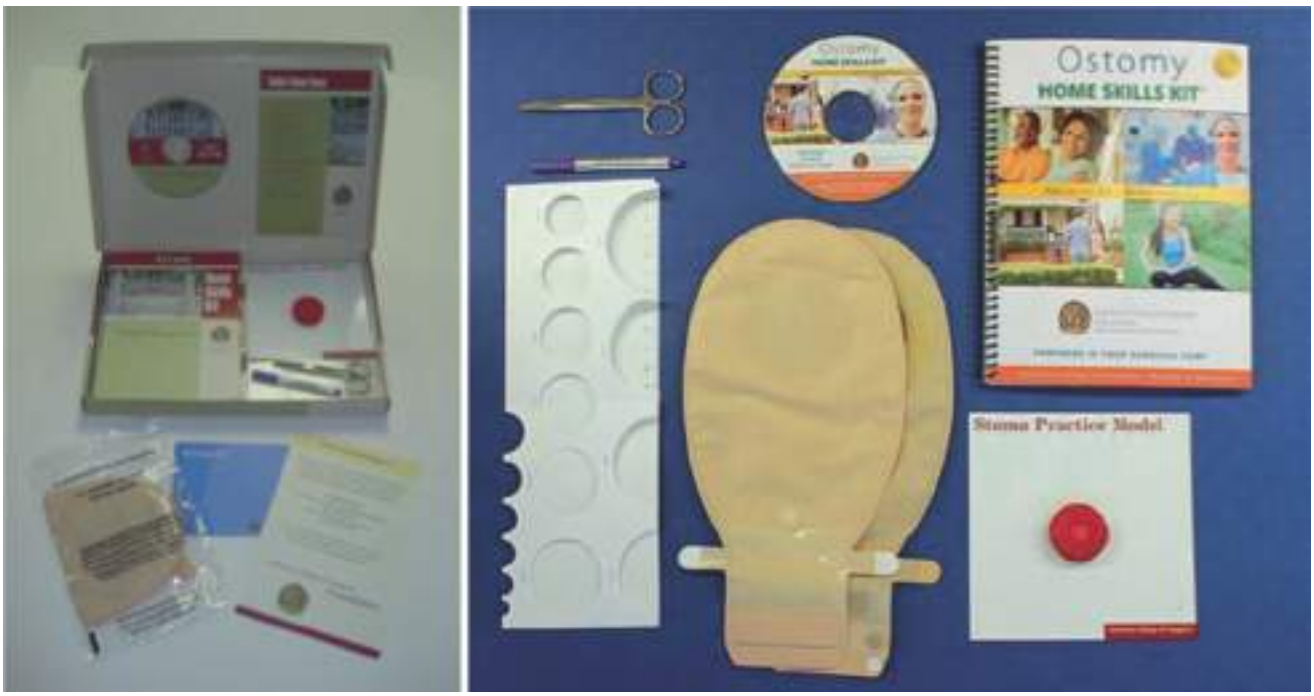

FIGURE 55-5. The American College of Surgeons Ostomy Home Skills Kit (photo credit: American College of Surgeons).

educational effectiveness in the early postoperative period where by increasing the value of preoperative education. Chaudhri et al. reported that two, 45-min pre-op visits with audiovisual aids and instruction decreased time to stoma care proficiency from 9 to 5.5 days, decreased hospital length of stay from 10 to 8 days, and decreased unplanned provider encounters with a net cost savings of $2104 per patient [16]. Similarly, Younis et al. revealed preoperative patient education sessions reviewing stoma models, sample appliances, and supplies decreased inpatient length of stay from 14 to 8 days [17]. Free and low-cost, commercially prepared, preoperative resources are available from stoma supply manufacturers and through the American College of Surgeons (ACS). The ACS Ostomy Home Skills Kit (Figure 55-5) contains an instructional DVD demonstrating stoma care techniques, sample stoma supplies, and a plastic model stoma that allows the patient to simulate preoperative stoma care. The standardized interactive program has been developed by the American College of Surgeons (ACS) in collaboration with the American Society of Colon and Rectal Surgeons (ASCRS) and other societies and organizations. Over 55,000 kits have been distributed since release in 2010. Preliminary, unpublished data from the ACS reveal that patients receiving the Ostomy Home Skills Kit preoperatively were more confident with stoma care, were less likely to have problems, required less provider help once home, and were more satisfied with their care compared to patients receiving standard postoperative stoma education.

Technical Considerations of Stoma Creation

Small Bowel End Stoma

Small bowel end stomas are typically easy to create owing to the mobility of the robustly collateralized small bowel mesentery. Laparoscopic or open approaches may be used, although the laparoscopic approach is favored, if feasible [7]. After selecting the target small bowel segment, care is taken to ensure the mesentery is fully mobilized and all adhesions are freed to allow tension-free reach beyond the abdominal wall. Division of some mesenteric vessels may be necessary to obtain adequate reach, particularly in patients with a thick abdominal wall.

During open surgery, identification of mesenteric vessels can be assisted by transillumination of the mesentery with a light source, providing guidance on which vessels to preserve or sacrifice to sustain stomal perfusion, if needed. Akin to preparing bowel for an anastomosis, careful assessment of bowel perfusion can avoid ischemia-related stomal complications such as stenosis and retraction. Obese patients or those with thickened or inflamed small bowel mesentery may require additional lengthening maneuvers detailed later in this chapter (see section “Special Considerations: The Difficult Stoma”).

Once adequate mobilization of the small bowel segment is obtained, a cylindrical stoma trephine is created at the previously marked stoma site. For an end ileostomy with normal

caliber bowel and mesentery, the authors prefer to excise an approximately 2-cm diameter skin disk and vertically divide the subcutaneous tissues down to the level of the anterior rectus sheath without "coring" or removing subcutaneous tissues. During open surgery, an assistant's two fingers firmly pushing a folded gauze sponge anteriorly at the intended point of peritoneal entry may ease trephine creation by compressing the tissue girth and ensuring the trephine cylinder remains orthogonal to the abdominal wall (Figure 55-6). The anterior rectus sheath is incised with a 3-cm vertical incision. The exposed fibers of the rectus muscle are carefully split with a large clamp to allow lateral and medial distraction of the split rectus muscle to expose the posterior rectus sheath. Special care is taken to ensure all fibers of the rectus muscle and inferior epigastric vessels are completely split and retracted to avoid pesky muscular bleeding. With the posterior rectus sheath exposed, cautery is used to make a 3-cm vertical incision directly onto the assistant's gauze sponge, whereby completing the stoma trephine. Passage of one or two fingers through the completed trephine gently dilates and confirms trephine size. If necessary, the trephine diameter can be further enlarged by making a radial skin incision at the skin level or extending either anterior or posterior rectus sheath incisions.

Laparoscopic approaches follow the same general principles as open surgery. After assuring adequate mobilization laparoscopically, an abdominal wall trephine is made. If an extraction site is present, a trephine can be made akin to open surgery with an assistant using two digits pressing upward. If no extraction site exists, careful trephine creation is needed to avoid injuring intra-abdominal contents while incising the posterior rectus sheath and peritoneum. Once the trephine is completed, pneumoperitoneum is quickly lost and it can be difficult to locate target segment of bowel through the small trephine. An extra-small plastic sleeve wound retractor placed in the stoma trephine may aid visualization. The authors suggest placing a locking atraumatic bowel grasper on the tip of target loop of bowel, left immediately under the peritoneal side of the stoma trephine so that the bowel can easily be visualized once pneumoperitoneum is lost. Once the abdomen is desufflated, the laparoscopic bowel grasper can be directed to a stoma trephine. Once the target bowel is identified through the trephine, it can then be transferred to a Babcock clamp placed through the trephine.

For both open and laparoscopic techniques, the previously mobilized bowel segment is carefully delivered through the properly sized trephine with assistance of a Babcock clamp. To avoid stoma retraction, 5–6 cm of small bowel and corresponding mesentery should be completely pulled through and be left above the level of the skin. Care should be taken to carefully coax the corresponding bowel mesentery through the trephine without injury or avulsion. A bimanual approach may be necessary to gently push and guide the bowel mesentery from the peritoneal surface while the surgeon is gently pulling the bowel at the skin. The blunt side of an Adson tissue forceps can be used as a shoehorn and assist the stoma mesentery eviscerate if it lodges at the rectus sheaths or subcutaneous tissues. Additional techniques are described to help coax the difficult stoma through the abdominal wall later in the chapter (see section "Special Considerations: The Difficult Stoma"). With an adequate length of bowel exteriorized through the abdominal wall, the stoma should be assessed for tension, viability, and mesenteric bleeding. A persistently dusky stoma may be related to mesenteric vascular injury, venous outflow occlusion from a narrow trephine, or unintentional vascular division during mesenteric mobilization and should be revised prior to closing the abdomen. Typically, the stoma is left for maturation until all other abdominal wounds are closed to minimize incisional contamination.

Once all remaining abdominal wounds are closed and protected from topical contamination, the end ileostomy is matured to ideally protrude 2–3 cm. Ileostomy maturation is necessary to cover and protect the eviscerated bowel serosa with mucosa, whereby shielding it from the caustic bowel effluent which can cause inflammatory serositis and ileostomy stricture. If the ileostomy was stapled closed, the staple line is excised and the full thickness of the bowel wall is everted. Occasionally, thick or fatty mesentery may require careful debulking to allow complete bowel wall eversion. Multiple interrupted absorbable sutures are used to suture the everted bowel wall to the skin (Figure 55-7). Classically, such "Brooke" sutures also incorporate a seromuscular purchase of the bowel at the skin level that fixes the everted structure at the skin. Sutures should carefully be placed through the dermis, but not the epidermis, to avoid mucosal cellular implants that have been reported to migrate along suture lines and colonize the epidermis with ectopic mucosal islands. Such dermal mucosal islands are thought to secrete mucus on the peristomal skin and interfere with stoma appliance adhesion [18]. The finished end small bowel stoma should ideally protrude 2–3 cm from the skin that distances the skin–appliance sealing interface from the point of stool egress that improves sealing and decreases complications [7, 10]. Flush or inadequately protruding small bowel stomas may be fraught with leakage since caustic liquid small bowel contents can easily leak underneath the stoma flange causing painful, excoriated, weeping skin wounds that are difficult to pouch. Ileostomy heights less than 2 cm are associated with problems, and the height of the stoma is inversely proportional to likelihood of complications [19]. Since a significant portion of end stomas will be permanent, the surgeon should take great care in making the perfect stoma, which may save the patient, surgeon, and family a lifetime of frustration.

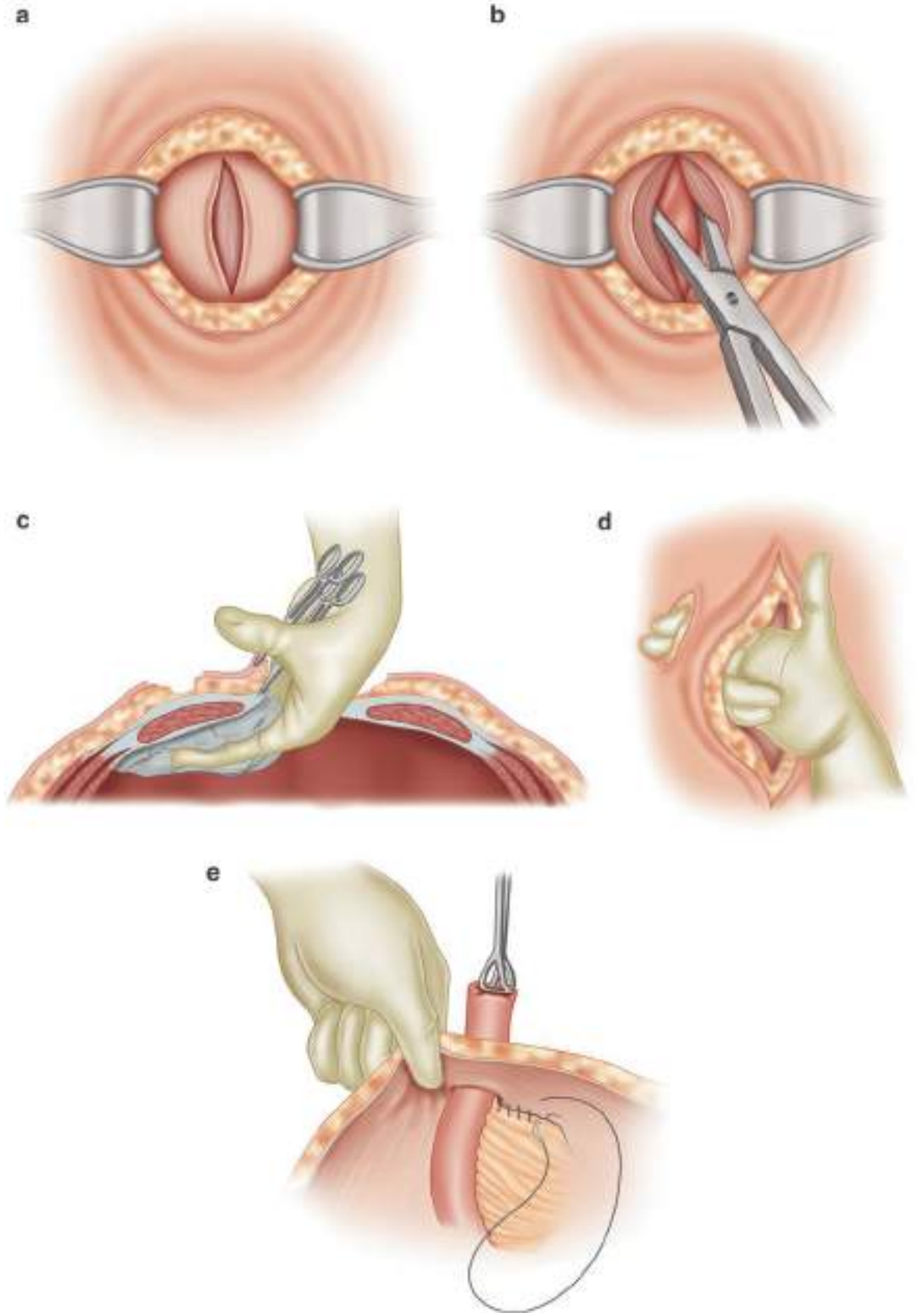

FIGURE 55-6. Creation of an end small bowel stoma. (**a**) A 2-cm skin disk is excised and the subcutaneous tissues are split to the level of the anterior rectus sheath. (**b**) The anterior and posterior rectus sheaths are incised vertically and the rectus muscle is split. (**c**) An assistant may assist in stoma creation by pushing anteriorly using a folded sponge to protect intra-abdominal contents. (**d**) Two fingers are passed through the completed stoma trephine to assure adequate sizing. (**e**) The ileostomy is eviscerated with assistance of a Babcock clamp.

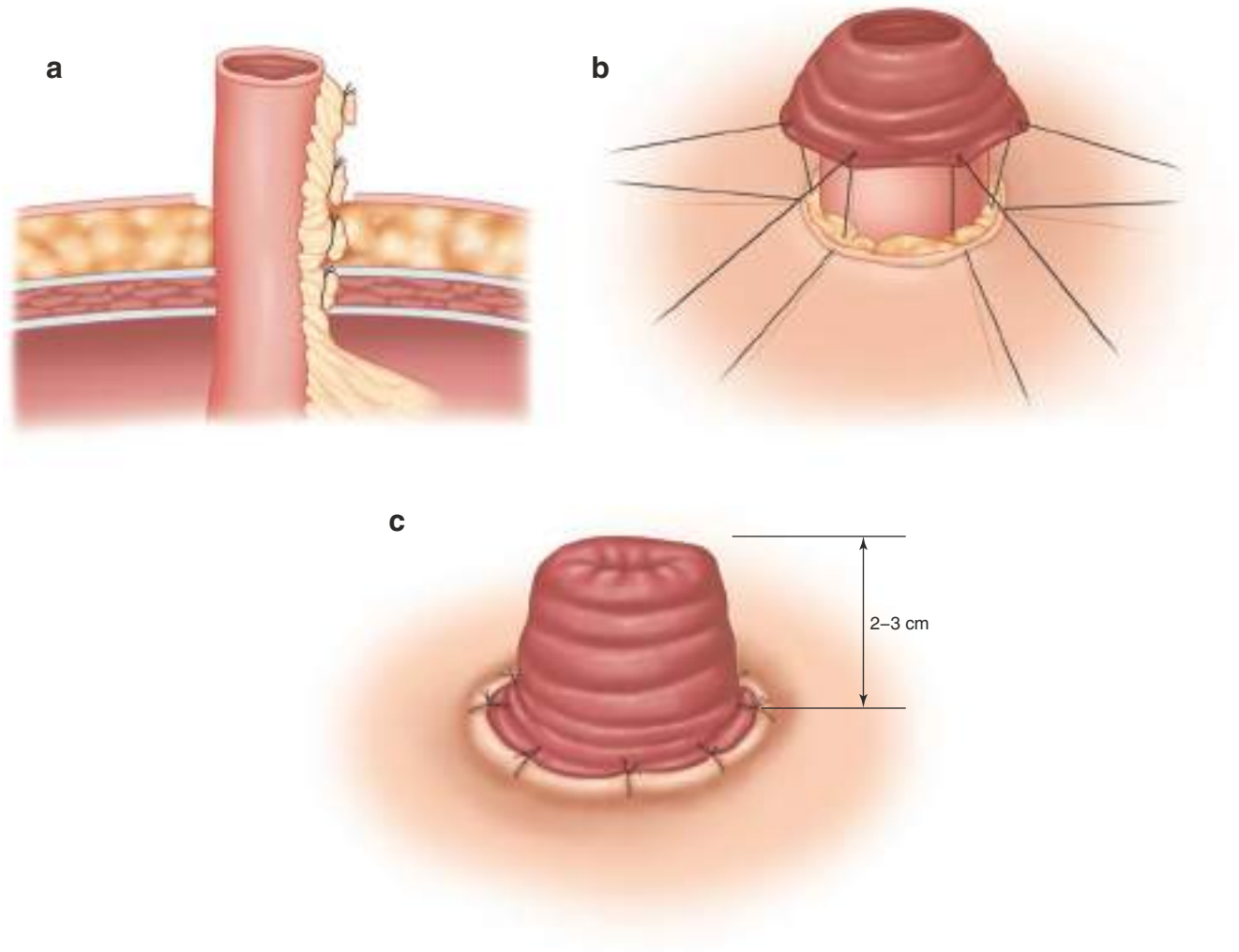

FIGURE 55-7. Maturation of an end small bowel stoma. (**a**) An adequately mobilized, tension-free, length of small bowel is eviscerated through the stoma trephine. (**b**) Multiple interrupted absorbable sutures are used to mature the stoma. (**c**) The completed small bowel stoma should ideally protrude 2–3 cm from the skin level.

Small Bowel Loop Stoma

Small bowel loop stomas are fashioned with either laparoscopic or open techniques with a segment of well-mobilized bowel free of adhesions. For open loop stomas, a fine-tipped clamp is passed to create a small defect at the bowel wall–mesentery interface and a thin Penrose drain or umbilical tape is passed underneath the bowel (Figure 55-8). Some prefer to place different colored seromuscular marking stitches to orient the bowel limbs and prevent twisting and inadvertently maturing the distal limb of the loop. Alternatively correct bowel orientation can be insured by drawing an arrow on the anti-mesenteric border of the bowel, indicating the proper direction of intestinal flow. A 2.5-cm diameter stoma trephine is made at a previously marked site using the previously described technique. Generally, the stoma trephine is made slightly larger for loop stomas than end stomas, and the final trephine typically accommodates two fingers easily. The Penrose drain is then used to safely pull the loop of bowel through the stoma trephine while minimizing trauma to the bowel. The surgeon confirms that there is no twisting of the mesentery. The blunt paddle-like back end of an Adson forceps is again helpful if the bowel is caught at the fascia or dermal level. The Penrose drain may be exchanged for a plastic stoma rod to temporarily support the bowel loop above the skin until adhesions form between the trephine and bowel wall, although the utility and type of a supporting rod is debatable [20]. If used, the rod should not be under significant posterior tension and additional bowel should be mobilized or pulled through the trephine if the rod is causing a deep indentation. Laparoscopic loop stomas are made similarly to laparoscopic end stomas as detailed above.

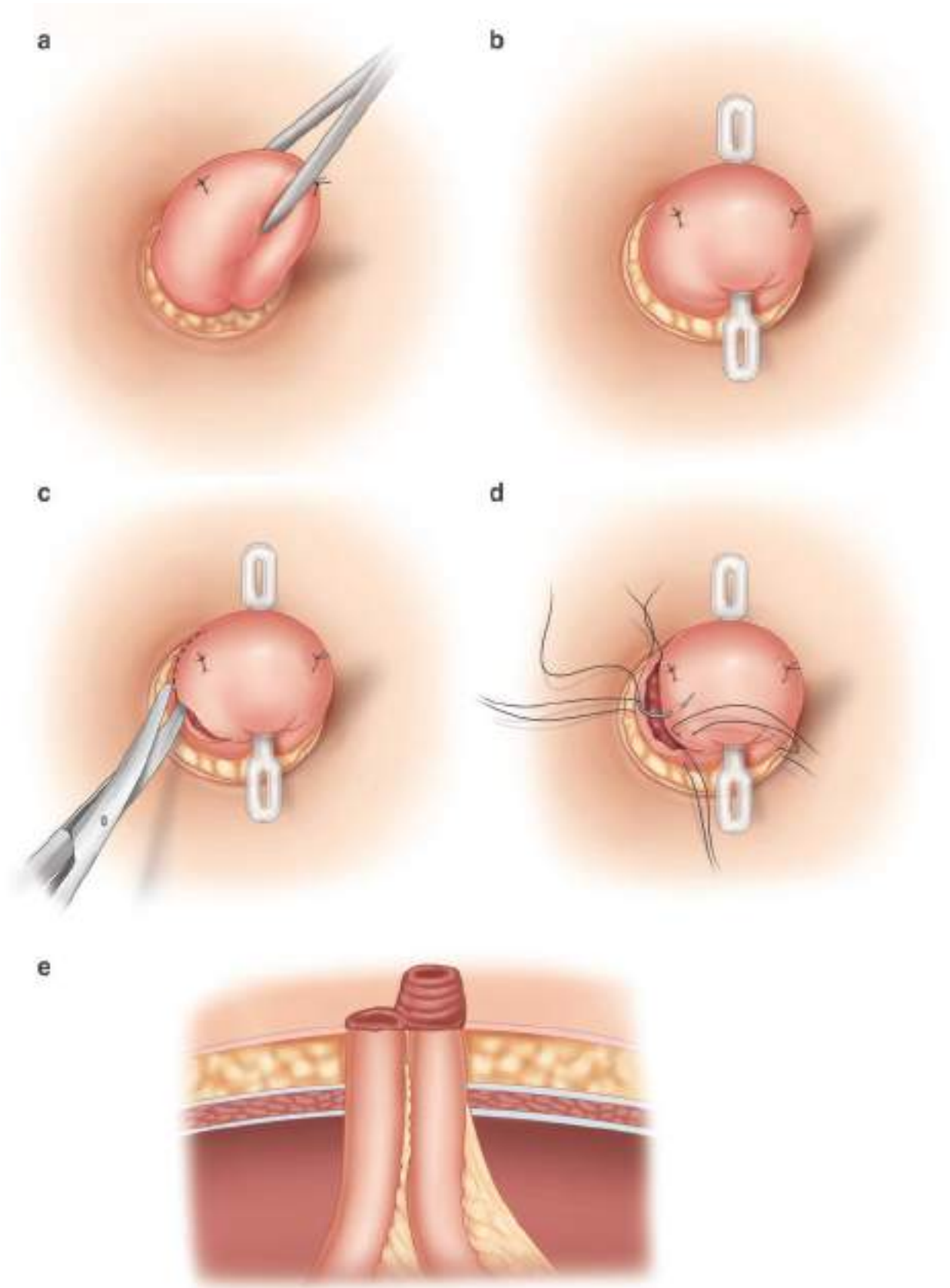

FIGURE 55-8. Creation of a loop small bowel stoma. (**a**) A narrow Penrose drain is passed through a mesenteric defect and used to gently pull the target loop through the stoma trephine. (**b**) The Penrose drain may be exchanged for a stoma rod. (**c**) The distal segment of the loop stoma is opened at the skin level. (**d**) The distal "hood" of small bowel is then everted and sutured over the proximal limb to create a spout. (**e**) The completed small bowel loop stoma.

Following closure and protection of all abdominal wounds, a near-circumferential incision is made along the distal limb bowel wall at the level of the skin. The mesenteric portion of the bowel wall is left intact and is not divided. Absorbable sutures are used to secure the defunctioned segment to the dermis. The remaining "hood" of bowel is then everted with the blunt back end of an Adson clamp and sutured to the dermis. As with end small bowel stomas, the proximal bowel limb should protrude 2–3 cm from the skin when finished allowing a watertight fit between the stoma appliance and the peristomal skin whereby decreasing postoperative stoma-related complications. When used, the stoma rod is typically removed in 3–5 days once adhesions have formed assuming there is no tension between the rod and skin. Although loop stomas are often considered temporary, they should be constructed durably in the event that distal intestinal continuity cannot be restored. The use of intra-abdominal anti-adhesion materials may be considered to decrease adhesions and possibly ease subsequent reversal at temporary ostomy sites [7, 21–23].

End Colostomy

Creation of an end colostomy follows similar techniques as described for small bowel stomas, but the tenuous colonic blood supply requires special consideration. Both laparoscopic and open approaches can be used. For either approach, great care should be taken to assuredly and completely mobilize the intended segment of colon so that several centimeters of bowel reaches above skin level in a tension-free manner. Unlike the relatively mobile small bowel mesentery, the colonic conduit and mesentery may require substantial mobilization depending upon the level of diversion. An end sigmoid colostomy may not require significant mobilization due to the redundant nature of the sigmoid loop in a thin patient; however, a proximal end descending colostomy may require full mobilization of the splenic flexure with high vascular ligation to obtain sufficient reach in an obese patient. The authors strongly suggest that the surgeon treats the colonic conduit akin to an anastomosis by eliminating tension with adequate colonic mobilization and assuring adequate perfusion. Confirming pulsatile blood flow from the marginal artery during colonic division helps to assess adequate perfusion of the colostomy. It may be helpful to excise all epiploic appendages from the anti-mesenteric bowel wall easing eventual evisceration.

For open end colostomies, once the segment of colonic conduit is chosen and prepared, a 2.5-cm diameter stoma muscle-splitting trephine is fashioned at the site of previous marking using the previously described techniques. An end colostomy may require a larger trephine depending upon the bowel caliber and mesentery thickness. Epiploic appendages may be excised to ease colon passage through the abdominal wall trephine. The colon is passed through the stoma trephine with a Babcock clamp and eviscerated. The surgeon confirms a pink, well-perfused stoma rests comfortably for 3–4 cm above the skin level without tension or retraction. Following closure and protection of abdominal wounds, the colostomy is opened everted and sutured to the skin to produce a colostomy that protrudes 1–2 cm. Typically, the solid nature of colostomy effluent is not toxic to surrounding skin, and a lengthy stoma eversion is not necessary. If necessary, a colostomy can be made flush with the skin, but the authors suggest that a small protrusion helps patients with stoma pouching and skin care. Once matured, the colostomy should be evaluated to confirm adequate perfusion with a pink glistening mucosa. Laparoscopic end colostomies utilize the same principles as detailed above.

Loop Colostomy

A loop colostomy is typically fashioned from the non-peritonealized sigmoid or transverse colon, although any segment of colon can be used in a loop configuration with adequate mobilization via open or laparoscopic techniques. After identifying the target segment of colon, an assessment of reach and mobilization is performed assuring the colon loop reaches several centimeters above the previously marked stoma site without tension. For open surgery, a narrow Penrose drain is passed through an avascular recess at the junction of the mesentery and colon wall. After creating an approximately 3-cm diameter trephine using aforementioned techniques, the colon loop is gently pulled through the trephine and delivered over a stoma rod. Following closure and protection of abdominal incisions, the loop colostomy is matured by incising along the long axis of the bowel and maturing the cut edge of bowel to the skin circumferentially (Figure 55-9). The matured loop colostomy may be quite large depending upon the bowel caliber, mesenteric thickness, and postoperative edema. As with loop small bowel stomas, loop colostomies may be temporary or permanent and should always be constructed durably if stoma reversal is inadvisable. Laparoscopic

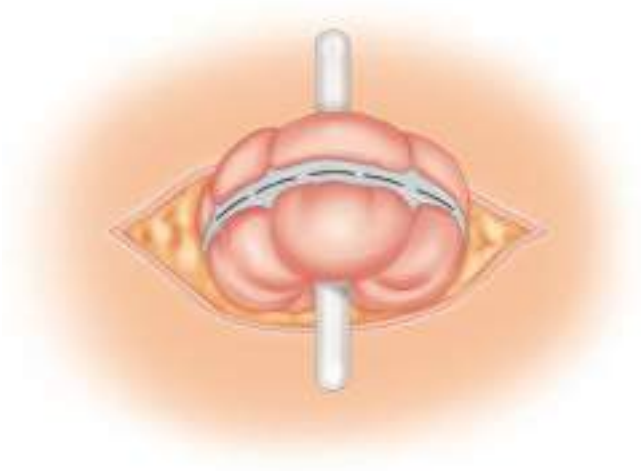

FIGURE 55-9. Creating an incision along the long axis of the colon to create a loop colostomy.

techniques follow similar principles as detailed above. As with loop small bowel stomas, use of intra-abdominal anti-adhesive products may be considered with temporary loop colostomies to potentially ease future reversal [7].

Postoperative Care for the Stoma

Early Inpatient Postoperative Care

Immediately after creation, the stoma will become edematous and swell to two to three times the original size. The stoma will shrink to normal size after approximately 4–6 weeks. The new stoma should be monitored daily and assessed for color, viability, and retraction and should remain pink and moist and protrude well. If a stoma rod was used, the rod is typically removed between 3 and 5 postoperative days or when centripetal tension decreases and the rod easily slides out. The stoma rod can be left for longer periods of time for difficult or tenuous stomas.

Both small bowel and colonic stomas do not typically function immediately. Stoma outputs initially resemble small volumes of serosanguinous or mildly bilious thin fluid without particulate matter described as "bowel sweat." Bowel function will recover with time and stoma outputs will increase. Colostomies tend to produce gas first, followed by liquid stool, and ultimately more solid waste as time proceeds—although this cadence can be variable. Small bowel stomas tend to function sooner than colostomies. Even during fasting, small bowel stomas will produce significant volumes or dark green bilious outputs. As diet is advanced, particulate materials intensify and small bowel effluent becomes increasingly thicker. As described earlier, small bowel stoma outputs can be high leading to profound dehydration and electrolyte abnormalities. As early postoperative bowel function returns, a deluge of backlogged bowel contents may rush out producing initially high stoma outputs. Small bowel stoma outputs generally taper with time, but may require dietary and medical interventions if outputs are persistently high (see section "High Output Small Bowel Stomas"). Over 30 % of new ileostomy patients may experience dehydration with early postoperative readmission rates exceeding 15 % [24]. Recent studies show that perioperative stoma care pathways focusing on patient education, standardized discharge criteria, output logs, visiting nurse care, and early follow-up may decrease postoperative readmissions related to dehydration and should be strongly considered for new ostomates [7, 25].

Patient-centered postoperative stoma education should begin as soon as the patient can participate. Since approximately half of stoma care is provided by a spouse and a quarter of stoma care is provided by an offspring, caregiving family members should participate in stoma education [11]. The ultimate goal is to train the patient and caregivers to become proficient in caring for the stoma and troubleshoot problems. Postoperative patients typically follow a graduated program that focuses on both knowledge and skills training for emptying, applying, and troubleshooting common stoma problems. Many new ostomates are only capable of emptying a stoma pouch at the time of discharge. As a result, patients are often discharged home lacking knowledge on how to manage common pouch-related issues. Unpublished data from the American College of Surgeons revealed only 53 % of home-going new ostomates were capable of applying a new pouch and only 28 % were able to fix pouch leaks. As a result, 45 % of all new home-going ostomates worried about self-care, 40 % felt sad and/or depressed, and 62 % were uncomfortable leaving home. As a result, many institutions bridge postoperative stoma care and education into the outpatient domain with home nursing.

Postoperative Outpatient Care

ASCRS believes that optimal care for patients undergoing ostomy surgery includes preoperative and postoperative care by an ostomy nurse specialist, such as a WOCN-certified nurse [7]. Periodic stoma assessment and educational reinforcement should continue following discharge from stoma surgery, particularly in the early postoperative period when stoma-related complications are most frequent. Attention should be paid to stoma outputs and the frequency that the stoma flange is changed, which is a good surrogate for peristomal skin quality and leakage. Ideally, a flange should last 3–5 days between changes. More frequent appliance changes may indicate improper technique, inappropriate appliance, peristomal skin disease, or a poorly located or constructed stoma. A recent survey indicated that a scheduled postoperative visit with a certified wound, ostomy, and continence nurse (WOCN) revealed that over 60 % of new ostomates had peristomal skin irritation that was unrecognized in nearly half of patients. Once identified and treated, stoma-specific quality of life improved [26]. Additionally, structured postoperative group sessions may prove beneficial to the ostomate even in the late postoperative period [27]. Ostomy support groups, which are organized online and in person, may provide ongoing support for novice and experienced ostomates alike [28].

Stoma Appliances

Stoma appliances come in a variety of sizes and configurations, but generally consist of an adhesive flange (wafer) that seals to the skin and a collecting bag which may come in one or two piece models (Figure 55-10). Two-piece appliances allow the collection bag to completely detach from the flange and allow inspection of the stoma without completely removing the flange and may be advantageous in the early postoperative period while the stoma is examined daily. Stoma flanges generally comprise a pectin-like adhesive wafer ring surrounded by waterproof tape-like layer. The inner diameter of the ring comes in various sizes and can often be trimmed

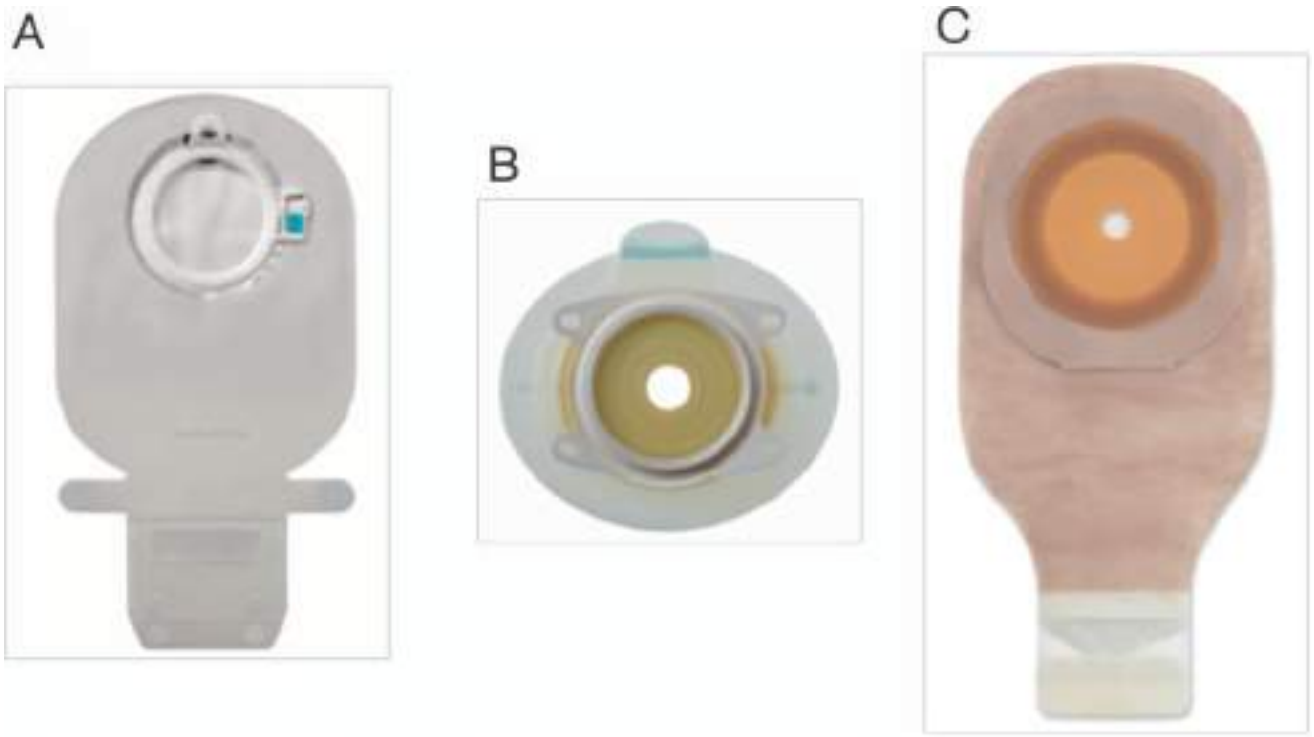

FIGURE 55-10. (**a**) Two-piece stoma appliance with flange and pouch (photo courtesy of Coloplast). (**b**) One-piece stoma appliance and belt (photo courtesy of Hollister). (**c**) One-piece stoma appliances (photo courtesy of ConvaTec).

with scissors to accommodate larger or irregularly shaped stomas. Generally speaking, the wafer should be trimmed to the exact size of the stoma leaving little to no peristomal skin exposed to bowel contents. Disposable stoma sizing templates are available from most stoma supply manufacturers. Appropriate sizing and trimming of stoma appliances is crucial—particularly during the first 6 weeks as stoma edema subsides. Survey data indicate that the average ostomate places a new flange every 4–5 days. The flange should be changed every 3–7 days depending upon peristomal skin care needs [29].

Collection bags come in a variety of sizes in both clear and opaque models based on patient preference. Venting charcoal filter bags may be used to help patients with high gaseous outputs. High output bags may be used to connect to a leg collection system akin to a Foley catheter. Bags should be emptied at the discretion of the patient. New small bowel stoma patients are encouraged to log outputs for the first several weeks and monitor for high outputs.

Specialized stoma appliances may be necessary depending upon the condition of the peristomal skin, stoma morphology, and body habitus. Convex stoma appliances feature a bowl-shaped wafer that assists sealing flush or retracted stomas. Elastic stoma belts may be used to bolster skin sealing for leak-prone stomas. Stoma paste and preformed stoma barrier rings may be used to improve sealing between the peristomal skin and wafer and may be particularly useful when skin folds or scars create an uneven peristomal skin surface. A variety of skin adhesives, protectant wipes, adhesive removers, and topical powders are available to assist with difficulties surrounding the peristomal skin.

Stoma Complications

Stoma problems are ubiquitous and profoundly impact ostomate quality of life, but can often be mitigated with proper care and education in collaboration with stoma care professionals. National Surgical Quality Improvement Program data showed a 37 % unadjusted complication rate for elective cases involving a stoma and 55 % for emergency operations [30]. Stoma-specific complication rates are even higher when considering patient-reported outcomes (Table 55-2). Early stoma-related complications such as leakage, peristomal dermatitis, and dehydration tend to arise from stoma management issues that can be remedied with stoma care and education. Prolapse, stenosis, and parastomal hernia are late-term stoma-related complications that require surgery for definitive correction. Although specialized stoma care nursing is available at many institutions, recognition, care, and management of stoma-related complications are under the purview of the colorectal surgeon.

Table 55-2. Stoma complications

Complication	Incidence rates (%)
Retraction	0–22
Parastomal hernia	0–40
Stoma prolapse	0–10
Stoma necrosis	0–7
Peristomal skin problems	10–42
Total complications	12–72

Adapted from Salvadalena G. Incidence of complications of the stoma and peristomal skin among individuals with colostomy, ileostomy, and urostomy: a systematic review. J Wound Ostomy Continence Nurs. 2008;35(6): 596–607 [31]

Stomal Ischemia: Necrosis, Retraction, and Stenosis

Poorly perfused stomas can necrose in the early postoperative period (Figure 55-11a). Arterial insufficiency is the most common cause of stoma necrosis; however, venous ischemia can rarely arise from fascial obstruction within the trephine. Loop stomas, which preserve collateralized mesenteric vasculature proximal and distal to the stoma, are more resistant to ischemia than end stomas, which require mesenteric division and typically rely upon unidirectional arterial flow. Proper stoma creation techniques can help avoid ischemia-related stoma complications by assuring adequacy of bowel perfusion. Intra-operative assessments of mesenteric pulses, pulsatile bleeding from the cut edge of the mesentery, nuisance bleeding from the cut edge of the bowel wall, and mucosal evaluation can mitigate risk of stoma ischemia and related complications.

Akin to ischemic colitis, marginally perfused stomas may demonstrate variable degrees of ischemia with regard to timing, length, and depth of the ischemic bowel segment, rendering early postoperative assessment of stoma viability crucial. Stoma ischemia typically begins with mucosal pallor and progresses to petechiae, cyanosis, and purple-black mucosal necrosis. Mild stomal ischemia may cause a limited, partial-thickness, mucosal necrosis and slough, but deeper bowel wall layers may remain viable. The most distal edge of the stoma, typically matured to the peristomal skin, is the segment most vulnerable to ischemia. As the everted bowel wall courses proximally, perfusional viability gradient may be seen where ischemia may transition to a viable bowel wall.

Identification of the proximal extent of the ischemic stoma is crucial and can often be identified with a bedside "test-tube" examination. A lubricated clear glass test tube is inserted through the stoma os while a flashlight is directed down the stomal lumen. The illuminated glass permits bedside mucosal evaluation for the length of the tube, allowing the surgeon to assess the proximal extent of mucosal ischemia along the stomal conduit. Management of early postoperative stoma ischemia varies between small bowel and colonic stomas. Any stoma with early evidence of sub-fascial ischemia (i.e., posterior to abdominal wall fascia) should be revised, since deep ischemia may progress to frank intraperitoneal necrosis and perforation. A colostomy appearing viable anterior to the fascia may be carefully observed without revision, since intraperitoneal perforation is unlikely, and solid colostomy outputs can be reasonably pouched even if distal stoma necrosis renders the stoma flush with the skin. A partially viable permanent end ileostomy with significant ischemia of the muscularis, however, should be revised in the postoperative period in suitable operative candidates since distal necrosis may result in a flush ileostomy that is difficult to pouch.

Long-term mild ischemia may result in late-term stoma stenosis and retraction (Figure 55-11b). Non-ischemic stomal retraction can be seen in patients with inadequately mobilized stoma conduits and the obese. Akin to ischemic colitis, necrosis and atrophy of the bowel conduit may cause variable degrees of stomal stricturing and/or retraction that may necessitate surgical revision depending upon symptom severity. Asymptomatic mild stoma stenosis or retraction can be carefully observed provided an adequate seal is maintained with pouching and the peristomal skin remains healthy (Figure 55-12). Skin level symptomatic colostomy stenosis can be locally revised provided the majority of the supra-fascial colon is normal. Sub-fascial stomal stenosis may require intra-abdominal approaches to mobilize a new segment of well-perfused bowel enabling creation of a new stoma. A chronically retracted colostomy can be observed absent stenosis or pouching problems; however, a difficult-to-pouch small bowel may require local revision or complete resection and creation of a new stoma.

Peristomal Skin Disorders

Peristomal skin disorders are the most commonly occurring complication for ostomates [31]. Although skin irritation can occur at any time during the course of the stoma, dermatologic conditions are most commonly seen in the early postoperative period as the ostomate learns proper stoma care techniques. Up to 70 % of new ostomates may have peristomal dermatitis, which is often unrecognized by the patient [26, 32, 33]. Fortunately, most peristomal skin complications arising from a well-constructed and properly located stoma can be successfully managed with local wound care.

Most peristomal skin irritation arises from poorly fitted or improperly sized appliances that expose vulnerable peristomal skin to potentially caustic stoma effluent (Figure 55-13). Leakage viciously begets leakage as irritated peristomal skin weeps exudative fluids that hinder stoma appliance adhesion, which further worsens leakage, excoriation, and appliance maladhesion. Leakage often requires frequent appliance changes, which inflicts additional mechanical stripping trauma to vulnerable peristomal skin. Pouch leaks and peristomal skin excoriation are treated best with a critical reappraisal of pouching apparatus and sizing. Care should be

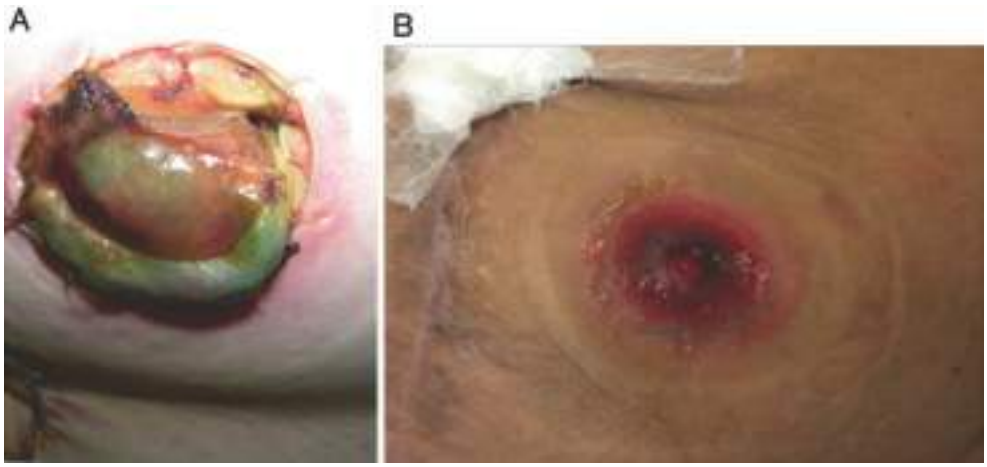

FIGURE 55-11. (**a**) Acute postoperative stoma necrosis with mucocutaneous separation [photo credit: Wound, Ostomy, and Continence Nurses Society (http://www.wocn.org/page/ImageLibrary)]. (**b**) Chronic ileostomy ischemia leading to retraction, stenosis, difficulty pouching, and peristomal erosions (photo credit: Adam Stein, MD).

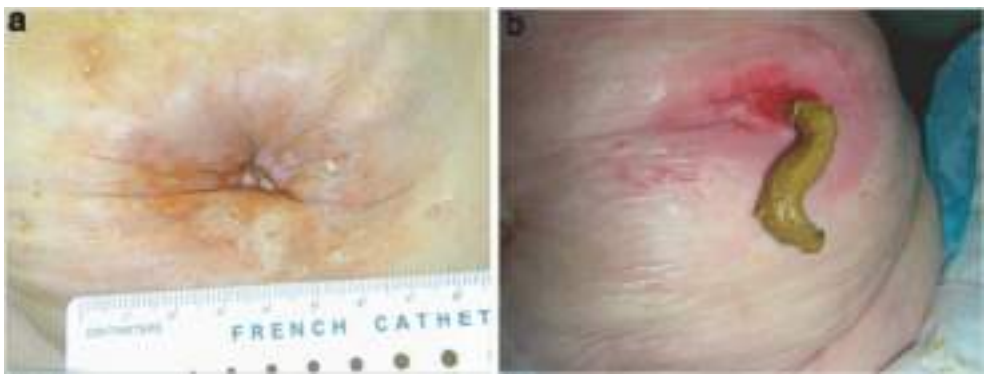

FIGURE 55-12. Chronic stoma stenosis [photo credit: Wound, Ostomy, and Continence Nurses Society (http://www.wocn.org/page/ImageLibrary)].

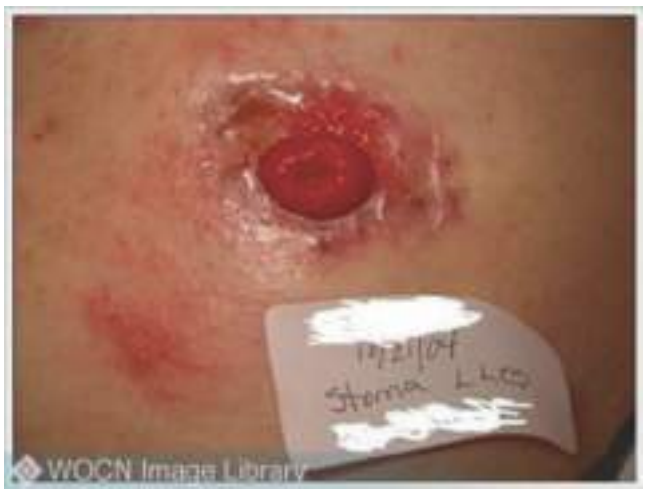

FIGURE 55-13. Peristomal skin excoriation and ulceration attributed to ill-fitting stoma appliance [photo credit: Wound, Ostomy, and Continence Nurses Society (http://www.wocn.org/page/ImageLibrary)].

taken to ensure the stoma flange aperture is sized and trimmed to fit the mucocutaneous junction perfectly so that no skin is exposed to stoma effluent. Flush or poor-fitting stomas may benefit from a convex pouching system, which may improve sealing at the mucocutaneous junction. Protective skin barrier wipes can be used to create a thin polymeric layer to improve and protect skin integrity at the pouch–skin interface. Weeping superficial peristomal skin excoriation can be treated with a thin layer of topical stoma powder. Peristomal contour issues such as peristomal indentations, skin folds, and mucocutaneous separation may be filled with stoma paste to "caulk" under-the-flange leakage.

Fungal peristomal infections typically appear as reddened, shiny patches with satellite papules involving the skin underlying the stoma appliance flange [33]. *Candida albicans*, the most common skin fungus, can proliferate in the warm moist environment at the skin–appliance interface causing itching, irritation, and pain. A fungal infection is first treated by removing and assessing the pouching system for occult leaks that add to skin moisture and irritation. Topical antifungal nystatin powder is then applied and rubbed into the irritated peristomal skin. Excess powder is then brushed off and a skin sealant is typically applied over the powder to enable application of a new stoma appliance. This process is repeated with each appliance change until the rash resolves which usually occurs within 1–2 weeks. In rare cases, topical miconazole and clotrimazole may be required for treatment of resistant fungal dermatitis.

The importance of assessing the peristomal skin cannot be overstressed, particularly in the early postoperative period. High-risk patients, such as those with low health literacy, poor support systems, and emergently created stomas, should be paid special attention. Additionally, obese ileostomy patients are at a higher risk of developing peristomal skin issues owing to the liquid nature of effluent and stoma creation challenges seen in thick abdominal walls [34]. As postoperative stoma edema subsides, the first several postoperative weeks require gradual adaptations in the pouching system to accommodate a shrinking stoma. New home-going ostomates should be made aware that the stoma diameter will gradually shrink and that the flange aperture should be trimmed smaller over time. Since the majority of peristomal skin disorders can be treated with pouching adjustments, postoperative WOCN support, if available, is an immensely valuable tool for the duration of the patient's stoma. Studies indicate a majority of ostomates do not realize a treatable dermatologic condition exists [32, 34], and when treated, can expect an improvement in quality of life [26]. To that end, routine postoperative follow-up with a stoma care professional, such as a WOCN-certified nurse, is recommended [7, 29].

Peristomal Pyoderma Gangrenosum

Pyoderma gangrenosum is a rare inflammatory skin disease characterized by painful ulcers with well-defined erythematous or violaceous undermined borders (Figure 55-14) [35]. Approximately 0.5–5 % of patients with inflammatory bowel disease can develop peristomal pyoderma gangrenosum. Pyoderma gangrenosum is also associated with rheumatoid arthritis, paraproteinemia, or hematologic malignancy in half of patients, but may be idiopathic in 25–50 % of patients [35–37]. Peristomal pyoderma gangrenosum can be seen in approximately 0.6 % of ostomates; however, some postulate the actual incidence may be higher due to underdiagnosis [36]. For unclear reasons, peristomal pyoderma is associated with female gender, autoimmune disorders, and obesity in IBD patients [36–38]. Pyoderma, although poorly understood, is felt to arise from pathergy arising from local skin trauma, which may explain a predilection for arising in the peristomal skin.

Diagnosis of peristomal pyoderma gangrenosum is made clinically and requires a high index of suspicion. Lesions characteristically begin spontaneously with a firm, pink, or

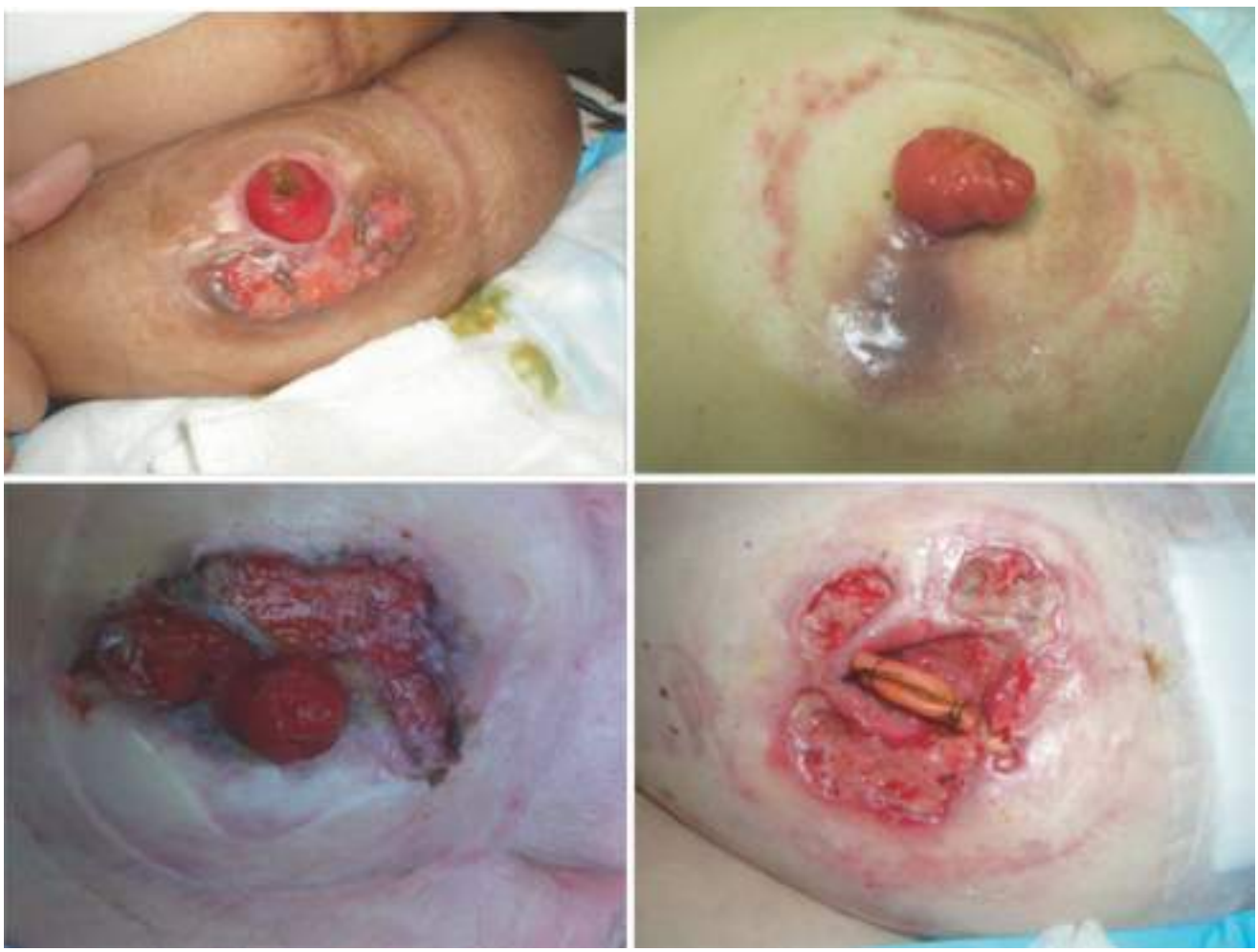

FIGURE 55-14. Peristomal pyoderma gangrenosum (photo credit: Janice Colwell, APRN, CWOCN).

purple hemorrhagic nodule at the peristomal skin in contact with the stoma appliance. The nodule typically enlarges and ulcerates rapidly, to produce a painful and occasionally purulent ulcer with a raised border [35]. Thin bridges of persisting epidermis may be seen spanning the ulcer. Biopsies of the ulcer margin typically reveal nonspecific epidermal neutrophil infiltration, edema, and perivascular lymphocyte infiltration. Although skin biopsies may exclude other dermatologic processes such as malignancy and infection, biopsies are usually not helpful in diagnosing pyoderma due to a lack of pathognomonic histologic findings [39, 40].

There is currently no standard treatment algorithm for pyoderma gangrenosum. Management of peristomal pyoderma utilizes a multidisciplinary approach to treat causative underlying disorders with early and aggressive wound and stoma care [39]. Pyoderma often parallels intestinal IBD activity and may indicate occult, active, intestinal disease. Topical, intra-lesional, and systemic steroids and antibiotics have been used to successfully treat peristomal pyoderma [41]. Following a stepwise approach, increasingly powerful systemic immunomodulators and biologics have also successfully healed peristomal pyoderma [39]. Absorbent-type dressings such as protective foam, calcium alginate, and hydrogel dressings covered with an occlusive dressing can be used to create a protective dry barrier over the wound while controlling for wound seepage [40]. Treatment efficacy can be assessed by monitoring the characteristically raised and undermined wound edge that flattens as the wound heals [39].

A combination of intra-lesional steroid injections and ulcer debridement has been reported to completely heal 40 % and partially heal an additional 40 % of parastomal pyoderma patients [42]. These acceptable results should be interpreted cautiously, however, since over 50 % of treated patients ultimately required stoma re-siting for disease control. A 50 % healing rate with medical therapy including a combination of topical, intra-lesional, and systemic steroids and antibiotics, systemic cyclosporine, and infliximab has also been reported [36]. Ultimately, stoma re-siting may be necessary for treatment refractory peristomal pyoderma, but relocation does not guarantee against pyoderma recrudescence.

Peristomal Varices

Akin to esophageal, gastric, and rectal varices, portosystemic venous shunts may also develop between the stoma and abdominal wall arising to peristomal varices in the setting of chronic portal hypertension. Parastomal varices are identified as a circumferential blue or purple subcutaneous ring extending from the mucocutaneous junction to the peristomal skin (Figure 55-15). Additional clinical findings of parastomal varices include raspberry appearance of the stoma, visibly dilated stomal submucosal veins, peristomal caput medusa, and easy bleeding hyperkeratotic skin [43]. Peristomal varices may also be found within the stomal lumen. Commonly seen in IBD patients with concomitant primary sclerosing cholangitis, parastomal varices can also

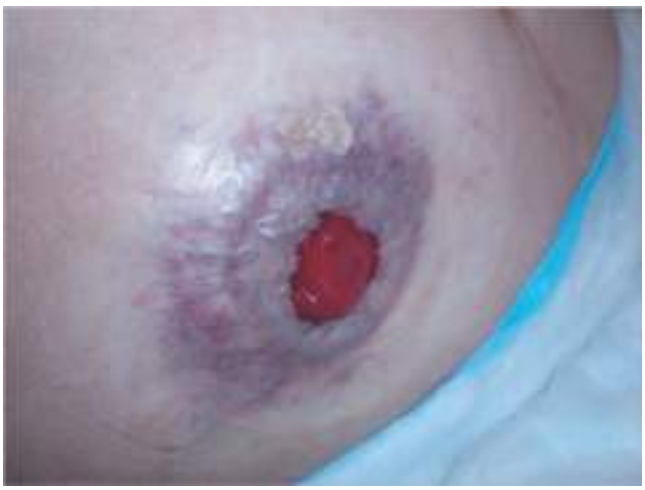

FIGURE 55-15. Peristomal varices (photo credit: Janice Colwell, APRN, CWOCN).

be seen in ostomates with alcoholic cirrhosis and those with extensive metastatic burden to the liver. The incidence of peristomal varices is unknown, but may occur in 27–50 % of ostomates with portal hypertension [44, 45].

Peristomal variceal hemorrhage can be heavy and occasionally life-threatening. Approximately 40 % of patients with parastomal varices will bleed and require transfusion, with the average time from stoma formation to first hemorrhage being 70 months [43]. Following stabilization and correction of any coagulopathy, hemorrhage can typically be first treated with local measures such as digital pressure, application of epinephrine soaked gauze, and suture ligation [46]. Suture ligation of the bleeding varix is not typically durable but may temporize heavy bleeding. Approximately 85 % of patients will re-bleed after local non-operative management of parastomal hemorrhage [43]. Portal decompression, most commonly with a transjugular intrahepatic portosystemic shunt (TIPS), is approximately 5 times more effective than local non-operative measures in durably treating hemorrhage and cured variceal bleeding in nearly 80 % of patients [43, 47, 48]. Moreover, liver transplant may be indicated depending upon the etiology of liver failure, but may only be possible for a fraction of patients with stomal varices [43]. Alternative non-operative treatments using injection sclerotherapy, octreotide, and percutaneous embolization may effectively treat parastomal varices [43, 44, 49–51]. Following local treatments, proper and gentle stoma care with a flexible flange should be employed since the friable varices dwell at the skin–pouch interface [52].

Surgical mucocutaneous disconnection may be employed when local therapy fails and portal decompression is not possible. This local surgery involves a cylindrical incision around the mucocutaneous junction to the level of the anterior fascia with identification and ligation of varices and rematuration of the stoma. Preoperative peristomal infiltration of dilute epinephrine may assist with hemostasis during this potentially bloody procedure [46]. The surgeon should pre-

pare for significant blood loss and necessary blood products should be available for transfusion. Varices will recur over time, but the local procedure can be performed repeatedly, if needed. Stoma re-siting procedures can be carefully considered for suitable variceal patients experiencing concomitant pouching difficulties arising from a parastomal hernia or poorly constructed stoma. The risks of this highly morbid procedure in a high-risk patient need to be cogently balanced with anticipated benefits and life expectancy.

While a stoma is not always avoidable, special situations may arise where portal hypertensives and early cirrhotics can be offered stoma-sparing surgery with the goal of potentially avoiding parastomal varices. Stoma avoidance is particularly germane in the setting of primary sclerosing cholangitis (PSC)-associated inflammatory bowel disease where reports of peristomal variceal hemorrhage can occur in up to 53 % of patients within 4 years of total proctocolectomy with end ileostomy [53]. Since patients with ulcerative colitis and PSC can successfully undergo restorative proctocolectomy with an ileal-pouch anal anastomosis (IPAA) and avoid a permanent stoma and varices [54, 55], IPAA is the treatment of choice [56]. If necessary, IPAA may be performed safely following TIPS or liver transplant [57, 58]. Although IPAA avoids a permanent stoma, unexplained pouchitis can develop in over 50 % of patients with PSC within 4 years of pouch creation [55].

Stoma Prolapse

Bowel proximal to an end stoma may intussuscept through the matured stoma creating stoma prolapse (Figs. 55-16 and 55-17). Loop stomas may prolapse bowel from either limb. Stoma prolapse is categorized as fixed or sliding depending upon the mobility of intussusceptum. A mobile sliding prolapse classically describes the problematic variant that can be seen in up to 8 % and 47 % of end and loop stomas, respectively [59]. Stoma prolapse is theorized to arise from a combination of a mobile bowel mesentery, increased intra-abdominal pressure, enlarged stoma trephine, or fixation failure of the opposing everted stomal serosa surfaces. Stoma prolapse ranges from mild cosmetic concerns to moderate difficulties pouching, up to rare and extreme cases of incarceration and strangulation.

Minimally symptomatic stoma prolapse may be managed with reassurance, modification of stoma appliances, and addition of an external fixation device. Significantly symptomatic stoma prolapse may require surgical revision in suitable operative candidates via local parastomal or open abdominal approaches. Sundry, heterogeneous, and anecdotal reports describe various stoma prolapse repair techniques, but no compelling method prevails. In the absence of steadfast evidence, conventional wisdom dictates local procedures are first attempted relegating more extensive intra-abdominal procedures for recurrent or complicated prolapse. Prolapsing temporary loop stomas are best treated with timely reversal. Prolapsing permanent stomas can be treated with local amputation of the prolapse with re-anastomosis, local excision of the stoma and intussusceptum with de novo stoma creation, or prolapse reduction and fixation. Some advocate concomitant seromyotomies to promote serosa-to-serosa bonding along the apposed serosal surface of the everted matured stoma to minimize future prolapse.

Intra-abdominal correction of stoma prolapse has been described using myriad techniques, largely focusing on fixation of the intussusceptum and corresponding mesentery.

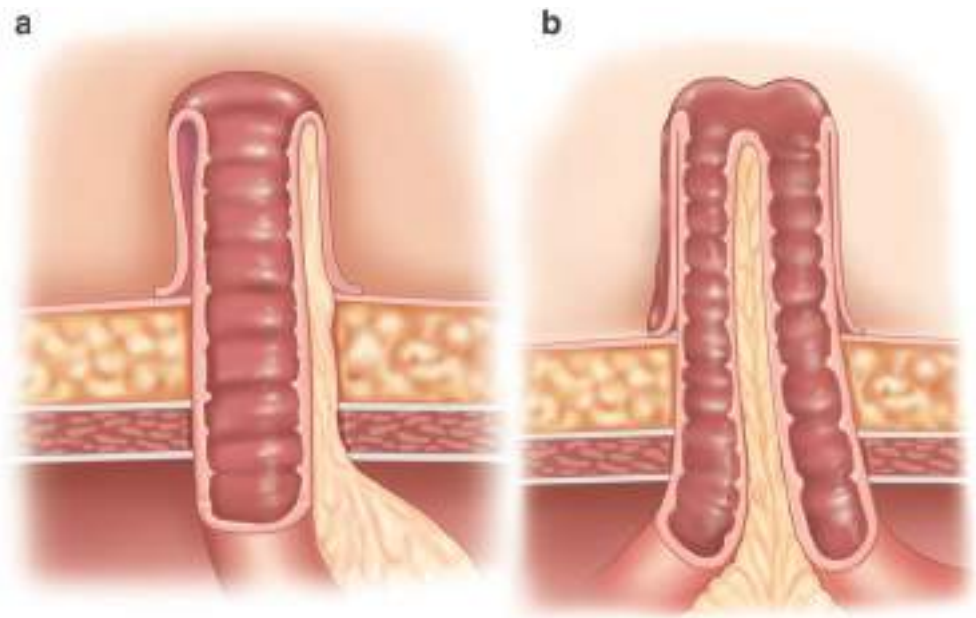

FIGURE 55-16. (**a**) Prolapsed end stoma. (**b**) Prolapsed loop stoma.

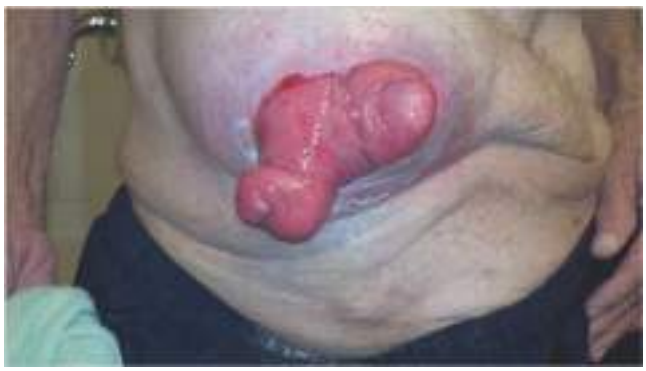

FIGURE 55-17. Prolapse of a prolapsed loop transverse colostomy [photo credit: Wound, Ostomy, and Continence Nurses Society (http://www.wocn.org/page/ImageLibrary)].

Intra-abdominal techniques may be preferable when prolapse is associated with concomitant parastomal hernia. Intra-abdominal approaches facilitate suture fixation of prestomal mesentery and/or bowel conduit directly to peritoneum with variable rates of success. Some propose routing pre-stoma conduit through a pre-peritoneal tunnel lateral to the linea semilunaris prior to exiting through a trans-rectus trephine, fixating bowel and mesentery intra-abdominally although the utility of this technique is debatable (Figure 55-18a). Prolapsing permanent loop colostomies commonly prolapse the distal limb and can be converted to an end or loop-end stoma by dividing the distal limb. Alternatively, the distal limb of a loop colostomy may be sutured to the peritoneum to limit excursion (Figure 55-18b). Ultimately, a prolapsing stoma can be moved to a new site using any of the above adjuncts to mitigate future prolapse, although isolated stomal prolapse without associated parastomal hernia rarely benefits from stoma relocation.

Rarely, prolapsed stomas will become incarcerated and reduction may become increasingly difficult to reduce as cumulative lymphatic and vascular compression worsens stomal engorgement and edema. Besides attempts to reduce a viable incarcerated prolapse may be aided with sedation, anxiolytics, and analgesics, whereas strangulated prolapse mandates immediate surgery. Topical ice and table sugar have been reported to decrease edema within the prolapsed stoma and ease reduction. Incarcerated prolapse may rarely progress to infarction and require immediate surgery (Figure 55-19).

Transient short-segment stomal "pseudoprolapse" may be seen during pregnancy owing to increased intra-abdominal pressure related to uterine displacement of abdominal viscera. Such prolapse is typically less than 3 cm long and resolves following delivery. Pregnancy-related pseudoprolapse does not typically merit surgical revision unless symptoms persist beyond the postpartum period [60].

Parastomal Hernia

A stoma, by definition, is an intentionally created hernia. Invariably, nearly all hernias will enlarge over time as intra-abdominal forces fatigue tissue [61]. A stoma trephine is susceptible to the same continuous intra-abdominal pressures and may enlarge over time to allow unintended protrusion of intra-abdominal contents whereby creating a parastomal hernia (Figure 55-20). As a result, many argue nihilistically that with time, every stoma will ultimately develop a parastomal hernia. The incidence of parastomal hernias is widely estimated between 30 and 50 %; however, detecting the true numerator is limited by heterogeneous definitions, observation periods, and means of diagnosis [62]. Increasing waist circumference, age, and stoma trephine diameter have been associated with parastomal herniation [63, 64]. Parastomal hernias range from small hernias incidentally found on imaging to large hernias containing significant lengths of bowel and omentum (Figure 55-21). Pain, obstruction, disdainful bulges, and pouching difficulties can arise from parastomal hernias, but a significant proportion are asymptomatic. Physical detection of an occult parastomal hernia may require complete removal of the stoma appliance assembly, careful digitation of the stoma, and examination of the patient in the standing position using Valsalva maneuvers. An abdominopelvic computed tomography (CT) scan may be necessary to detect an occult parastomal hernia in obese patients since abdominal wall thickness may obfuscate physical examination findings. Special positioning (e.g., prone or lateral) or maneuvers to increase intra-abdominal pressure (cough, straining, or Valsalva) during the CT scan may help identify an occult parastomal hernia. Therefore, patients who will be undergoing a CT may be coached by the surgeon to strongly Valsalva when told by the technician to hold still for the actual X-ray.

The need for parastomal hernia repair is dictated by the degree of symptoms. An asymptomatic parastomal hernia does not mandate repair. Mild symptoms arising from a parastomal hernia may be ameliorated with appliance modifications or a modified abdominal binder or stomal support belt (Figure 55-22). Suitable-risk patients with intermittent obstructions, intolerable discomfort, and significant pouching difficulties attributable to a parastomal hernia may be considered for elective repair. Incarcerated hernias causing complete obstruction or worrisome for strangulation require immediate surgery.

Given the high prevalence of parastomal hernias, several methods for parastomal hernia repair have been reported over the past half-century, but the majority of published data lies within small case series. Surgical approaches have been divided into three broad categories: local repair, transabdominal repair, and re-siting [62]. Local repair involves a peristomal incision remote to the stoma wafer area with

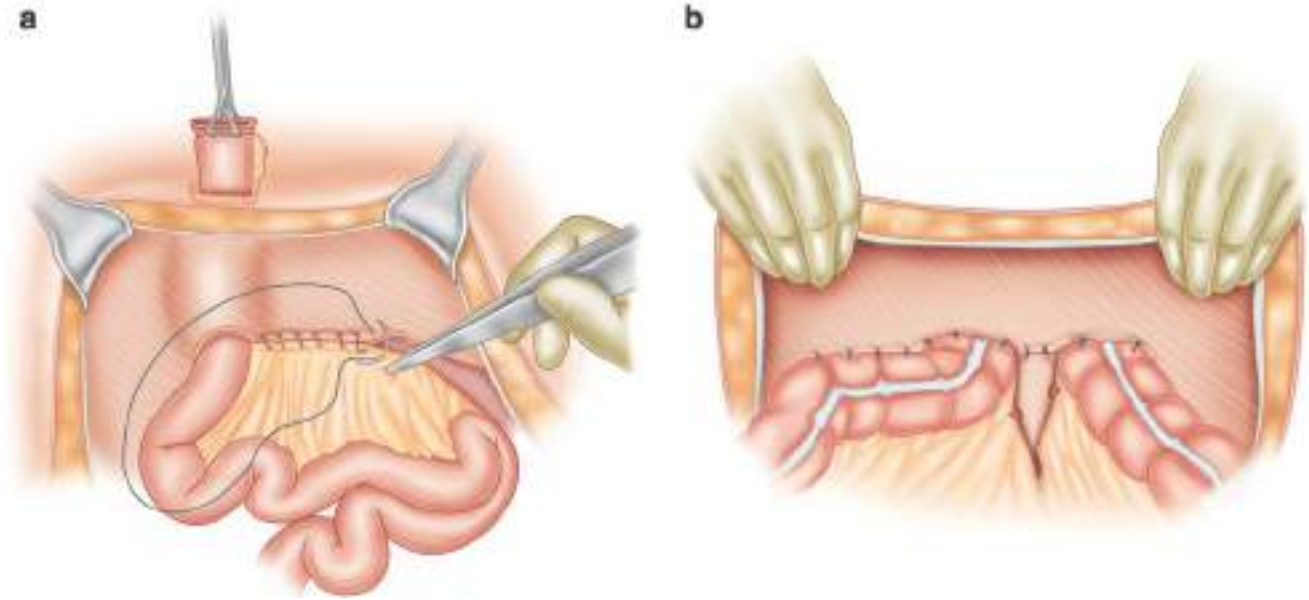

FIGURE 55-18. (**a**) Retroperitoneal tunneling of an end ileostomy with suture pexy of the pre-stomal mesentery to limit prolapse. (**b**) Suture pexy of the distal limb of a loop colostomy to mitigate prolapse of the distal limb.

FIGURE 55-19. Stomal prolapse with distal ischemia and infarction [photo credit: Wound, Ostomy, and Continence Nurses Society (http://www.wocn.org/page/ImageLibrary)].

reduction of hernia contents, hernia sac excision, and suture closure of the hernia defect. Mesh overlay reinforcement may or may not be used (Figure 55-23). Local primary suture repair is an attractive option due to avoidance of a laparotomy, but obtaining tension-free repair is impossible. As realized with ventral hernia repair techniques, primary repair and on-lay mesh techniques have higher rates of recurrent parastomal hernia and are considered inferior to trans-abdominal approaches with mesh underlay [61, 65]. Stoma relocation, although attractive and more effective than local primary repair [66], can be a significant undertaking that jeopardizes midline and former stoma site hernias and does not guarantee against herniation at the new site.

FIGURE 55-20. Parastomal hernia.

Trans-abdominal mesh underlay repair of parastomal hernias offers theoretical advantages to local repair since the same intra-abdominal forces responsible for hernia protrusion are also securing the intra-abdominal reinforcement. As a result, the European Hernia Society has adopted underlay mesh repair as the standard method for repairing incisional hernias [61], and it seems plausible to extrapolate the same rationale to

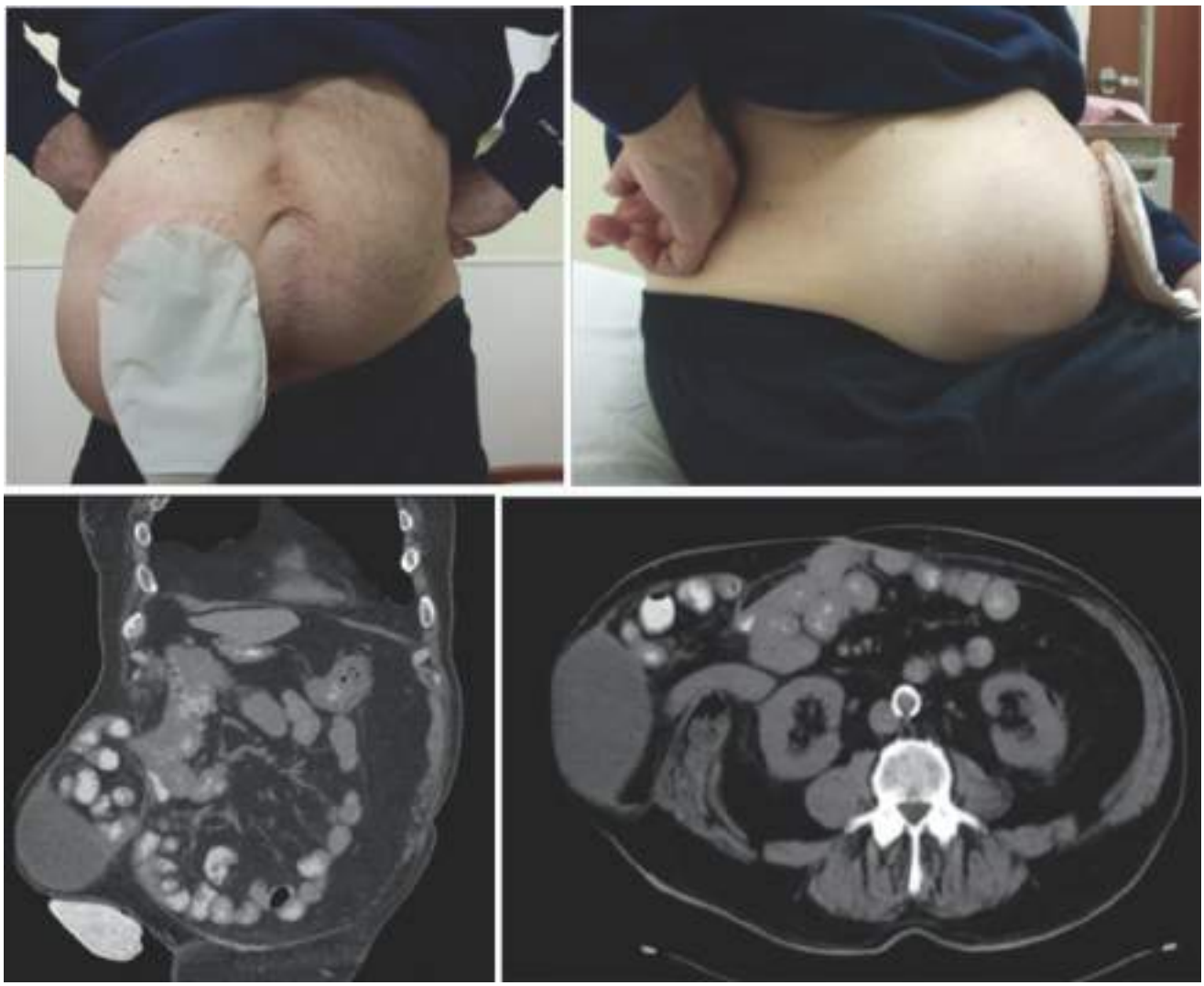

FIGURE 55-21. A 77-year-old man with a 19-year-old end ileostomy with a large parastomal hernia and seroma.

FIGURE 55-22. Stomal support hernia belt (photo courtesy of Nu-Hope Laboratories).

parastomal hernia repairs. Trans-abdominal approaches can be used through laparoscopic or open techniques using a variety of biologic and permanent prosthetic meshes. Both open and laparoscopic approaches involve lysing all abdominal wall adhesions to identify the stoma trephine and completely reduce hernia contents. Typically an intra-abdominal mesh is then fixed in intraperitoneal or retro-rectus position using either a "keyhole" slit or Sugarbaker underlay to cover and reinforce

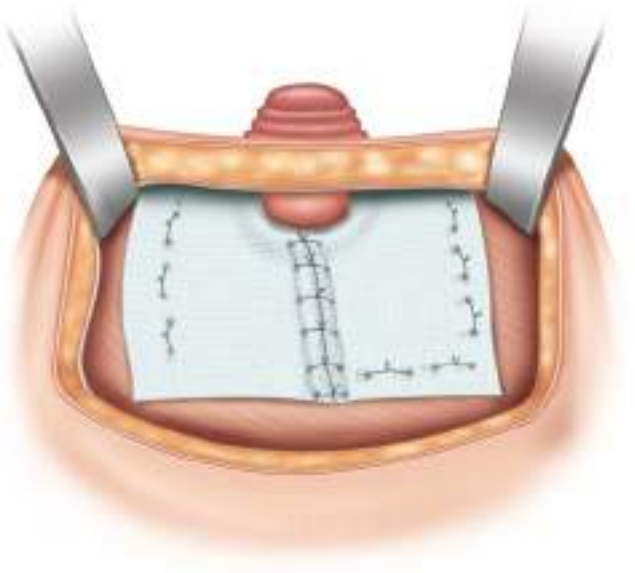

FIGURE 55-23. Local repair of parastomal hernia with prosthetic mesh overlay.

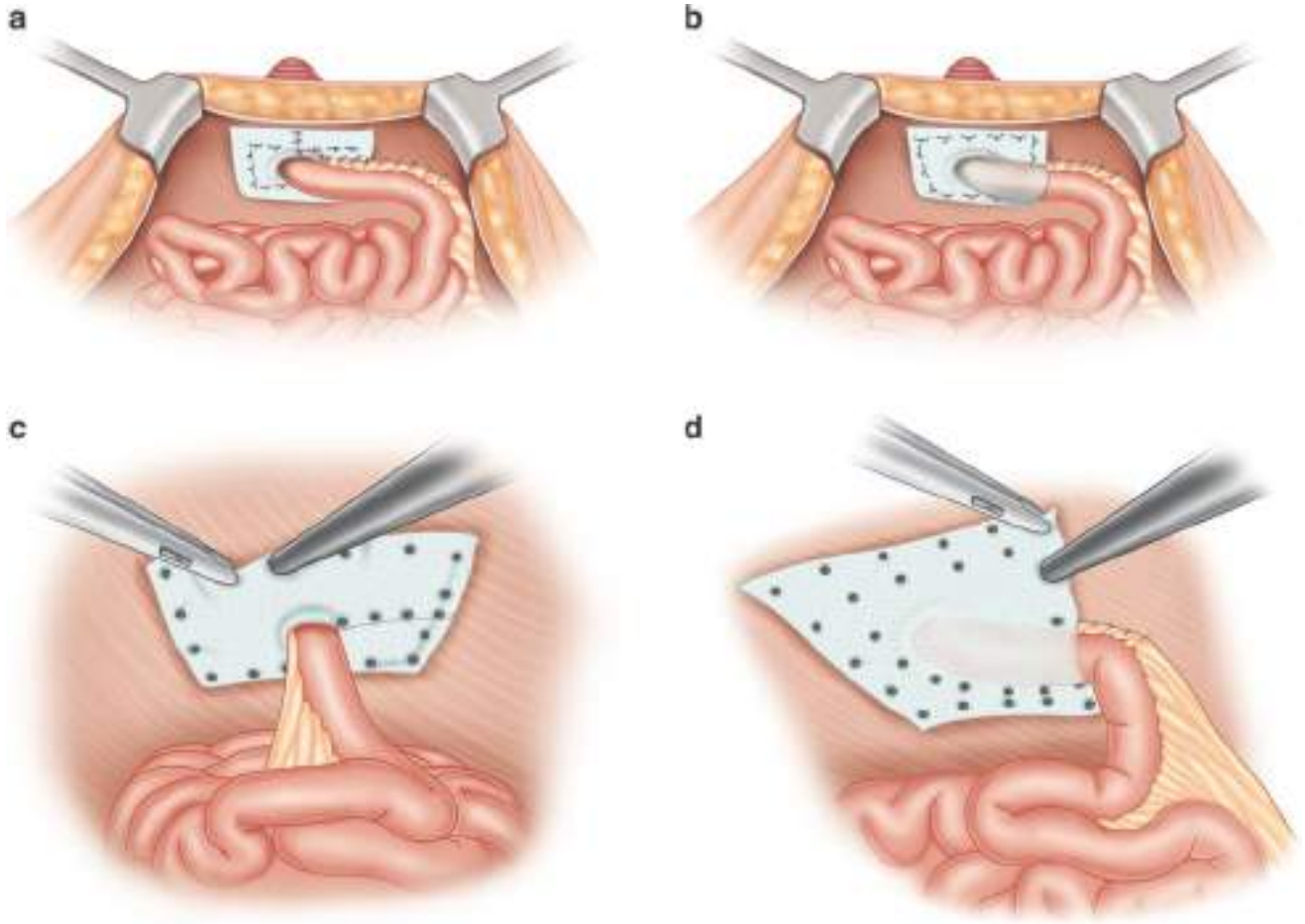

FIGURE 55-24. Intra-abdominal parastomal hernia repair with (**a**) open "keyhole," (**b**) open Sugarbaker overlay, (**c**) laparoscopic "keyhole," and (**d**) laparoscopic Sugarbaker techniques with "double crown" tack technique.

the trephine and surrounding abdominal wall (Figure 55-24) [67]. Hernia repair mesh can be fixed to the abdominal wall through a variety of techniques. A percutaneous suture-passing device can be used to obtain trans-fascial mesh fixation with suture. Two concentric circles of tacks can be used to secure the mesh perimeter to form a "double crown" of mesh fixation (Figure 55-24d). Typically, a combination of trans-fascial suture fixation and tacks is used to robustly fix the mesh to the abdominal wall, but care must be taken not to obstruct or impinge upon the bowel conduit, particularly with the Sugarbaker technique.

The discussion of mesh selection is particularly relevant at the time of this text's publication, owing primarily to an overwhelming variety of mesh types for the surgeon to choose. Permanent non-absorbable prosthetic mesh and bioabsorbable substrates have been used for parastomal hernia repair with variable early success [68], but no particular mesh has demonstrated superiority. Surgical dogma has historically contraindicated the use of permanent prosthetic meshes in contaminated fields out of concern of mesh infection. Use of costly, infection-resistant, biologic meshes in potentially contaminated fields (such as a stoma) initially appeared to avoid theoretical concerns of mesh infection; however, several recent studies suggest that cheaper permanent prosthetic meshes may be equally safe for contaminated hernia repairs, which questions the value-added benefits of costly biologic meshes at this time [69–72].

Despite the high prevalence of parastomal hernias, evidence-based guidance determining the optimal surgical approach is hampered by a bevy of heterogeneous, retrospective, case series lacking steadfast definitions, standardized management algorithms, and clinical trials [73]. The best evidence at this time arises from a large systematic review and meta-analysis that evaluated 30 studies comparing local versus intra-abdominal repair techniques [73]. In this study, which excluded stoma re-siting, the authors found recurrence rates approaching 70 % with local primary suture repair and recommended this technique be abandoned. The authors further report that open and laparoscopic intra-abdominal approaches with mesh have similar effectiveness, but laparoscopic Sugarbaker approaches are superior to keyhole configuration when mesh is used.

Since the above meta-analysis, a complex approach combining open stoma relocation, retro-muscular dissection, posterior component separation, and retro-muscular mesh placement for parastomal hernia repair was reported for 48 patients [74]. The midline incision, former stoma site, and new stoma site were reinforced with a variety of meshes. In this challenging patient group, a variety of meshes were used in patients with a mean BMI of 31, 70 % of which had simultaneous incisional hernia, and each having undergone an average of 4.3 prior repair attempts. The authors report encouraging recurrence rate of 11 % at a mean follow-up of 13 months. While encouraging, results are early and the surgery was a feat: the mean operative time was 258 min and subsequent length of stay was nearly 11 days. Nonetheless, this "belt and suspenders" approach may be useful for patients with recurrent parastomal hernias with concomitant midline incisional hernias.

The high incidence of parastomal hernia and post-repair recurrence has led several investigators to evaluate the use of prophylactic implanted mesh at the time of permanent end colostomy creation to avoid hernia formation. The majority of studies and subsequent pooled meta-analyses have shown placement of prophylactic mesh to be effective in reducing, but not eliminating, parastomal hernias [75–79]. In a prospective randomized trial of patients undergoing permanent end colostomy, placement of a lightweight polypropylene prosthetic mesh underlay decreased clinical parastomal hernia from 41 to 15 % and radiographic parastomal hernia from 44 to 22 % at a mean follow-up of 29 months without mesh-related complications [77]. The exact type, size, and mesh location are debatable. A multicenter, prospective randomized trial evaluating usage of intra-abdominal placement of biologic mesh for permanent stomas showed no beneficial effects of mesh implantation [80]. ASCRS suggests that lightweight polypropylene mesh may be placed at the time of permanent ostomy creation to decrease parastomal hernia rates [7]. A this time, it is difficult to explicitly define the role of routine mesh placement for permanent stomas. First, mesh and mesh implantation can be costly and not innocuous. Added to the fact that only a fraction of parastomal hernias require repair and prophylactic mesh is not completely effective in preventing hernias, the cost–benefit balance of routine mesh use is murky. For patients undergoing creation of a permanent colostomy with expected long-term postoperative survival, routine placement of an affordable mesh appears to be a reasonable practice based on the best information available at this time; however, the authors acknowledge this practice is in infancy and await additional evidence to definitively address this fluid concept.

Peristomal Abscess

Rarely, an ostomate may develop a peristomal abscess. Peristomal tenderness, swelling, and erythema may indicate a subcutaneous collection. Peristomal abscesses are typically seen in the early postoperative period resulting from intraoperative contamination; however, late peristomal abscesses can be seen in the setting of penetrating Crohn's disease of the stoma or from an intra-abdominal source. Initial management of a peristomal abscess includes drainage via image-guided or standard operative techniques. To avoid pouching problems, the drainage catheter should either be inserted remote to the peristomal skin–appliance interface or directly through the mucocutaneous junction (Figure 55-25). If fistulization from the stoma is suspected following drainage, further endoscopic or radiographic evaluation may determine if the abscess is arising from a diseased stoma.

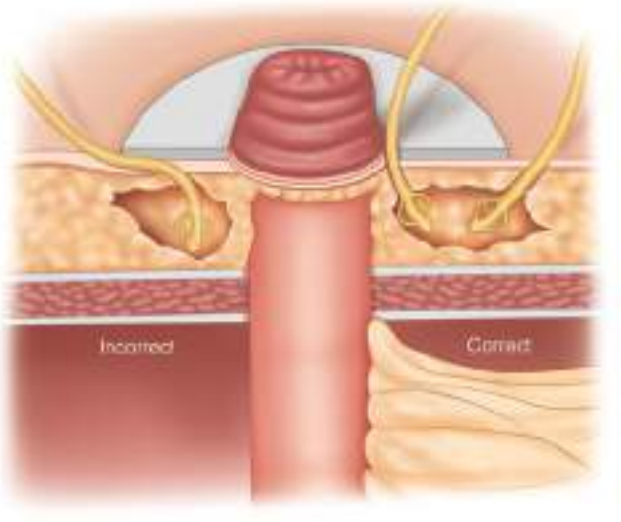

FIGURE 55-25. Percutaneous drainage of a parastomal abscess.

High Output Small Bowel Stomas

Normal ileostomy outputs are typically between 800 and 1200 mL/day, and outputs exceeding 1200–2000 mL/day are considered to be high [81]. High stoma outputs can cause severe fluid, electrolyte, and nutritional deficiencies and are typically seen with small bowel stomas and rarely proximal (i.e., ascending or proximal transverse) colostomies. High output stomas can be transiently seen in the new ostomate as ileus resolves and the initial deluge of bowel contents exits the body. Approximately half of postoperative high output stomas will resolve spontaneously within 2 weeks [81]. With time and resumption of a normal diet, stoma outputs typically plateau to a level proportional to the length of remaining proximal bowel, but high outputs can commonly necessitate treatment. This section will focus on small bowel stomas (ileostomy, jejunostomy), the most common culprit in high output situations.

Once postoperative ileus resolves and stomal outputs reach a steady state, daily output assessments determine the need for treatment. Small bowel stomas outputting less than 1200 mL/24 h are usually well tolerated without clinical derangements and do not typically require treatment.

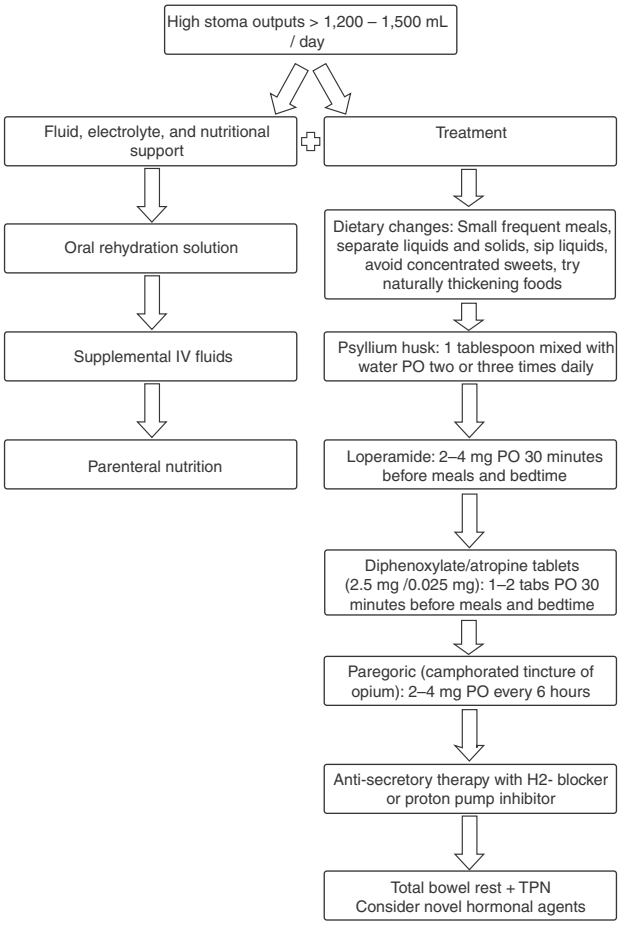

FIGURE 55-26. Proposed management algorithm for management of high output small bowel stomas.

Outputs between 1200 and 1500 mL/day are borderline high and may cause problems for some ostomates. Persistently high stoma outputs can be treated with dietary, behavioral, and medical means via a proposed algorithm described in Figure 55-26. Behavioral alterations include avoidance of large bolus feedings in lieu of smaller, more frequent aliquots. Large meals can be replaced with smaller frequent meals, fluids can be sipped rather than gulped, and solids and liquids can be consumed at different times to minimize bolus effects. Concentrated sweets including juice, soft drinks, and candy should be limited to decrease the effects of osmotic diarrhea. Breads, crackers, peanut butter, and bananas may naturally thicken stoma outputs and help decrease volumes. The addition of psyllium powder mixed in water helps to absorb excess fluid from the intestinal tract and thicken outputs. Hypotonic oral fluid restriction (500–1000 mL/day) and treatment with the cheap and easily made World Health Organization oral rehydration solution (Table 55.3) [82] help limit sodium loss and may produce a more favorable osmotic intestinal gradient [81]. It has been shown that most high output patients can avoid IV fluid and electrolyte supplementation if oral intake is restricted to 500–1000 mL/24 h of oral rehydration solution [83].

TABLE 55-3. Oral rehydration solution

Ingredients
- 3/8 tsp salt (sodium chloride)
- ¼ tsp table salt substitute (potassium chloride)
- ½ tsp baking soda (sodium bicarbonate)
- 2 tbsp + 2 tsp sugar (sucrose)
- Add tap water to make 1 l
- Optional: Nutrasweet® or Splenda® based flavoring of choice, to taste

Directions: Mix dry ingredients with water and serve. Best sipped slowly over long periods of time

Contains 27 g of sucrose, 70 mEq/L of sodium, 20 mEq/L of potassium, and 30 mEq/L of bicarbonate. The final osmolarity is approximately 245 mOsm/L

tbsp tablespoon, *tsp* teaspoon

Following dietary and behavioral changes, pharmacotherapy may be required to manage high output stomas. Medical therapy typically begins with stepwise titration of antimotility agents beginning with loperamide and adding diphenoxylate/atropine. It is useful to take such antimotility agents approximately 30 min before meals (three times daily) to preemptively slow transit time before eating. Rarely, intestinal transit may be so rapid that tablet medications do not have enough time to completely dissolve, leaving elixir forms of antimotility agents preferable. Anti-secretory therapy with either H2 or proton bump blocking agents may be added to decrease stoma outputs by reducing gastric secretions. If dietary, anti-secretory, and antimotility therapies fail, oral opium tincture (Paregoric, camphorated tincture of opium) or oral codeine phosphate can be added. Paregoric can be costly and can cause sedation and is typically added as a later measure for recalcitrant high output stomas. Common medicines to manage high output stomas are detailed in Table 55.4.

Unexpected and persistently high stoma outputs merit a work-up to exclude other potentially treatable causes. Cross-sectional abdominal imaging or a small bowel fluoroscopic series should be performed to exclude a partial bowel obstruction, which can cause paradoxically high outputs. High outputs can be caused by small bowel Crohn's disease, which can be evaluated with small bowel enteroscopy through the stoma or cross-sectional imaging. *Clostridium difficile* enteritis is a reported cause of both small and large bowel high output stomas and can be evaluated with stool testing. Steatorrhea may develop in patients with significant ileal resections and can be treated with oral cholestyramine. Pancreatic insufficiency may rarely cause persistently high stoma outputs and can be remedied with a trial of pancreatic enzyme replacements.

During periods of high stoma outputs, fluid, electrolyte, and nutritional support may be necessary. Periodic surveillance of serum electrolytes, daily weights, and strict recording of inputs and outputs guide resuscitation and replacements. Short gut situations with a high jejunostomy may not respond to standard therapies and may require parenteral fluids or nutrition. On rare occasions with critically proximal stomas, patients may require fasting and total parenteral nutrition as a last resort to sustain euvolemia.

Table 55-4. Common medicines for control of high output stomas

Medication	Starting dose	Maximum daily dose
Psyllium	1 tablespoon BID	1 tablespoon TID
Loperamide tab	2–4 mg PO QID	16 mg (4–8 tabs)
Loperamide liquid	2–4 mg PO QID	80 mL (16 mg)
Diphenoxylate-atropine tab	2.5–5 mg PO QID	20 mg (4–8 tabs)
Diphenoxylate-atropine liquid	2.5–5 mg PO QID	40 mL (20 mg)
Codeine tab	15–30 mg PO QID	240 mg (60 mg PO QID)
Codeine elixir	15–30 mg PO QID	240 mg (80 mL)
Paregoric 0.4 mg morphine/1 mL Paregoric (45 % alcohol)	5 mL PO QID	37.5 mL PO QID (150 mL/day)
Opium tincture 10 mg morphine/1 mL opium (19 % alcohol)	0.3–1 mL PO QID	1.5 mL PO QID (6 mL/day)

Adapted from Parekh and Seidner [3]

Octreotide, a somatostatin analogue; teduglutide, a glucagon-like peptide 2 analogue; and human growth hormone all show promise in managing the most recalcitrant high output stoma associated with short gut syndrome [84, 85].

Stoma Reversal

Preoperative Preparation

The surgeon should have a clear understanding of the patient's anatomy prior to attempting stoma reversal. For patients with a stoma created by another surgeon, it is crucial to review the prior operative and pathology reports to understand the surgical indications, encountered pathology, and remaining anatomy. Record review is particularly important when reversing an end colostomy performed for diverticulitis or malignancy, since additional resection of the distal stump, descending colon, and splenic flexure mobilization may be needed to complete an adequate resection. Close or threatened margins found on oncologic pathology reports may merit endoscopic anastomotic evaluation to exclude cancer recurrence prior to stoma reversal. Endoscopic mucosal evaluation may be helpful prior to reversing stomas in IBD, ensuring that disease activity is controlled in the defunctioned bowel before attempting reversal, but the endoscopist must be aware that diversion colitis may grossly and histologically mimic IBD [86].

If a diverting loop stoma was used to protect a distal anastomosis, the authors prefer to use a lower gastrointestinal fluoroscopic contrast study to exclude anastomotic leak, stricture, and obstruction prior to stoma reversal. Similarly, for patients undergoing reversal of an end stoma, preoperative fluoroscopic and endoscopic studies are important to evaluate the remaining anatomy and quality of both distal and proximal segments of bowel—particularly when reversing another surgeon's stoma. Fluoroscopic abnormalities can be further examined with endoscopy allowing mucosal evaluation, tissue sampling, and anastomotic dilation, if needed. Coloanal, distal colorectal, and ileal pouch-anal anastomoses may be additionally assessed and gently dilated with digital rectal exam. Several groups espouse selective, rather than routine, use of lower GI contrast studies for anastomotic evaluation prior to stoma reversal and note that most anastomotic complications can be diagnosed without imaging [87–91]. Although intra- and postoperative surprises are not completely avoidable, the authors feel preoperative evaluation including record review, imaging, and endoscopy is the best way to avoid unexpectedly complex stomal reversals.

Timing

Timing of stoma reversal may impact the ease of the procedure. Diverting loop stomas are typically reversed within 2–3 months after creation once the surgeon is satisfied with the distal anastomosis (or pathology) that required diversion. Limited evidence suggested that loop ileostomy reversal performed less than 8.5 weeks following coloanal or ileoanal anastomosis may be associated with increased risk of complications [92]. Recently, several small studies have challenged this notion. A Turkish study showed that 88 % of loop ileostomy patients could be reversed during the same admission as the index operation without increasing morbidity, whereby avoiding high rates of stoma-related complications [93]. Nineteen patients undergoing loop ileostomy reversal within 10 days of the index operation revealed increased rates of wound infections, but otherwise similar complication profiles compared to normal interval closure patients [94]. Another retrospective study revealed patients who underwent loop ileostomy reversal less than 12 weeks from the interval operation had less postoperative nausea and vomiting than patients closed after 12 weeks [95]. Results from a Scandinavian prospective randomized trial comparing loop ileostomy reversal at 2 versus 12 weeks after low anterior resection are in press at the time of this publication and are eagerly awaited to provide evidence-based guidance to surgeons [96]. Until more rigorous evidence is available supporting safe early closure, the authors recommend loop ileostomy closure at approximately 8–12 weeks postoperatively as dictated by the clinical situation.

The use of adjuvant chemotherapy introduces another consideration in the timing of stoma reversal. If adjuvant chemotherapy is planned, conventional wisdom dogmatically

dictates keeping a diverting stoma through the duration of treatment to minimize postoperative reversal complications and diarrhea. Conversely, chemotherapy may further compound dehydration resulting in readmission for up to 11 % of ileostomy patients [97] and ostomates must be monitored carefully for dehydration during chemotherapy. A recent small retrospective review showed that loop ileostomy reversal in the midst of colorectal cancer chemotherapy had comparable morbidity and cancer-related outcomes in select patients compared to post-chemotherapy reversal [98], although this practice is not widely adopted at this time. Patient choice plays a large role in this situation, and a thorough discussion is helpful in choosing the ideal time for stoma reversal.

The optimal time for end stoma reversal remains a contentious issue with conflicting guidance in the literature [99]. It is generally considered that early postoperative adhesions become less tenacious and vascular with time, which may ease a challenging intra-abdominal dissection. Retrospective comparisons between early (<15 weeks) and late (>15 weeks) end colostomy reversal detail similar morbidity, but increased length of stay, subjective adhesion density scores, and small bowel injuries favoring later surgery [100]. An older study associated early Hartmann's reversal (<3 months) with increased leaks, sepsis, and death compared to colostomy reversals taking place after 6 months [101]. Although small series have shown no timing-dependent outcome differences [99, 102], the balance of low-level evidence suggests delaying end stoma reversal for 3–6 months eases future surgery in patients having undergone open end colostomy creation.

Technical Consideration of Loop Stoma Reversal

Once the surgeon is satisfied with the quality of the protected distal anastomosis (or pathology) (see section "Preoperative Preparation"), loop colostomy or ileostomy reversal can typically be performed as a local procedure through a peristomal circular incision under general anesthesia. The entire abdominal midline should be included and prepared in the operative field; in the rare event an unplanned laparotomy is required. A circumferential skin incision is made just outside the mucocutaneous junction and sharply deepened until subcutaneous fat is seen (Figure 55-27). Clamps may be placed on the skin rim to retract the stoma anteriorly to expose the interface between the serosal surfaces of the bowel limbs and the subcutaneous tissues. A cylindrical sharp dissection is performed on the serosal surfaces of the bowel limbs heading posteriorly until the anterior rectus sheath is encountered. If the patient is obese and the fascia is deep, clamps can be used to grasp and elevate the fascia; alternatively, radial 1–2 cm counter-incisions extending from the cut skin edge may allow deeper exposure. The rectus muscle is dissected from the bowel serosa and can be distinguished from the bowel by the longitudinal orientation of muscle fibers. Circumferential dissection continues until the abdomen is entered. Limited intra-abdominal adhesiolysis is performed to enable adequate mobilization of the bowel loop for eventual anastomosis and fascial closure. Care should be taken to avoid injury to the stoma mesentery during dissection, especially during loop colostomy reversal since marginal artery injury can result in distal colonic ischemia.

If the stoma is everted, sharp adhesiolysis may be used to flip the everted bowel wall into a normal configuration. The skin disk and mucocutaneous junction is excised and debrided back circumferentially to soft and supple bowel suitable for closure. Partial and full thickness bowel injuries can rarely occur during loop stoma closure. Bowel assessment can be performed by injecting dilute povidone-iodine solution via a bulb syringe while digitally occluding each bowel limb to pressurize the dissected bowel limbs and evaluate for injury (Figure 55-28). Injuries can be suture repaired or resected depending upon the nature and location of injury. Rarely, tenacious adhesions or deep bowel injury may require

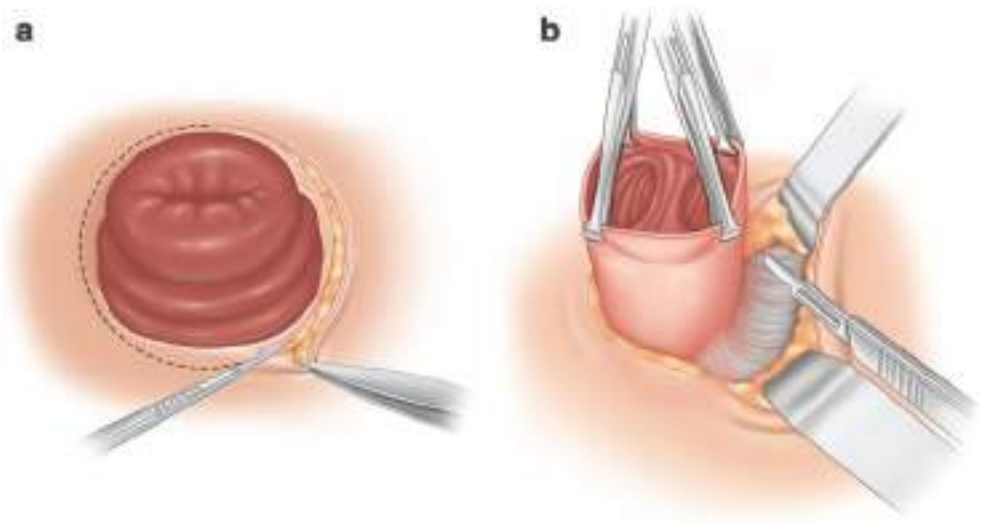

FIGURE 55-27. (**a**) Incision of the stomal mucocutaneous junction. (**b**) Elevating the stoma with clamps to expose the subcutaneous stomal dissection.

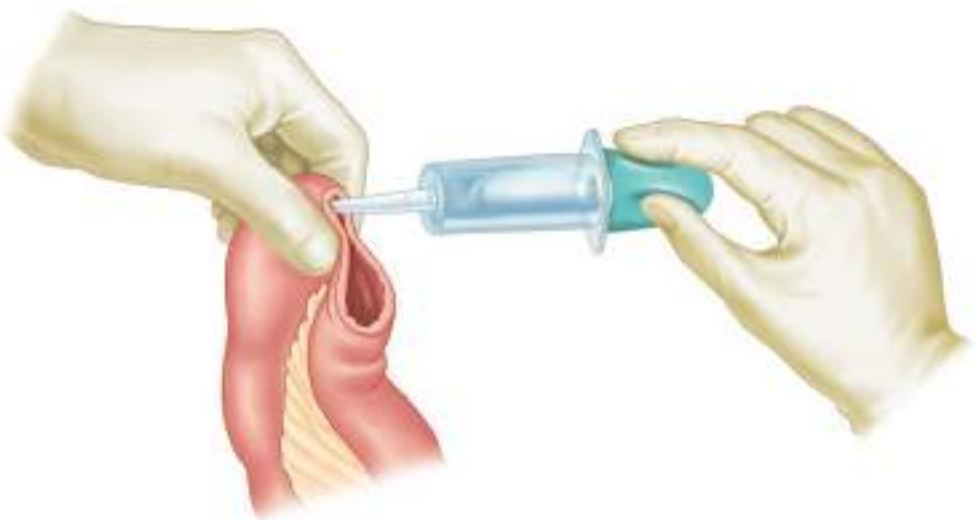

FIGURE 55-28. Pressurized leak testing of injured bowel during loop stoma closure.

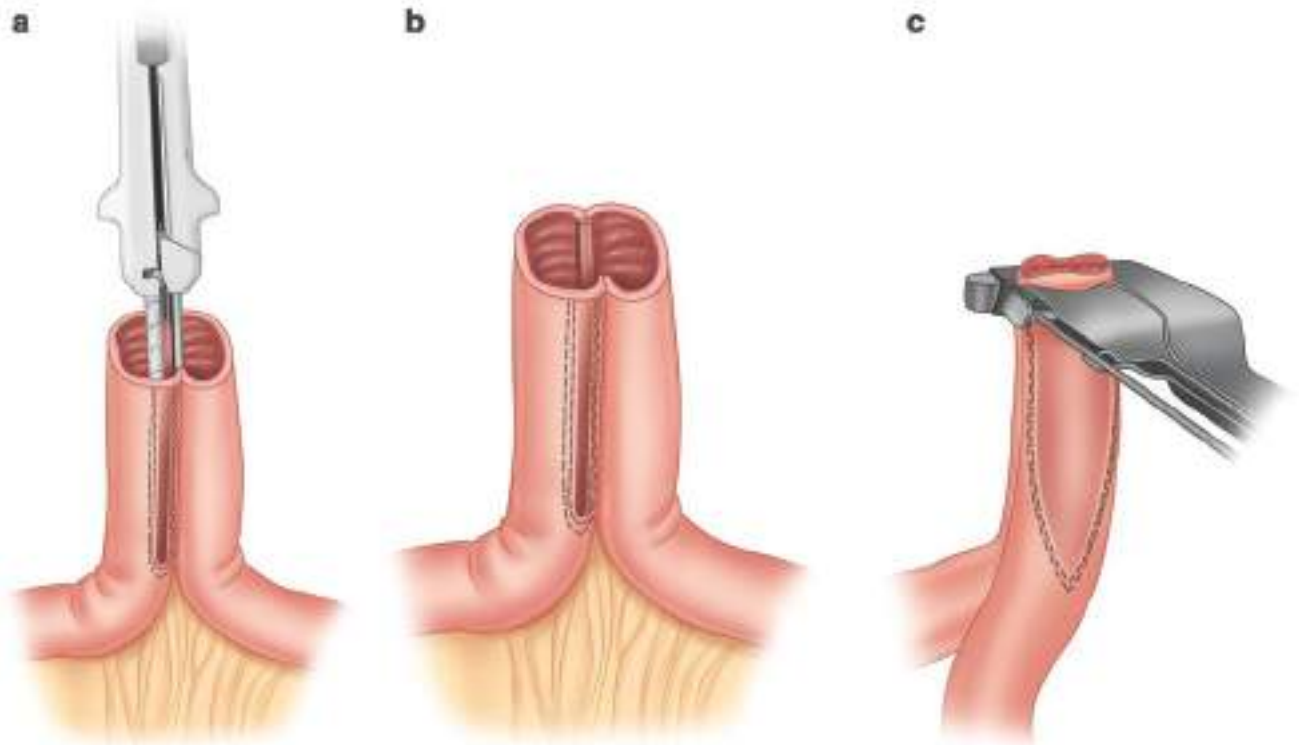

FIGURE 55-29. A stapled side-to-side anastomosis.

a laparotomy for repair. The bowel portions that comprised the stoma can be resected or left in situ at the surgeon's discretion. Once the bowel is adequately mobilized and inspected, a stapled or hand-sewn closure is performed.

A side-to-side (functional end-to-end) stapled closure is performed by inserting the limbs of a linear cutter stapler (GIA type) into each limb of the loop stoma (Figure 55-29). Care is taken to ensure the limbs are opposed along the anti-mesenteric surfaces prior to firing the stapler. The common portion of bowel wall that connects both bowel limbs may be divided or resected to improve anti-mesenteric opposition. The common enterotomy is then closed with either suture or an intersecting fire of another GIA- or TA-type stapler. The completed anastomosis may

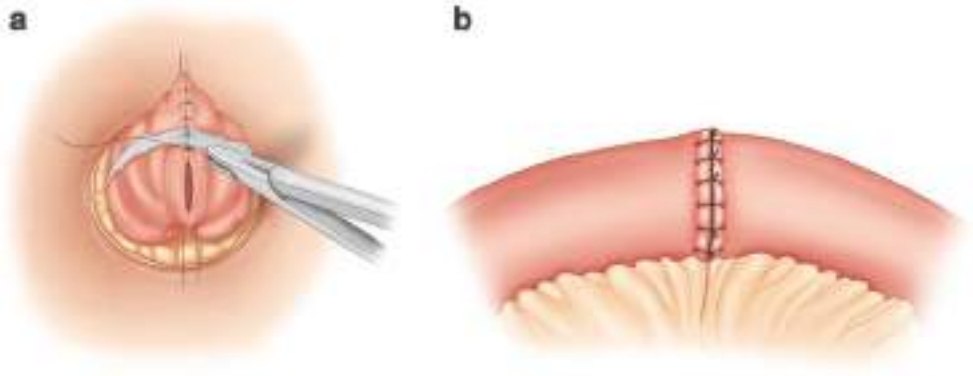

FIGURE 55-30. Handsewn loop closure for (**a**) colostomy and (**b**) ileostomy.

be oversewn at the discretion of the surgeon and a suture (i.e., "crotch stitch") may be placed at the confluence of the bowel limbs. Alternatively, a hand-sewn anastomosis is performed with either running or continuous suture in one or two layers to longitudinally close the defect (Figure 55-30). The completed anastomosis is then reduced into the abdomen. Adequate intra-abdominal adhesiolysis must be completed prior to fascial closure to avoid injury to bowel adherent to peritoneum. The fascia is closed with interrupted or running suture. The skin can be closed with or without a drain, left partially open with wicks, or left completely open to heal secondarily.

Mode of loop ileostomy closure has long been a source of debate amongst surgeons based largely on preference and training pedigree. Several meta-analyses and three single-center prospective randomized control trials have shown stapled and loop closures are equivalent with regard to anastomotic leakage, wound infection, overall complications, and cost; however, stapled closure was faster, caused less postoperative bowel obstruction, and was associated with shorter hospital stays [103–107]. It is postulated that the narrow luminal diameter produced with hand-sewn closure techniques is prone to edema and early obstruction compared to widely patent stapled anastomoses. Recently, a large multicenter trial showed stapled and hand-sewn anastomoses to have similar rates of postoperative bowel obstruction [108]. As a result, ASCRS Clinical Practice Guidelines (CPG) state that stapled and hand-sutured techniques are both acceptable for loop ileostomy closure [7].

Wound closure at the former stoma site is also a contentious issue that has been studied extensively. Several studies have compared various techniques including traditional linear wound closure, closure over a suction drain, and skin-level purse-string cerclage technique (which leaves a small opening at the center of the wound). Purse-string techniques are shown to have significantly lower wound infection rates and improved patient satisfaction [109, 110]. ASCRS CPG recommends stoma-site skin re-approximation should be performed when feasible, and purse-string skin closure may have advantages compared with other techniques [7].

Technical Considerations of End Stoma Reversal

Undoubtedly, reversal of an end stoma can be a substantial surgical undertaking and may be a larger operation than the initial stoma creation. The patient and surgeon should be prepared for an extensive and potentially hostile operation. In addition to the preoperative preparation described above, the surgeon may selectively use ureteral stents to aid in ureteral identification in a potentially hostile operative field. A fully prepared surgeon should have pelvic retractors, proctoscopes, EEA sizers, and vaginal retractors available in the operating room. Lastly, the surgeon should note the adequacy of the current stoma and site. If the current stoma site is in a poor location, the patient can be marked for a new stoma site should a temporary loop ileostomy be required.

Once the surgeon is satisfied with the quality of the protected distal anastomosis (or pathology), an end stoma can be reversed using open or laparoscopic approaches [111, 112]. The patient is typically placed in modified Lloyd-Davis (low lithotomy) or split leg position allowing access to the anus. For open reversal of an end stoma, the stoma is prepared in the surgical field. A sterile, countable, gauze sponge and adherent plastic drape can be used to sequester end colostomy contamination from the midline wound. The abdomen is entered sharply and adhesions are lysed to identify the bowel conduit leading to the end stoma. The distal bowel conduit is identified, and may be mobilized if necessary, and inspected for anastomotic suitability. In case of a rectal stump, scarring and retraction may rarely require mobilization and resection of the previous rectal closure line; however, it is crucial to ensure that the anastomosis is in the rectum and not sigmoid (see below). Once adequate intra-abdominal adhesiolysis is performed, the stoma is mobilized back into the abdomen by incising the stomal mucocutaneous junction and cylindrically dissecting subcutaneous adhesions until the abdominal dissection is met (Figure 55-31a). Care is taken to avoid mesenteric injury and devascularization of the stoma since bowel length preservation may aid in reaching low pelvic anastomoses.

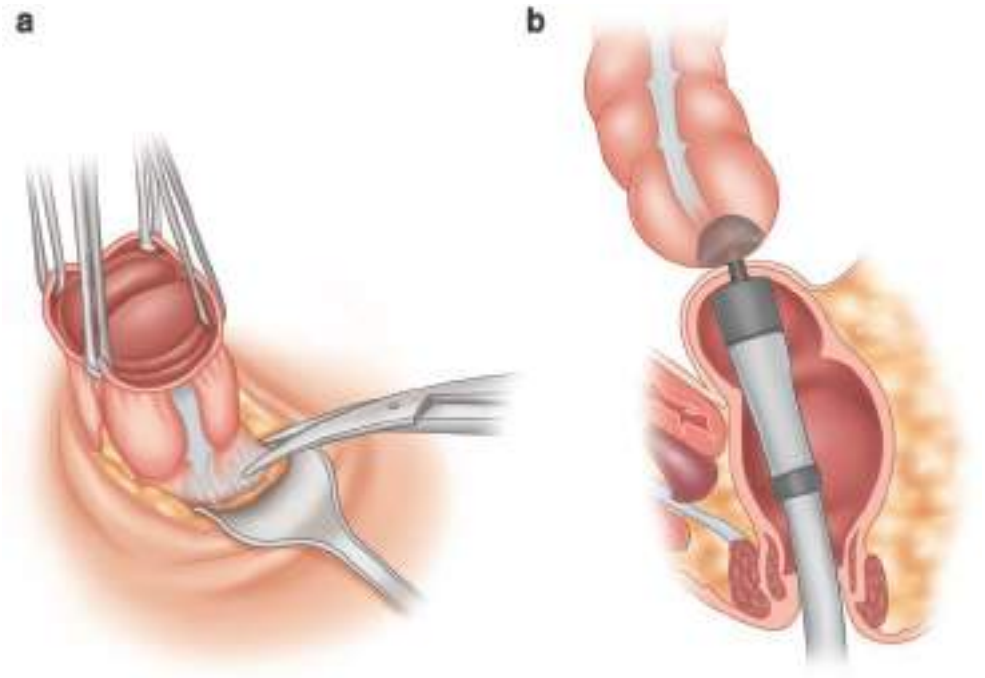

FIGURE 55-31. (**a**) Mobilization of an end colostomy. (**b**) Stapled end-to-end colorectal anastomosis.

After the end stoma is reduced into the abdomen, the surgeon may need to perform additional mobilization of the former stoma to obtain tension-free reach to the target distal bowel. For end ileostomy reversals, generous small bowel mobility does not typically require much additional mobilization. Colorectal anastomoses may require additional lengthening maneuvers including mobilization of the flexures and high vascular ligation to obtain tension-free reach into the pelvis. For an end colostomy reversal following sigmoid diverticulitis, the surgeon must ensure the adequacy of the initial resection at time of stoma reversal with particular attention paid to previous resection margins. Occasionally, a surgeon may create a sigmoid stump rather than a rectal stump during emergency surgery, and a completion sigmoid colectomy may be necessary at the time of stoma reversal to ensure an adequate diverticular resection. Similarly for cancer, the oncologic adequacy of the initial resection must be assessed and remedied at the time of stoma reversal, which may require additional bowel resection or lymphadenectomy.

Once the distal and proximal bowel conduits are adequately mobilized and prepared, an anastomosis is created with either stapled or hand-sewn techniques at the surgeon's discretion. For colorectal anastomoses following Hartmann's procedure, a stapled end-to-end anastomosis (EEA) is commonly performed (Figure 55-31b). For stapled anastomoses, the surgeon must ensure the stapler can easily be passed to the transected rectal staple line. This may not always be easy or possible since the rectal stump can become corrugated, contracted, entrapped, or lost in a hostile pelvis. Lighted deep pelvic retractors, proctoscopes, vaginal retractors, EEA sizers, and copious lubrication may aid in identification of the rectal stump. If the stapler is unable to be advanced fully to the proximal rectal transection line, the end of the colon can be anastomosed to the side of the anterior rectal wall, but the end-to-side anastomosis must be several centimeters from the proximal rectal margin to avoid ischemia to the remaining bridge of rectal wall. Moreover, if an anterior end-to-side rectal anastomosis is performed, the surgeon must assure the vagina and/or bladder is fully mobilized away from the intended rectal anastomotic site to avoid catastrophic iatrogenic fistulas. An anastomotic air-leak test should be performed to interrogate anastomotic quality. If a leak is discovered, the anastomosis can be resected and recreated, revised, or protected with a diverting loop ileostomy at the surgeon's discretion.

Laparoscopic end stoma reversal with colorectal or ileorectal anastomosis is predicated upon the same principles and techniques described above, but are modified to reflect the nuisances of laparoscopy. After similar preoperative work-up and positioning, surgery typically commences with incision of the mucocutaneous stomal junction and subcutaneous stomal dissection. Once the stoma is completely freed from peritoneal attachments and un-everted, the anvil to an EEA stapler is secured in place and the anvil–stoma combination is reduced into the abdomen. The former stoma site is occluded with a airtight, twisted, plastic, wound retractor or plugged with a balloon-tipped Hasson trocar as pneumoperitoneum is generated. Additional laparoscopic working ports are placed to complete the necessary adhesiolysis, pelvic dissection, and rectal mobilization exactly as performed for an open procedure. An intracorporeal EEA stapled rectal anastomosis is then completed as described above.

TABLE 55-5. Select published complications rates for stoma reversal [99, 108, 112, 113, 116, 125–127]

Stoma reversal type	Loop ileostomy reversal (%)	Loop colostomy reversal (%)	End colostomy reversal with colorectal anastomosis (%)
Superficial surgical site infection	3–13.5	5–20	14–43.8
Deep space infection/leak	2–4	2–4	1.5–21
Bowel obstruction/ileus	5–16	4	23
Hernia (clinically diagnosed)	0–50	2–38	3–31

Stoma Reversal Complications

Loop stoma reversal is often considered a minor procedure when compared to the index operation; however, complications can occur more frequently than most surgeons acknowledge (Table 55.5). Regardless of technique, loop ileostomy reversal is generally well tolerated with low risk of anastomotic leakage; however, early wound infections and late-term incisional hernias may occur. Reversal of an end stoma is associated with high morbidity, and stoma reversal is often more challenging than the initial operation. Given the gravity of some end stoma reversals, proper surgical planning is essential to assure the best surgical outcomes, while preoperative patient counseling can best manage perioperative patient expectations.

Special Considerations

The Difficult Stoma

Increasing rates of obesity present a particular challenge to the colorectal surgeon. Unfortunately, obesity is associated with increased risk of stoma-related complications [10], so the patients who require the highest quality stomas to avoid problems paradoxically can be the most challenging stomas to create. Acutely inflamed and chronically foreshortened bowel mesentery also may hinder stoma creation, even in thin patients. Special tips and tricks can help the surgeon create difficult stomas in complex situations. Since stoma height has been identified as an independent risk factor for problematic stomas, it is not surprising that the majority of tips involve means of obtaining adequate, tension-free reach of an adequate length of stomal conduit above skin level.

Simple measures are first employed when dealing with the difficult stoma. In obese patients with a thick abdominal wall, the surgeon may find the supra-umbilical abdominal wall to be thinner whereby easing reach and minimizing tension on a stoma (Figure 55-32). In the super morbidly obese, a subxiphoid loop transverse colostomy may be the easiest stoma to create if temporary diversion is necessary. If superior stoma sites are not plausible, and the surgeon still struggles to deliver bulky bowel through a thick abdominal wall, the stoma can be delivered in a stepwise fashion. First, the subcutaneous tissues can be completely elevated off of the anterior rectus sheath and the stoma can be delivered completely through the muscular layer. The stoma can then be delivered through the subcutaneous tissues and skin in a second step. Alternatively, use of a plastic sleeve wound retractor with or without water-soluble lubricant may provide a slick conduit to help deliver thickened bowel and mesentery through a challenging trephine. Some advocate performing subcutaneous lipectomy to minimize abdominal wall distance; however, this may lead to a difficult-to-pouch recessed stoma and should be used judiciously, if at all.

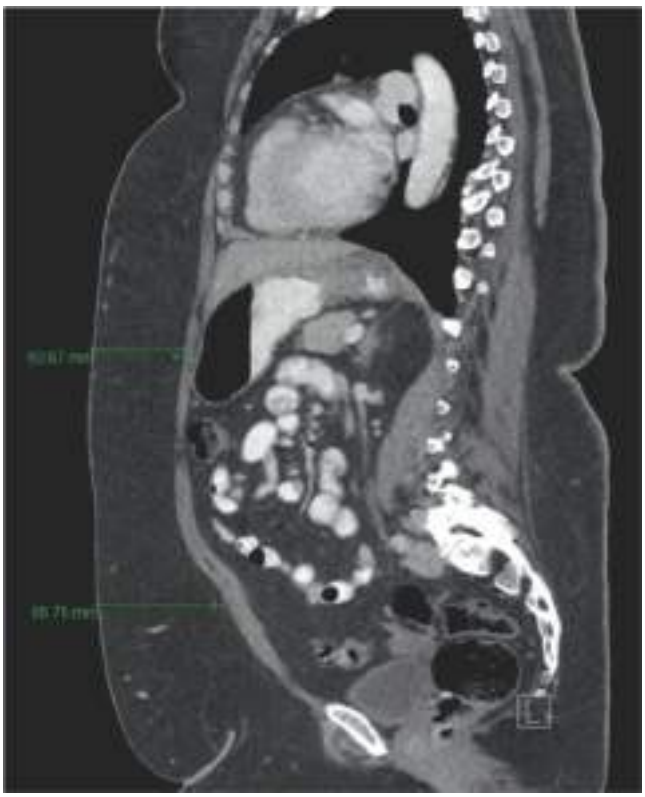

FIGURE 55-32. The abdominal wall may be thinner above the umbilicus in the obese patient, easing creation of a potentially difficult stoma.

A loop-end stoma is a unique ostomy configuration that may allow additional reach of an end ileostomy (Figure 55-33) or colostomy (Figure 55-34) in obese patients or those with a foreshortened mesentery. The loop-end stoma

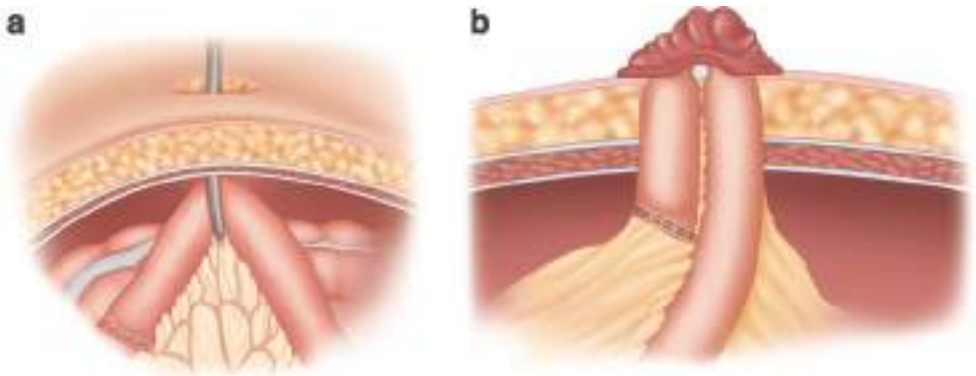

FIGURE 55-33. Loop-end ileostomy.

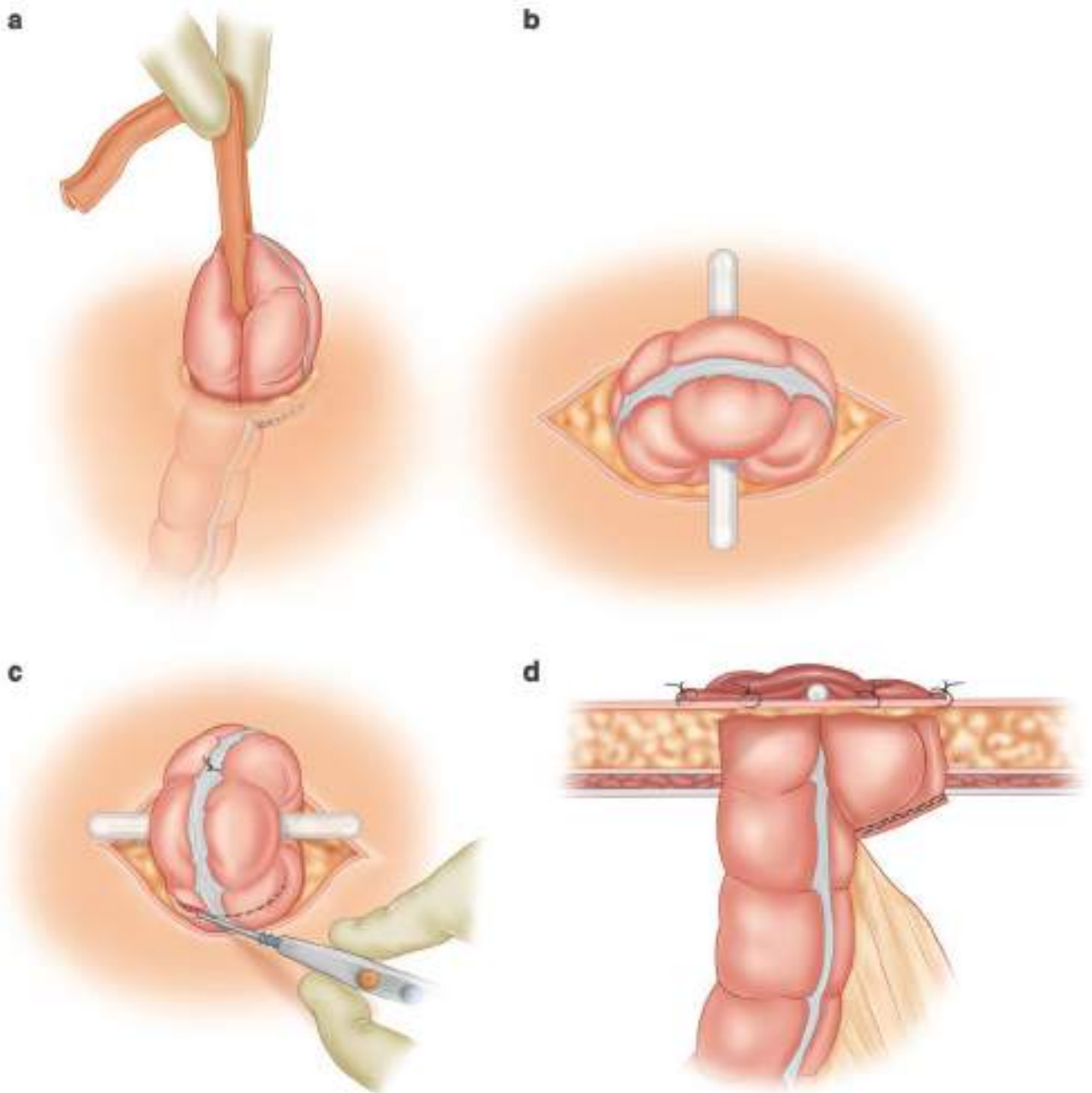

FIGURE 55-34. Creation of a loop-end colostomy.

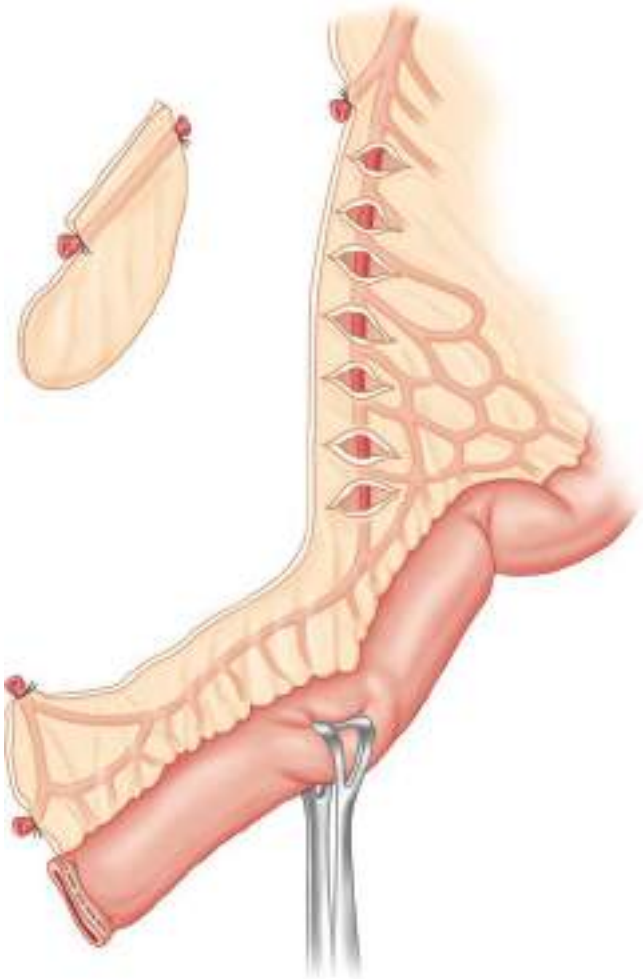

FIGURE 55-35. "Pie crusting" of the bowel mesentery to obtain additional length prior to stoma creation. If a difficult end ileostomy is fashioned from the terminal ileum, the surgeon may find it helpful to ligate the ileocolic artery proximally to obtain reach.

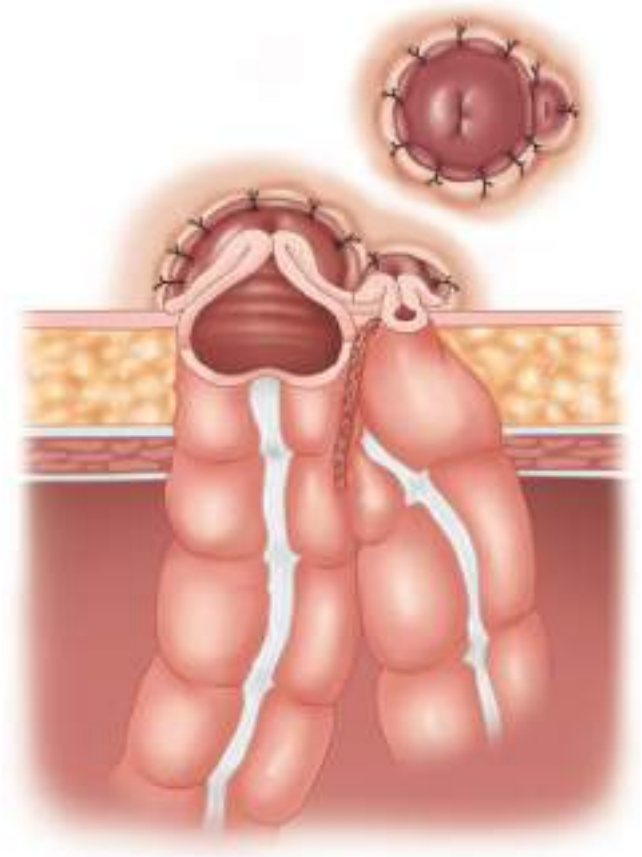

FIGURE 55-36. A Prasad-type end-loop colostomy.

configuration is useful when the tip of the intended stoma conduit is tethered by the mesentery and the bowel immediately proximal to the end is more mobile. The loop-end arrangement preserves the mesentery to the entire stoma, whereby assuring adequate perfusion. A loop-end stoma is created similarly to a loop stoma, which is aided by passing a narrow Penrose drain through a mesenteric defect at the mesentery–bowel interface to deliver the loop. The stoma is matured as a loop ileostomy or colostomy as detailed previously (see section "Technical Considerations of Stoma Creation").

Two to three centimeters of additional bowel reach can be obtained by sequentially scoring the peritoneal surface of the stomal mesentery perpendicular to the course of the vessels (Figure 55-35). Such "pie crusting" should be carefully performed by only dividing the peritoneum while protecting the underlying vessels. In the case of a small bowel stoma, both peritonealized mesenteric surfaces may need to be scored to obtain maximum reach.

In the acute setting when it may be inadvisable to create an anastomosis, both segments of bowel may be exteriorized in a Prasad-style end-loop stoma (Figure 55-36). This configuration is most commonly used when there is a bowel perforation related to diverticulitis or trauma but may be employed in any situation when primary anastomosis is inadvisable. The unique aspect of this stoma is that both bowel limbs are exteriorized and eventual re-anastomosis may often be performed with a local procedure without laparotomy.

Challenging situations may require the surgeon to compromise on the tenets of stoma creation and the ideal stoma at the ideal location with the ideal bowel segment may not be possible. If a surgeon is forced to decide between making a poor stoma in a good location versus making a good stoma in a poor location, a general consensus amongst stoma care professionals is that a poor stoma in a good location is the lesser of two evils [12]. Rarely, thickened bowel and mesentery may prohibit stoma eversion and maturation. In these cases where eversion and maturation is not possible, the

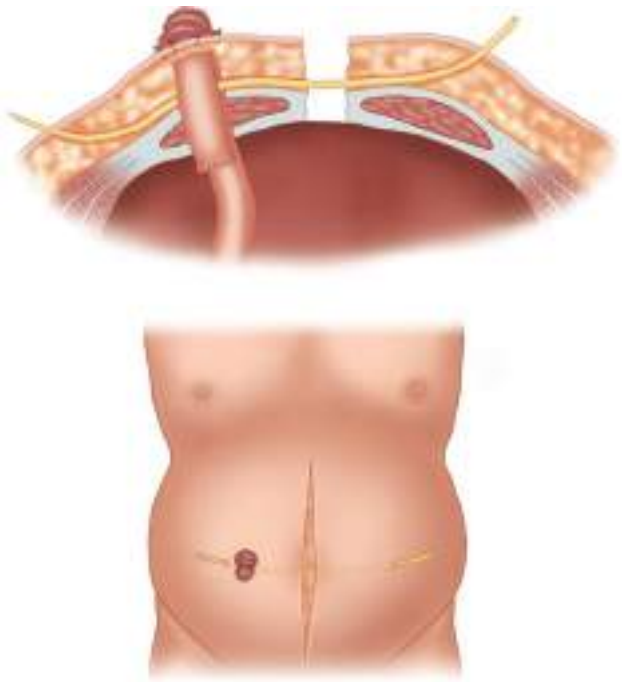

FIGURE 55-37. Supporting a difficult loop enterostomy at the fascial level with a filiform catheter.

stoma can be simply opened without maturation and secured to the skin well above skin level. While reactive serositis and late-term stricture may develop, this temporizing measure may get the patient through until the bowel is suitable for stomal revision or reversal. Seldom, a remarkably hostile abdomen may prohibit stoma delivery through a traditional stoma trephine despite exhausting all lengthening maneuvers. In these rare situations, a stoma may be fashioned through the midline incision. Although a stoma placed in an incision is prone to wound and hernia problems, it may temporize or palliate an otherwise unsustainable surgical situation. Infrequently, a heavy mesentery or friable bowel may cause a stoma support rod to tear through the mesenteric aspect of a loop stoma. Instead, the bowel can be supported by two stoma rods placed alongside one another to distribute the tension over a greater surface area. Alternatively, the mesentery can be braced at the fascia level rather than the skin level. In this method, a long malleable or pliable tube (e.g., thin chest tube, filiform, follower, plastic vascular tunneling device) is passed through a skin incision remote from the stoma site down to the anterior fascia of the abdominal wall where it pierces an avascular portion of the stoma mesentery before rising through the skin on the opposite side of the stoma (Figure 55-37). This tube is subsequently removed in several days when the stomal bowel and mesentery adhere to the subcutaneous tissues and are at minimal risk for retraction.

Temporary Fecal Diversion: Loop Ileostomy Versus Loop Colostomy

The ideal level of temporary protective fecal diversion following colorectal or coloanal anastomosis has long been debated by colorectal surgeons. It is generally acknowledged that loop ileostomy and loop colostomy have similar complication rates, but different complication profiles [7]. Clinical and patient-reported outcomes between temporary loop ileostomy versus loop colostomy have been compared in several recent trials and meta-analyses with inconsistent results [113–115]. Loop ileostomies, although more prone to dehydration, re-admission, and post-reversal obstruction, are found to have less post-closure sepsis and less pre- and postoperative hernias and may offer improved quality of life compared to loop colostomy [116–118]. ASCRS CPG recommends loop ileostomy preferentially over transverse loop colostomy for temporary fecal diversion in most cases, but acknowledges that there may be particular circumstances favoring a loop transverse colostomy [7]. For instance, a distal colorectal obstruction may best be palliated with a transverse loop colostomy that allows both afferent diversion and efferent retrograde venting. Additionally, a transverse loop colostomy may be easier to fashion in the obese than a loop ileostomy (see section "The Difficult Stoma").

Genitourinary Stomas

Although colorectal surgeons do not typically perform reconstructive genitourinary procedures, familiarity with such procedures is important for several reasons. First, a colorectal surgeon may be asked to help with stoma care and complications and assist with urinary stoma revisions. Additionally, a thorough understanding of urinary stoma construction and anatomy can prove invaluable during urgent and emergent re-operations on patients with previous genitourinary reconstructions. Moreover, genitourinary reconstruction may be necessary for patients with locally advanced pelvic malignancies that require multi-visceral resection. Lastly, patients with neurogenic bowel and bladder may require synchronous urinary and fecal diversion, so conscientious understanding of the urologic aspects of a synchronous operation is crucial.

The simplest reconstructive urinary diversion is the ileal conduit (Figure 55-38) [119]. This procedure typically harvests a 10–15 cm segment of ileum (typically at least 15–20 cm proximal to the ileocecal valve) to serve as a conduit between ureters and the skin. Enteric continuity is restored with an ileo-ileostomy and the left ureter is tunneled through a sigmoid mesenteric defect. Both left and right ureters may be anastomosed separately (in a "Bricker" fashion) or sewn together and a single ureto-ileal performed

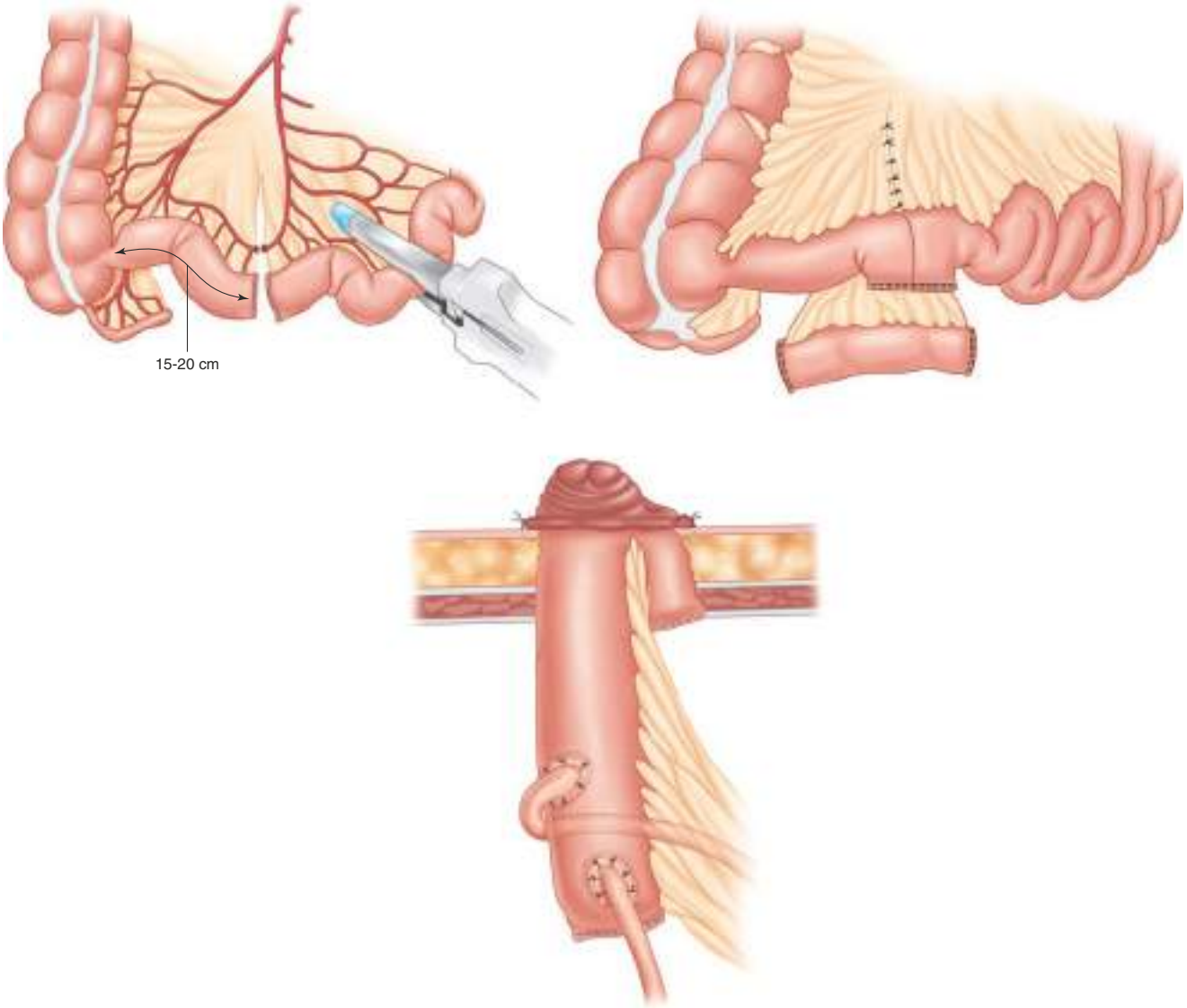

FIGURE 55-38. The ileal urinary conduit: (**a**) a segment of mid ileum is resected, (**b**) an ileo-ileostomy is created, and (**c**) the harvested ileal conduit is anastomosed to the ureters and matured as a stoma.

(called a "Wallace" anastomosis). The proximal end of the conduit is usually oversewn to limit stone formation. The open end of the conduit is delivered through a stoma trephine and matured to the skin. The stoma is matured in either an end or loop-end configuration. The surgeon must be keenly aware of the left ureter's aberrant course during re-operation and left colon mobilization. Moreover, the tenuous ileal conduit mesentery must be preserved at all costs during re-operation, since inadvertent injury can result in conduit infarction and convert a simple adhesiolysis to an extensive and complex urinary reconstruction. The mesentery for the conduit will always be inferior to the new ileo-ileostomy.

Urologic surgeons may augment or replace urinary bladders with harvested ileal segments for myriad indications [120]. Akin to the ileal conduit, a similar segment of mid ileum is harvested and configured as either a panel or pouch to augment or reconstruct the bladder to increase its capacity. Regardless of the ileal configuration, enteric continuity is restored with an ileo-ileostomy and a fragile mesenteric pedicle spans from the closed mesenteric defect to the pelvis. This ileal mesentery pedicle can be a nidus for obstruction and internal herniation, and extreme care should be taken to preserve the mesentery to avoid devascularization of the reconstructed urinary bladder.

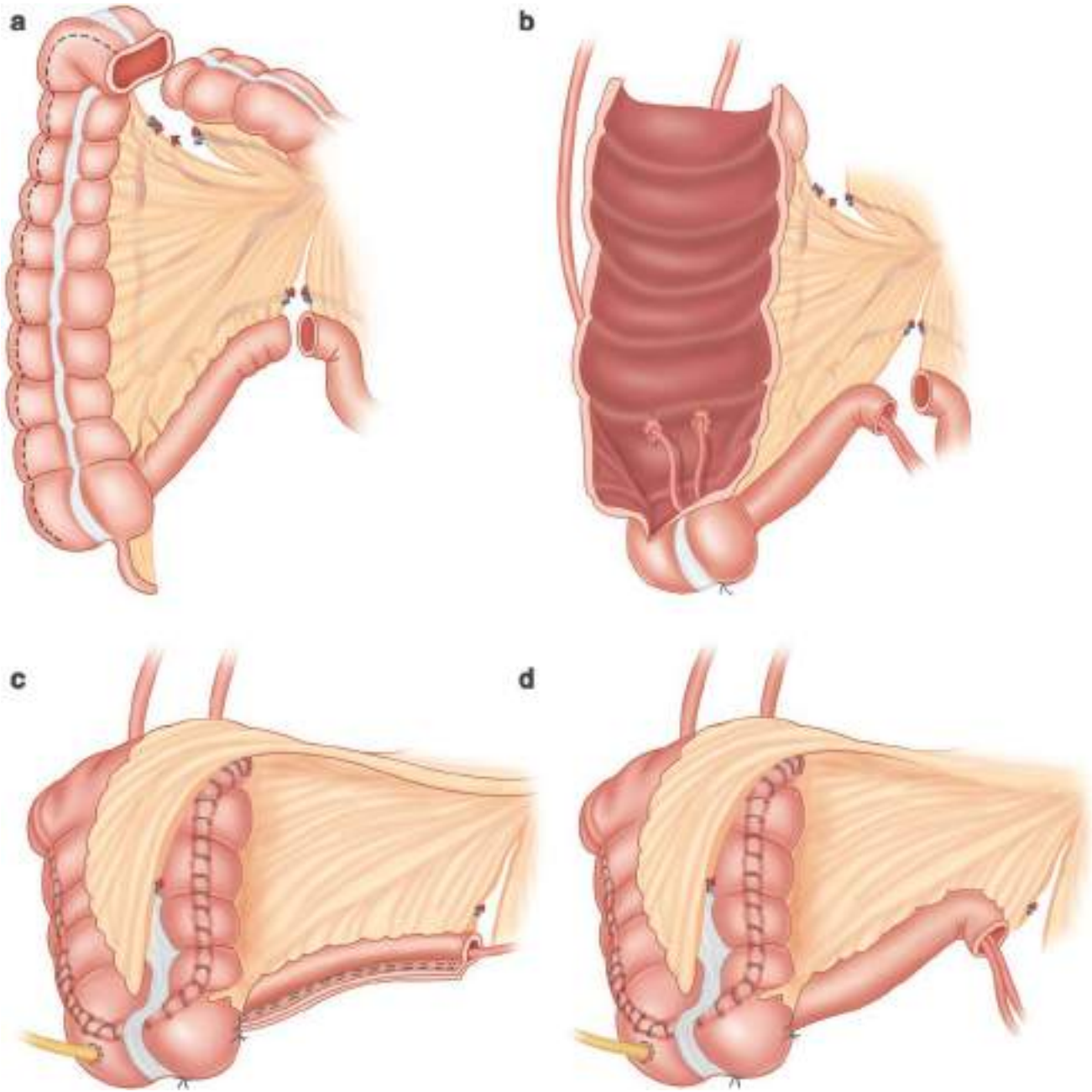

FIGURE 55-39. The Indiana pouch.

Several types of catheterizable urinary stomas may provide appliance-free urinary continence to patients in need of genitourinary diversion. These catheterizable stomas are brought to the umbilicus or the right lower quadrant. Most pouches are created from the right colon with the appendix or the terminal ileum as the channel for catheterization. An Indiana pouch follows similar principles as the ileal conduit; however, the right colon and ileum are harvested en bloc to create a large intra-abdominal urinary reservoir (Figure 55-39) [121]. The ileocolic segment is anastomosed to the bilateral ureters, and a narrow, skin-level, stoma is created that serves as a valve and permits intermittent catheterization. A Mitrofanoff appendicovesicostomy utilizes an appendiceal conduit to create a catheterizable stoma for the

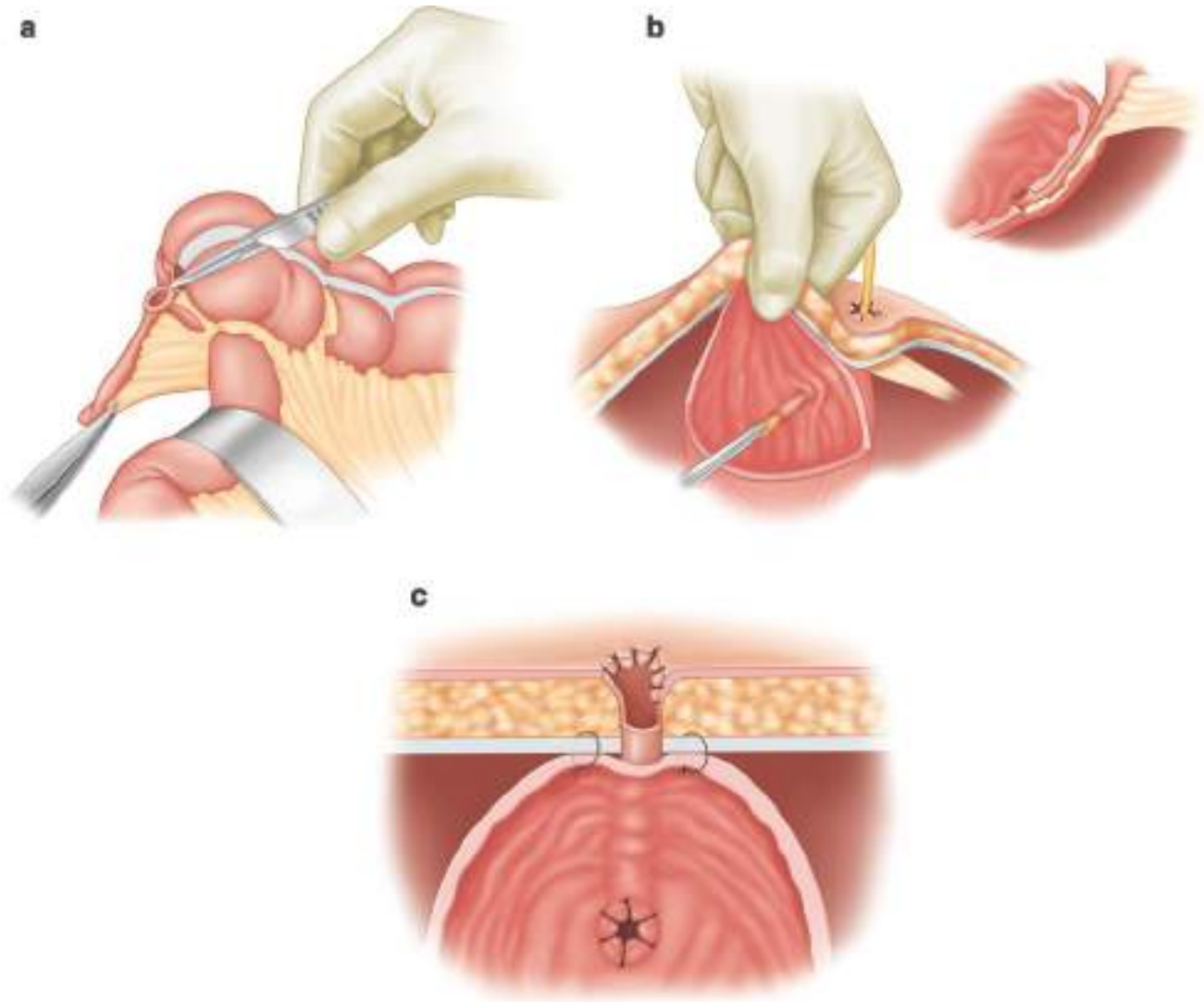

FIGURE 55-40. Mitrofanoff appendicovesicostomy.

bladder or neobladder (Figure 55-40) [122]. A Monti conduit is similar to the Mitrofanoff appendicovesicostomy but utilizes a pedicled segment of tubularized ileum to create a narrow, catheterizable, urostomy (Figure 55-41) [123].

The Turnbull Blowhole Colostomy

Rarely, difficult situations may arise where colectomy or proper fecal division is inadvisable due to prohibitively high operative risk. For example, gravid patients with fulminant colitis may be unsuitable for colectomy out of concern of patient or fetal demise. Occasionally, profound comorbidities such as sepsis or cardiovascular collapse may also make a total colectomy inadvisable. In these situations, a limited upper midline laparotomy with loop ileostomy and Turnbull blowhole colostomy can be fashioned quickly to divert and decompress a toxic colon until the patient can sustain a proper resection (Figure 55-42) [124]. In these challenging situations, a limited 10-cm supra-umbilical laparotomy can be made to accommodate a hand to explore the abdomen. A loop ileostomy can be made through a separate stoma trephine and the loop of transverse colon can be brought out through the midline incision. The midline fascia is closed around the bulge of the transverse colon loop and then a watertight seal is created between the seromuscular surface of the colon and

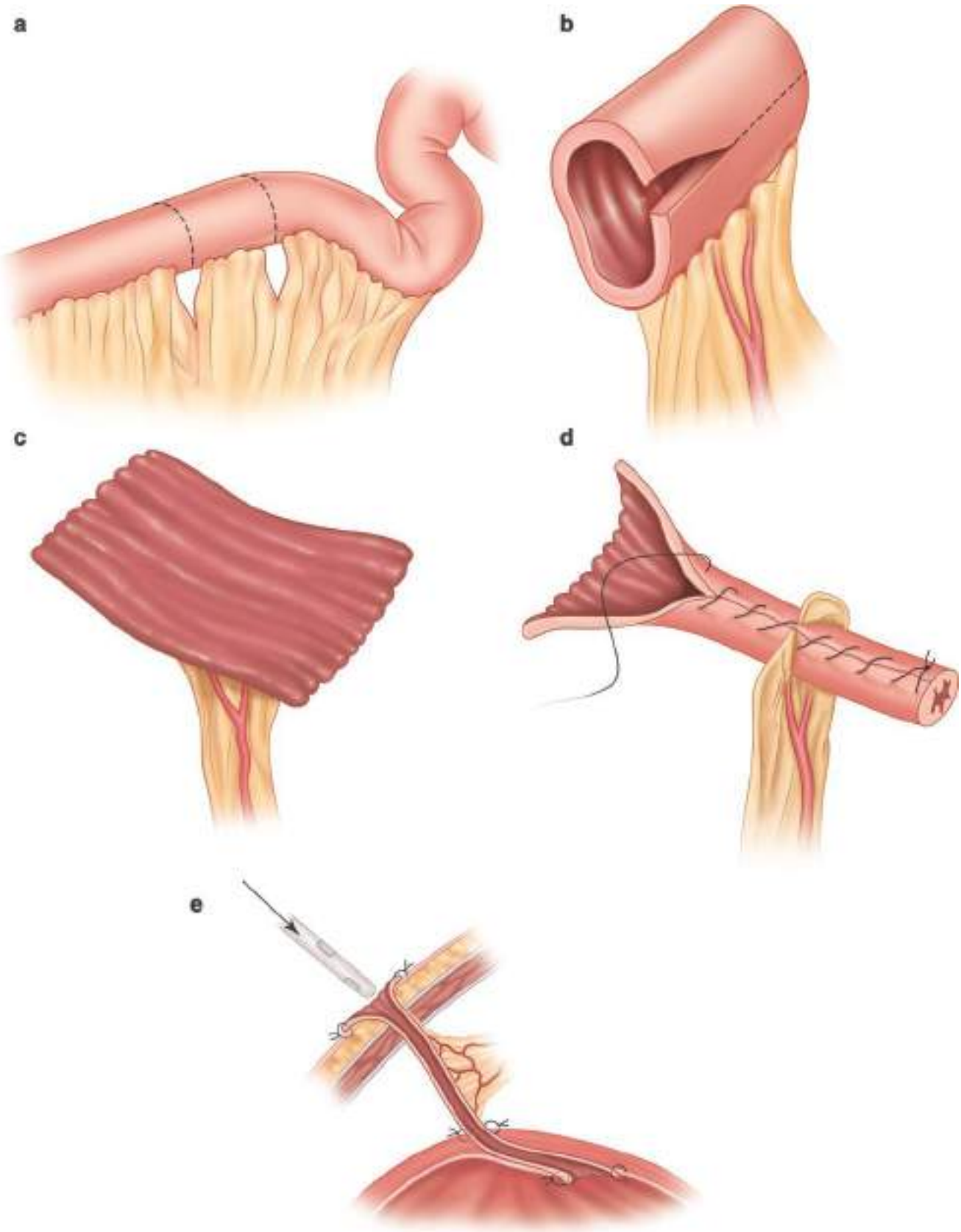

FIGURE 55-41. The Monti procedure.

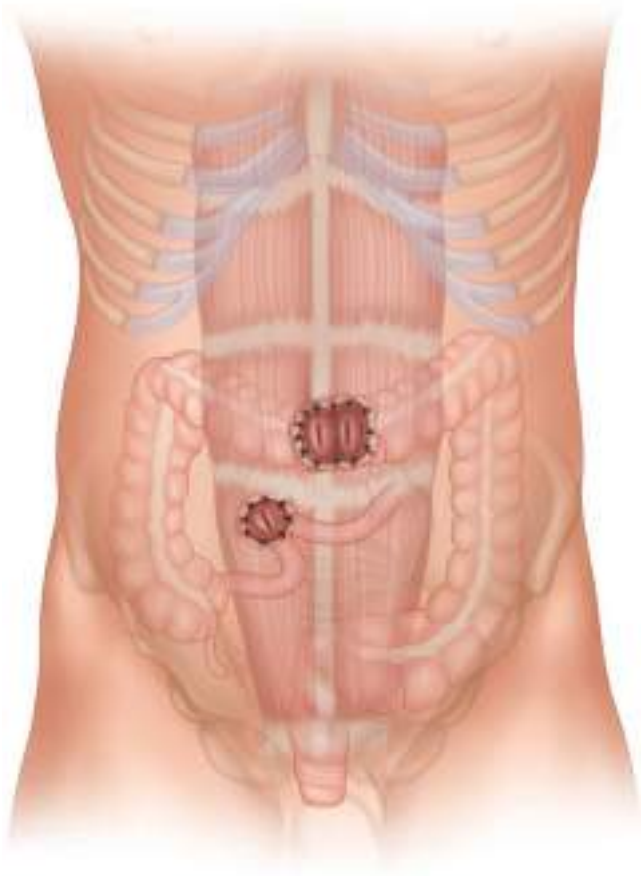

FIGURE 55-42. The completed Turnbull blowhole colostomy and loop ileostomy.

the surrounding peritoneum with one or two layers of continuous suture (Figure 55-43). Once the peritoneal cavity is sequestered from potential bowel spillage, the colon is incised and the bowel edge is sutured to the skin. The ileostomy is then matured. The blowhole stoma is suboptimal due to prolapse and pouching difficulties owing to the flat nature of the stoma, but it can be a useful temporizing adjunct when no other options exist.

For rare patients too ill to tolerate a general anesthetic, the Turnbull blowhole colostomy can be performed under local anesthesia with the aid of a fluoroscope. A fluoroscopic projection of the upper abdomen is obtained with the patient supine on the operating table. The colon is identified fluoroscopically by its characteristic bowel gas pattern and a metallic coin is then used to mark the intersection of the transverse colon and the midline. The spot is then marked and local anesthetic is infiltrated through the subcutaneous tissues and a 4-cm midline incision is made directly over the colon. Local anesthetic is infiltrated layer by layer as the fascia and peritoneum are carefully divided and the abdomen is entered. The anterior seromuscular surface of the colon is grasped through the incision and sutured circumferentially to the peritoneum to limit intra-abdominal stool contamination. A colotomy is made and the stoma is fasted to the skin as described above.

Ileostomy and Foodstuff Bolus Obstruction

Early postoperative edema may cause transient ileostomy obstruction at the level of the rectus fascia. Such edema typically subsides before return of bowel function, but lasting edema can cause an obstruction. In the setting of bowel obstruction symptoms, ileostomy obstruction may be suspected when there is peristomal pain with either thin, nonbilious, hydrops-type fluid ileostomy effluent or no output at all. Cross-sectional imaging may reveal an abrupt transition in bowel caliber as the stoma traverses the abdominal wall. If acute postoperative ileostomy obstruction is suspected, a 14-18-French Foley (or red rubber) catheter can be gently placed at the bedside to bypass the level of obstruction and decompress the bowel proximal to the ileostomy. To place a catheter, a two-piece stoma appliance should be used. With the stoma flange in place and bag removed, a well-lubricated catheter is inserted into the stomal os as small aliquots of water are gently injected through the catheter with a Toomey syringe to create a water cushion ahead of the catheter tip. Gentle pressure is applied to the catheter as water is injected to push the bowel wall away from the catheter tip whereby avoiding bowel wall injury and perforation. The catheter is advanced as long as resistance is not met beyond the fascial obstruction and secured to the stoma appliance with suture or dental floss to hold the catheter in place. If a Foley catheter is used, the balloon should not be blown up out of concern of injuring the bowel. The catheter should be used sparingly, as both short- and long-term use of indwelling stoma catheters can cause bowel perforation.

The relatively narrow luminal diameter of an ileostomy may occasionally cause bolus obstruction by non-digestible foodstuffs. High-residue foods such as nuts, seeds, shellfish, sausage casings, and raw produce are poorly digested and may pass through the ileostomy in large chunks. Rarely, such foodstuffs may become lodged within the ileostomy and require ileostomy irrigation to disimpact the food bolus. To irrigate an ileostomy, a Foley (or red rubber) catheter is placed as described above to a distance just beyond the fascia (typically <6 in. from the skin surface). A Toomey syringe is then used to slowly irrigate out the bolus obstruction with 30–50 mL aliquots of water until the bolus is dislodged. This process may take 1–2 h.

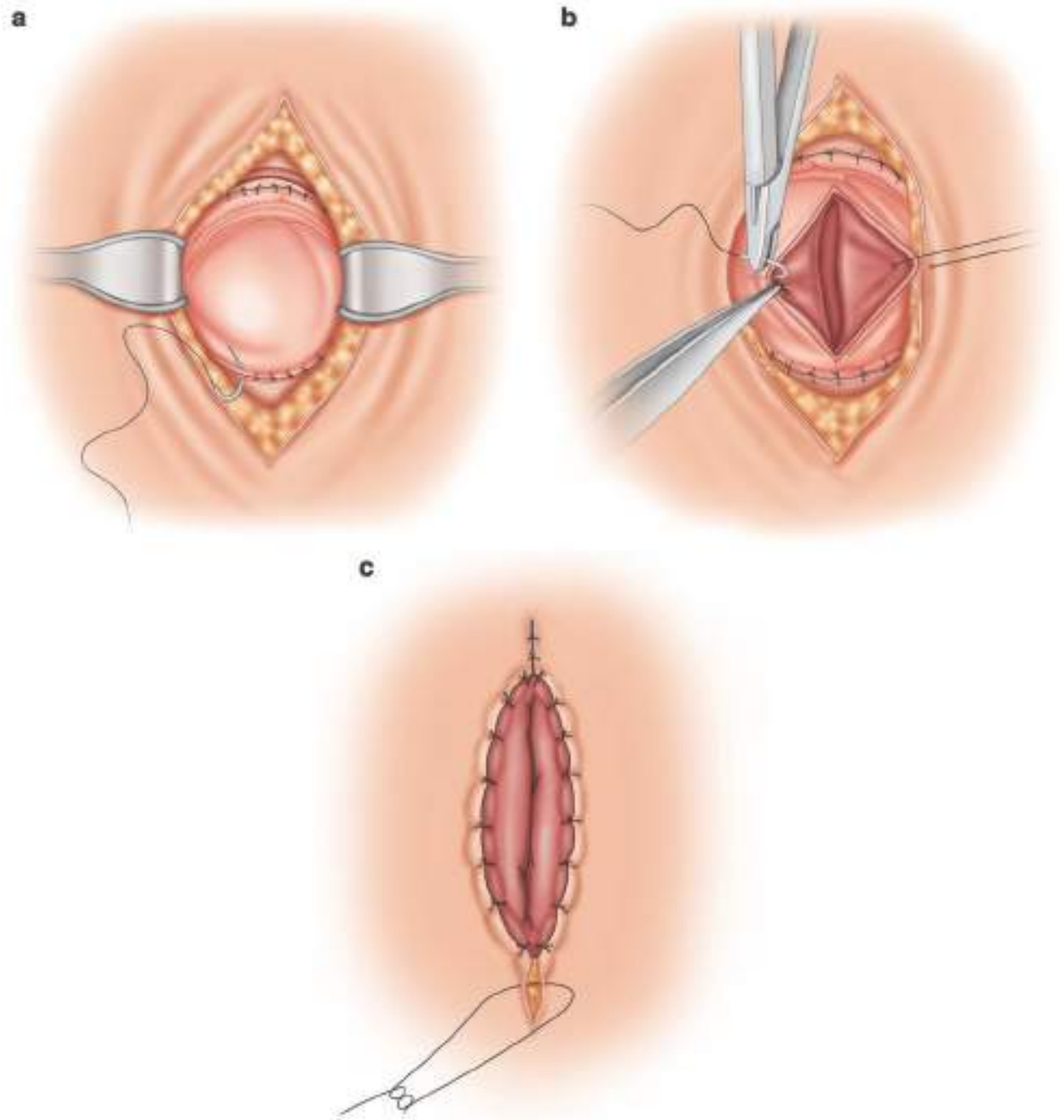

FIGURE 55-43. Creation of a Turnbull blowhole colostomy.

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Functional Complications After Colon and Rectal Surgery

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Key Concepts

- Low anterior resection syndrome (LARS) is extremely common after proctectomy with a multifactorial etiology including damage to sphincters, variations in RAIR, intestinal motility changes, autonomic and somatic nerve injury, and pelvic floor dysfunction.
- Radiation and pelvic sepsis may contribute to deterioration of bowel function.
- Symptoms may include incontinence to stool or flatus, urgency, fragmentation of stool, difficult evacuation, and a sense of incomplete evacuation.
- Alternative reconstructions utilizing colonic pouch or side-to-end anastomosis may be associated with better bowel function when compared to straight anastomoses.
- Pelvic nerve damage during TME can impair urinary and sexual function as well as bowel function.
- Sexual dysfunction occurs in both males and females and may manifest in women as dyspareunia and failure to lubricate with arousal. In men, erectile dysfunction and retrograde ejaculation may occur.
- Colorectal surgeons may underappreciate the magnitude of bowel dysfunction after rectal cancer resection and its impact on quality of life.
- There is no accepted treatment algorithm for bowel dysfunction after proctectomy; symptom control utilizing medications to slow and bulk stools, protection of the perianal skin, physical therapy, colonic irrigation, and in some cases sacral nerve stimulation are currently recognized therapies.

Introduction

Colorectal cancer is the third most common cancer in men and women in the United States and approximately one-third of these cases are rectal cancers [1]. Total and partial mesorectal excisions (TME) are commonly performed, and although colorectal surgeons are very adept at discussing potential complications of these operations, they may not be as thorough in the discussion of functional outcomes. Bowel dysfunction after low colorectal or coloanal anastomoses is extremely common and underappreciated. This dysfunction has been termed: low anterior resection syndrome (LARS). This chapter will discuss symptoms, etiology, and current treatment recommendations. Additionally, other potential functional problems that may be seen after a proctectomy will be covered.

Low Anterior Resection Syndrome

Symptoms and Prevalence

During rectal cancer resection, sphincter-preserving surgery has been considered desirable to permanent stoma if oncologic outcomes are equivalent. The introduction of high-resolution imaging along with the tailored use of neoadjuvant radiation therapy has improved the ability of the surgeon to accomplish sphincter preservation [2]. However, the presumption that quality of life (QOL) would be improved without a permanent stoma has not borne out in the literature [3]. Both a Cochrane review and a meta-analysis indicated that QOL was equivalent between those who underwent abdominal perineal resection (APR) and those with sphincter preservation [4]. Although this finding has not been fully elucidated, many patients experience altered bowel function after low anterior resection (LAR), potentially offsetting the benefits of preserved intestinal continuity [3]. It is estimated that 50–90 % of patients undergoing LAR experience at least some degree of bowel dysfunction postoperatively [5]. The constellation of symptoms including fecal incontinence, urgency, frequent small bowel movements, and clustering of stools has been referred to as low anterior resection syndrome (LARS) [5]. Other postoperative problems after LAR include evacuatory dysfunction [4]. A pragmatic definition

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of LARS is any disordered bowel function after rectal resection leading to a detriment in quality of life [4]. After LAR, oncologic outcome is naturally the primary parameter evaluated; however, bowel function is more commonly being emphasized and studied [6].

The reported incidence of LARS is variable, depending on the definition, the particular study, length of follow-up, and tools used for symptom assessment. Fecal incontinence may occur in 6–87 % of LAR patients, with 5–87 % having urgency, and 8–75 % of patients reporting three or more bowel movements per day [2]. LARS may also be accompanied by tenesmus, rectal or anal pain, difficult defecation, impotence, and dyspareunia [2]. Skin irritation resulting from multiple bowel movements can also be debilitating.

In a recent international multicenter study, Juul and colleagues correlated LARS and quality of life. The study included 796 patients from 4 different countries. Patients completed a questionnaire which provided a LARS score (Figure 56-1) and the EORTC QLQ-C30 questionnaires. Patients with major LARS dysfunction fared worse than those with no LARS issues in global QOL, physical, emotional, role, social functioning, and fatigue. These findings held true for patients with major LARS symptoms when compared to those with minor symptoms [5]. Diarrhea had the strongest correlation to a decreased in QOL [5].

Previous accepted philosophy regarding LARS was that the bowel dysfunction was transient, mainly resolving 12 months after surgery [4]. Long-term studies now report the presence of adverse effects up to 15 years after surgery, with the prevalence of fecal incontinence varying from 0 to 71 % and evacuatory disorders from 12 to 74 % [4]. Chen et al. examined patients who had undergone LAR/TME with a median follow-up of 14 years and found 42 % suffered from major LARS symptoms and 22 % had minor LARS symptoms [7]. These long-term results suggest that LARS results from permanent changes rather than short-lived postoperative inflammation and healing [4].

Etiology of LARS

The exact pathophysiology of LARS remains unclear; however, it appears to be multifactorial. Several studies have demonstrated that anatomical, sensory, and muscular changes have likely been altered by LAR surgery [8]. Other contributing factors include neorectal capacity, compliance, sphincter function, pelvic floor function, colonic motility, and postprandial bowel response [8].

Several studies have concentrated on physiologic changes after LAR surgery. Patients with LARS can have loss of the rectoanal inhibitory reflex (RAIR)—reflecting disordered internal anal sphincter function and anorectal sampling alteration [2]. This alteration may lead to poor discrimination between liquid or gas contents in the rectum [2]. Absence of RAIR has been correlated with poor bowel function and when found to recover (over time), the patient may experience a reduction in nocturnal urgency and incontinence [2]. Persistent disturbance in RAIR has been associated with long-term fecal soiling [2]. A study by Kakodkar et al. examined anorectal function in normal healthy volunteers compared to preoperative and postoperative values in patients undergoing LAR/TME surgery. The authors found that bowel dysfunction can continue 1 year after surgery. Poorer outcomes were associated with a lower reservoir capacity, shortened high-pressure zone, and an absent RAIR [9].

Some studies evaluating anal sphincter function after LAR have shown a decrease in mean anal resting pressure and maximum squeeze pressure that does not recover over time (4, 10). These changes may be due to direct injury to the sphincter complex during stapler insertion [2]. Efthimiadis et al. reported a significantly decreased anal resting pressure, loss of RAIR, and unchanged squeeze pressures [10]. By 6 months, they noted these changes recovered. They suggest that decreased compliance of the neorectum lowers the capacity of the reservoir, leading to more frequent stools. Reduced reservoir compliance also leads to increased pressure as stool fills the neoreservoir. Higher pressure in the neorectum and lower anal canal pressure can result in frequent stools and soiling, even with small volumes of stool [10]. Small, poorly compliant reservoirs have also been found to have sensory alterations that contribute to incontinence [2]. A direct association between decreased rectal compliance and deterioration in fecal continence scores has been reported [4].

It has been postulated that the unfavorable functional results such as fecal urgency and incontinence noted with LAR are due to the reduced neoreservoir volume with conventional end-to-end colorectal or coloanal anastomosis. This has led to the development of alternative configurations of the proximal colon in an effort to improve the reservoir [4]. These will be discussed in depth later in this chapter.

Other research has focused on the association between intestinal motility and LARS. Emmertsen et al. reported that patients with major LARS problems had an increased postprandial response and higher neorectal pressures after eating compared to patients without LARS, suggesting that severe bowel dysfunction after LAR/TME may be related to abnormal gastrointestinal motility [8]. Another study also indicated that LARS patients with high stool frequency had increased contractions and increased neorectal tone in response to a meal whereas normal healthy patients did not [8]. Animal studies have shown increased number and duration of colonic migrating complexes after LAR, equivalent to high amplitude propagating contractions responsible for mass movement of stool in humans [4]. A study of meal-induced colonic motility reported significantly earlier contractions in patients with increased bowel frequency compared to those without [4]. In a study of 60 patients after LAR, 26 had small, irregular waves at the site of the neorectum and the presence of these waves was associated with fecal soiling, urgency, and multiple evacuations [4].

The aim of this questionnaire is to assess your bowel function.

Please tick only one box for each question. It may be diffiult to select only one answer as we know that, for some patients, symptoms vary from day to day.

We would kindly ask you to choose one answer which best describes your daily life. If you have recently had an infection affecting your bowel function, please do not take this into aaccount and focus on answering questions to reflect your usual daily bowel function.

Do you ever have occasions when you cannot control your flatus (wind)?

☐ No, never
☐ Yes, less than once per week
☐ Yes, at least once per week

Do you ever have any accidental leakage of liquid stool?

☐ No, never
☐ Yes, less than once per week
☐ Yes, at least once per week

How often do you open your bowels?

☐ More than 7 times per day (24 hours)
☐ 4-7 times per day (24 hours)
☐ 1-3 times per day (24 hours)
☐ Less than once per day (24 hours)

Do you ever have to open your bowel again within one hour of the last bowel opening?

☐ No, never
☐ Yes, less than once per week
☐ Yes, at least once per week

Do you ever have a strong urge to open your bowels that you have to rush to the toilet?

☐ No, never
☐ Yes, less than once per week
☐ Yes, at least once per week

FIGURE 56-1. LARS score questionnaire. Adapted from Emmertsen K, Laurberg S. Low anterior resection syndrome score: development and validation of a symptom-based scoring system for bowel dysfunction after low anterior resection for rectal cancer. Ann Surg 2012;255(5):922–8 [8].

Autonomic denervation may also contribute to poor functional outcome despite standardization of surgery and TME to preserve autonomic nerves [2]. A Japanese study showed that preservation of the colonic and pelvic nerves resulted in less stool fragmentation [8]. It is suggested that the partially denervated colon might contribute to fragmentation of stools due to the absence of a negative feedback of the defecation reflex [8].

Rectal evacuatory dysfunction is also described as part of LARS. This includes infrequent defecation, incomplete rectal emptying, and excessive straining [4]. A suggested mechanism is loss of rectoanal coordination, manifesting as

impaired rectal contraction and paradoxical anal contraction [4]. Patients with a rectal evacuatory disorder can also have lowered rectal sensation possibly due to impairment of the parasympathetic and sympathetic nerve supply to the rectum [4].

Risk Factors for LARS

Incontinence is multifactorial in LARS patients. Worse functional outcomes have been associated with a lower anastomotic distance to the anal verge, male gender, and younger patients [2, 3, 6, 11] Any form of pelvic sepsis—anastomotic leak/dehiscence or abscess—can lead to scarring and reduction in the neorectum compliance. This leads to a poorly distensible neorectum and reduced storage capacity [2, 3, 11].

Some studies have indicated that preoperative radiation is also a risk factor for fecal incontinence after LAR [6]. Radiation may affect bowel function through several mechanisms. Radiation effects are dose dependent, altering the rectal musculature, innervation, and a direct effect on sphincter morphology [2]. Bowel function can also be altered secondary to radiation-induced small bowel toxicity and pelvic neuropathy [2]. Results from the Dutch TME trial demonstrated that 39 % of patients who had a TME alone were incontinent at 5 years compared to 62 % of those treated with surgery and preoperative radiotherapy [6]. In a study performed by Parc et al., patients with a neorectal reservoir who received neoadjuvant chemoradiation reported more frequent bowel movements per day and more nocturnal urgency for up to 24 months following surgery compared to patients without radiation [12]. Short-term radiotherapy also can have a detrimental effect. One study found that short-course radiotherapy had a negative effect on sexual function and daily functional activities [4].

A recent large population-based study of patients who had undergone LAR/TME found that patients who suffered from major LARS were more likely to have had neoadjuvant radiation compared to those without radiation [3]. Higher rates of LARS were found in patients with total versus partial TME and those with a symptomatic anastomotic leak. Younger (<64 years) patients and females also had a higher risk of major bowel dysfunction [3]. The study found no differences in functional outcomes between different anastomotic reconstruction types or short versus long-course radiation [3]. These results are dissimilar to other studies that demonstrated worse function in males and worse function after short-course radiation [11]. With regard to radiation, it is important to keep in mind that few prospective studies evaluated LARS in relation to contemporary radiotherapy protocols [4, 11]. Therefore, prospective studies utilizing modern radiation therapy are needed to elucidate the relationship of LARS to radiation therapy.

Evaluation of Bowel Dysfunction After LAR

Several QOL questionnaires and fecal incontinence scoring systems have been used to quantify LARS. The LARS score (Figure 56-1) is calculated from a validated scoring instrument evaluating bowel function after sphincter-preserving surgery for rectal cancer [12]. The questionnaire has been developed and validated in a nationwide cohort of Danish patients who received LAR with or without radiotherapy for localized rectal cancer between 2001 and 2007. The instrument was designed to reflect the severity of bowel dysfunction and its impact on QOL [12]. Questions pertaining to incontinence of stool or gas, symptoms of urgency, number of bowel movements, and clustering of bowel movements per day are included [5]. A composite score between 0 and 20 indicates “no LARS,” 21–29 “minor LARS,” and 30–42 “major LARS” [5]. This questionnaire has been translated into numerous languages. It correlates with many of the scales in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core Module (EORTC QlQ-C30) [12].

Studies have shown that rectal cancer specialists lack an understanding of which bowel dysfunction symptoms truly matter to patients after sphincter-preserving surgery. Additionally, despite the high prevalence of LARS, care providers do not appreciate how these symptoms affect QOL [12]. Chen et al. found considerable discrepancy between the specialists’ perspective of what mattered to the patient and the patient’s actual views [7]. For instance, few clinicians realized the importance patients placed on incontinence to flatus and its impact on them. Likewise most clinicians overestimated the importance of liquid and solid stool incontinence while underestimating the impact of urgency and clustering on QOL [7]. Thus, postoperatively, it is crucial for rectal cancer specialists to ask that right questions, inquire as to what bothers the patient the most, and identify LARS. This will allow appropriate and timely management of symptoms. It is also important to provide pertinent, honest information to the patient prior to rectal cancer treatment [7].

Treatment for Bowel Dysfunction After LAR

There is currently no specific treatment consensus or treatment algorithm for LARS. Current therapies target distressing symptoms and include medications such as loperamide and codeine, the use of pelvic floor physiotherapy and biofeedback, and rectal irrigation [11]. Studies specifically looking at medications to treat LARS are lacking and represent a focus for future studies.

Pelvic floor rehabilitation targets the same therapies as when used for other forms of fecal incontinence. This includes pelvic floor muscle training, biofeedback, and rectal balloon training [6]. Visser at el performed a systematic review that showed incontinence scores significantly

improved in 4/5 studies and stool frequency decreased in 2/5 studies after pelvic physical therapy in patients with LARS [6]. QOL measures, vitality, and mental functioning on SF-36 also improved. Rehabilitated patients had less depression and better self-perception in FIQL scores [6]. One study demonstrated improved functional outcomes based on anorectal pressures and rectal capacity, but two other studies did not show any differences in physiologic measures [6]. The authors concluded that pelvic floor rehabilitation is useful for improving functional outcome after LAR [6]. Another study that was retrospective and non-randomized evaluated 70 patients who underwent biofeedback for LARS. There was significant improvement in fecal incontinence scores and decreased bowel frequency [4]. Therefore, it appears that pelvic floor physical therapy and rehabilitation may be an important treatment option for some LARS patients.

Retrograde Colonic Irrigation

Retrograde colonic irrigation (RCI) has also been proposed as a potential treatment option for fecal incontinence and stool fragmentation after LAR. Also known as transanal irrigation (TAI), water is introduced into the rectum and left colon. The irrigation is designed to assist in the evacuation of feces. The impact of RCI varies considerably. Koch et al. reported that 57 % of patients became "mostly" continent with RCI. Fourteen percent still reported trouble controlling flatus and 29 % had difficulty controlling liquid stools. The side effects were mild and the procedure is inexpensive and noninvasive [13]. Therefore, this represents another treatment in the armamentarium of doctors caring for LARS patients.

Sacral Nerve Stimulation

Sacral nerve stimulation (SNS) has shown promising early results in small studies of patients with fecal incontinence after rectal resection [4]. SNS improves function by decreasing antegrade colonic motor activity and increasing retrograde activity [4]. In a 2015 systematic review of SNS for the treatment of LARS, an overall intention to treat success rate of 74.4 % was found [11]. Of the 34 patients who had enough improvement to warrant permanent stimulator placement, 32 (94.1 %) had treatment "success" [11]. Patients reported subjective and objective improvement in LARS symptoms. Incontinent episodes decreased in all studies [11]. Another study utilizing SNS to treat LARS reported decreased nocturnal defecation, fragmentation, urgency, and soiling. SNS also led to an improvement in the time to defer defecation [11]. Thus, SNS appears to be a promising therapy for some patients with LARS.

Colorectal Reconstructions and Effects on Function After Colorectal Surgery

As surgeons have been able to attain a higher incidence of sphincter preservation when operating on low rectal cancers, an increasing frequency of bowel dysfunction has been reported. The first reported anastomoses were typically straight (SA) colorectal or coloanal [13]. Analysis of the functional outcomes after LAR with SA led to a description of a wide spectrum of symptoms including urgency, frequency, stool fragmentation, and fecal incontinence. It was speculated that reduced reservoir volume related to the bowel used for a conventional end-to-end colorectal or coloanal anastomosis contributed to urgency and fecal incontinence. In an effort to improve bowel function, surgeons developed alternative configurations of the proximal bowel used for the anastomosis with the goal to improve the function of the neoreservoir [4, 14]. The colonic j pouch (CJP), the transverse coloplasty (TC), and the side-to-end anastomosis (STEA) have been utilized to improve the function and capacity of the neorectal reservoir with the goal of improving bowel function (Figure 56.2).

Colonic J Pouch

The colonic j pouch (CJP) is constructed by folding the sigmoid or descending colon onto itself and stapling the antimesenteric walls to create a larger lumen (Figure 56-2). There have been several prospective randomized studies comparing the SA with the CJP. The CJP led to reduced bowel frequency, less fragmentations, fewer spasms, and less urge incontinence for up to 12 months when compared to SA [13]. There have been fewer studies that looked at longer-term results. While most studies still reported some functional advantage, one study noted the functional improvement with the CJP apparent at 1 year disappeared by 24 months [15]. In contrast, others reported decreased frequency and stool fragmentation in CJP patients at 24 months and at 5 years [13]. Fecal continence was better at 3, 4, 5, and 9 years when compared to SA [13]. A meta-analysis performed by Heriot and colleagues confirmed these long-term results. In 2240 patients, those with CJP had decreased daily frequency, decreased fecal urge incontinence, less incomplete evacuations, and used less antidiarrheal medications at 1 and 2 years when compared to patients with SA [15].

Initially the size of the CJP mirrored the ileal J pouch. Comparison of bowel function in patients with a larger pouch (>6–12 cm) versus a shorter (4–6 cm) CJP showed no differences in clinical outcomes or complications. However, difficult or incomplete defecation was found to be higher in patients with longer pouches [16]. Patients with longer CJP were also noted to require more laxative for defecation [16]. Hence, a CJP of 4–6 cm was felt to be the ideal size.

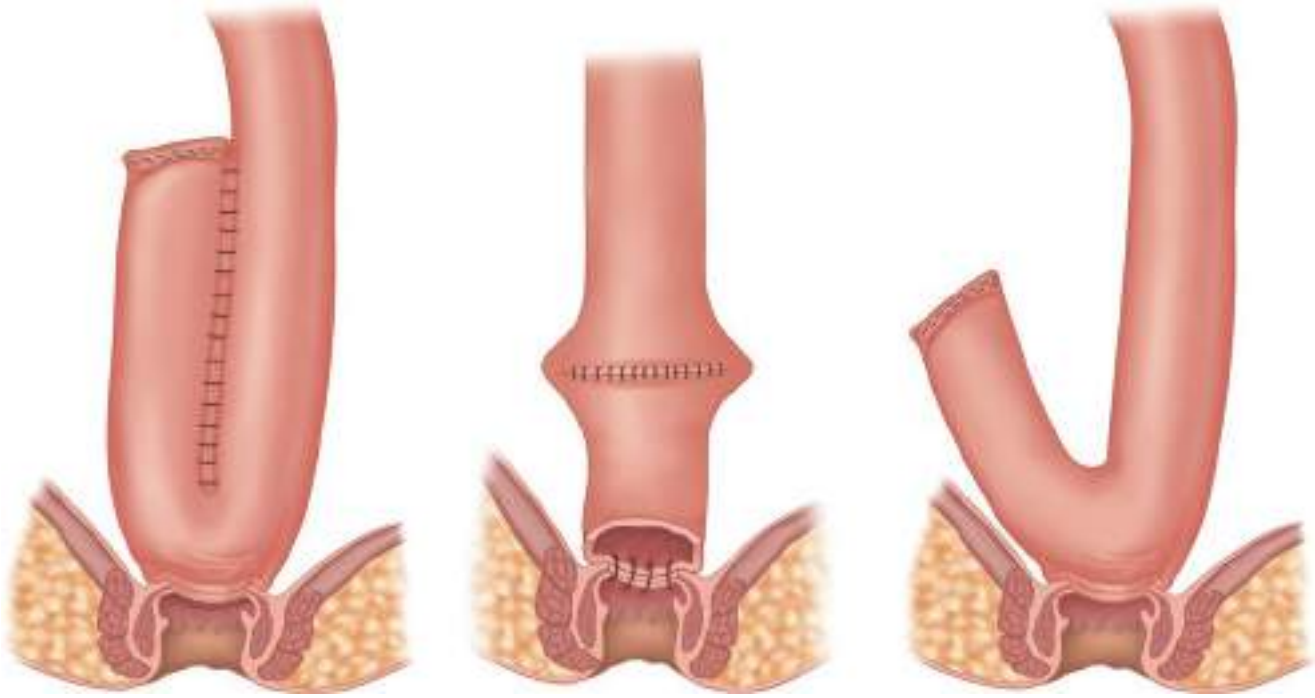

FIGURE 56-2. Alternative colorectal anastomotic reconstructions after low anterior resection.

Transverse Coloplasty

A transverse coloplasty (TC) construction is an alternative colorectal reconstruction that was first described in 1999 and first performed in humans in 2001 [17]. TC involves cutting the colon wall longitudinally for 7–10 cm between the taenia, starting at approximately 4 cm from the distal cut edge of the colon [17]. The colotomy is then closed transversely and looks similar to a Heineke–Mikulicz stricturoplasty (Figure 56-2). Although TC was thought to decrease the evacuation difficulties that were found with CJP, multiple studies did not illustrate any significant differences [15, 17]. In a multicenter randomized prospective trial, Fazio and colleagues did show functional benefits of the CPJ when compared to TC [18]. There was less stool fragmentation and less digestive spasms after CPJ when compared to TC at 4, 12, and 24 months. Other outcomes such as urge incontinence and antidiarrheal medication use were not significantly different. They also did not find any functional advantage of TC over SA. Therefore, adoption of TC has recently slowed secondary to nearly equivalent functional outcomes and at least one study showing higher anastomotic leak rates [19].

Side-to-End Anastomosis

The side-to-end anastomosis (STEA) is another alternative reconstruction after a low anterior resection (Figure 56-2). This technique was described by Baker in 1950 and has gained popularity in the United States, Germany, and France. An anastomosis is created 3–6 cm upstream from the cut edge of the proximal colon on the antimesenteric side to the distal rectum or anal canal [13]. The open end of the proximal colon is then closed. A few prospective studies have looked at functional outcomes after STEA. In short- and long-term follow-up, most do not show any significant differences in bowel function when compared to CJP. Two studies did show less evacuation difficulties [13]. Siddiqui et al. performed a meta-analysis on studies comparing STEA and CJP. Only urge incontinence was less after STEA at 6 months, but this was no longer significant after 24 months [20]. Anastomotic leak rates may be lower after STEA compared to SA. However, the leak rate appears similar when comparing STEA with CJP [7, 13]. Evacuation problems may also occur with STEA. Utilizing a 3 cm vs. 6 cm blind limb of the STEA seemed to be associated with less evacuation problems [21].

In summary, in an effort to reduce bowel dysfunction after a low anterior resection, a CJP or STEA may be utilized. The size of the CJP should be 4–6 cm and the blind limb of the STEA should be 3 cm to reduce the risk of difficulty in evacuation of stool.

Sexual and Urologic Dysfunction After Surgery for Rectal Cancer

Nerves of the Pelvis

Sexual and urologic dysfunction after proctectomy is multifactorial; however, the main etiology is related to direct injury to the pelvic nerves. There are several locations where

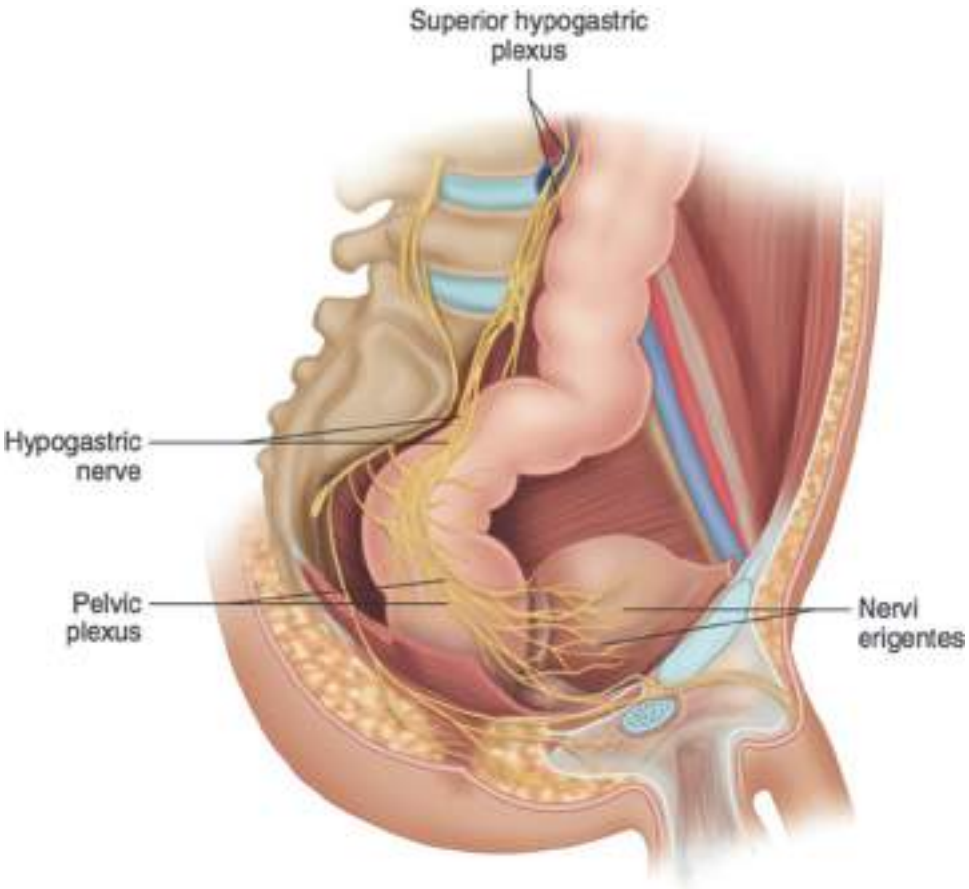

FIGURE 56-3. Pelvic nerve anatomy and potential sites of injury. Damage to the superior hypogastric plexus during high ligation of the interior mesenteric artery (IMA) or to the hypogastric nerves of the sacral promontory during mobilization of the upper mesorectum results in retrograde ejaculation. Damage to the pelvic plexus during the lateral dissection or to the nervi erigentes or the cavernous nerves while dissecting the anterior plane may result in erectile dysfunction.

pelvic nerves can be damaged during TME (Figure 56-3). Within the pelvic plexus, there are both sympathetic and parasympathetic nerves. The sympathetic roots originate from L2 and L3. They comprise the superior hypogastric plexus (or the aortic plexus), which becomes the hypogastric plexus under the parietal peritoneum at the level of the aortic bifurcation. At the sacral promontory, these fibers form the hypogastric nerves, which run laterally to the internal iliac arteries and ureters, to join the pelvic autonomic plexus at the lateral pelvic wall. The parasympathetic fibers originate from S3 to S4 in males and from S2 to S4 in females. They run along the nervi erigentes and the inferior hypogastric plexus.

Below the peritoneum, the hypogastric plexus sits anterior and lateral to the rectum. The inferior hypogastric plexus is the autonomic pelvic plexus on the lateral pelvic wall, in close proximity to the prostate in males. In females, it is anterior and lateral to the rectum, running by the vagina and cervix. The parasympathetic fibers are responsible for erection, increasing blood flow to the penis or clitoris, as well as providing lubrication to the vagina. The sympathetic fibers are responsible for ejaculation and orgasm. These sympathetic fibers also inhibit the detrusor muscle, stimulating contraction of the bladder neck, affecting the urinary continence mechanism [22–25]. With the adaption of total mesorectal excision and a focus on pelvic nerve-sparing surgical technique, the incidence of sexual dysfunction is lower but still significant. The ligation of the inferior mesenteric artery and dissection of the retrorectal space can cause damage to the superior hypogastric plexus and/or hypogastric nerves at the sacral promontory. This can result in retrograde ejaculation. Anterolateral dissection and division in the area described as the "lateral ligament" can damage the pelvic plexus resulting in erective dysfunction. Dissection in the anterior plane particularly on the rectal side of Denonvilliers' fascia can damage the nervi erigentes or cavernous nerves and also lead to erectile dysfunction. Perineal dissection can indirectly or directly damage the pudendal nerve (Figure 56-3) [14, 26].

Sexual Dysfunction After Surgery for Rectal Cancer

The goal of rectal cancer surgery is to remove the tumor and cure the patient. However, negative outcomes like sexual dysfunction can result from this therapy. There has been more awareness and focus on sexual dysfunction in men (versus women) after surgery for rectal cancer and interestingly this is not always discussed preoperatively [25]. Sexual

dysfunction in men consists of erectile dysfunction (ED) and retrograde ejaculation. However, difficulty with orgasm and libido and issues with body image are also reported [27]. Postoperative female sexual dysfunction includes problems with vaginal lubrication, dyspareunia, arousal, and orgasm. These problems are harder to quantitate. With advances in the surgical technique of TME, the incidence of sexual dysfunction has been reduced but remains a significant postoperative problem. Besides nerve damage, other risk factors include significant blood loss, preoperative radiation, anastomotic leak, and the presence of a stoma [28]. Validated tools that have been developed to evaluate sexual dysfunction after rectal cancer surgery include the International Index of Erectile Function (IIEF), the Female Sexual Function Index (FISI), and the EORTC QLQ-C30 and EORTC QLQ-CR38 to measure QOL in colorectal cancer patients.

Studying patients who were sexually active before surgery, Hendren et al. reported that 29 % of women and 45 % of men after proctectomy for rectal cancer perceived deterioration in their sexual function [27]. Only a small percentage of patients recalled a preoperative discussion regarding the risk of sexual dysfunction after surgery [27]. Patients may be embarrassed to discuss this highly personal topic. Therefore, healthcare providers should counsel patient preoperatively regarding potential risks and initiate the conversation postoperatively in an effort to address concerns.

Retrograde ejaculation can be treated with medications including tricyclic antidepressants, antihistamines (chlorpheniramine), and decongestants like ephedrine sulfate and phenylephrine, which can help close the bladder neck during ejaculation [29, 31]. For patients reporting ED postoperatively, a trial of sildenafil citrate, tadalafil, or vardenafil can be considered. At low dose, these medications do not cause erection but can increase blood flow to the area around nerves to promote healing [30].

Sexual dysfunction in females after rectal cancer resection has not been examined extensively. There are both physiologic etiologies and components of body image that contribute to sexual dysfunction. Besides nerve injury which can lead to decreased clitoral sensation and vaginal lubrication, dyspareunia can also be secondary to fibrosis after radiation leading to reduced pliability of the vagina [34]. Medications and creams which improve lubrication along with pelvic floor physical therapy have been the mainstay of treatment. Newer treatments, such as flibanserin, warrant further investigation.

Urologic Dysfunction

Bladder dysfunction commonly happens after pelvic surgery and can occur in 30–70 % of patients after surgery for rectal cancer. Damage to the visceral nerves during proctectomy can decrease bladder sensitivity. Injury of the sympathetic nerves via damage to the hypogastrics may be responsible for female urgency and stress incontinence [32]. The patient may experience loss of the filling sensation of the bladder secondary to denervation of the detrusor muscle. This can also predispose patients to voiding problems and overflow incontinence. Posterior bending of the bladder that may occur during and following abdominoperineal resection can also contribute to voiding dysfunction. Persistent incomplete emptying of the bladder due to any of the above mentioned mechanisms may predispose patients to urinary tract infections.

Some patients may have preexisting urinary dysfunction as a result of age, chronic inflammation, benign prostate enlargement, or prostate cancer in males and stress incontinence or urgency in multiparous females. In addition, any damage to the pudendal nerves can contribute to decreased bladder sensitivity and impotence. Postoperative urinary symptoms are often temporary and only 10 % of patients will require medical or surgical treatment. Any voiding issue that persists after 3 months may be permanent, requiring more aggressive management [29].

Perianal Skin Irritation After Colorectal Surgery

Skin irritation is common after rectal cancer surgery. This results from frequent and/or loose stools and improper wiping techniques. Additionally, pliability of the skin can be reduced from chemoradiation further compounding the problem. Frequent bowel movements result in constant wiping which excoriates the top layer of the delicate skin around the anus. In addition, digestive enzymes in fecal matter have been noted to contribute to irritation of the perianal skin [33, 35]. The first-line of treatment is skin protection that is provided by barrier creams. Two examples are Desitin™ or Balmex^{R}. The barrier cream should be applied like frosting to fully coat the area. When wiping after defecation, the patient should wipe against the cream and avoid completely wiping it off. If there is a fungal component, antifungal powders or creams should be added. For severe itching and pain, a short course of steroid cream can provide dramatic relief (particularly for itching). However, the use of steroid cream should be confined to short-term use since it has the potential to thin the skin [33]. Counseling is helpful regarding wiping and having the patient avoid the urge to “over-wipe.” Use of wet toilet paper also lessens the friction upon the anal skin with wiping. Using warm baths or showers after bowel movements and colonic irrigation with enemas or tap water may also eliminate stool from sitting on the skin or leaking from the rectum after defecation. An enterostomal therapy nurse or skin care nurse specialist may be invaluable to provide additional suggestions for patients with resistant skin irritation.

Managing stool frequency and consistency are also important. Fiber supplements are recommended in an attempt to bulk the stool. Patients are advised to take agents such as psyllium mixed in the least amount of fluid in an attempt for the fluid in the stool to saturate the ingested fiber. The use of antidiarrheal medications such as diphenoxylate hydrochloride/atropine sulfate or loperamide are trialed to slow stool frequency. The patient can take up to eight doses of each of these two types of medications daily; however, this amount typically is not needed. They should take one pill in the morning upon awakening and then titrate the dose. The medication should be taken *before* meals (not after defecation as the package insert may advise). Loperamide can be obtained in a liquid form and the dose can further be titrated down if the 2 mg pill slows the bowel motility too much.

Conclusions

Functional outcomes after colorectal surgery are now becoming recognized as important contributors to quality of life and measures of our performance as surgeons. The significance of postoperative function should be a focus of preoperative discussion as technical advances now allow more sphincter-preserving surgeries at the risk of increased bowel problems. Bowel dysfunction along with urinary and sexual dysfunction can significantly impact and lessen quality of life postoperatively. The cause of these functional disorders is multifactorial including damage to the anal sphincters, variations in RAIR, intestinal motility changes, autonomic and somatic nerve injury, and pelvic floor dysfunction. Compliance of the neorectum, pelvic sepsis, and radiation can also contribute to postoperative dysfunction. Important steps the surgeon can take to lessen the risk of dysfunction after proctectomy include proper TME technique, avoidance of nerve injury, creation of a healthy, tension-free anastomosis, consideration of alternative colorectal reconstructions (colonic J pouch or side-to-end versus a straight anastomosis), and avoidance of amenable risks factors for pelvic sepsis. Also, the appropriate selection of patients for sphincter preservation cannot be understated. When bowel dysfunction does occur, initial treatment focuses on optimizing the patient's diet and alterations in bowel habits. For more severe symptoms, biofeedback, colonic irrigation, and sacral nerve stimulation have been found to improve function. Stool bulking and decreasing stool frequency along with barrier creams can improve perianal skin irritation after colorectal surgery. For patients who report urinary or sexual dysfunction, medications may improve symptoms. Lastly, pelvic floor rehabilitation with biofeedback should also be considered as this may improve the quality of life after LAR.

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Part V
Pelvic Floor Disorders

57
Common Tests for the Pelvic Floor

Dana R. Sands and Amy J. Thorsen

Key Concepts

- Pelvic floor disorders affect a significant portion of the population and account for relevant portion of patients seen in colorectal clinics.
- Proper history and thorough physical examination is the cornerstone of the evaluation of patients suffering from functional disorders.
- Specialized tests to evaluate structure and function augment the evaluation of this complex patient population.

Introduction

Disturbances in bowel evacuation and continence are common in North America.

In a population based study of nearly 2000 non-pregnant women, Nygaard et al. found 15.7 % of women had at least one pelvic floor disorder. In women aged 80 or older, the prevalence approached 50 % [1]. Although 9 % of women in this study experienced symptoms of fecal incontinence, another recent survey found nearly 20 % of women age 45 or older have experienced accidental bowel leakage at least once per year [2]. Constipation appears to be a more frequent complaint of patients, affecting up to 20 % of North Americans [3–5]. The direct annual costs associated with ambulatory care for pelvic floor disorders were estimated at $412 million dollars in 2006, compared to $262 million in 1997 [6]. As the population ages, health care expenditures in treating pelvic floor disorders are expected to escalate. Given the psychosocial stresses that accompany pelvic floor disorders, the true cost of these disorders to society is probably extremely underestimated.

Functional disorders account for approximately a quarter of a typical colorectal practice's referrals. A traditional approach is to start the evaluation ruling out significant pathology, such as neoplastic or inflammatory bowel disease, with lower endoscopy. This chapter will focus on the next steps in evaluating patients with fecal incontinence, obstructive defecation, and rectal prolapse. Pelvic floor testing includes anatomic evaluations, functional investigations, and exams that evaluate both anatomy and function of the pelvic floor.

History

A detailed history is critical in the management of patients with pelvic floor disorders. Patients will often give limited details, and self-diagnose ("I have hemorrhoids") to avoid feeling embarrassed about their condition. The patient should be comfortable and clothed during the interview. The onset, duration, and evolution of symptoms should be elicited. Patients should be queried about other possible pelvic floor complaints; rectal prolapse can easily cause constipation or bowel leakage, and symptoms of fecal incontinence may develop after years of obstructed defecation. A high incidence of urinary incontinence and vaginal vault prolapse is prevalent in these patients, and presently there are treatment options that can address multi-compartment complaints in these complex patients.

Addressing stool consistency is key, as well as the factors that may have changed it. Diet changes, food intolerances, and allergies should be identified. Changes in medications and supplements can cause disturbances as well. Surgeries such as cholecystectomy and gastric bypass surgery often alter stool consistency and frequency.

Trauma to the pelvic floor—whether it be surgical, obstetric, or psychological—is also common. Previous surgeries for hemorrhoids, fissures, or fistulas may affect sphincter integrity. Posterior compartment prolapse and dyssynergic defecation may be seen after hysterectomy or cystocele repair. Vaginal delivery, especially that associated with forceps or vacuum instrumentation, can cause sphincter injury, levator avulsion, and pudendal nerve injury. A history of sexual abuse and underlying psychological disturbances are

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often significant factors that need to be addressed for successful management of these patients.

Questionnaires

Unlike hypertension or diabetes, the response to treatment of pelvic floor disorders cannot be assessed by measuring a vital sign or following serial laboratory values. Pelvic floor disorders have multiple symptom components, and eliciting these details can sometimes be difficult in a patient that is embarrassed. Lastly, each individual's situation is different; the impact of once weekly liquid stool incontinence will affect a teacher differently than a patient homebound due to other medical conditions. Hence, symptom scales and quality of life questionnaires can be an important clinical and research tool in managing the pelvic floor patient.

Fecal Incontinence

Fecal incontinence has been graded and scored in a variety of ways. Grading scores assign a value to a specific kind of incontinence. Values tend to reflect physician impression of severity based on sphincter function; i.e., incontinence to solid stool is graded more severe than incontinence to liquid stool. Severity scales, more commonly utilized by clinicians and researchers, screen for different types of incontinence, assign a value for each category, and produce a summary score based on the total of values per category. Severity scores may differ in their inclusion of the symptoms of incontinence to flatus, mucous incontinence, staining, urgency, pad usage, and lifestyle variation. Inclusion of more symptoms may be seen in severity scales that involved patients in their development. Although inclusion of more aspects of anal incontinence may more accurately reflect the patient experience, some of these measures may duplicate some aspects of the symptoms within the score and may add in components of impact instead of severity. Urgency is a common component that can be difficult to measure, but it may also be reflected significantly in lifestyle alteration. Pad usage may better reflect patient meticulousness or concomitant urinary incontinence rather than be a discrete component of fecal incontinence severity. Pad usage also appears to be less common in male patients with fecal incontinence [7].

Jorge and Wexner [8] developed the first scoring system to take into account both pad usage and lifestyle alteration as well as the consistency and frequency of fecal incontinence [Cleveland Clinic Florida Fecal Incontinence Score (CCF-FIS)] (Table 57-1). All types of incontinence, and all categories, are weighted equally. There are five frequency categories which aid in discrimination for change for patients with both frequent and infrequent anal incontinence. In an internet based study assessing the prevalence of fecal incontinence in women age 45 or older, women who sought care for their condition had a mean score of 10.7, versus a mean of 7.5 in women who did not seek care for their symptoms [2]. Today, the CCF-FIS is one of the most widely used scores in assessing the severity of fecal incontinence.

In 1999, Vaizey et al. [9] introduced a modification of the CCF-FIS scale. Adjustments included diminishing the significance of pad usage, including a measure to account for the use of antidiarrheal medications, and inclusion of a measure to note the presence of urgency. Although five frequency categories are maintained, the lowest frequency measured, "never" is equal to less than once per four weeks. Hence patients who have anal incontinence less than this frequency can have a total score of 0, equal to "perfect continence." The need to use a pad or constipating medication is present or absent, and not measured in frequency. Urgency, described as "the ability to defer defecation 15 minutes," is also given a single score if present, despite if this is a symptom the patient experiences daily or rarely. The Vaizey or St. Mark's incontinence score appears to correlate with patients' perception of bowel control. When 423 patients ranked their perception of control on a scale of 0–10, a significant correlation ($r=-0.52$) was seen with their Vaizey score. This correlation was maintained despite patient age, gender, or type of incontinence, and was sensitive to change with treatment [10].

A weighted scale utilized in measuring incontinence is the Fecal Incontinence Severity Index (FISI). In contrast to other scoring systems, the FISI is the first continence severity score to involve patients in its development [11]. The FISI was developed in a multicenter trial sponsored by the American Society of Colon and Rectal Surgeons. Thirty-four patients and twenty-six colon and rectal surgeons ranked a grid of four types of anal incontinence (gas, mucus, liquid, and solid) at five different frequencies. A frequency category to include multiple accidents per day was included, but episodes of frequency less than once per month were not

Table 57-1. Cleveland Clinic Florida/Wexner Fecal Incontinence Grading Scale [8]

	Never	Rarely (<1/month)	Sometimes (>=1/month, <1/week)	Usually (>+1/week, <1/day)	Always (>=1/day)
Solid	0	1	2	3	4
Liquid	0	1	2	3	4
Gas	0	1	2	3	4
Wears pad	0	1	2	3	4
Lifestyle alteration	0	1	2	3	4

included. Severity assessment rankings for surgeons and patients correlated very highly [11]. Surgeons tended to assign higher weight to infrequent episodes of solid stool incontinence compared to patients. This may reflect the surgeon's impression of sphincter integrity as being a measurement of severity, whereas the patient's ranking may more reflect personal hygiene and social embarrassment. Many patients comment that loss of solid stools is easier to manage than loss of liquid stools.

When the FISI is administered, a decision needs to be made whether to use the physician or patient weighting. Although the physician weight may better imply severity in terms of sphincter function, the patient weight may better reflect patient satisfaction to treatment. Given the calculations required to determine the FISI, the score is more cumbersome tool to use in the clinical setting.

Although some severity scales include a measurement of lifestyle alteration, the true impact of fecal incontinence for an individual patient cannot be captured when measuring severity alone. The Fecal Incontinence Quality of Life Scale (FIQL) was developed as a collaboration between the American Society of Colon and Rectal Surgery and the University of Minnesota Clinical Outcomes Research Center. The FIQL, through 29 questions, taps aspects of life for patients with fecal incontinence that may interfere and affect social functioning and self-image. The results are tabulated in four subscale scores: Lifestyle, Coping/Behavior, Depression/Self Perception, and Embarrassment (Table 57-2) [12]. Bordeianou et al. [13] examined the relationship between fecal incontinence severity and its relationship to quality of life prospectively in 502 patients. Fecal incontinence severity correlated moderately with disease specific (FIQL) quality of life, and only weakly with generic quality of life (SF-36). Based on these results, the authors recommended using both questionnaires when evaluating treatments for fecal incontinence.

Constipation

Frequency of bowel movements is a common measurement of severity of constipation by both patients and physicians. This fails to take into account other factors, such as incomplete emptying, difficult evacuation, and pain experienced by these patients. Although many constipation scores exist, some include components measuring symptoms of irritable bowel syndrome or upper gastrointestinal disorders. Several scoring systems may be useful to the colorectal surgeon.

The Cleveland Clinic Florida Constipation Score (CCF-CS) [14], developed in 1996, is a score commonly used in clinical trials in the treatment of obstructive defecation. Eight variables are assessed (frequency of bowel movements; difficult or painful evacuation; completeness of evacuation; abdominal pain; time per attempt; type of assistance including laxatives, digitations, or enemas; number of unsuccessful attempts at evacuation in a 24-h period; and duration of constipation). Seven items are scored at a frequency of 0 (none of the time) to 4 (all of the time), and one item at 0–2. A cut-off score of 15 suggests constipation, with a score of 30 indicating severe constipation.

The Patient Assessment of Constipation-Symptom (PAC-SYM) is a brief, easily administered questionnaire that provides a score developed to assess symptom frequency and severity based on the Rome II criteria. Three symptom subscales—abdominal, rectal, and stool—are evaluated through 12 items on a scale of 0–4, with 4 being the most severe. The PAC-SYM does not clearly discriminate constipation subtypes, but has demonstrated excellent discriminant validity between those patients with constipation who have responded to interventions and those who have not [15].

To evaluate the impact of symptoms, the Patient Assessment of Constipation-Quality of Life was developed in 2005 [16]. Twenty-eight items are grouped into four subscales: physical discomfort, psychosocial discomfort, worries and concerns, and satisfaction. The scores range from 0 to 96, with lower scores corresponding to a better quality of life.

Physical Examination

A complete physical exam should be performed on the pelvic floor patient. Although the prone jack-knife position is preferred by many colorectal specialists, a perineal exam in the left lateral decubitus position may be more acceptable to these patients. The perineum should be inspected for thinning, scars, fistulas, excoriation from soiling, or prolapsing hemorrhoids that can contribute to symptoms. A patulous appearing anus may indicate a rectal prolapse. Clinical neurologic function can be assessed by checking sensation to pinprick as well as the presence of the anocutaneous wink reflex. By lightly stroking the perianal skin, the external anal sphincter should reflexively contract via the reflex arc between nociceptors of the pudendal nerve, integration by spinal cord segments S2–S4, and motor efferents to the external sphincter.

Digital rectal examination can detect anorectal masses, strictures, or fecal impactions that can cause symptoms. An assessment of function can also be obtained by noting anal resting tone, the increment and durability of the patient's squeeze, and the ability of the puborectalis to relax when the patient pushes. Rectoceles can be noted and occasionally internal intussusception can be appreciated. Anoscopy and proctoscopy can aid in the diagnosis of hemorrhoid or mucosal prolapse, proctitis, and neoplastic disease.

Gynecological assessment may help detect other pelvic floor disorders that require treatment. Inspection of the introitus at rest may reveal evidence of postmenopausal atrophy, lichen sclerosus, and even evidence of a cystocele or rectocele. With the vulva parted, a patient may more likely

TABLE 57-2. Fecal Incontinence Quality of Life Scale [12]

Q1. In general, would you say your health is:

(1) Excellent
(2) Very Good
(3) Good
(4) Fair
(5) Poor

Q2. For each of the items, please indicate how much of the time the issue is a concern for you due to accidental bowel leakage. (If it is a concern for you for reasons other than accidental bowel leakage then check the box under Not Apply, (N/A).)

Due to accidental bowel leakage	Most of the time	Some of the time	A little of the time	None of the time	N/A
a. I am afraid to go out.	1	2	3	4	( )
b. I avoid visiting friends.	1	2	3	4	( )
c. I avoid staying overnight away from home.	1	2	3	4	( )
d. It is difficult for me to get out and do things like going to a movie or church.	1	2	3	4	( )
e. I cut down on how much I eat before going out.	1	2	3	4	( )
f. Whenever I am away from home, I try to stay near a restroom as much as possible.	1	2	3	4	( )
g. It is important to plan my schedule (daily activities) around my bowel pattern.	1	2	3	4	( )
h. I avoid traveling.	1	2	3	4	( )
i. I worry about not being able to get to the toilet in time.	1	2	3	4	( )
j. I feel I have no control over my bowels.	1	2	3	4	( )
k. I can't hold my bowel movement long enough to get to the bathroom.	1	2	3	4	( )
l. I leak stool without even knowing it.	1	2	3	4	( )
m. I try to prevent bowel accidents by staying very near a bathroom.	1	2	3	4	( )

Q3. Due to accidental bowel leakage, indicate the extent to which you AGREE or DISAGREE with each of the following items (If it is a concern for you for reasons other than accidental bowel leakage then check the box under Not Apply, (N/A).)

Due to accidental bowel leakage	Strongly agree	Somewhat agree	Somewhat disagree	Strongly disagree	N/A
a. I feel ashamed.	1	2	3	4	( )
b. I cannot do many of the things I want to do.	1	2	3	4	( )
c. I worry about bowel movements.	1	2	3	4	( )
d. I feel depressed.	1	2	3	4	( )
e. I worry about others smelling stool on me.	1	2	3	4	( )
f. I feel like I am not a healthy person.	1	2	3	4	( )
g. I enjoy life less.	1	2	3	4	( )
h. I have sex less often than I would like to.	1	2	3	4	( )
i. I feel different from other people.	1	2	3	4	( )

(continued)

TABLE 57-2. (continued)

j. The possibility of bowel accidents is always on my mind.	1	2	3	4	( )
k. I am afraid to have sex.	1	2	3	4	( )
l. I avoid traveling my plane or train.	1	2	3	4	( )
m. I avoid going out to eat.	1	2	3	4	( )
n. Whenever I go someplace new, I specifically locate where the bathrooms are.	1	2	3	4	( )

Q4. During the past month, have you felt so sad, discouraged, hopeless, or had so many problems that you wondered if anything was worthwhile?
(1) Extremely So—to the point that I have just about given up
(2) Very Much So
(3) Quite A Bit
(4) Some—Enough to bother me
(5) A Little Bit
(6) Not at All

Scale scoring

Scales range from 1 to 5, with 1 indicating a lower functional status of quality of life. Scale scores are the average (mean) response to all items in the scale (e.g., add the responses to all questions in a scale together and then divide by the number of items in the scale. Not Apply is coded as a missing value in the analysis for all questions.)

Scale 1. Lifestyle, ten items: Q2a Q2b Q2c Q 2d Q2e Q2g Q2h Q3b Q3l Q3m

Scale 2. Coping/Behavior, nine items: Q2f Q2i Q2j Q2k Q2m Q3d Q3h Q3j Q3n

Scale 3. Depression/Self Perception, seven items: Q1 Q3d Q3f Q2g Q3i Q3k Q4

Scale 4. Embarrassment, three items: Q2l Q3a Q3e

reveal anterior or posterior vaginal wall prolapse or stress urinary incontinence when asked to cough. Speculum examination assesses the cervix, if present, as well as the integrity of the vaginal epithelium. Pelvic floor strength can be assessed by placing the examining digit about 2 cm inside the introitus, hooking the pelvic floor muscles, and asking the patient to squeeze to prevent "passing gas." Bimanual examination of the vagina and rectum can assist in the clinical detection of enteroceles if widening of the rectovaginal septum is appreciated when the patient bears down.

Commode examination is extremely helpful in assessing patients for possible rectal or hemorrhoid prolapse. Vaginal wall prolapse and perineal descent may also be detected simultaneously. The patient is asked to sit on the commode or on a specialized chair (with the buttocks spread and reassurance that there are protective absorbent pads on the floor). The patient is asked to bear down as if defecating. A mirror is used to assess for any vaginal or rectal protrusion or if the patient is on a commode, they lean forward and the anal area is then viewed.

Anatomic Evaluation

Ultrasound 2D

Ultrasonography is the determination of an object's properties by measuring the transmission of sound waves through that object. The appearance of tissue on the ultrasound screen represents its echogenicity compared to surrounding structures. Lesions that return minimal echo, such as water, will appear black on the screen and are **anechoic**. Tissue that reflects more waves than the neighboring tissues will appear whiter, or **hyperechoic**, on the monitor. Tissue that reflects ultrasound beams less than the adjacent tissues appear darker, or **hypoechoic**, on the screen. Collagen and fat, which can be mixed into the striated fibers of the puborectalis muscle and external anal sphincter, tend to have higher reflectivity and will appear hyperechoic, whereas muscle with its high water content, such as the smooth muscle of the internal anal sphincter, tends to be hypoechoic.

In the late 1980s and early 1990s, St. Mark's Hospital first described the utility of evaluating patients with fecal incontinence with endoanal ultrasound. External anal sphincter defects were accurately identified and findings correlated highly with needle electromyography (EMG) mapping [17–19]. Given ultrasonography had similar accuracy and improved patient tolerance, endoanal ultrasound has replaced needle EMG in the anatomic assessment of patient with bowel incontinence.

Endoanal ultrasound can identify patients that may benefit from surgical sphincter repair with overlapping sphincteroplasty [20]. This procedure requires an isolated sphincter injury, and is not useful in patients without sphincter injuries or in patients with multiple sphincter defects in different locations. Endoanal ultrasound may also play an essential

role in selecting patients for other treatment options, including the artificial anal sphincter [21, 22] sacral nerve stimulation [23–25], and injectable biomaterials [26–28].

Anal ultrasonography is also used in the assessment of treatment results. Obstetric sphincter defects repaired primarily at the time of delivery may increase in size with time, and the size of the defect corresponds to an increased risk of fecal incontinence [29]. Several studies have demonstrated that patients with persisting sphincter defects after overlapping sphincteroplasty have impaired outcomes [20, 30]. Endoanal ultrasound can also evaluate anatomic outcomes after treatment of fecal incontinence with injectable biomaterials [27, 31].

Evaluation of anal sphincter integrity with endoanal ultrasound is a critical step in planning the operative repair of most rectovaginal fistulas [32, 33]. Preoperative anal ultrasound may change operative strategy and improve surgical success in treating patients with cryptoglandular anal fistulas [34–38]. Anal fistulas secondary to Crohn's disease may have characteristic findings on ultrasound. The presence of a hypoechogenic rim with a surrounding hyperechoic region around abscesses and fistulae has been designated the Crohn's Ultrasound Fistula Sign (or CUFS) and may represent a peri-fistula inflammatory process specific to Crohn's disease [39]. Further, Blom et al. [40] have suggested that on three-dimensional endosonography, Crohn's fistulae are more often bifurcating in structure, are wider than cryptogenic fistulae, and tend to contain more hyperechoic debris. Endoanal ultrasound can also be used to determine the appropriate timing of seton removal in patients treated with infliximab therapy for perianal Crohn's disease. If setons are not removed until the fistula tract is narrow and minimal hypoechoic inflammatory changes are seen on ultrasound, Schwartz et al. demonstrated long-term healing in 76 % of patients [41].

Prior to the procedure, the patient is instructed to perform two enemas to eliminate any residual stool that may interfere with imaging. At our institution, the exam is performed in the left lateral decubitus position. When a 2D probe is used, this is placed in the upper anal canal after lubrication of the probe and anal canal. Correct placement is confirmed by seeing the characteristic horseshoe pattern of the hyperechoic puborectalis muscle (Figure 57-1). Images at the different levels of the anal canal are acquired by manual withdrawal of the probe. The normal mid-anal canal appears as two intact concentric circles: an inner hypoechoic internal sphincter and an outer hyperechoic external sphincter (Figure 57-2). The distal anal canal is noted by the absence of the internal sphincter and presence of the hyperechoic subcutaneous external sphincter only. Given its short length, it can be difficult to identify sphincter injuries at this level.

Applying digital pressure to the posterior vaginal wall during the exam can facilitate identifying anterior sphincter injuries as well as allow perineal body measurement. This is defined as the distance between the hyperechoic finger and the inner aspect of the internal anal sphincter [42]. A perineal body measurement <10 mm has been associated with an anterior sphincter injury [42].

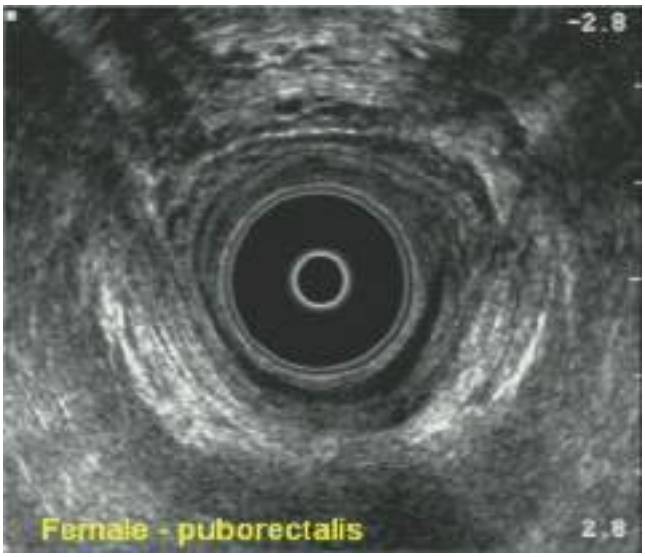

FIGURE 57-1. Female puborectalis.

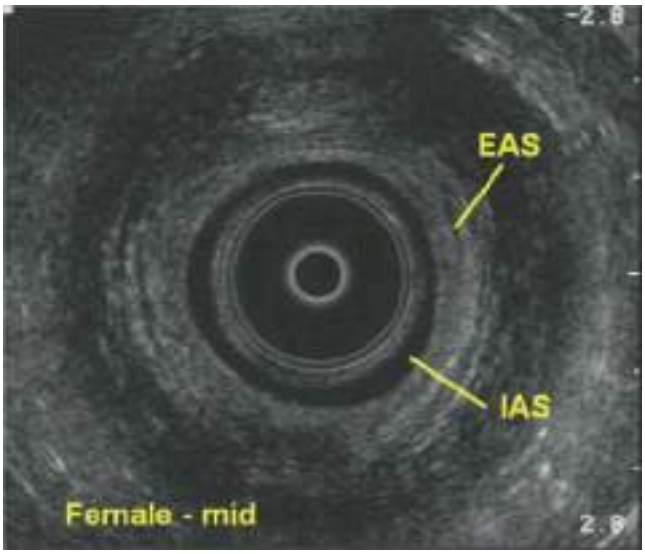

FIGURE 57-2. Female mid-anal canal.

During review of the images, abnormalities of the internal and external sphincters are recognized. Scarring, thinning, and hypertrophy of the structures may be noted. The angle of sphincter disruption can be measured (Figure 57-3a).

The interpretation of endoanal ultrasound is operator dependent, especially in the evaluation of external anal sphincter integrity [43]. The external anal sphincter has similar echogenicity to its surrounding tissues, which increases the difficulty of visualizing its borders on endoanal ultrasound. Using 2D probes, a false positive anterior sphincter defect may be identified in 5–25 % of normal patients; accu-

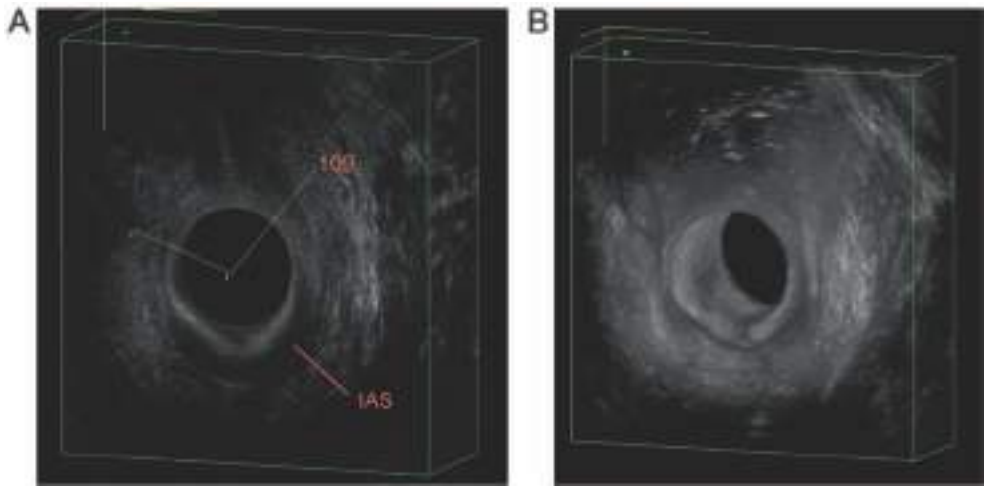

FIGURE 57-3. (**a**) Endoanal ultrasound revealing combined external sphincter defect (measuring 109°) with significant retraction of the internal sphincter (IAS). (**b**) The external sphincter defect can be more easily appreciated on 3D rendered imaging.

racy can be improved by limiting imaging to the distal 1.5 cm of the anal canal [44].

Ultrasound 3D

With the development of three-dimensional endoanal ultrasound, the visualization of the sphincter anatomy is facilitated and the diagnostic accuracy improved [45]. In our institution (AJT), endoanal ultrasound is performed using a Pro Focus 2202 Ultrasound scanner (Bruel and Kjaer, Naerum, Denmark) and a 6- to 16-MHz probe (type 2050; Bruel and Kjaer) with depth of focal zone 0.5–2.5 cm. This probe enables automatic volumetric acquisition of images over a 6 cm axis without movement of the probe. The tip of the probe is placed at the level of the puborectalis, and we use the 13 MHz frequency for evaluating patients with fecal incontinence. After recording the dataset, images can be reconstructed and manipulated in the coronal, sagittal, and axial planes. The software permits visualization of anatomic structures from different angles and distances can be accurately measured. Volume rendering software provides reconstructions to improve visualization performance.

Christensen et al. evaluated the differences between 2D and 3D ultrasound in the evaluation of anal sphincter injury. Inter-observer agreement was 98.2 % in 3D ultrasound compared with 87.9 % with two-dimensional imaging [46]. Rendering software features may help improve visualization of the borders of the internal and external sphincter from surrounding structures, as well as aid in evaluation of external anal sphincter atrophy (Figure 57-3b) [47]. With sagittal and coronal imaging, anal sphincter length can be assessed. In the absence of sphincter injury, significant shortening of the anterior external anal sphincter can be seen after vaginal delivery [48]. West et al. found loss of sphincter volume in parous females did not correlate with symptoms of fecal incontinence [49].

Dynamic US

Given the limitations of physical examination, the concerns of ionizing radiation, and the costs and accessibility of dynamic magnetic resonance imaging, pelvic floor ultrasound is emerging as a viable option in imaging and understanding pelvic floor dysfunction. Unlike other modes of dynamic imaging, meshes and tapes can be seen on ultrasound. The clinical applications for pelvic floor ultrasonography are listed in Table 57-3 [50].

Three separate probes are used to perform pelvic floor ultrasound in four separate steps. The majority of the exam is performed in a modified lithotomy position (frog-legged). An enema prep is recommended for anorectal scanning. Dynamic imaging is performed with the patient at rest, during cough, with squeeze, and with push. Video clips are saved for subsequent review.

Transperineal scanning is performed with a 6 MHz linear transducer such as the B-K 8802 probe. The probe is placed with minimal pressure on the perineum from the mons pubis to the anal margin. Dynamic midsagittal images of the pelvis are recorded with this probe. Transvaginal ultrasound is then performed with a biplane probe, such as the B-K 8848 transducer with a 3D mover. This allows axial and midsagittal imaging of the anterior compartment and the posterior compartment. The transducer should be placed lightly into the vagina without significant pressure on the surrounding structures to prevent distortion of the anatomy. Dynamic images are again obtained and stored. Transvaginal assessment is then completed with a 360-degree rotational probe, such as

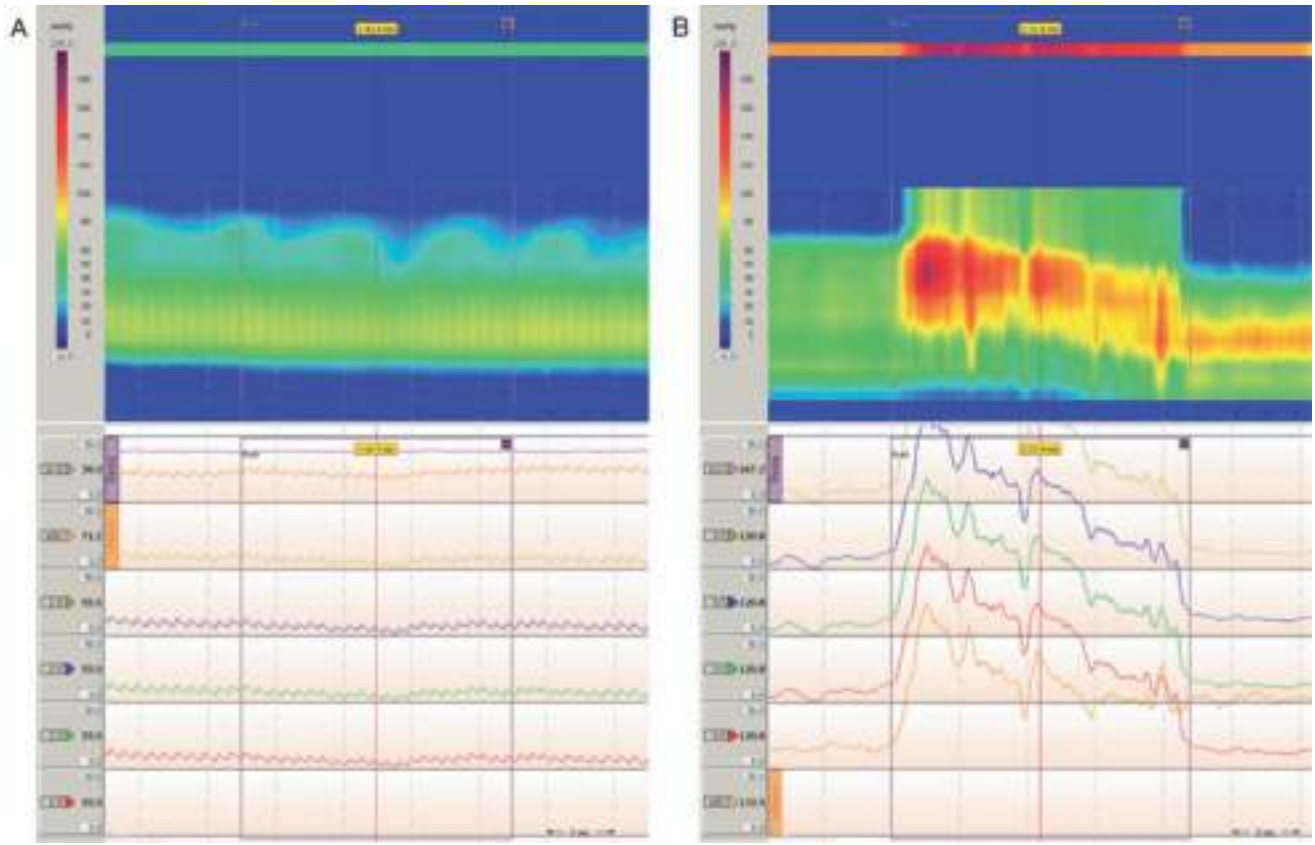

FIGURE 57-4. Appearance of Valsalva on high-resolution manometry. (**a**) Normal relaxation. (**b**) Paradoxical contraction.

TABLE 57-3. Indications for dynamic pelvic floor ultrasound [50]

Urinary incontinence
Symptoms of voiding dysfunction
Recurrent urinary tract infection
Fecal incontinence
Pelvic organ prolapse: cystocele, enterocele, rectocele, uterine prolapse
Symptoms of obstructed defecation: straining at stool, chronic constipation, vaginal or perineal digitation, and sensation of incomplete bowel emptying
Suspected pelvic floor dyssynergy
Pelvic, vaginal, or anal pain
Follow-up after pelvic floor surgery

the B-K 2052 probe. Static images are achieved and later analyzed at four axial planes [51]. Lastly, endoanal ultrasound is performed with the 2052 or similar transducer as previously described.

In static imaging, transvaginal ultrasound may reveal levator trauma not seen on endoanal ultrasound, given the levator ani attachments to the pubic rami can be easily visualized. Levator ani avulsion has been associated with decreased pelvic floor strength [52, 53]. DeLancey et al. found women with pelvic organ prolapse have an odds ratio of 7.3 for having a major levator injury compared with asymptomatic women [52].

Dynamic transperineal ultrasound has been evaluated and compared with standard defecography. In an early study, good agreement was seen in the diagnoses of rectocele, rectoanal intussusception, and rectal prolapse. No differences were noted in the measurement of the anorectal angle at rest, anorectal junction position at rest, or anorectal junction movement during straining. The anorectal angle at strain was also similar [54]. More recent studies have suggested trans-

perineal ultrasound has a lower detection rate for prolapse compared with defecography [55, 56].

An alternative technique, called echodefecography, has been described by Murad-Regadas [57, 58]. A 3D 360-degree probe, such as the B-K 2050 or 2052, is used to perform the exam. The patient is examined in the left lateral decubitus position after a cleansing enema. For scan 1, the probe is placed into the anal canal, and a scan of the distal 6 cm is obtained at rest. The angle between the puborectalis and a line perpendicular to the axis of the anal canal is measured. In scan two, the same anatomy is scanned with 15 s at rest, 20 s of maximal push, and 15 s of rest. Comparing scans 1 and 2, normal relaxation is noted if the angle increases by a minimum of one degree; paradoxic contraction is noted if the angle decreases by at least one degree. For scan 3, 120–180 ml of ultrasound gel is introduced into the rectum. The transducer tip is placed at 7 cm from the verge. The anatomy is scanned for 15 s at rest, 20 s at maximal push, and 15 s at rest, similar to scan 2. During this examination, middle and posterior compartment prolapse, such as rectocele, intussusception, and enteroceles may be noted.

Using the Murad-Regadas technique, echodefecography was compared with defecography in 86 women evaluated at six centers. Echodefecography identified 37 of 42 rectal intussusceptions, but identified an additional four not seen on traditional defecography. There was good concordance in identifying grade 3 enteroceles, however, grades 1 and 2 enteroceles could not be identified with the ultrasound technique. Anismus was identified more commonly in the echodefecography group, and two rectoceles may have been missed by the technique due to insufficient straining [59].

Using dynamic endoanal ultrasonography, in a protocol similar to the method described above, Vitton et al. compared their technique to dynamic MRI and traditional defecography in the evaluation of posterior compartment disorders. Using defecography as the gold standard, concordance rates were similar between ultrasonography and magnetic resonance imaging. Patients strongly preferred the ultrasound exam over the other two procedures [60]. Given the exam is not performed upright, similar to dynamic MRI, there is concern the exam may be less sensitive for prolapse compared with defecography. However, for surgeons who have ultrasound available in their office, dynamic ultrasonography may be a convenient method of tricompartment imaging of pelvic floor dysfunction.

MRI

Magnetic resonance imaging has been used to assess sphincter integrity in the evaluation of fecal incontinence [61–63]. Images can be generated either with an external phased array coil or with an endoanal coil. The latter may be less commonly available and more uncomfortable for the patient. Endoanal ultrasound appears to be superior in evaluating the internal anal sphincter [64]; both methods appear to be equivalent at detecting external anal sphincter integrity [64, 65]. Magnetic resonance imaging of the anal canal may better detect external sphincter atrophy that can adversely affect the outcomes of sphincteroplasty [66, 67]. Given the lower costs and accessibility, endoanal ultrasound is presently the more commonly performed exam in the anatomic evaluation of patients with fecal incontinence. The utility of magnetic resonance imaging in the dynamic evaluation of pelvic floor function is discussed later in this chapter.

Functional Evaluation

Anal Manometry

The study and recording of pressures in the anal canal has been practiced for over a century. Gowers described measuring the pressures in the anal canal of patients with spinal cord injuries in 1877 [68]. Early investigators sought to determine the contribution of the internal and external sphincters to overall anal canal pressure and function [69].

Anal manometry offers physicians valuable information regarding several aspects of anorectal function. For this reason, it is one of the most commonly utilized diagnostic tests in the evaluation of pelvic floor function. Manometry has been described in the evaluation of patients with fecal incontinence [70], constipation [71, 72], anal pain [73], fissure [74], and Hirschsprung's disease [75].

There are several systems and probes utilized to perform manometry, each with its own potential advantages and disadvantages. There are no standardized protocols that can create challenges in interpretation. In addition, age and gender have been shown to influence results [76].

The basic equipment necessary to perform manometry consists of a probe to sense pressure, a recording device, a monitor, and software system for analysis.

The probes can be either water perfused or solid state including the newer high-resolution and high-definition technologies. A non-latex balloon is tied to the end of the probe where a final pressure sensor is located to measure rectal pressures and reflexes.

Water perfused catheters utilize a thin plastic tube with 4–8 radially situated side holes. There is a central channel for balloon inflation. A pneumohydraulic pump is used to attain a consistent perfusion rate of 0.2–0.4 ml/min [77]. Pressure is measured at each of the side holes within the anal canal. This system is advantageous with respect to cost, however, potential shortcomings are the inability to measure in the sitting position and the potential artifact due to reflexes triggered by the sensation of the fluid in the anal canal. Proper calibration is essential.

Solid-state microtransducer is a thin flexible tube with embedded microtransducers which provide a direct measurement of pressures within the anal canal. These catheters are

more expensive and fragile but are felt to give more accurate and reproducible results [78].

High-resolution manometry represents the newest technological advance in the evaluation of anal function. Initially reported for the evaluation of esophageal function [79], high-resolution manometry has gained traction in the realm of anorectal physiologic testing [80]. Several probes are currently available (Table 57-4).

These devices provide enhanced resolution and greater detail due to the increased number of sensors. The sophisticated software provides the user with easy to understand color topographic analysis of the anal canal pressures. This can lead to improved understanding of the anal canal function. When compared to water perfused systems, high-resolution anal manometry was found to correlate well with respect to pressure measurements, but was noted to have decreased variability during the dynamic portions of the study as well as decreased time to perform the study [81]. Some have noted an increase in measured resting and squeeze pressure using the high-resolution probe compared to the water perfused probe. It was theorized that this increase, which was consistent, was a result of improved sensitivity of the measurements with the 256 sensors in the high-resolution probe [82].

Manometry Technique

Patients do not need formal bowel prep for this study. After an attempted evacuation attempt prior to the procedure, or there is significant residual stool, an enema can be given. It is important to provide proper education to the patient prior to the procedure as anxiety can lead to unreliable results.

The patient is placed in the left lateral decubitus position and a digital rectal examination is performed. Particular attention is paid to the presence of any anal abnormalities on examination such as blood, masses, or tenderness. Postoperative patients with a low anastomosis should be evaluated for stenosis or disruption prior to placement of any probe, catheter, or balloon.

As has been previously mentioned, there is no standardized technique for the manometric evaluation of the anal canal. The basic concept is that of a balloon tipped catheter placed within the anal canal with the balloon in the distal rectum to measure pressures during various maneuvers. The water perfused systems can utilize a station pull through technique, whereby the catheter is inserted to the 6 cm level and static measurements at rest and squeeze are taken at 1 cm intervals along the length of the anal canal. The continuous pull through technique measures pressures along the length of the anal canal as the catheter is slowly withdrawn, rather than taking incremental measurements. High-resolution probes have the advantage of simultaneous measurement of pressure within the entire canal as the sensors are situated over the length of the probe within the anus.

After initial probe placement, a period of equilibration is necessary in order to allow the anal sphincter to return to baseline activity. This typically takes about 5 min. Several wave patterns are seen which demonstrate the intrinsic nature of the internal sphincter.

Slow waves are the most common. They occur with a frequency of 10–20/min and are low amplitude. They have an increasing frequency in the lower anal canal and may cause an upward movement of rectal contents, possibly playing a role in continence [83].

Ultraslow waves are high amplitude and occur with a frequency of less than 2/min. These are associated with anal hypertonia but also can be found in normal subjects [77].

Intermediate waves occur with a frequency of 4–8/min. These are the least common and are seen in patients with neurologic injury.

The components of the examination include measurements of static pressure at rest and squeeze, dynamic measurements with cough and Valsalva, assessment of the rectoanal inhibitory reflex (RAIR) as well as evaluation of rectal sensation and compliance.

Resting Pressure

The concept of anal canal "tone" has long been understood. Through the early work of Masius in animal models, the spinal cord reflex contribution to anal canal resting pressure became known in the late 1800s [84]. The internal anal sphincter tone is the primary determinant of the resting pressure. It is recognized, however, that up to 30 % of the resting pressure can come from the external anal sphincter tone and 15 % from the anal cushions themselves [85, 86]. Pressures are recorded within the anal canal with the patient at rest after the equilibration period. The resting pressure is defined as the difference between the intra-rectal pressure and the anal canal pressure. The stationary or continuous pull

Table 57-4. Anorectal manometry probes

	Manufacturer	Diameter	Length	Sensors/row	Rows	Interval
HRAM	Given Imaging, Yokne'am Illit, Israel	4.2 mm		10	12	6 mm
3d HRAM	Medical Measurement Systems, The Netherlands	4 mm	15 cm	1–4	8	10 mm
3d HDAM	Given Imaging, Yokne'am Illit, Israel	10.75 mm	10 cm	16	16	4 mm

through technique can be used. The high-resolution probe will allow for measurements along the length of the canal without moving the probe, thereby reducing the chance of unintentional excitation of the internal sphincter by the movement of the probe. The standard probe is placed 5 cm above the anal margin. After equilibration, measurements are taken at either 1 cm intervals or continuously as the probe is withdrawn by a motorized pulling device at a rate of 5 mm/s.

The sphincter length can be calculated with the pull through technique by measuring the length of the anal canal where the pressure is at least 5 mm greater than the intra-rectal pressure. The high pressure zone is defined as the length of the anal canal over which the pressures are greater than half the maximum resting pressure [87].

Controversy exists over the effect of gender on mean resting pressure. While several studies suggest that men have higher pressures, the larger series with evenly matched groups have failed to show this difference [88]. Age has been shown to have an influence on resting pressure as well, correlating with decreases in both genders in older age groups [89].

Squeeze Pressure

The squeeze pressure is obtained by placing the probe within the anal canal and asking the patient to contract the anal muscles. It is important to avoid the use of accessory muscles of contraction. The squeeze pressure should be generated by the external anal sphincter. The intra-rectal pressure is subtracted from this number. In order to truly isolate the striated muscle contribution, the resting pressure can be subtracted to determine the squeeze increment. This measurement will assess the contribution of the external anal sphincter and puborectalis only. The duration of squeeze can also be measured as the time that a patient can sustain squeeze pressure greater than 50 % of the maximal squeeze pressure [90]. Decreased squeeze pressures are frequently the result of external anal sphincter dysfunction, correlation with other physiologic studies can determine the etiology (traumatic or neurologic). A diminished squeeze duration has historically been associated with fecal incontinence [91], however, more recently, researchers have found an inverse relationship between external anal sphincter fatigue and incontinence [92].

Cough Reflex

A rapid rise in intra-abdominal pressure, such as with cough, causes a reflex contraction of the external anal sphincter. This is the normal state and is mediated by a polysynaptic pathway of spinal origin. The cough reflex is preserved after mid thoracic spinal injury but lost with cauda equina lesions [93]. The cough reflex helps to maintain continence during rapid rise in intra-abdominal pressure.

Valsalva

Relaxation of the external anal sphincter during Valsalva maneuver facilitates defecation. Conversely, contraction of the striated puborectalis or external anal sphincter during attempted defecation will result in constipation secondary to outlet obstruction [94]. Non-relaxation or paradoxical contraction of these muscles can be demonstrated at the time of anal manometry. After an equilibration period, the patient is asked to feign defecation. It is expected to visualize an increase in the intra-rectal pressure with a concomitant decrease in the anal canal pressures. Failure to decrease or an increase in anal pressures with feigned defecation can aid in the diagnosis of dyssynergic defecation. Four types of dyssynergic defecation have been described:

Type 1 Intra-rectal pressure rises with an increase in intra-anal pressure.
Type 2 No intra-rectal pressure increase, increase in intra-anal pressure.
Type 3 Intra-rectal pressure rises, no/minimal change in intra-anal pressure.
Type 4 No intra-rectal pressure increase, no/minimal change in intra-anal pressure.

Care must be taken in the correlation of manometric findings of non-relaxation of the sphincter and clinical findings. It has been demonstrated that paradoxical sphincter contraction is also a common finding in healthy patients as well at the time of manometric evaluation, presumably a result of patient's unease during the procedure itself [95]. It has even been demonstrated that patients with non-relaxation at the time of manometry can go on to have normal testing when the manometry was repeated in the patients home setting [96]. Figure 57-4 demonstrates the normal and paradoxical responses to Valsalva seen on manometric evaluation.

Rectoanal Inhibitory Reflex

The rectoanal inhibitory reflex (RAIR) can be elicited by filling a balloon within the rectum. The volume required in approximately 50 cc but can be larger in conditions of megarectum and hyposensitivity [97]. Distension of the rectal wall causes an initial contraction of the external sphincter followed by a relaxation of the internal anal sphincter. This was first noted by Gowers in 1877 [68] and is felt to aid in the sampling mechanism of the anal canal. This mechanism allows discrimination of solid liquid and gas has been shown to be an important component of continence [98]. Presence of the reflex confirms a functioning myenteric plexus and therefore the absence of Hirschsprung's disease. The absence of a reflex is associated with Hirschsprung's disease and visceral neuropathy [99]. It should be noted that the absence of a reflex is often related to technical factors such as inadequate balloon volume. In the event of a negative reflex, testing at several levels within the canal and at a larger balloon

volume may elicit the response. Fecal incontinence and constipation have been associated with altered patterns of the RAIR [100, 101]. Figure 57-5 demonstrates the rectoanal inhibitory reflex seen on high-resolution anorectal manometry.

Rectal Sensation

Rectal sensation is assessed by incrementally inflating a balloon in the rectum with small volumes. The patients first sensation and urge to defecate and maximum tolerated volumes are recorded. The rectum itself does not contain pain sensing nerve fibers. The rectum is sensitive to distension via mucosal receptors and nerves in the pelvic fascia and pelvic floor musculature via the S2–4 nerve roots [102]. Alteration in rectal sensation is associated with fecal incontinence and constipation:

- First sensation: the lowest volume of air that the patient senses a fullness in the rectum.
- Urge to defecate: the lowest volume of air that produces a sustained desire to defecate.

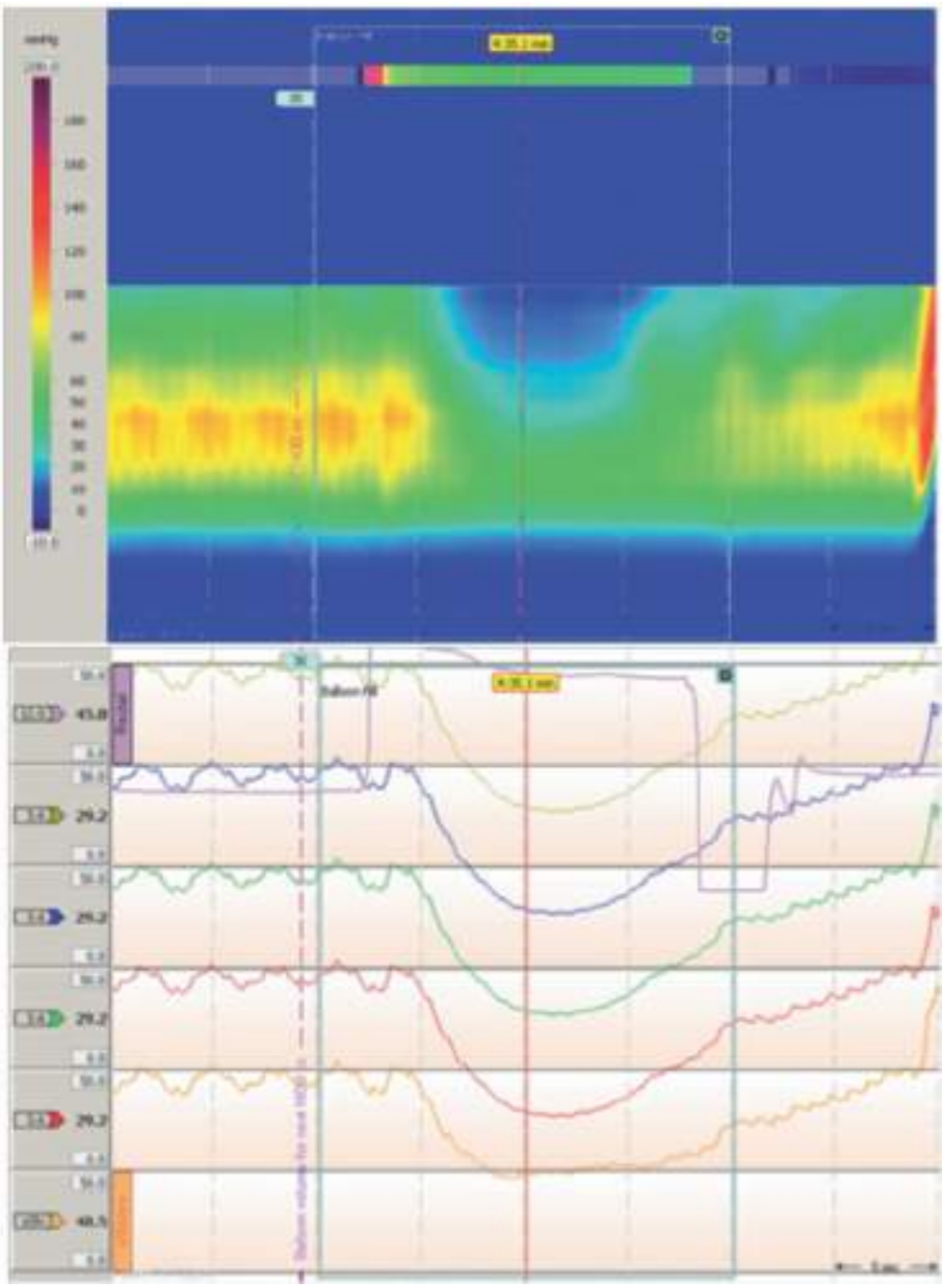

FIGURE 57-5. Appearance of RAIR (rectoanal inhibitory reflex) on high-resolution manometry.

- Maximal tolerated volume: the maximum volume that a patient can tolerate. It is of note that most balloons can hold 300 cc, so if the maximum tolerated volume is 300 cc, the rectum may have dramatically decreased sensation.

Compliance

Rectal compliance measures the distensibility of the rectum. This can be altered in conditions such as proctitis and after radiation. The balloon is inflated and the change in rectal pressure with the change in volume is calculated.

Balloon Expulsion

The balloon expulsion test is a relatively simple method to grossly assess evacuatory function. As is often the case in pelvic floor physiology testing, there is no standardized method of performing the test. In general, a balloon attached to catheter is placed into the rectum and inflated. In the seated position, the patient attempts to expel the balloon. The ability and time taken to expel the balloon are measured.

Variables in the technique include the type of balloon, the material used to fill, the amount filled (standard 50 cc vs. volume that produces urge to defecate [103]).

Most studies use 1 min as the cut-off point for the normal time taken to expel the balloon [104].

Neurophysiologic Testing

The neurophysiologic evaluation of the anorectum provides important functional evaluation of the anal canal. Electromyography records electrical activity of the external anal sphincter and puborectalis muscles during rest, squeeze, and attempted defecation. The integrity of the motor unit is assessed. EMG can be used as a tool to map the anal sphincter and identify defects. First described in 1930 [105], historically, EMG was the gold standard for evaluating sphincter defects, More recently, however, ultrasound was found to have high correlation with EMG [106]. EMG still remains a useful tool in the detection of sphincter defects when the ultrasound is inconclusive as can be the case in areas of dense scarring. In addition to the potential of anal sphincter mapping, the EMG can be used to identify areas of injury, where prolonged action potentials and polyphasic responses will be seen. With severe injury, or complete denervation, electrical silence will be noted. In areas that have undergone repair and reinervation, the action potentials will be prolonged and the regrouping of muscle fibers will create polyphasic potentials. The irregularity of the motor unit potentials has been correlated with neurologic injury [107]. There are four methods of EMG assessment:

- concentric needle
- monopolar wire
- single fiber
- surface anal plug.

Needle EMG

Needle EMG provides the examiner with detailed information about the electrical activity of the anal sphincter muscle. Quadrant by quadrant, the examiner can assess the function of the motor units. The test, while informative, is often not well tolerated. Although no longer a mainstay in the evaluation of anal sphincter defects, concentric needle EMG is important in the evaluation of neurogenic fecal incontinence [108, 109].

Surface

The surface anal electrode (Figure 57-6) has the advantage of increased patient comfort as no needles are used. The study provides a global assessment of anal sphincter function but cannot provide isolated quadrant activity. This technique is useful in the evaluation of constipation and dyssynergia. The technology is commonly used in biofeedback therapy as well. The anal canal responses to squeeze and attempted defecation are recorded. The absence of a needle insertion reduces the potential for a false recording due to pain. The expected response to attempted defecation is a decrease in electrical activity. Failure to decrease or an increase in activity

FIGURE 57-6. Surface EMG (electromyography) electrode.

constitutes non-relaxation or paradoxical contraction of the puborectalis, respectively. Correlation between the anal sponge and needle EMG has been well established in evaluation of constipated patients [110, 111].

Pudendal Nerve Terminal Motor Latency

Pudendal nerve terminal motor latency (PNTML) measures the time taken from stimulation of the nerve intrarectally to measurement of a muscular response at the level of the anal sphincter. The technique was first described by Kiff and Swash from St. Mark's Hospital in 1984 [112, 113]. A disposable electrode was introduced in 1988 [114]. The Dantec St. Mark's electrode is most commonly used to assess PNTML (Figure 57-7). Stimulating electrodes at the fingertip and receiving electrodes situated 4 cm distally at the base of the finger allow for measurement of the muscular response to nerve stimulation. The study has been shown to be reproducible with low intra- and inter-observer variability [115]. After placement of the electrode, the examiner inserts the finger into the anal canal and after localization of the coccyx posteriorly, the finger is brought laterally to the ischial spine while delivering electrical impulses. Once the nerve is located, the time measured to elicit a muscular response is recorded. Normal latency is 2.0±0.2 ms [116]. The study is technique dependent and a learning curve has been reported [117]. PNTML has been advocated in the evaluation of fecal incontinence, rectal prolapse, and constipation. Its clinical significance has been debated particularly with respect to patients with incontinence. Studies of patients suffering from idiopathic incontinence found no association with incontinence severity or manometric findings [118], while others draw a direct correlation with manometric findings [119]. These discrepancies may be attributable to the complex and multifactorial etiology of fecal incontinence. The test is still utilized in the evaluation of fecal incontinence and other functional disease states to evaluate the integrity of the pelvic floor innervation.

Transit Testing

Assessment of the transit time of the gastrointestinal tract is an integral component of the evaluation of constipation and

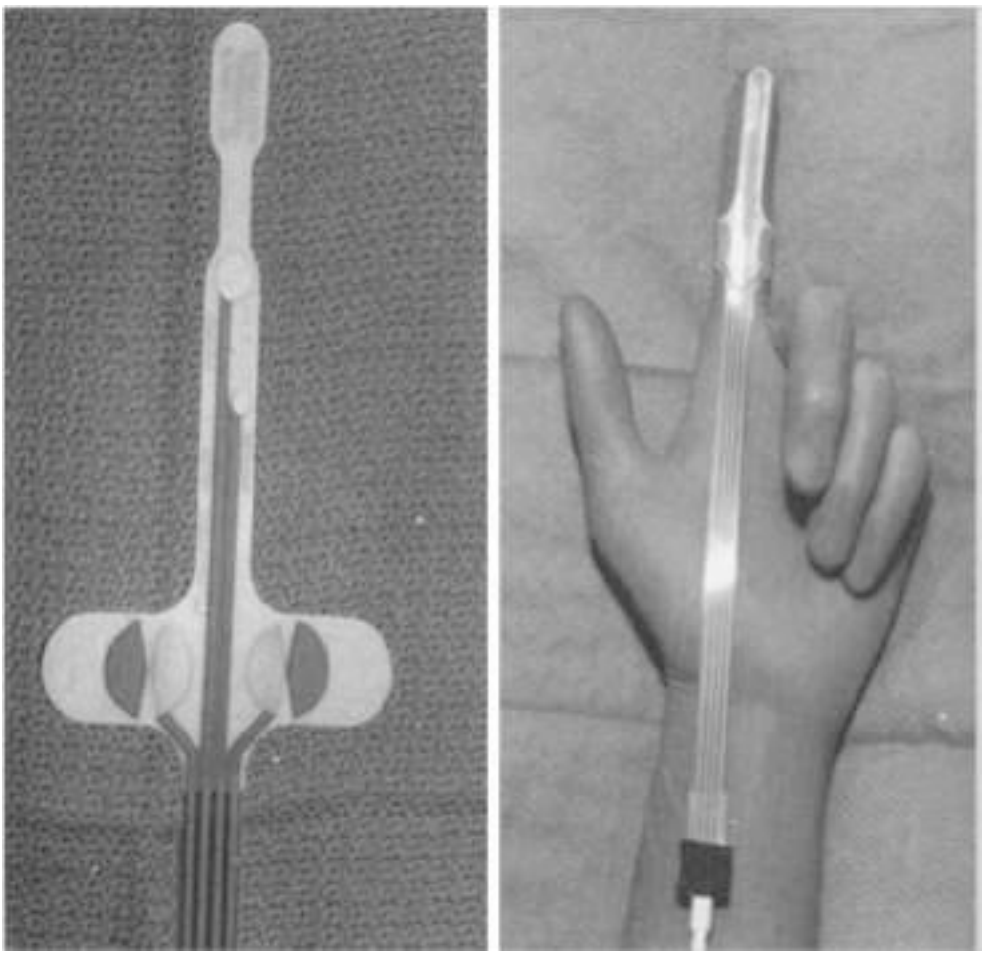

FIGURE 57-7. St. Mark's electrode.

other colorectal complaints. Historically, this was accomplished with ingestion of radio-opaque markers. More recently, however, advances in technology have given physicians the ability to understand segmental transit times as well as the whole gut transit time. There are four main methods to assess GI transit: radio-opaque markers, scintigraphy, breath testing, and most recently, the wireless motility capsule. Each method has its advantages and drawbacks with respect to cost, radiation exposure, and information provided.

Radio-Opaque markers

The ingestion of radio-opaque markers to assess gastrointestinal transit has been utilized since the 1960s. In 1969, the first reports utilized solid cylindrical pellets specifically to assess colonic transit. These were modified to a cut section of radio-opaque polythene tubing. The patients ingested 20 pellets and serial radiographs were taken of both the patient and the stools passed [120]. Fortunately, the technique was simplified to include only abdominal radiographs and stool transport to the radiology suite is no longer necessary. Currently, a single capsule containing 24 markers (Sitzmark Radio-opaque Markers, Konsyl Pharmaceuticals Inc, Fort Worth, TX) is ingested and serial radiographs are taken. There are several protocols for the study, however, all require cessation of all laxatives 48 h prior to and for the duration of the study. The simplest protocol utilizes plain abdominal X-rays on days 1, 3, and 5. A normal study requires passage of 80 % of the markers by day 5. The number and distribution of the markers are noted. Patients with colonic inertia will have greater than five markers evenly distributed throughout the colon (Figure 57-8). Outlet obstruction should be considered with there is a stacking of markers at the rectosigmoid junction [121]. The X-ray on day 1 will document grossly normal gastric and small bowel transit if all of the markers are located in the colon at this point. There are alternate techniques, which require the ingestion of multiple distinct capsules (1/day for 3 days) followed by an abdominal X-ray on day 4. The segmental transit times are then calculated by the distribution of the markers [122].

These marker studies have the benefit of decreased cost; however, the patient is subjected to the ionizing radiation of the serial X-rays.

The use of radio-opaque markers has been described to evaluate small bowel transit [123], however, this technique requires repeated fluoroscopic examination and radiation exposure.

Breath Testing

Breath testing has been described for the evaluation of several conditions including carbohydrate malabsorption, intolerance, and bacterial overgrowth. In the evaluation of gastrointestinal transit, breath testing can provide estimation of both gastric emptying and orocecal transit time.

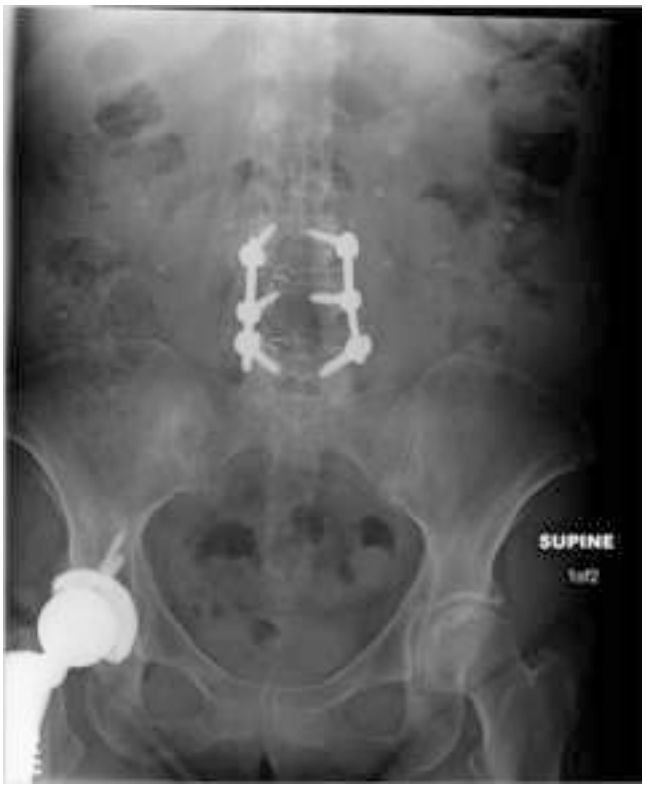

FIGURE 57-8. Abdominal radiograph demonstrating retention of radio-opaque markers.

Gastric emptying is assessed using nonradioactive isotope. ^{13}C-labeled substances are ingested and metabolized after passing the pylorus. Ultimately, there is conversion to $^{13}CO_2$, which is exhaled. Several substances can be labeled to measure the solid and liquid phases of gastric emptying. Breath samples are collected for 4 h. Both mass spectrometry and infrared analyzers have been used to detect and measure the presence of $^{13}CO_2$ [124]. The results can be affected by pulmonary conditions resulting in CO_2 retention.

Orocecal transit time is frequently assessed with the use of the lactulose breath test. Hydrogen is the measured component. The premise is that the lactulose, a nonabsorbed sugar, is ingested and the anaerobic bacteria of the GI tract, found in the colon, metabolize it producing CO_2 and H_2. The H_2 is absorbed and circulated to the lungs where it is ultimately exhaled and measured in breath samples. The time taken to increase the exhaled H_2 ppm greater than 20 ppm is considered to represent the orocecal transit time. This time is not a true representation of small bowel transit time as it can be affected by conditions that delay gastric emptying. Normal orocecal transit time ranges between 40 and 170 min [125]. It is known that approximately 15–20 % of people are "non-fermenters" and will not produce hydrogen at all. Conditions

such as bacterial overgrowth can lead to a false and early rise in the measured breath hydrogen.

This technique has been validated in comparison with scintigraphy with lactulose and avoids the use of radioactive isotopes [126]. Scintigraphy without lactulose was shown to have a decreased transit time when compared to studies performed with lactulose [127]. Presumably, this was related to the osmotic effects of the lactulose and should be considered in the evaluation of H_2 breath tests.

Scintigraphy

The use of nuclear medicine to assess gastrointestinal transit has been most commonly described for the evaluation of gastric transit. Initial reports in 1970 describe the use of ^{129}Cs [128]. Since this time, as is the case with many tests of GI physiology, there has been little standardization of testing methods. In an attempt to simplify and standardize the technique, international controls were established in 2000. ^{99}Technetium labeled fat free egg substitute or egg whites are given in a low fat meal. The percentage of retained gastric contents is measured at 60, 120, and 240 min. Delayed gastric emptying is defined as residual of greater than 10 % at 4 h [129].

Small intestinal scintigraphy has largely been used in research settings due to its limited availability and lack of standardization. Recent reports of evaluating small bowel transit in the setting of a whole gut transit time have attempted to better define the study [130]. Utilizing a standard ^{99}Tc labeled solid meal and ^{111}In water, gastric emptying, followed by small bowel and colonic transit was measured. The percent of the meal that reached the cecum at 6 h was calculated. The colonic transit was evaluated by assessing the pattern of the tracer and percent excretion at 24, 48, and 72 h. A recent position paper by the American and European Neurogastroenterology and Motility Societies found strengths in the quantitative information provided but drawbacks in the lack of standardization, cost, radiation exposure, and time taken to complete the study [131]. Colonic scintigraphy has also been evaluated. Studies have shown the ability to delineate segmental colonic transit [132]. The clinical implications of these findings are still unclear. Colonic transit scintigraphy also has limited availability and requires radiation exposure and repeated imaging.

Wireless Motility Capsules

The wireless motility capsule represents the newest technology used in the evaluation of gastrointestinal transit. The device is ingested orally and records temperature, pH, and pressure as it passes through the GI tract. It has been approved by the FDA for evaluation of gastroparesis in 2006 and colonic transit in the setting of constipation in 2009. The technology had the advantages of the avoidance of all ionizing radiation, performance in the ambulatory office setting, standardization of technique with the ability to assess motility in all portions of the GI tract. The WMC (smartPill; Given Imaging Corp, Yokne'am Illit, Israel) is a single use indigestible capsule that measures 26.8 mm × 11.7 mm. The pH, temperature, and pressure sensors are housed within the capsule that transmits data every 20 s for 24 h then every 40 s for the remainder of the study. The battery lasts for a minimum of 120 h. The activated capsule is ingested by the patient and a data receiver is worn for the next 5 days. At the completion of the study, the receiver interfaces with a laptop and the data is interpreted. Prior to the study, an overnight fast is required. All medications that can affect motility or pH are discontinued prior to the test. After ingestion, a standardized meal is consumed. Following this, the patient is kept NPO for 6 h to assess gastric emptying time. Following this initial period, patients can eat and drink normally. They are asked to record meals, sleep, and bowel movements for the duration of the study. Use of the WMC is contraindicated in patients with dysphagia, strictures, or anatomic bowel obstruction. An initial drop in pH signifies passage of the capsule from the stomach in to the small bowel. A subsequent drop in pH signifies passage in to the cecum. If the ileocecal valve is incompetent, this change might not be observed [133]. In patients where the pH drop is not observed, changes in pressure wave frequency of amplitude may signify the passage from small bowel into the colon [134]. Abrupt decrease in temperature is noted when the capsule exits the body. With this information, gastric emptying, small bowel transit, colonic transit, and whole gut transit times can be determined [135].

Anatomic and Functional Evaluation

From the surgeon's viewpoint, the use of dynamic imaging of the pelvic floor is crucial in evaluating patients with obstructive defecation. Dynamic imaging can differentiate between functional causes, such as anismus, and mechanical etiologies, such as intussusception and rectal prolapse. The use of dynamic imaging in patients with pelvic floor prolapse may better identify patients requiring multi-compartment repair and prevent recurrences [136, 137]. Given surgical correction of rectal intussusception (RI) can improve bowel continence [138], and the possibility that sacral neuromodulation may be less effective in treating fecal incontinence in patients with high grade RI [139], dynamic imaging is performed routinely in some centers in the evaluation of fecal incontinence.

Defecography

Defecography, also referred to as evacuation proctography, assesses dynamic changes in rectal wall, anal canal, vaginal, and pelvic floor morphology during the defecation process

[140, 141]. Although many centers use retrograde rectal and vaginal contrast, some may add bladder contrast to perform dynamic pelvicography [142]. Others advocate the use of oral contrast or peritoneal contrast to better delineate enteroceles and peritoneoceles [143, 144]. The rectal barium contrast is thickened to simulate stool weight and consistency. The volume introduced may be standard [144] or tailored to the individual until a strong, sustained urge to defecate is achieved [145]. The patient is then comfortably placed on a radiolucent commode attached to a fluoroscopic table. Images may be obtained in the lateral and occasionally in the antero-posterior view. A disposable plastic bag collects evacuated barium below the commode.

One of the advantages of defecography is that it is performed in the upright sitting position. This may approach more physiologic conditions, allowing the natural movement of the abdominal muscles, the weight of the intestines, and the influence of gravity's effect on rectal evacuation be evaluated [140]. Images are obtained when the patient is asked to squeeze and contract the external sphincter and puborectalis, at rest, and with Valsalva. If the patient digitates to facilitate or initiate evacuation, images during these maneuvers are performed.

A recent report of defecography in normal volunteers reported a mean radiation dose of 0.6 mSv (effective dose 01–1.0 mSv) [146]. Goei and Kemerink estimated the mean effective dose at 4.9 mSv for female patients and 0.6 mSv for males, given the testes receive only scattered radiation [147]. For comparison, an individual's environmental radiation exposure is estimated at 2.5–3.0 mSv/year, and the effective dose from a single barium enema would be 7.0 mSv.

Normal Parameters

The pubococcygeal line (PCL) refers to a line between the tip of the coccyx and the pubis. Given it is a static, unchangeable point, it is used to assess the mobility of the pelvic floor. In a normal patient, no more than one third of the rectum will lie below this line; perineal descent can be noted if a greater percentage of rectum lies below the PCL. Radiologists often define the presence of pelvic organ prolapse when pelvic viscera descend below the PCL [148].

The anorectal angle (ARA) refers to the angle between the anal canal and the posterior rectal line. At rest, the ARA approximates 90°. With squeeze, the imprint of the puborectalis muscle on the posterior rectal wall increases, and the ARA should decrease to about 75°. This is associated with elevation of the anorectal junction (ARJ), the highest point of the anal canal [149]. With strain, the puborectalis should normally relax, decreasing its imprint on the posterior rectum, increasing the anorectal angle to 110–180°, and allowing the ARJ to descend no more than 3.5 cm from its resting position. A lack of relaxation of the puborectalis with strain and persistent impression of the muscle on the posterior rectum can be consistent with anismus or paradoxic contraction of the pelvic floor [150]. A common criticism of the clinical value of ARA measurement is high intra- and inter-observer variation [151, 152].

Rectocele

A rectocele is a bulging of the rectal wall. Usually this is a ventral wall bulge in female patients given laxity in the rectovaginal septum (Figure 57-9). Lateral and posterior rectoceles have also been described in male and female patients [153]. Rectoceles are very common, and may be seen in up to 93 % of asymptomatic females, regardless of parity [146]. The size of the protrusion from the anterior rectal wall can be measured; rectoceles smaller that 2 cm are regarded as clinically insignificant. The pattern of deformation as well as the degree of emptying of the rectocele is noted during defecation. If the patient admits to using perineal or vaginal digitation, the impact of the maneuver in assisting evacuation can be observed during imaging.

Rectal Intussusception

Rectal intussusception represents the invagination of the rectal wall by more than 2 cm during straining. The invagination can be circumferential or asymmetric, and the extent may be intra-rectal or intra-anal [154, 155]. Rectal intussusception is also common, and may be seen in up to 39 % of symptomatic patients [156] and 20 % of asymptomatic volunteers [146]. Rectorectal intussusceptions are often asymp-

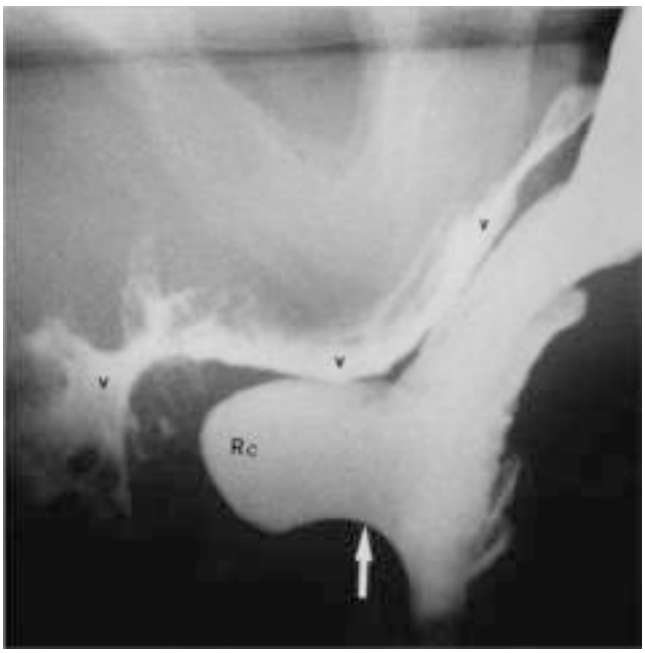

FIGURE 57-9. Fluoroscopic defecography with vaginal (v) and rectal contrast. An anterior rectocele (Rc) is noted; the size can be measured from the expected anterior rectal wall (*arrow*) to the anterior aspect of the protrusion.

tomatic, whereas rectoanal intussusceptions may cause symptoms of fecal incontinence, obstructive defecation, or rectal pain.

Rectal Prolapse

Rectal prolapse occurs when full thickness rectal wall protrudes past the anus. Dynamic imaging can evaluate whether the prolapse is isolated to the posterior compartment, or whether it is associated with anterior and middle pelvic compartment prolapse. Combined multi-compartment pelvic prolapse repairs appear to be safe and have lower rates of symptomatic recurrence [136, 137].

Enterocele and Sigmoidocele

An enterocele refers to the presence of small bowel loops in the pouch of Douglas [157]. If oral contrast is used, opacified loops of small bowel can be seen in the rectovaginal septum. If there is no contrast, widening of the rectovaginal septum is indicative of an enterocele's presence. A sigmoidocele occurs when redundant sigmoid colon fills the peritoneal sac in the pouch of Douglas. Although sigmoidoceles are less common than enteroceles, both pathologies cause symptoms of incomplete evacuation.

Descending Perineum Syndrome

Perineal descent has been described as both a dynamic and static measurement in the defecography literature. During Valsalva, the anorectal junction (ARJ) descends normally. A descent of more than 3.5 cm may indicate perineal hypermobility [158, 159]. This can result in nerve and muscle stretch with resultant loss of function. Other patients have an abnormal position of the perineum at rest, and subsequently have no ability to move the pelvic floor with push [160]. An abnormal perineal position does not appear to correlate with severity of symptoms [161]. Descending perineum syndrome can be caused from chronic constipation and be associated with fecal incontinence.

Dynamic MRI

Given the complexity of pelvic floor anatomy and the concerns of the carcinogenic effects of ionizing radiation, dynamic MRI has been advocated as a viable alternative to cystoproctography. Advances in magnetic resonance imaging allow rapid acquisition of dynamic images with improved spatial resolution and soft tissue details in a single breath. Images can also be analyzed in multiple planes. The majority of studies are performed in a closed configuration MR in the supine position. Rectal contrast consisting of ultrasound gel or a gadolinium based MR contrast mixed with potato starch is instilled via a rectal catheter [162, 163]. The patient performs the same maneuvers as described with fluoroscopic defecography, and the images and video loops are analyzed for the same parameters (Figure 57-10).

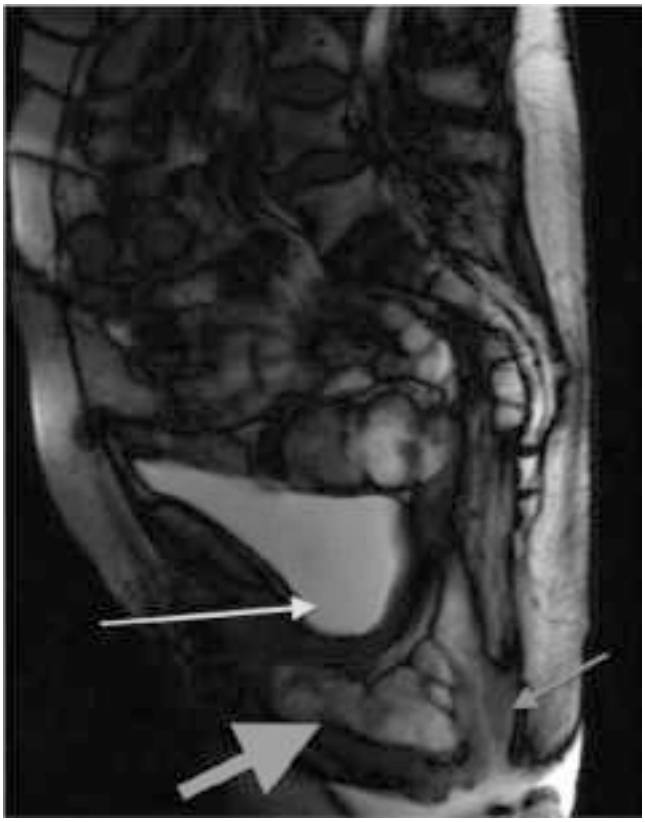

FIGURE 57-10. MR Defecography. The *short thin arrow* marks a rectal intussusception, associated with an enterocele (*short thick arrow*). The *long thin arrow* marks a cystocele. *Courtesy of Dr. Sidney Walker, Center for Diagnostic Imaging, Minneapolis, MN.*

One of the main criticisms of dynamic MRI is that it is not performed in the physiologic state: the upright sitting position. When performed upright in an open magnet system, images have a lower signal to noise ratio with less soft tissue resolution, with subsequent loss of detail in evaluation of pelvic supporting structures. This leads to increase interobserver variation in determining reference points [164, 165]. In a comparison of fluoroscopic cystoproctography with dynamic pelvic MRI, MRI underestimated prolapses that are not rectoceles by 10–15 % [166]. Critics also note that patient embarrassment is a limitation with both examinations, but this can be exacerbated when requesting the patient to defecate in the supine position [167].

Conclusion

Disorders of bowel evacuation and continence are distressing to patients, and the factors leading to dysfunction are frequently multifactorial. Although each test has its limitations, anatomic and functional evaluation of the pelvic floor and gastrointestinal tract aids the evaluating surgeon in the diagnosis and treatment of these conditions.

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58
Evaluation of Constipation and Treatment of Abdominal Constipation

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Key Concepts

- There are three constipation subtypes which can be differentiated by symptoms and diagnostic testing, although there can be overlap between subtypes.
- Initial treatment of constipation includes behavioral modification and medication.
- Surgical management of constipation is reserved for severe slow transit constipation that is not responsive to medications.

Prevalence

Constipation is an extremely common complaint and in North America alone it is estimated that 63 million people suffer from constipation. The prevalence has been estimated between 2 and 27 % and accounts for 2.5 million physician visits annually [1, 2]. Women report a two- to three-fold higher incidence of constipation than their male counterparts. In a survey study of 600 healthy women from Spain, almost a third had functional constipation symptoms [3]. In another study of patients presenting to European tertiary care centers for idiopathic constipation, 92 % were women, and furthermore, women were more likely to have a diagnosis of slow transit constipation [4]. There is a higher incidence of constipation in non-Caucasians as well as individuals with less education and lower income. Additionally, multiple studies have found older patients have a higher prevalence of constipation, particularly over the age of 65 [5–8].

Etiology of Constipation

Defecation is a complex process that results from stool formation, gastrointestinal motility, and pelvic floor function. Constipation may result from dysfunction of any portion of the defecatory process. Contributing factors may include diet, medications, neurologic or endocrine disorders, psychosocial issues, colonic disease, or pelvic floor abnormalities (Table 58-1). Often patients may have constipation with no identifiable cause.

Rome Criteria and Constipation Subtypes

In an effort to standardize the definitions associated with constipation, a symptom-based classification was established by consensus approach. The most recent iteration was created by the Rome Committee in 2006 and is termed the Rome III Criteria [9]. For functional constipation, criteria (Table 58-2) must be met for the last 3 months, with symptom onset at least 6 months prior to diagnosis [10].

Constipation can be further categorized into the following subtypes: slow transit constipation, normal transit constipation, or pelvic constipation. Slow transit constipation or abdominal constipation is a motility disorder and stool moves through the colon at a slow rate. In some patients, only the colon is affected, while in others, there may be involvement of other portions of the gastrointestinal tract. Patients with slow transit constipation may not have bowel movements for days to weeks at a time, despite using laxatives and enemas. Normal transit constipation, also termed constipation predominant-irritable bowel syndrome, is a functional disorder characterized by normal transit through the gastrointestinal tract, however, stools are hard and defecation may be difficult. Additionally, patients may complain of abdominal pain and bloating that is relieved by defecation. Pelvic constipation includes lack of coordination of the pelvic floor during defecation, rectal hyposensitivity, or constipation from impingement, such as rectocele, enterocele, and sigmoidocele. There may also be associated full thickness rectal prolapse, internal intussusception, and solitary rectal ulcer syndrome. Pelvic constipation results in

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TABLE 58-1. Factors associated with constipation lifestyle, medications, medical illness, psychological, colonic structure/function, pelvic floor abnormality

Lifestyle
Inadequate fluid intake
Inadequate fiber intake
Inactivity
Laxative abuse
Medications
Opiates
Anticholinergics
Iron
Medical illness
Neurologic
Spinal cord dysfunction/damage
Parkinson's disease
Multiple sclerosis
Endocrine/metabolic dysfunction
Diabetes mellitus
Hypothyroidism
Hyperparathyroidism
Electrolyte abnormalities
Uremia
Hypercalcemia
Porphyria
Psychological
Depression
Anorexia
Psychiatric illness
Sexual abuse
Colonic structure/function
Cancer
Crohn's disease
Irradiation
Endometriosis
Hirschsprung's disease
Chagas disease
Pelvic floor abnormality
Nonrelaxing puborectalis
Anal stenosis
Rectocele/enterocoele/sigmoidocele

TABLE 58-2. Rome III criteria for functional constipation

1. Must include *2 or more* of the following[a]:
a. Straining during at least 25 % of defecations
b. Lumpy or hard stools in at least 25 % of defecations
c. Sensation of incomplete evacuation for at least 25 % of defecations
d. Sensation of anorectal obstruction/blockage for at least 25 % of defecations
e. Manual maneuvers to facilitate at least 25 % of defecations
f. Fewer than 3 defecations per week
2. There are insufficient criteria for irritable bowel syndrome
3. Loose stools are rarely present without the use of laxatives
4. There are insufficient criteria for irritable bowel syndrome

[a]Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

excessive straining, need for digital manipulation, and incomplete evacuation. Each of these constipation subtypes may occur either in isolation or in various combinations, which may create treatment challenges. The focus of this chapter is to discuss the evaluation and management of slow transit constipation; irritable bowel syndrome and obstructed defection will be discussed in detail elsewhere.

History and Physical Examination

Evaluation of constipation should always begin with a thorough history (Table 58-3) and physical examination. Information collected should include details regarding stool consistency, caliber, and frequency as well as onset and duration of symptoms. Stool consistency can be described using the Bristol Stool Form Scale (Figure 58-1). A stool diary kept by the patient which details stool form and frequency may provide valuable data for providers. The patient should be questioned regarding dietary intake, fluid consumption, and exercise habits. Patients may note bloating, pain with defecation, and need for significant straining or digital maneuvers to evacuate, which may aid physicians in differentiating between constipation subtypes. Finally, a detailed medical history, including psychiatric illness, and surgical history should be obtained. Patients complaining of constipation have a 20–30 % incidence of physical and sexual abuse and therefore this must also be specifically queried [11]. Medication history, including over-the-counter medications, fibers, laxatives, and enemas, should be noted. Scoring systems and constipation-specific quality of life indices may be helpful in determining severity and effect of constipation (see Chap. 57 for details).

TABLE 58-3. History for patients with constipation

Bowel habit frequency
Stool consistency[a]
Onset and duration of symptoms
Straining during defecation and need for manual maneuvers
Dietary history
Exercise habits
Laxative use
Medication history
Medical history
Physical and sexual abuse history

[a]As depicted in the Bristol Stool Scale, see Figure 58-1

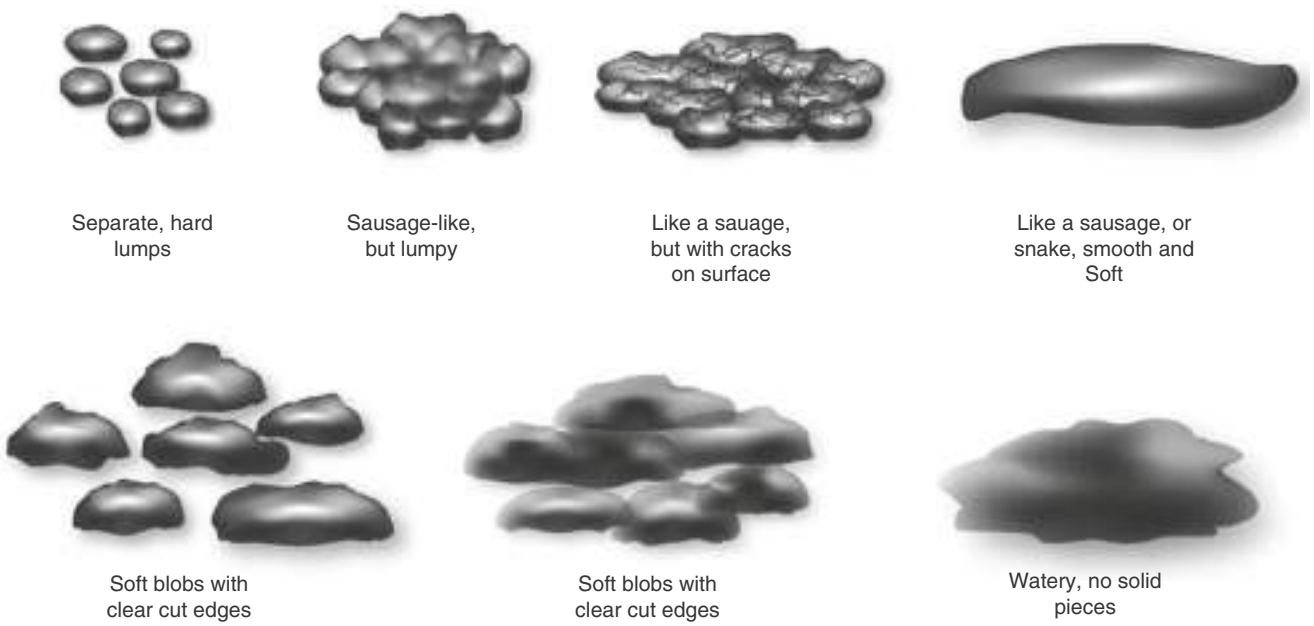

FIGURE 58-1. Bristol stool scale. *With permission from Lewis SJ, Heaton KW. Stool Form Scale as a Useful Guide to Intestinal Transit Time. Scand J Gastroenterol. 1997;32(9):920–924 © Taylor and Francis 1997* [83].

Physical examination, while important, is often unremarkable in patients with constipation. The abdominal examination may be notable for distention. Examination of the pelvic floor should include digital rectal examination and the patient should be asked to contract and relax the sphincter muscles to assess for dyssynergia. The presence of a rectocele should be noted. Anoscopy is used to evaluate the anorectal mucosa for abnormalities. Valsalva should be performed on the commode and the perineum should be studied for perineal descent and prolapse of the rectum, bladder, or uterus.

Diagnostic Testing

Initial laboratory testing for slow transit constipation should include a complete blood count, chemistry panel, calcium level, and thyroid function tests to exclude metabolic abnormalities such as diabetes, hyperparathyroidism, or hypothyroidism. Colonoscopy is appropriate to rule out a mechanical obstruction from malignancy or strictures related to diverticular disease or inflammatory bowel disease. Additional radiologic or functional testing may be beneficial for patients who are not responsive to medical therapy (Figure 58-2). These tests may help to distinguish between constipation subtypes and most commonly include transit studies, anorectal testing, and defecography.

Colonic transit studies provide an estimate of gastrointestinal motility. There are three general ways of assessing transit time: radiopaque markers, scintigraphy, and capsule studies. The most commonly performed transit studies involve radiopaque markers. There are several procedural variations of these studies [12, 13], however, most often they include ingestion of radiopaque markers by the patient and abdominal radiographs taken after 5 days. During the study period, patients are advised not to take laxatives. In normal subjects, at least 80 % of the markers should pass within 5 days; if more than 20 % of the markers are retained in the colon, the transit study is considered abnormal (Figure 58-3). If the markers are distributed throughout the colon, slow transit constipation is suggested. Traditionally, markers distributed mostly in the rectosigmoid colon suggest obstructed defecation, however, this has been challenged by Cowlam et al. who examined 108 patients with functional constipation [14]. Their findings demonstrated that patients with obstructed defecation had no difference in marker distribution as compared to other functional constipation patients, and therefore they could not be diagnosed alone based on markers. Other studies have also questioned the accuracy of interpreting this type of transit study [15].

Colonic scintigraphy involves ingestion of an isotope (indium 111 or technetium 99) in a coated capsule or with a test meal. Gamma camera images are subsequently obtained

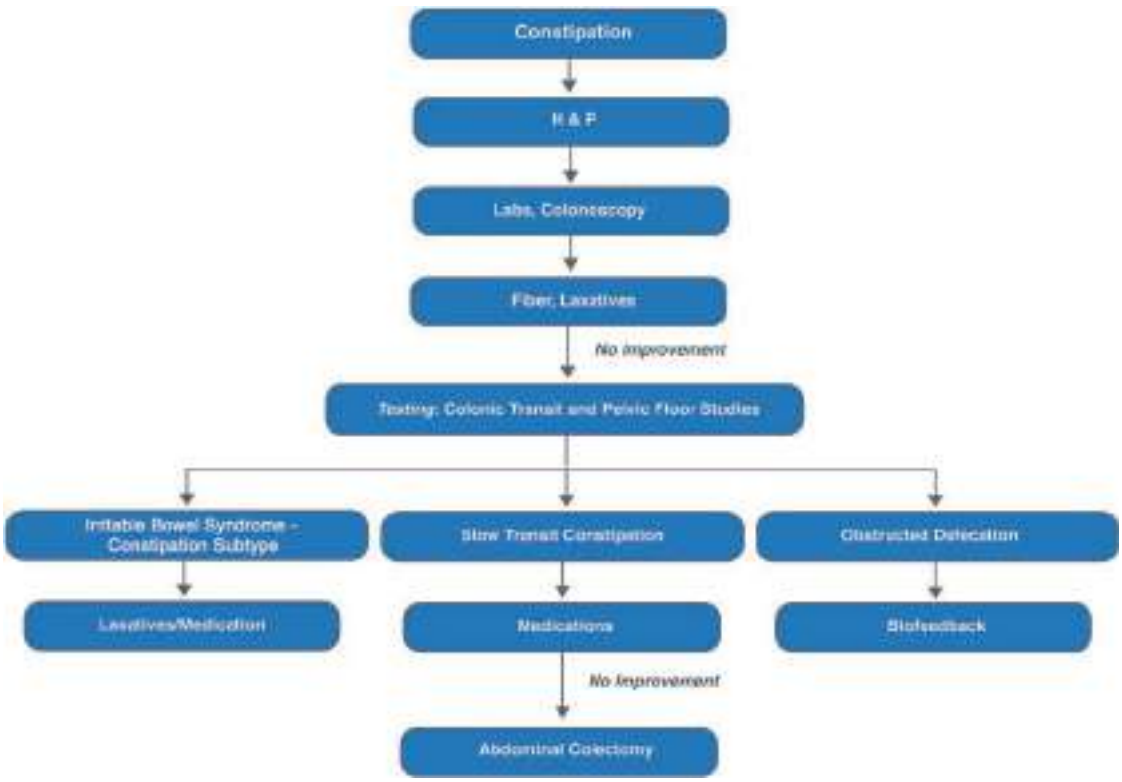

FIGURE 58-2. Workup and treatment schematic for constipation.

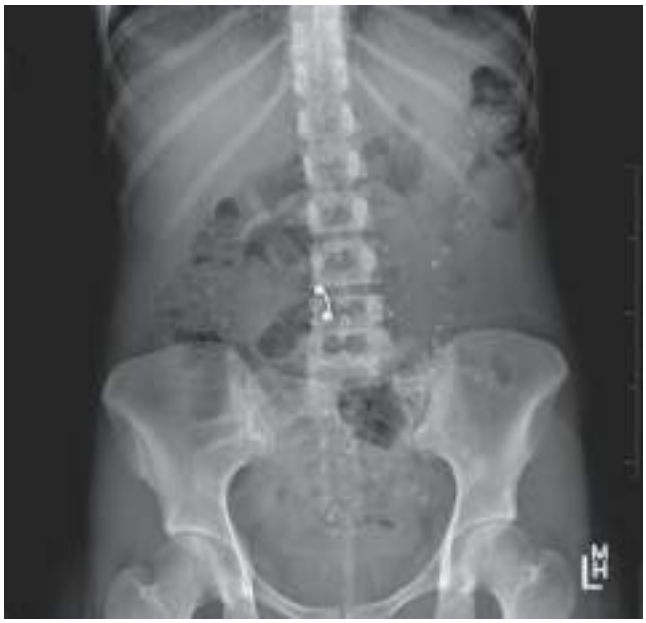

FIGURE 58-3. Radiopaque marker study 5 days following ingestion of the Sitz marker capsule.

and transit times are generated by following the passage of the isotope through the intestinal tract. Eising et al. studied 32 patients with constipation and were able to distinguish between slow transit constipation and obstructed defecation [16]. Scintigraphy studies have been demonstrated to be reliable [17], however, cost and availability limit use.

The wireless motility capsule is a newer technology which allows for measurement of gastric, small bowel, and colonic transit times using pH change and temperature. The capsule has been demonstrated to have good sensitivity and specificity for evaluating colonic transit [18] and when compared to radiopaque markers, an 87 % agreement was demonstrated in differentiating slow versus normal colonic transit [19].

There are several examinations which may be performed to determine anorectal and pelvic floor function. Anal manometry evaluates resting and squeeze pressures in the anorectum and provides information regarding rectal sensation. Anal manometry can diagnose pelvic floor dysfunction, and if the rectal anal inhibitory reflex (RAIR) is present, a diagnosis of Hirschsprung's disease can be excluded [20]. Rectal electromyography may demonstrate non-relaxation of the pelvic floor. Additionally, rectal balloon expulsion provides a simple assessment of ability to evacuate. Failure to evacuate the balloon suggests dyssynergia.

Defecography allows for dynamic study of the rectum and pelvic floor. Contrast is inserted into the rectum and vagina, and fluoroscopy is performed during defecation. It may identify paradoxical contraction of the pelvic floor, internal intussusception, full thickness rectal prolapse, rectocele, or enterocele, which can contribute to obstructed defecation. Dynamic MRI similarly gives an impression of the pelvic floor during defecation of contrast, but is not available in all centers.

Slow Transit Constipation

In slow transit constipation or colonic inertia, there is diminished colonic propulsion resulting in markedly reduced stool frequency. The clinical presentation may be somewhat varied and patients may suffer from abdominal pain, bloating, nausea, and incomplete defecation. A diagnosis of slow transit constipation must be confirmed by transit studies. Once the diagnosis is made, the first step in management is medical treatment.

Medical Management of Slow Transit Constipation

The management of constipation should always begin with appropriate counselling, which includes listening to and validating the patient's complaints. It is important for patients to understand that daily bowel movements are not necessary and that there is a large variation in bowel habits across the normal population. The majority of patients have between 3 and 20 bowel movements per week [21], and men have increased stool frequency compared to women [22]. Minimizing patient anxiety can often go a long way.

Behavioral modifications are usually touted as the first step towards treating constipation and this includes increasing hydration and exercise, as well as dietary and medication changes. Some studies report that constipation is more prevalent in patients with sedentary lifestyles and that physical activity may increase stool transit time [23, 24]. Other studies have reported no such association between constipation and activity levels [25]. Despite this conflicting data, increased physical activity is often recommended for constipated patients; however, there is no direct evidence that exercise improves constipation. Fluid intake is also often encouraged in patients with constipation and is thought to soften stool and make it easier to pass. However, there is minimal evidence to support that increasing oral fluid intake improves constipation, except in dehydrated patients [26]. There are extensive lists of medications which contribute to the development of constipation. These medications should be reviewed and minimized, and alternatives should be considered when appropriate.

There are many medical treatments available for chronic constipation (Table 58-4). These include bulking agents, osmotic laxatives, colonic irritants, softening laxatives, and medications.

Lack of dietary fiber intake may contribute to the development of constipation. Fibers are bulking laxatives considered to be first-line therapy for the treatment of constipation. There have been studies which have demonstrated their benefit [27, 28]. Fiber is found in grains, fruits, vegetables, nuts, seeds, and beans and can be categorized as either soluble or insoluble. Examples of fiber include psyllium (Metamucil®,

Table 58-4. Medical therapy for treatment of slow transit constipation

Medical therapies	Examples
Bulking laxatives	Psyllium
	Methylcellulose
	Calcium polycarbophil
Osmotic laxatives	Lactulose
	Sorbitol
	Magnesium salts
	Polyethylene glycol
Stimulant laxatives	Senna
	Cascara
	Bisacodyl
Softening laxatives	Mineral oil
	Docusate
	Glycerine
Serotonin receptor agonists	Tegaserod
	Prucalopride
Prosecretory agents	Lubiprostone
	Linaclotide

Konsyl®), methylcellulose (Citrucel®), and calcium polycarbophil (Fibercon®). They soften and increase the size of the stool bolus by absorbing and retaining fluid with the stool. Therefore, fiber must be ingested with sufficient amounts of fluid to reach efficacy. Recommended daily fiber intake is between 25 and 35 grams. Side effects of fiber consumption include abdominal bloating and flatulence.

Osmotic laxatives promote accumulation of large volumes of fluid in the colon lumen by osmosis. The osmotically active particles can be derived from sugars or salts such as sucrose-based sorbitol and lactulose. Lactulose is degraded in the colon yielding the production of fatty acids, hydrogen, and carbon dioxide. MiraLAX® (polyethylene glycol 3350) is an over-the-counter osmotic laxative that increases the frequency of bowel moments and softens the stool. It is one of the most commonly recommended laxatives, found to be safe and effective for everyday use. Osmotic laxatives can also be based on nonabsorbable ions, commonly derived from magnesium or phosphate. Examples are magnesium hydroxide (Milk of Magnesia®) or sodium phosphate (Fleets® Phosphosoda). Caution must be exercised in patients with renal insufficiency as hypermagnesemia and renal failure can result. Polyethylene glycol-based products such as NuLYTELY or GoLYTELY are used in many bowel cleansing regimens but can also be used for constipation. However, chronic use can lead to electrolyte disturbances and dehydration.

Colonic irritants stimulate colonic motility, thereby diminishing constipation. Examples are anthracene derivatives, which include senna and cascara and are found in Senekot® and Pericolace®. Bisacodyl is another irritant and can be found in the agent Dulcolax®. Long-term use can generate a characteristic brown discoloration of the mucosa called melanosis coli. Additionally, sustained use of anthracene irritants may lead to poor colon function and therefore, such use is discouraged.

Softening laxatives change the stool composition, creating softer stools and they include mineral oil and docusate (Colace®). Mineral oil coats the stool, creating an emulsion. Docusate is a detergent which allows increased absorption of fluid into the stool bolus and there is conflicting data regarding its efficacy [29].

Enemas and suppositories are used to stimulate bowel movements. Strategies include promotion of defecation through rectal distension (saline enema), rectal irritation (soapsuds, bisacodyl), or physical softening of the stool (glycerine). Enema therapy can be habituating and therefore providers should be mindful of this potential dependency.

There are several medications which have been used to treat slow transit constipation. Lubiprostone (Amitiza®) is a bicyclic functional fatty acid which activates chloride channels to increase intestinal chloride secretion. This facilitates stool transit and has been demonstrated to be beneficial in the treatment of constipation [30, 31]. Common side effects include nausea, headaches, and diarrhea. Linaclotide (Linzess®) in a peptide agonist of guanylate cyclase which increases colonic smooth muscle cell contraction and promotes bowel movements. Studies have shown improvement in constipation over placebo [32, 33]. Both lubiprostone and linaclotide are approved for the treatment of slow transit constipation and constipation predominant-irritable bowel syndrome in the USA.

In patients taking opioid medications, methylnaltrexone and alvimopan can increase motility [34–37]. However this benefit does not seem to extend to patients with idiopathic constipation. Tegaserod, a 5-HT_4 receptor agonist, was initially introduced for the treatment of irritable bowel syndrome and subsequently extended for the treatment of slow transit constipation. It was later removed from the market because of findings that the drug was associated with increased risk of cardiovascular disease. To avoid these deleterious effects, a more selective 5-HT_4 agonist, prucalopride, has been developed. While prucalopride has been shown to increase number of bowel movements, it is not currently approved for use in the USA [38, 39].

Surgical Therapy of Slow Transit Constipation

Surgical therapy for constipation should only be considered after nonsurgical therapy has been completely exhausted. A thorough diagnostic workup, including transit studies confirming slow transit constipation, is important in order to select the appropriate operative treatment and to aid in preoperative counselling regarding outcome. In patients diagnosed with generalized intestinal dysmotility including both upper and lower gastrointestinal tracts, the incidence of recurrent constipation has been shown to be much higher than in patients with colonic inertia alone [40]. Given that constipation is a functional disorder, it is extremely impor-

tant to set patient expectations regarding outcomes and possible postoperative issues.

Abdominal Colectomy

In patients with constipation for whom surgical management is indicated, abdominal colectomy is usually the treatment of choice. Lane first reported this idea in 1908 when he published his series describing resolution of constipation symptoms in two-thirds of patients. The surgical procedure remains essentially unchanged since its initial description, although minimally invasive techniques have been successfully applied to this procedure [41, 42] and are commonly performed.

Webster et al. reported results in 50 patients who underwent total abdominal colectomy [43]. In the immediate postoperative period, 42 % of patients experienced complications, most commonly ileus. Anastomotic leak occurred in 4 %. Five patients had persistent constipation. At 12-month follow-up, patients averaged 3 stools per day and the most common complaint was abdominal pain in 19 % of patients. The majority of patients rated their results as "good" or "excellent." Regarding long-term follow-up, Pikarsky et al. reported results in 50 patients who underwent total abdominal colectomy at a median follow up of 106 months (range 61–122 months) [44]. Data was gathered via telephone interviews and the average frequency of bowel movements was 2.5 (range 1–6). Two patients required enemas/laxatives and two patients required antidiarrheal medications. Six patients had small bowel obstructions postoperatively, three of whom required laparotomy. Overall, patients were satisfied with their bowel function and had sustained benefit.

Variations of the procedure include subtotal colectomy with ileosigmoid anastomosis and subtotal colectomy with cecorectal anastomosis. These variations have been developed to reduce unwanted side effects of diarrhea and electrolyte abnormalities following total abdominal colectomy. Cecorectal anastomosis was suggested by Sarli et al. in an effort to leave a physiologic reservoir for colonic bacteria and thereby maintain normal postoperative stool consistency [45]. They reported their results in 19 patients at a median follow up of 64 months. Thirteen patients reported solid stool consistency, one reported constipation, and five reported diarrhea with the need to take antidiarrheals. In a follow up study of the same cohort of patients, 88.2 % reported that they would undergo surgery again given the same preoperative conditions [46]. In an effort to compare functional outcomes between ileosigmoid and cecorectal anastomoses, Feng et al. compared 79 patients who underwent ileosigmoid or cecorectal anastomosis at a mean follow up of 2 years [47]. Defecation frequency increased and abdominal pain and bloating diminished in both groups. However, more patients in the cecorectal group complained of persistent constipation, and overall ileosigmoid anastomosis led to higher patient satisfaction.

In 1999, Knowles et al. reviewed 32 series, which included ten or more patients treated for constipation with colectomy. There was a great deal of variation between the publications regarding data collection, preoperative workup, and surgical technique [48]. However, the overall success rate ranged from 39 to 100 %, with median reported to be 86 %. The median number of daily bowel movements was 2.9 (range 1.3–5) and the median frequency of incontinence was 14 % (range 0–52 %). The frequency of recurrent constipation was 9 % (range 0–33 %). Persistent abdominal pain was present in 41 % of patients. Additionally, because of poor functional outcomes, 5 % (range 0–28 %) of patients eventually underwent permanent ileostomy creation.

Given that constipation is a functional disorder, quality of life studies are extremely important in understanding patient outcomes. Hassan et al. evaluated 110 patients who underwent total abdominal colectomy with ileorectal anastomosis at a median follow up of 11 years. Prospectively collected annual functional surveys were available for 85 patients and demonstrated that 98 % of patients had improvement in constipation and 85 % were satisfied with their outcome. Additional quality of life questionnaires were completed by 59 respondents demonstrating that all reported their constipation improved, 83 % did not require any antidiarrheal agents and 85 % were satisfied with their bowel function.

FitzHarris et al. similarly sent quality of life questionnaires to 112 patients who previously underwent total abdominal colectomy with ileorectal anastomosis for constipation and had a 67 % response rate [49]. Of those, 81 % of patients were pleased with their frequency of stools. However 41 % reported abdominal pain, 21 % reported fecal incontinence, and 46 % had some diarrhea, and these symptoms negatively impacted quality of life scores. In a smaller study, Thaler et al. surveyed patients using the SF-36 Health Survey and found that while all patients had relief of constipation, patients had significantly lower quality of life scores compared with the general population [50]. More recently, Zutshi et al. surveyed 69 patients who underwent colectomy with ileorectal anastomosis at a median follow up of 10.8 years. Of the 35 respondents, 77 % reported that surgery was beneficial, but results of the SF-36 demonstrated low mental and social functioning scores [51]. These data must be considered when counselling patients and setting appropriate postoperative expectations.

There are special circumstances which should be noted. In some patients, concomitant pelvic floor dysfunction may be present. This may be diagnosed with defecography, electromyography, and anorectal manometry. Bernini et al. studied 16 patients with slow transit constipation and pelvic floor dysfunction who underwent a colectomy by distributing questionnaires [52]. Preoperatively, all patients underwent biofeedback, which resulted in pelvic floor relaxation confirmed by electromyography. Postoperatively 43 % of patients had complete resolution of constipation symptoms, six patients complained of incomplete evacuation, and three patients complained of diarrhea and incontinence. Only nine

patients were satisfied with the surgical outcome. More recently, Reshef et al. compared 144 patients who underwent colectomy for slow transit constipation with and without obstructed defecation [53]. At a median follow up of 43 months, 88 patients were available for phone interview. Short- and long-term outcomes were found to be equivalent between groups as was patient satisfaction. They concluded that total abdominal colectomy can be offered to patients with slow transit constipation with concomitant obstructed defecation.

Another group of patients that deserves mention are patients with associated small bowel and gastric dysmotility, or global dysmotility. Zmora et al. reviewed patients who underwent total abdominal colectomy and had preoperative small bowel transit studies [54]. There was no difference in postoperative function between patients that have normal and abnormal transit studies. Mollen et al. found similar results in a study of 21 patients [55]. However, Glia et al. studied 17 patients and found a trend towards better long-term results following colectomy in patients with normal preoperative antroduodenal manometry [56]. While these results are not definitive, preoperative functional evaluation for global dysmotility is still recommended. If concomitant delayed gastric or small bowel motility is determined, colectomy is not absolutely contraindicated; however, patients should be warned that they may have persistent postoperative abdominal symptoms.

Finally, patients with a history of sexual trauma have been shown to require more medical care for abdominal complaints following colectomy for constipation [57]. For this subset of patients, preoperative preparation should include evaluation and treatment of psychosocial/psychiatric issues as well as pelvic floor dysfunction and a discussion of possible postoperative abdominal symptoms.

Segmental Colectomy

In an effort to reduce the diarrhea associated with abdominal colectomy, some surgeons have advocated the use of segmental colectomy for the treatment of slow transit constipation. In some published reports, segmental colectomy has resulted in improvement of constipation [58, 59]. You et al. reported a group of 28 patients who underwent segmental colectomy based on the distribution of markers in the colon, of which three patients experienced recurrent constipation [60]. Similarly, Lundin et al. performed segmental resections on 28 patients studied preoperatively with radiopaque markers and scintigraphy and found to have impaired transit in one segment [61]. After a median follow up of 50 months, 23 patients were satisfied with the outcome, whereas five patients required additional surgery for constipation. Rectal sensation, based on preoperative manovolumetry, was diminished in patients who experienced treatment failure. Similar findings were demonstrated more recently by Ripetti et al., in 15 patients with slow transit constipation, seven underwent left-sided colectomy while the rest underwent total colectomy [62]. All but one patient in the segmental colectomy group had symptom improvement. In each of these studies, patients underwent careful and extensive evaluation prior to surgery and it must be reemphasized that evaluation by radiopaque markers may not be exact.

Proctocolectomy with Ileal Pouch Anal Anastomosis

Proctocolectomy with ileoanal pouch (IPAA) reconstruction has been described for slow transit constipation. Keighley et al. performed IPAA in patients who previously underwent total colectomy with ileorectal anastomosis and had recurrent difficulty with defecation [63]. Four of these patients subsequently underwent excision of their pouches because of dissatisfaction with functional results. The authors no longer recommend IPAA for slow transit constipation. Another group performed proctocolectomy with IPAA for 15 patients having less than one bowel movement per week with slow transit constipation and rectal inertia [64]. Preoperative workup in these patients demonstrated abnormal transit studies and abnormal defecography, specifically megarectum or rectal dysmotility. Two patients subsequently underwent pouch excision for intractable pelvic pain. At follow up, patients had a mean stool frequency of 5 per day and reported significant improvement in quality of life scores following surgery. Overall, this is a small and well-selected group of patients and proctocolectomy should be chosen carefully if being considered for slow transit constipation. Additionally, before considering pouch creation for constipation, pelvic floor relaxation should be studied and confirmed otherwise patients may have continued difficulty with defecation.

Ileostomy Creation

Fecal diversion for the treatment of slow transit constipation tends to be reserved for those patients who fail other surgical management. In a review of patients who underwent surgical intervention for constipation, 2–25 % of patients who underwent other surgical management went on to have end ileostomies [65]. Additionally, for those who may not tolerate colon resection, who have concomitant fecal incontinence or in whom it is uncertain as to whether the patient will benefit from colon resection, creation of a loop ileostomy may be an appropriate alternative. Loop ileostomy is relatively simple to reverse should the patient not derive the anticipated benefit. Scarpa et al. retrospectively reviewed outcomes in 24 patients with ileostomies created for constipation: 9 end ileostomies and 16 loop ileostomies [66]. One patient had persistent constipation after stoma creation with bloating and

infrequent output. Four patients underwent ileostomy closure, two of whom had recurrent constipation. Patients undergoing ileostomy creation should be warned that they may have persistent symptoms, especially if global intestinal motility is suspected. While it may seem to be an extreme measure, ileostomy creation is beneficial in some patients.

Antegrade Colonic Enema

The concept of the antegrade colonic enema (ACE) is to washout the colon via enemas delivered to the cecum. The concept was first described by Malone et al. for the treatment of fecal incontinence in children, and later the indications were extended to include intractable constipation. In the original technique, the appendix is reversed and a non-refluxing, catheterizable appendicocecostomy is created, through which the enemas are delivered [67]. There have since been many modifications to this procedure, including utilizing the appendix in situ, stoma creation using the ileum and/or cecum, permanent catheter implantation, and left colon placement [68–70].

While originally described in children, this procedure is increasingly used in the adult patients although the reported success rates are inferior [71–73]. This procedure is less invasive than colectomy and there is avoidance of an ileostomy or colostomy. Lees et al. reported that in 32 patients who underwent the ACE procedure for constipation, satisfactory function was achieved in 47 % at a mean follow up of 36 months [74]. Similarly, Worsoe et al. reported results in 69 patients who underwent ACE for constipation. Patients were surveyed regarding continued use of ACE and symptom resolution and 42 % reported success at a median follow up of 75 months [75]. Revisions of the stoma are common, and most often required for stenosis or leakage. Using an indwelling catheter reduces stenosis, but wound infection and long-term catheter dislodgement are common [70].

Sacral Nerve Stimulation

Sacral nerve stimulation is most widely utilized for the treatment of urinary and fecal incontinence. This therapy involves electrical stimulation of the sacral nerve roots. Patients undergo a test phase to determine if there is a therapeutic benefit and if so, the permanent device is implanted. Sacral nerve stimulation has been shown to increase bowel frequency, improve defecation, and reduce laxative use [76, 77]. While the exact mechanism which improves constipation is unknown, sacral nerve stimulation has been shown to increase colonic propagating sequences [78]. The largest series reported by Govaert et al. included 117 patients with constipation, of which 75 had slow transit constipation diagnosed by a transit study. All underwent percutaneous nerve evaluation (PNE), of which 52 % responded to therapy during the initial test period [79]. The success rate of PNE was lower in patients with slow transit constipation versus patients with normal transit constipation. A prospective European study was conducted in 62 patients with constipation. Transit studies were available for 27 patients prior to implantation and 20 patients had prolonged transit. At 6 months following sacral nerve stimulation, only nine patients had prolonged transit ($p=0.014$). In subjects with normalized transit times, defecation frequency increased from a median weekly stool frequency of 2.7–6.5 at 6 months [80]. Studies by Ortiz et al. [81] and Graf et al. [82] reported much lower success rated for sacral nerve stimulation in constipated patients. Further long-term studies and detailed evaluation of patient selection are indicated. At present, sacral nerve stimulation is not approved in the USA for use in patients with constipation.

Conclusion

Constipation can range in presentation from minor annoyance to a significant disruption of daily life. Initial management should include behavioral modification, fiber supplementation, or laxatives. In patients requiring additional therapy, differentiating between constipation subtypes is necessary and can be accomplished by a good history, transit studies, and pelvic floor testing. For patients with slow transit constipation who do not respond to medical management, surgical intervention may be appropriate. Care of the constipated patient requires patience, compassion, and the ability to tailor treatments to the individual.

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59
Obstructed Defecation

M. Shane McNevin

Key Concepts

- Obstructed defecation syndrome is characterized by excessive straining at stool, incomplete rectal evacuation, and perineal splinting.
- The primary treatment for patients with obstructed defecation is dietary management and pelvic floor physical therapy.
- The primary treatment of patients with overt pelvic prolapse and obstructed defecation is surgical repair of the prolapse.
- Symptoms of obstructed defecation are not as reliably relieved as overt prolapse by surgical repair.
- Ventral mesh rectopexy or stapled transanal rectal resection are alternative surgical procedures which may more reliably relieve obstructed defecation symptoms.
- Sacral nerve stimulation may be an alternative for patients with rectal hyposensitivity and obstructed defecation failing non-operative management

Introduction

Pelvic floor disorders are a frequent source of morbidity in the developed world [1]. This is a much more common problem for women and almost one quarter of women in the USA will complain of at least one pelvic floor disorder in their lifetime. The incidence increases with age, parity, and obesity. Demand for pelvic floor services is expected to grow at twice the population rate in the future [2–4]. Suffice it to say that all of the medical specialties will frequently manage patients with pelvic floor complaints however colorectal surgeons will assume a disproportionate share of the diagnosis and management of patients with persistent or refractory symptoms of pelvic floor dysfunction.

Pelvic floor disorders typically present with overt pelvic organ prolapse and/or functional disorders of bowel or bladder evacuation. In the USA, 16 % and 9 % of women, respectively, will experience bladder or bowel incontinence. Pelvic organ prolapse affects 3 % of women [2]. Approximately 12–27 % of adults will seek care for constipation related complaints in their lifetime and over $1 billion is spent annually on constipation related goods and services [5]. Typically, constipation in association with pelvic floor disorders is manifested as obstructed defecation. Obstructed defecation syndrome is a well-defined symptom complex consisting of excessive straining at stool, need for perineal splinting, and incomplete rectal evacuation [6–8]. Not uncommonly, different manifestations of constipation co-exist, hence, global hindgut and pelvic evaluation is required for those treating this complicated group of patients [9–12].

This chapter will focus on disordered bowel evacuation in general and specifically on obstructed defecation syndrome. A review will be undertaken of the clinicopathologic features and clinical evaluation of the disorder, its frequent association with other manifestations of pelvic floor dysfunction and the outcomes of medical and surgical therapy for the disorder.

Etiology of Constipation

Lower gastrointestinal function involves the formation of stool, its transit through the hindgut and its subsequent expulsion from the body. As anyone involved in the care of the constipated patient knows, this is a complex and coordinated process and failure at any of the various points in the algorithm will result in constipation related complaints.

Unfortunately, constipated patients rarely present with a defined etiology of their constipation but instead will use various adjectives to describe their clinical situation. It is important that the patient be given the opportunity to clearly describe their symptom complex in their own words as our descriptors for defecatory dysfunction typically have different meanings for different people. Typically, symptom complexes are unique and dependent upon where in the process of

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TABLE 59-1. Etiology of constipation

Lifestyle
Inadequate fluid/fiber intake
Sedentary
Iatrogenic
Narcotics
Psychotropics/antidepressants
Antihypertensive/diuretics
Chronic laxative abuse
Medical conditions
Psychiatric disorders
Neurologic injury/degeneration
Hypothyroidism
Hyperparathyroidism
Diabetes mellitus
Renal insufficiency
Intrinsic colonic dysfunction
Benign/malignant obstruction
Hirschsprung's disease
Scleroderma
Functional bowel disorders
Colonic inertia
Irritable bowel syndrome, constipation predominant
Pelvic floor dysfunction

hindgut function failure occurs. Hence, a good and detailed history of the complaints and physical examination is frequently diagnostic and drives further testing and treatment options.

A wealth of different factors may affect lower gastrointestinal function (Table 59-1) and give rise to symptoms of constipation. A detailed history focuses on onset and duration of symptoms, stool frequency and consistency, dietary fiber and fluid intake, and associated medical and surgical history and medication usage. A history of physical, sexual or psychologic abuse, or dysfunction is not infrequently associated with constipation related complaints and should be explored [13, 14]. A bowel diary can be particularly helpful to objectify the patient's complaints if not clear based upon their subjective description. Physical examination should focus on abdominal findings such as distension, pain, or mass lesion. Anorectal and pelvic examination should focus on normal anorectal and genital anatomy and evidence of occult or overt pelvic prolapse. Patients should undergo endoscopic evaluation of the lower gastrointestinal tract as a matter of routine when evaluating new complaints centered on a change in bowel habits.

Functional Bowel Disorders

Over half of patients referred for specialty evaluation and care have functional bowel disorders [15]. The three main types are colonic inertia (slow transit constipation), constipation predominate irritable bowel syndrome (normal transit constipation), and obstructed defecation syndrome. Historical symptom description is usually diagnostic. Differentiation of the disorders or in patients exhibiting features of more than one etiology can be further evaluated with colon transit study (Sitz mark study; Figure 59-1) and pelvic floor testing [13].

Colonic inertia or slow transit constipation is characterized by infrequent (<1/week) bowel movements and cathartic dependence. Typically, patients will also describe significant symptoms of nausea, bloating, and fullness that do not necessarily improve with defecation. Many patients will deny the feeling of rectal fullness and need to stool. The diagnosis is established with colon transit study revealing elevated segmental and global colonic transit.

Constipation predominate irritable bowel syndrome or normal transit constipation is defined by the Rome criteria listed in Table 59-2. Most patients will have irregular bowel movements both in terms of consistency and frequency. Abdominal pain is a frequent co-morbid complaint that frequently improves with bowel evacuation. Colon transit evaluation frequently reveals normal segmental and global transit times.

Obstructed defecation is defined in Table 59-3. Typically it is characterized by the constant sense of rectal fullness and

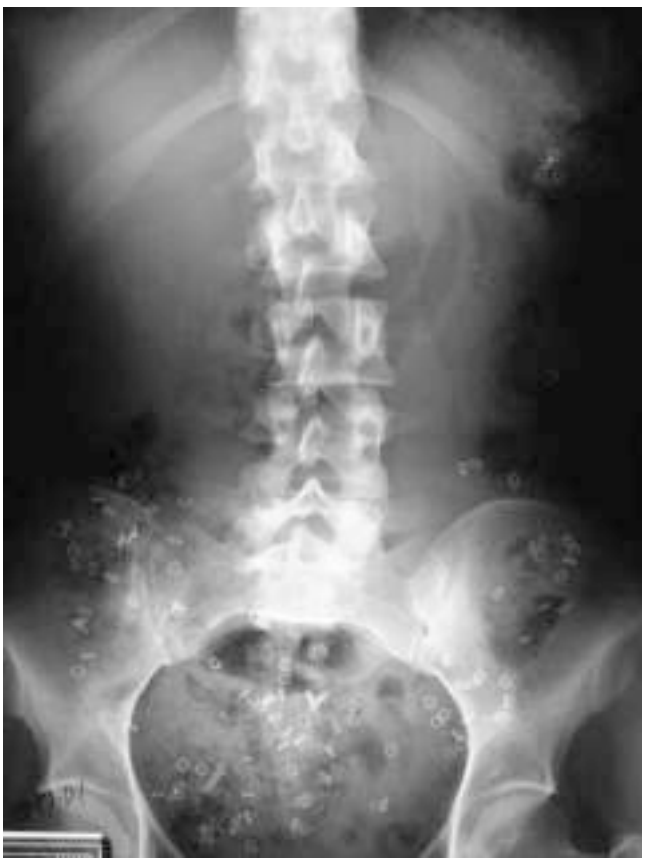

FIGURE 59-1. Sitz mark study. The radiograph demonstrates Sitz markers scattered throughout the abdomen and pelvis.

Table 59-2. Rome III criteria

Abdominal pain associated with
Improved with defecation
Change in stool frequency
Change in stool consistency
Altered stool frequency of consistency
Altered stool passage
Subjective bloating or distension

Table 59-3. Obstructed defecation syndrome criteria

Any of the following >25 % of the time
Painful, excessive straining
Incomplete or fragmented evacuation
Perineal splinting

painful excessive straining at stool. Patients also describe a sense of incomplete evacuation and fragmented bowel habits. Patients will often manually support or compress the perineum (splinting) during defecation. Patients also tend to defecate frequently, unlike the other functional disorders, and their symptoms tend to be relatively refractory to cathartic therapy. Fecal pseudo incontinence is also a frequent complaint due to the inability to completely evacuate the rectum. Colon transit study typically reveals elevated global transit times with delay only in the recto sigmoid region.

Defecation Mechanics

The act of rectal evacuation is a complex and coordinated action requiring the interplay of several anatomic and functional factors for successful completion (Figure 59-2). Rectal filling with stool induces distension of the rectum and the sense of need to evacuate. The rectal contents are sampled by transiently relaxing the internal sphincter and contracting the external sphincter, the so-called recto-anal inhibitory reflex, allowing discrimination of rectal contents. When answering the call to stool we assume a sitting or squatting position, which increases the intra-rectal and intra-abdominal pressure. We then relax the levator ani, specifically the puborectalis muscle, and anal sphincter complex and defecation ensues.

Any disturbance in this process be it pelvic floor anatomic abnormalities, disorders of anorectal sensation, and/or discoordinated pelvic floor musculature will result in symptoms that we associate with obstructed defecation syndrome.

Evaluation of Obstructed Defecation

Endoscopy

Obstructed defecation syndrome can be mimicked by many intrinsic obstructive disorders of the anorectum and pelvis, hence, a careful physical examination and endoscopic examination of the anorectum is imperative. Cross sectional imaging can be valuable in cases where extra-luminal obstructive pathology is suspected.

Colon Transit Study

Colon transit study is helpful in differentiating types of functional constipation when the history is unclear or disorders co-exist [13]. The study involves ingestion of radio-opaque markers followed by a series of radiographs over several days documenting the transit time through the hindgut. This is performed while withholding cathartics and pro-motility agents. The most objective interpretation is the Metcalf technique that quantifies the total and segmental transit times through the right, left, and rectosigmoid colon, respectively. Unfortunately, the technique is not standardized and difficult to reproduce across pelvic floor centers [16].

Balloon Expulsion Study

The balloon expulsion study can be a useful adjunct to the other testing modalities to evaluate obstructed defecation. It involves the placement of a fluid filled balloon within the rectum and then the timed expulsion of the balloon from the rectal vault. Chiaroni et al. found that an expulsion time in excess of 2 min revealed good correlation of findings from anorectal manometry and electromyography in constipated patients [17].

Anorectal Manometry

Anorectal manometry is helpful in evaluating the patient with obstructed defecation (Figure 59-3). The most important information gleaned is the rectal sensory thresholds depicted by the first sensation of rectal fullness, the urge to defecate, and the maximal tolerable volume, which may denote rectal hyposensitivity. Additional information obtained is the presence of the recto-anal inhibitory reflex denoting appropriate anorectal innervation, excluding the diagnosis of short segment Hirschsprung's disease, and mean resting and squeeze pressures which may be associated with non-relaxation of the pelvic floor [18, 19].

Anorectal Electromyography

Anorectal electromyography is primarily useful for the evaluation of patients with obstructed defecation. It senses electrical activity in the pelvic floor musculature during rest, squeeze, and push, and can be useful to identify patients with paradoxic contraction of the puborectalis. Patients with abnormal electromyography should undergo confirmatory testing with dynamic defecography [18, 19].

Defecation mechanics

Rectal filling/distension → rectoanal inhibitory reflex →defecation response →

sit/squat increasing intra-rectal and abdominal pressure→ levator ani relaxation →

strain → increased intra-rectal/abdominal pressure →defecation

FIGURE 59-2. Defecation mechanics.

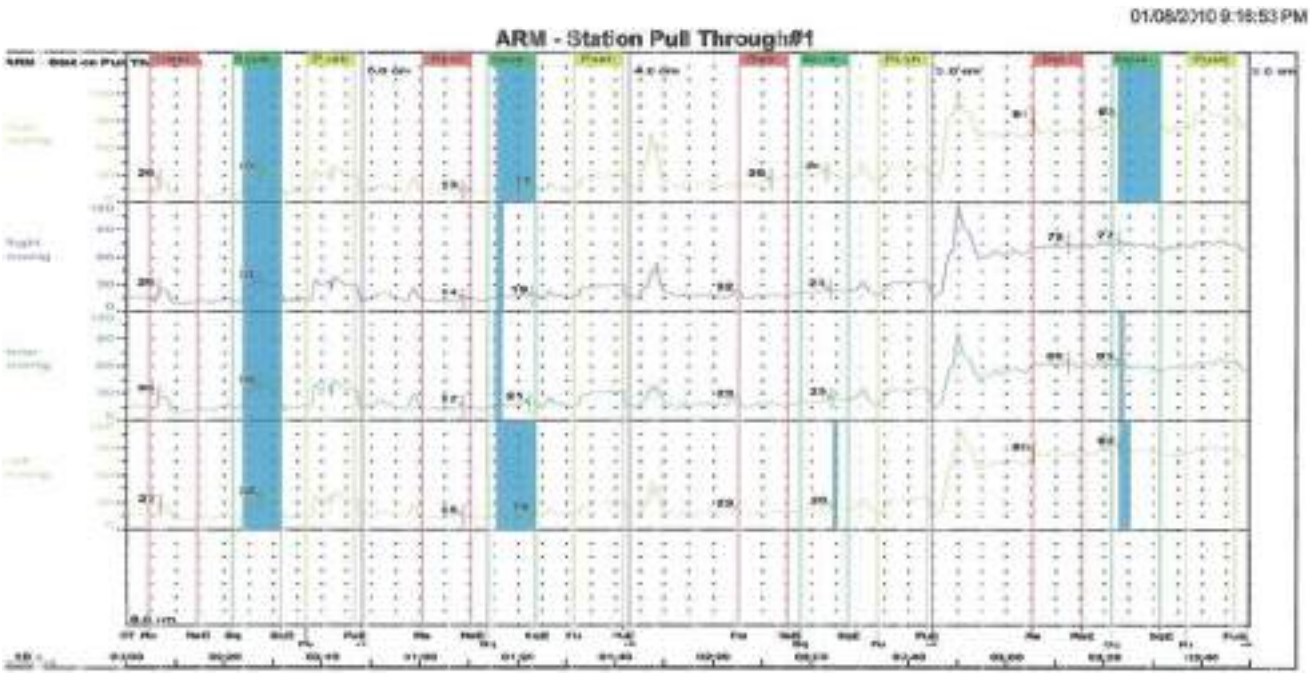

FIGURE 59-3. Sample of an anorectal manometry.

Defecography

Defecography is a particularly useful technique for the precise evaluation of the functional anatomy of the pelvic floor [13, 15, 20]. Defecography is performed with patient in the squatting position using a lateral fluoroscopic view as the patient expels a barium paste from the rectum (Figure 59-4). Further anatomic definition can be obtained by having the patient ingest oral contrast to opacify the small bowel, placement of contrast material within the vagina and bladder, and injection of water-soluble contrast material into the peritoneal cavity.

Magnetic resonance defecography and 3D ultrasonography have also been described as alternatives to traditional fluoroscopic defecography that obviates the need for radiation exposure and may improve the anatomic detail of the images obtained although quality comparative studies of the techniques are lacking [21–26].

Interpretation of Test Results

No one pelvic floor test is entirely diagnostic of pelvic floor dysfunction and a high degree of variability of test results both in terms of anatomy and function in symptomatic and healthy asymptomatic patients can be seen. This makes interpretation of results of pelvic floor tests challenging and determination of abnormal test results need to be made in conjunction with the history and physical examination findings of each particular patient [27, 28].

Etiology and Treatment of Obstructed Defecation

In evaluating and treating the patient with obstructed defecation multiple different and often co-existent etiologies and multiple different and often co-existent symptom complexes are present. Patients will also often present with significant existential anxiety regarding their symptoms. The most important first step is patient and careful listening and acknowledgment of the patient's symptoms and validation of the impact that these symptoms have on the patient's quality of life. Reassurance that, while the symptoms are quite obtrusive and debilitating, there is no significant underlying health or life threat, will allay many of the patient's fears. Keeping that in mind also informs treatment decisions. Our goal in treating these problems should be to provide as much

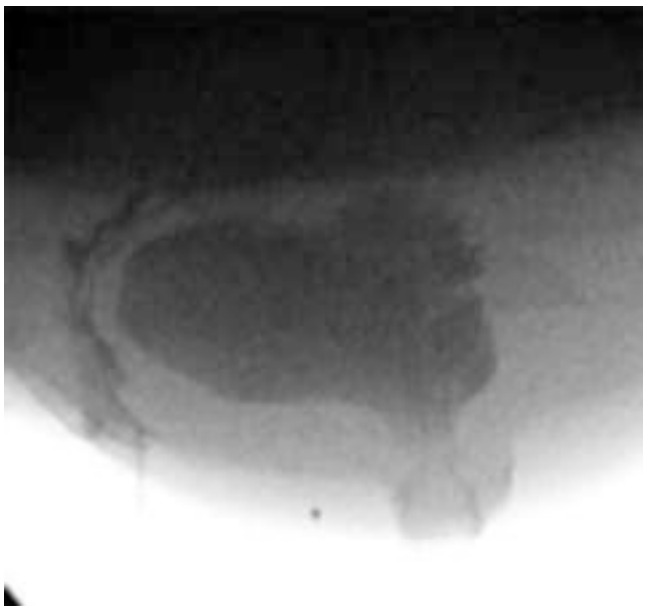

FIGURE 59-4. Defecography. This defecography demonstrates a large rectocele.

symptom relief as possible while exposing the patient to the least amount of risk and secondary treatment related side effects as possible.

With that in mind obstructed defecation as an isolated condition is primarily treated non-operatively. Traditional approaches have been to insure adequate hydration and fiber intake, modest daily physical activity, and pelvic floor physical therapy retraining [29–32].

Hydration/Lifestyle Modification

Recommended goals for daily hydration are 1–2 L/day of non-caffeinated fluids. This is typically in combination with increased fiber intake and daily exercise. As a stand-alone therapy, not surprisingly, increased hydration alone does not result in a change in bowel consistency or frequency [33]. Modest daily exercise has been shown to stimulate colonic motility and increase bowel frequency [34].

Fiber Intake

Recommended dietary fiber goals are 30–40 g/day of either soluble or insoluble fiber. Better outcomes are associated with increased hydration (>2 L/day). Quality studies documenting the efficacy of this approach are lacking and its use is primarily supported by small case series [35, 36]. Cathartic therapy, either stimulant or osmotic in nature, while important for certain etiologies of constipation is typically ineffective in management of obstructed defecation [37].

Pelvic Floor Physical Therapy Retraining

Pelvic floor physical therapy retraining is an essential component of comprehensive pelvic floor management. It is a more apt term to describe the comprehensive and complex bowel, bladder and pelvic floor treatment than the traditional term biofeedback. Biofeedback alone uses operant conditioning to reinforce positive behavior, thereby retraining the pelvic floor to optimize function. While widely used, techniques are not standardized and optimum techniques, frequency of encounters, and duration of therapy are unknown [38]. In many cases, a several week cycle (4–6 weeks with transition to a home program) of multiple pelvic floor exercises combined with a transanal probe (either electromyography or intra-rectal pressure monitor) displaying visual feedback to monitor pelvic floor activity during the squeeze-relax-push cycle is used. Pelvic floor physical therapy retraining uses, in addition to biofeedback, patient education on appropriate dietary management, proper defecation mechanics, and psychologic support of the patient as they learn techniques to manage their symptoms. The treatment sessions are typically performed by nurses or physical therapists with advanced training and interest in pelvic floor disorders. Outcomes can be very dependent on the affect and patience of the therapist and patient acceptance of this technique. Several studies in the last decade have demonstrated a therapeutic effect in patients with obstructed defecation [39–42]. Despite the lack of reproducible standardized techniques, it is a relatively inexpensive treatment option that has no treatment related risks or side effects satisfying our goals of obstructed defecation syndrome treatment.

Pelvic Organ Prolapse

Patients with pelvic organ prolapse present with prolapse symptoms, which is a sense of rectal or vaginal tissue protrusion, and/or functional obstruction of the rectum. Patients with isolated prolapse symptoms are usually reliably and durably improved with repair. It is important to keep in mind, however, that response of the functional rectal obstruction to repair of the anatomic prolapse is not as reliable, hence, it is important that surgeons and patients understand this and that their expectations for improvement are realistic [43, 44].

Rectal Prolapse: Overt

Patients with rectal procidentia typically present with rectal tissue protrusion with Valsalva or gravity that spontaneously reduces or requires manual reduction. Patients also frequently describe a mucous discharge and frequent bleeding, fecal incontinence, and obstructed defecation. Repair can be accomplished with either a trans-abdominal or perineal approach dependent upon patient age, medical co-morbidities,

prior surgery, body habitus, and performance status. Perineal procedures may be undertaken due to inability to tolerate an abdominal procedure at the cost of functional outcome and recurrence risk [45].

Abdominal rectopexy traditionally has been performed in healthy patients with good performance status. Laparoscopy and robotic technology have extended the indication in the elderly/frail population [46]. The procedure is conducted with posterior rectal mobilization and mesorectal fixation to the presacral fascia with or without mesh augmentation. A prominent side effect of this approach is persistence or worsening of obstructed defecation [47]. Sigmoid resection and preservation of the lateral rectal stalks have been associated with decreased postoperative obstructed defecation at the cost of increased surgical risk and elevated prolapse recurrence, respectively.

A newer alternative to posterior rectopexy is ventral mesh rectopexy [48]. This involves the anterior rectal mobilization and mesh fixation of the anterior rectum to the presacral fascia. Durable repair of the prolapse with this technique has been demonstrated and interestingly a lower incidence of persistent postoperative obstructed defecation is seen. This is also being explored as a treatment for obstructed defecation related to occult rectal prolapse. Most support for this technique comes from small, uncontrolled case series and objective and technical comparative results are lacking [49, 50]. See Chap. 60 for a complete overview of the treatment of rectal prolapse.

Rectal Prolapse: Occult

Occult or internal rectal prolapse is seen in patients presenting with isolated complaints of obstructed defecation or fecal incontinence. This is typically identified on defecography and complicating its association with obstructed defecation is the finding of radiographic internal prolapse in healthy, asymptomatic volunteers [51].

Initial treatment of this group of patients is non-operative with the techniques already described. Patients failing this approach with refractory, lifestyle-limiting symptoms can be considered for surgical intervention. It is important for patients and surgeons to recognize that inconsistent functional improvement is seen with surgical correction of the occult prolapse using the posterior rectopexy technique [44]. Ventral mesh rectopexy may become a valid option for this group of patients but objective studies documenting its efficacy are lacking at this time.

An alternative to posterior or ventral rectopexy for management of rectal intussusception is stapled transanal rectal resection (STARR). This may also be considered for some patients with rectoceles and refractory symptoms of obstructed defecation who have failed non-operative treatment. This approach uses a specialized transluminal gastrointestinal circular stapling device to resect the redundant anterior and posterior rectal walls, thereby reducing rectal volume and improving rectal sensitivity [52]. Results have been overall positive in terms of initial relief of the symptoms of obstructed defecation, though appreciable operative morbidity (up to 36 %) and long-term functional consequences including fecal urgency and incontinence, bleeding, rectovaginal fistula, persistent or recurrent obstructive defecation, and pelvic sepsis have all been described [53–57]. The difficulty in determining which patients would benefit from the STARR procedure along with the possible morbidity that can occur from the circular "anastomosis" have dampened the enthusiasm for this procedure.

Rectocele

Rectoceles arise from loss of anterior rectal support due to disruption of the rectovaginal fascia. This is typically related to traumatic disruption from prior obstetric trauma or simple age related decline in fascial integrity. Rectoceles are identified in up to 80 % of the adult population, the majority of which are asymptomatic and do not require treatment [58]. Symptomatic rectoceles come to clinical attention owing to overt vaginal prolapse and/or functional rectal obstruction (Figure 59-5). Associated symptoms may include anorectal or vaginal pain and sexual dysfunction. A detailed history and physical examination to define the presenting symptoms and its impact on quality of life is important. Clearly defining the problems most important to the patient and setting realistic expectations for medical and surgical treatment of this problem is critically important [2].

Patients whose primary complaint is posterior vaginal wall prolapse may be offered surgical reconstruction with the expectation of durable relief of their prolapse symptoms. Rectoceles can be repaired via the transvaginal (will be discussed in Chap. 63), transrectal, and transperineal approaches with or without levatoroplasty. The operative morbidity, risk of recurrence, vaginal anatomic distortion, and a significant risk of dyspareunia should not be underestimated and should be thoroughly discussed with the patient prior to surgery [59–61].

Many colorectal surgeons favor a transanal approach to repair of low rectoceles. Patients are typically placed in the prone position. A curvilinear incision is made over the poste-

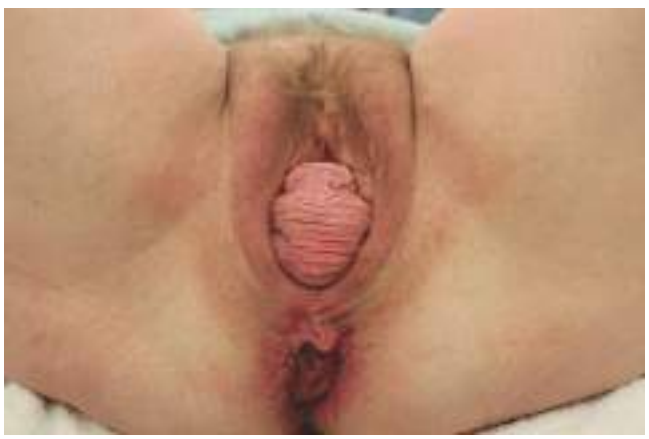

FIGURE 59-5. Rectocele.

rior rectal mucosa just 1–2 cm distal to the distal edge of the rectocele. Prepping the vagina and using the index finger in the vagina to outline the rectocele edges is helpful. The mucosa is dissected off the rectocele until it is 1–2 cm cephalad to the proximal rectocele edge. Then the cephalad edge is sutures to the caudad edge with simple or figure of eight absorbable sutures (2-0 polyglycolic acid). Confirmation of the complete obliteration of the rectocele is confirmed with the finger in the vagina to palpate the closure. The mucosa is then advanced down and re-approximated with the distal cut edge. Alternatively, this can be performed with the use of a stapler to remove the redundant tissue (Figure 59-6).

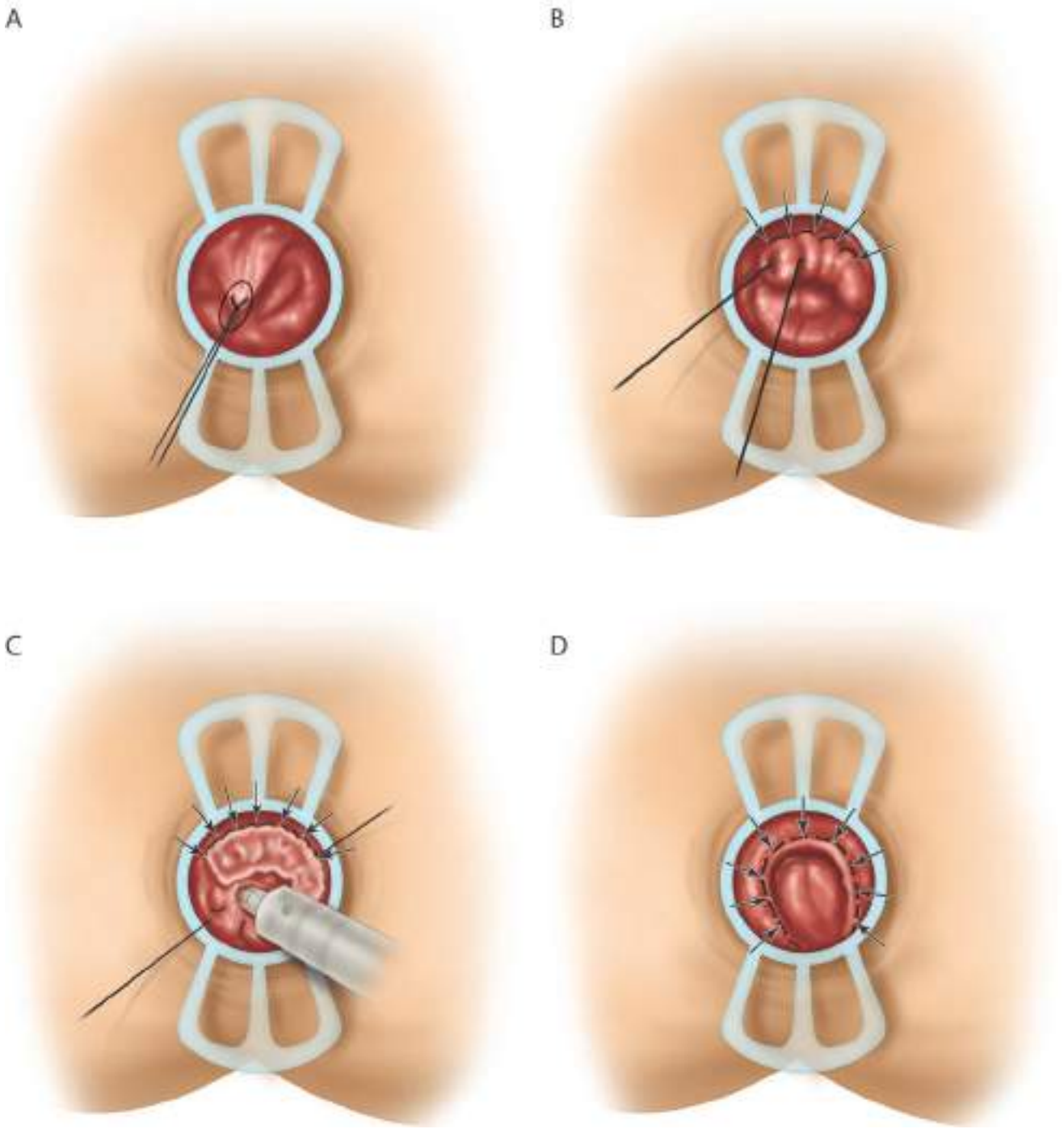

FIGURE 59-6. Transanal rectocele repair and mucosectomy (with a *circular stapler*). (**a**) The apex of the rectocele is identified and pulled down through a stitch (*circle*). (**b**) A running horizontal suture is placed through the base of the rectocele (*arrows*). (**c**) The exceeded prolapsed mucosa and the muscular layer were excised, keeping an opened wound with the edges joined by the previous manual suture (*arrows*). The pursestring suture is tied around the stapler's center rod. (**d**) The remaining stapled suture line (*arrows*).

In an attempt to lessen operative risk, improve recurrence rates, and lessen postoperative sexual dysfunction surgeons have utilized mesh based rectovaginal septal reconstruction. The technique remains controversial but most studies reveal no advantage in the use of mesh over native tissue repairs for posterior compartment defects. In light of this and in conjunction with the morbidity of mesh related complications leading to significant litigation, the technique has not been widely adopted. The clinical situation where mesh may be particularly advantageous is in cases of recurrent prolapse or patients at high risk of primary failure but only after carefully weighing the risks and careful discussion with the patient [62, 63].

Patients whose primary complaint is obstructed defecation in association with a rectocele are less reliably managed with surgical reconstruction [64–66]. These patients should be offered a trial of non-operative therapy as already discussed prior to consideration of surgical intervention. For patients failing non-operative therapy and who have significant lifestyle altering symptoms, all of the aforementioned rectocele repair techniques have been used with varying success and durability. It is very important that the patient have realistic expectations for improvement prior to undergoing surgical reconstruction.

Enterocele with or without Vaginal Vault Prolapse

Enterocele and vaginal vault prolapse may exist in isolation of each other, but are co-existent in the majority of cases. Patients present with complaints of vaginal prolapse and symptoms of obstructed defecation. Chronic pelvic and low back pain may also be present and is typically worse throughout the day while upright and relieved with recumbency. Dyspareunia is also a frequent complaint. As with other pelvic floor disorders, careful history and physical examination is essential. If an enterocele is clinically suspected, confirmation with defecography is usually definitive identifying the small bowel descending into the rectovaginal space (Figure 59-7). A less common finding is a sigmoidocele where a redundant sigmoid colon fixated at the rectosigmoid junction fills the rectovaginal space.

For symptomatic patients with a confirmed enterocele, sigmoidocele, or vaginal vault prolapse, intervention is appropriate. Again, anatomic prolapse symptoms are much more reliably repaired than are the functional bowel consequences of the disorder. Patients with primarily obstructed defecation, as the presenting symptom should be offered a trial of non-operative therapy prior to surgical intervention.

The surgical approach can be either trans-abdominal or transvaginal, and is often determined by overall patient performance status. For healthy patients with good performance status, an abdominal approach offers a more durable and functionally better repair. The gold standard is abdominal sacral colpopexy with either prosthetic or biologic mesh support. A number of plication procedures of the pouch of Douglas have been described to manage the enterocele and may be concomitantly performed [67]. Sigmoidoceles are most commonly addressed with an anterior resection. With surgeons increasingly facile with advanced laparoscopic or robotic techniques, this procedure has become less invasive [68, 69]. Multi-compartment prolapse is common and concomitant repair should be undertaken [70]. See Chap. 63 for additional information.

Patients with poor performance status or patients with relative contra-indications for abdominal surgery are considered for a transvaginal approach. Traditionally, the transvaginal approach has used sacrospinous ligament fixation to support the vaginal apex concomitant with high ligation of the enterocele sac [71]. For patients without any desire to preserve sexual function, a vaginal obliterative procedure, colpocleisis, is an attractive approach for its relative ease and safety [72]. For those patients who are inappropriate surgical candidates or who desire non-operative relief of their symptoms a pessary may be entertained [73].

Non-Anatomic Causes of Obstructed Defecation

Several different non-anatomic anorectal functional and pelvic support issues may negatively affect defecatory function and give rise to obstructed defecation. Another term frequently used to describe this complex is dyssynergic defecation but this term probably is better used interchangeably with obstructed defecation syndrome rather than as a descriptor of patients with obstructed defecation not associated with underlying pelvic prolapse. Paradoxic puborectalis contraction, rectal hyposensitivity often in conjunction with mega rectum, and abnormal perineal descent are often contributors to obstructed defecation syndrome.

Paradoxic puborectalis occurs when the levator ani is inappropriately contracted during initiation of defecation. In normal defecation, the levator ani is relaxed thereby straightening the anorectal angle, shifting the rectum posteriorly, and allowing comfortable bowel movement. When the puborectalis is inappropriately contracted the anorectal angle becomes more acute and rectal outlet obstruction ensues inhibiting rectal evacuation. Diagnosis is suggested by physical examination. Having the patient strain during digital rectal examination, the puborectalis is felt to contract against the examining finger. Confirmatory testing with a combination of anorectal electromyography and defecography is diagnostic. Conservative treatment with dietary modification and biofeedback results in improvement in 40–60 % of patients [74, 75].

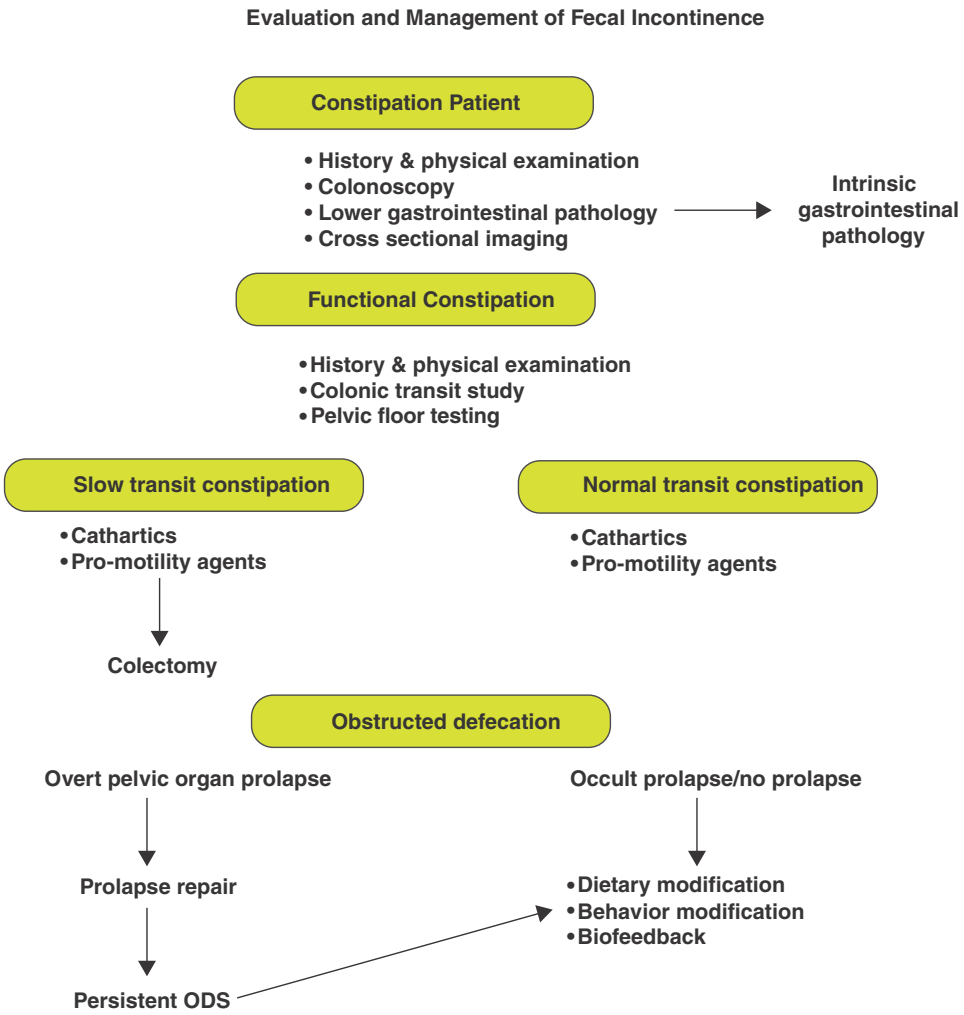

FIGURE 59-7. Algorithm for evaluation and management of functional constipation.

Rectal hyposensitivity is often seen concomitant with mega rectum. This is seen frequently in patients with neurologic or psychiatric impairment. However it is important to consider that a patient with megarectum could have short segment Hirschsprung's disease or a non-relaxing pelvic floor and these types of problems must be actively ruled out. Symptomatically, these patients present with typical obstructed defecation symptoms and may (or may not) have recurrent episodes of fecal impaction. Diagnosis is confirmed with defecography and anorectal manometry. Treatment is challenging and in conjunction with dietary and behavioral therapy, rectal stimulation with suppository, or enema therapy can be helpful. A technique being explored in clinical trials for this difficult group of patients failing nonoperative therapy is sacral nerve stimulation. Most studies published have grouped all forms of constipation together and have not clearly defined the etiology of refractory constipation. Overall results have been disappointing on an intent to treat basis but for the subgroup of patients that do benefit the results have been striking [76–78]. Knowles et al. in a randomized prospective double blind trial specifically treating patients with refractory obstructed defecation related to rectal hyposensitivity showed excellent results in terms of normalization of rectal sensation, ease of defecation, and improved Wexner scores in 10/13 patients. Eleven patients went on to permanent implant with nine patients have durable improvement at almost 2 years of follow-up [79].

Abnormal perineal descent results from loss of pelvic floor fascial integrity. Physical examination suggests the diagnosis when a pelvic floor bellows phenomenon is seen during straining. Defecography is diagnostic when descent greater than 2 cm past the static pelvic floor is seen. Treatment remains conservative with dietary manipulation and biofeedback. Unfortunately, treatment outcomes are relatively poor with less than 30 % experiencing major symptomatic improvement.

Fecal Diversion

As a last resort for patients with debilitating and refractory symptoms of obstructed defecation, fecal diversion may be considered. A very detailed and careful discussion clearly delineating the risks, benefits, and expected outcome of this therapy should be undertaken.

Algorithm for Evaluation and Management of Functional Constipation

An algorithm for evaluation and management of functional constipation is shown in Figure 59-7. Probably the single most important test to obtain is a good history and physical examination taken by a patient and empathetic surgeon. Further hindgut and pelvic floor functional testing is driven by the working diagnosis obtained in the initial encounter.

For patients with slow transit and normal transit constipation the initial treatment is non-operative with cathartic and pro-motility agents. Patients with slow transit constipation refractory to medical therapy may benefit from total colectomy but patients with normal transit constipation do not (Figure 59-8). A more detailed discussion of these disorders is undertaken in other sections of this text (see Chap. 58).

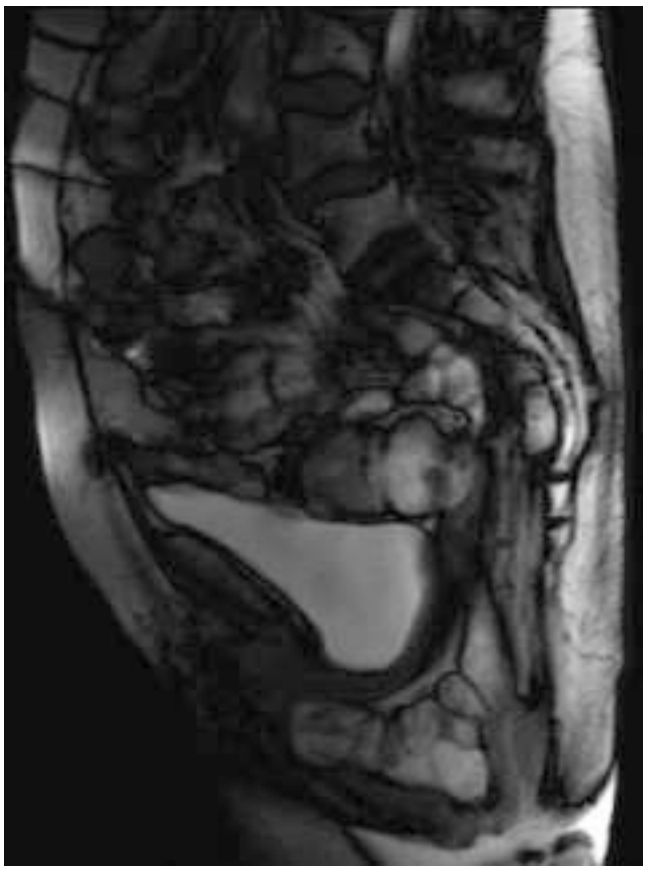

FIGURE 59-8. MR defecography demonstrating a cystocele, intussusception, and enterocele. Notice the small bowel loops extending down to the pelvic floor.

In patients with obstructed defecation, the most important first step is identifying whether patients have co-existing overt pelvic organ prolapse. For patient with overt pelvic prolapse, surgical correction of the prolapse is the first step, recognizing that the functional rectal outlet obstruction may or may not improve. For patients with isolated symptoms of obstructed defecation or persistent symptoms after pelvic prolapse repair, the initial treatment is non-operative with dietary and behavioral modification. Pelvic floor physical therapy retraining, while non-standardized, can be particularly effective. Recognizing the importance of the therapist in terms of their patience and empathy is critical to a successful biofeedback program.

For patients with refractory symptoms of obstructed defecation and significant lifestyle limitations due to the disorder, surgical intervention can be entertained. It is critically important that a detailed discussion of the goals, risks, and expected outcome of treatment be documented such that patient and surgeon expectations for improvement are realistic. In choosing an operative approach it is also important that we expose the patient to the least amount of risk and secondary treatment related side effects for this benign condition.

Conclusion

Patients with functional constipation are a challenging population that requires patient and empathetic care. The symptoms of this disorder are quite obtrusive and a major impediment to quality of life. A careful and methodical approach to evaluation and management of this group of patients can often result in major improvements. Considerable ongoing research, however, is still required to define the best practices and surgical techniques that may results in further functional benefits.

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60
Rectal Prolapse

Brooke Gurland and Massarat Zutshi

Key Concepts

- Individuals with rectal prolapse may complain of a myriad of symptoms: mucus discharge, rectal bulge, rectal bleeding, fecal incontinence, constipation, tenesmus, pelvic and rectal pain and pressure. Correction of the prolapse does not guarantee functional improvement.
- Successful outcomes measures after rectal prolapse surgery include both prolapse recurrence rates and functional outcomes. The surgeon should be familiar with different abdominal and perineal procedures to choose the best operation for each individual in the setting of initial and recurrent rectal prolapse.
- Laparoscopic ventral rectopexy is associated with functional improvement, low morbidity, and low recurrence rates but has a high learning curve for proficiency and advanced training may be required.
- Robotic rectopexy can be offered safely to patients and has advantages when suturing in the pelvis is required.
- The paradigm for treatment rectal prolapse in the elderly has changed from perineal to abdominal minimally invasive procedures in elderly and high risk patients.
- Rectal prolapse may coexist with vaginal prolapse and multidisciplinary evaluation and treatment should be considered in symptomatic patients.

Introduction

Rectal prolapse or procidentia is defined as extrusion of the full thickness of the circular folds of the rectum through the anal muscles beyond the anal verge. If the rectal wall is prolapsed but does not extend beyond the anus, it is called occult (internal) rectal prolapse or rectal intussusception. Both full-thickness and internal rectal prolapse should be differentiated from mucosal prolapse which occurs when only the rectal or anal mucosa protrudes beyond the anus. Several anatomic conditions are associated with rectal prolapse including a laxity of rectal attachments, a deep Pouch of Douglas cul-de-sac, lack of fixation of the rectum to the sacrum, and a large redundant sigmoid colon (Figure 60-1).

The peak incidence of rectal prolapse is reported in women aged 70 and may be associated with a spectrum of pelvic floor disorders such as vaginal prolapse (enterocele, cystocele, rectocele) and urinary incontinence. These disorders are generally attributed to multiparity and pelvic floor weakness [1]. Women are six times as likely as men to present with rectal prolapse [2]. Approximately one-third of female patients are nulliparous and younger women; men with rectal prolapse tend to suffer from disordered defecation, dysmotility, psychiatric comorbidities, eating disorders, and autism or developmental delays [3, 4].

Symptoms of rectal prolapse may include the feeling of a bulge, mucus drainage and/or fecal accidents, constipation, tenesmus, rectal pressure, pelvic pressure and pain, and rectal bleeding. These symptoms can be debilitating and can result in isolation and depression in affected individuals.

Fecal incontinence is reported in 50–75 % of patients with rectal prolapse [5]. Mucus discharge frequently is described early in the disease process and this can evolve into frank fecal accidents as the prolapsed segment keeps the sphincters open permitting stool to leak. Chronic stretch, trauma, and continuous stimulation of the rectoanal inhibitory reflex by the prolapsing tissue can result in permanent sphincter damage. Pudendal neuropathy has been demonstrated in 50 % of patients with prolapse [6] and may be responsible for denervation related atrophy of the external sphincter musculature [7].

Constipation is reported in 25–50 % of patients with rectal prolapse [5, 8] and may be associated with colonic dysmotility or pelvic floor dyssynergia. Chronic straining can lead to

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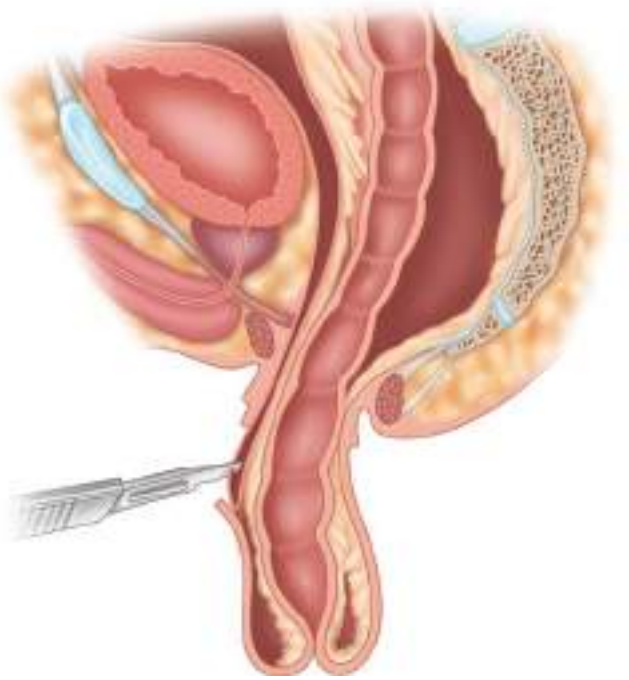

Figure 60-1. Cross section of rectal prolapse. Anatomical associations with rectal prolapse include laxity of rectal attachments, deep Pouch of Douglas, lack of fixation to the rectum, and redundant sigmoid colon.

rectal prolapse or the prolapse can induce outlet constipation with the intussuscepting bowel in the rectum creating a blockage of the outlet which is exacerbated by excessive straining.

Patient Evaluation

The evaluation of rectal prolapse should include a complete pelvic floor history and physical examination. An assessment of risk factors should be considered and treatment of constipation with fiber or laxatives should be considered. A screening evaluation with endoscopy in adults is performed to exclude coexisting conditions. If the diagnosis of rectal prolapse is suspected, but not detected on initial examination, the patient should be evaluated standing, squatting or on the commode in the straining position. If rectal prolapse is still elusive and the history is suggestive of a prolapse, the patient can be asked to photograph the prolapse at home. For those patients with vaginal prolapse or urinary symptoms, urogynecological examination and urodynamics should be considered for multidisciplinary pelvic floor repair. Additional testing such as anorectal physiology testing rarely changes the operative strategy but they can often guide treatment for associated functional abnormalities [9]. Defecography may reveal associated defects such as cystocele, vaginal vault prolapse, and enterocele that may require treatment [10, 11].

Non-operative Treatment

Non-operative treatment of rectal prolapse has shown to produce only temporary or symptomatic relief. Reduction of incarcerated rectal prolapse can be performed by coating the prolapse with table sugar to reduce edema and gently push the prolapse above the sphincters [12]. Biofeedback was used to improve postoperative function but has not been reported as a primary therapy [13].

Surgical Approaches for Rectal Prolapse

A single common theory for the cause of rectal prolapse has not been substantiated but the anatomic basis includes a deficient pelvic floor through which the rectum herniates. A deep pelvic cul-de-sac, attenuated ligamentous attachments to the rectum and presacral fascia, and a redundant sigmoid colon are frequently associated with rectal prolapse [14].

Surgery is the only curative treatment for rectal prolapse. A range of surgical procedures are available which differ with respect to approach: abdominal versus perineal. Additionally, the surgeon must decide about the method of fixation that will be used and if bowel will be resected. The optimal operation for rectal prolapse is unclear. Surgeons are inclined to individualize the patient's treatment when it comes to approach thus making it difficult to evaluate and compare results from case series. Low accrual rates for randomized trials and poor quality data continues to be a challenge when reviewing the literature for rectal prolapse surgery. Deen et al. performed a small randomized controlled trial ($n=20$) comparing perineal rectosigmoidectomy with an abdominal approach [15]. The recurrence rate was 10 % for the perineal group compared to 0 % for the abdominal group and functional results were better in the abdominal group. The PROSPER Trial compared the surgical treatments for rectal prolapse in 293 patients [16]. Seventy-eight abdominal procedures and 213 perineal procedures were performed. Overall, rectal prolapse recurrence rates were higher than anticipated but recurrence was not significantly different between groups.

Description of Surgical Interventions

Anal Encirclement

The Thiersch procedure involves reduction of prolapse and placement of a subcutaneous suture or mesh material to encircle the anus, thereby narrowing the anal canal. This procedure does not eradicate prolapse but prevents further descent by providing a mechanical barrier. It is associated

with recurrence rates ranging from 33 to 44 % but can lead to problems with severe outlet constipation. It is rarely recommended and only reserved for patients at high risk of anesthetic complications [17]. In some patients with rectal prolapse and a permanent colostomy, the treatment may be considered to prevent the symptoms of protrusion and mucus drainage.

Perineal Procedures

Delorme

A mucosal sleeve resection was described by Delorme in 1900 and involves stripping the mucosa of the prolapsed segment, plication of the muscle layers, and re-approximation of the mucosa (Figures 60-2, 60-3, 60-4, and 60-5). This procedure is advocated for patients with a short segment of full-thickness rectal prolapse or for patients who are considered "high risk" for abdominal procedures such as those with a "hostile abdomen." Procedure related operative complications are low but prolapse recurrence rates are high in the range of 16–30 % [18–20] (For a description of the procedure, please see Video 60.1 Delorme procedure, reproduced with the permission of the Department of Colon and Rectal Surgery, The Cleveland Clinic Foundation, Cleveland, OH, USA).

Perineal Rectosigmoidectomy

The perineal rectosigmoidectomy or the Altemeier procedure involves excising the prolapsing rectum and creating a low end-to-end stapled colorectal anastomosis or a sutured coloanal anastomosis (Figures 60-6, 60-7, 60-8, 60-9, 60-10, 60-11, and 60-12). This procedure can be combined with a levatorplasty to "tighten" the pelvic floor muscles with the goal to improve continence [21]. Fecal incontinence can be exacerbated after a perineal rectosigmoidectomy which may be due to loss of the rectal reservoir confounded by poor sphincter function. Recurrence rates have been reported as high as 20 % and complications rates (<10 %) include suture line bleeding, pelvic abscess, or anastomotic leak [22] (For a description of the procedure, please see Video 60.2 Altemeier procedure, reproduced with the permission of the Department of Colon and Rectal Surgery, The Cleveland Clinic Foundation, Cleveland, OH).

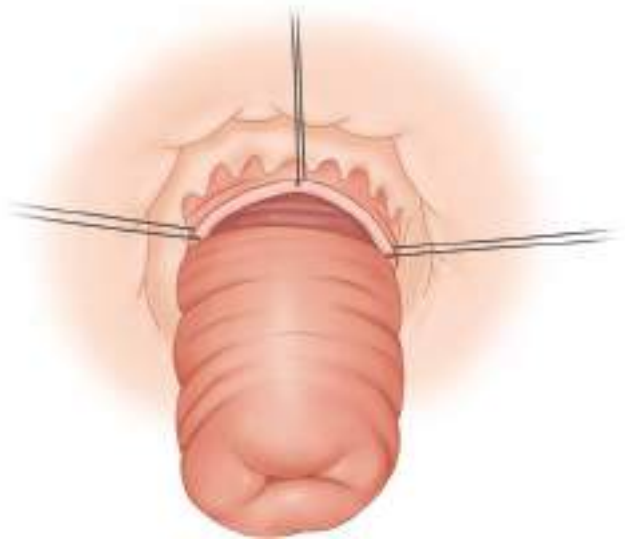

FIGURE 60-2. Delorme procedure. Two centimeters proximal to the dentate line, a circular line is marked out in the mucosa with the bovie. The area is injected with a vasoconstricting agent. An incision is then made through the mucosa but not full thickness through the entire rectal wall. The bovie is an excellent means to make the mucosal incision.

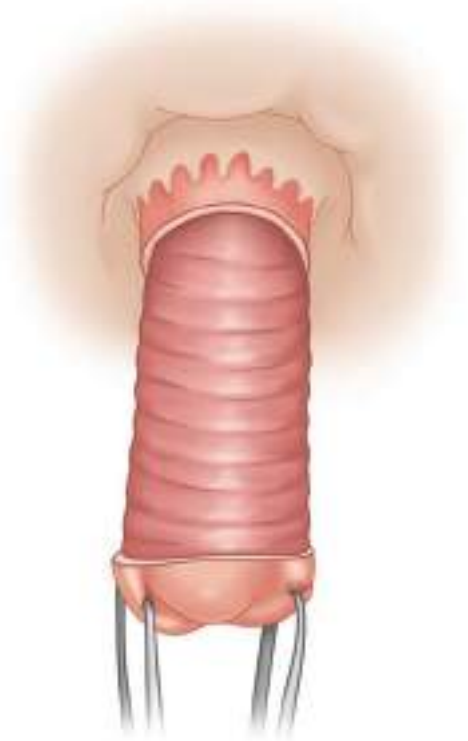

FIGURE 60-3. Delorme procedure. Working cephalad, a sleeve of mucosa is dissected off the muscular layer of the rectal wall. Liberal injection of saline with or without a vasoconstricting agent assists in developing the correct plane. Care is taken to achieve meticulous hemostasis as there are penetrating vessels in this plane of dissection which will need to be tied or coagulated.

Abdominal Procedures

Transabdominal Rectopexy

The goal of rectopexy is to anchor the rectum to the sacrum. This can be performed by open, laparoscopic, or robotic techniques. Fixation of the rectum with suture was first described by Cutait. The suturing is done to correct telescoping

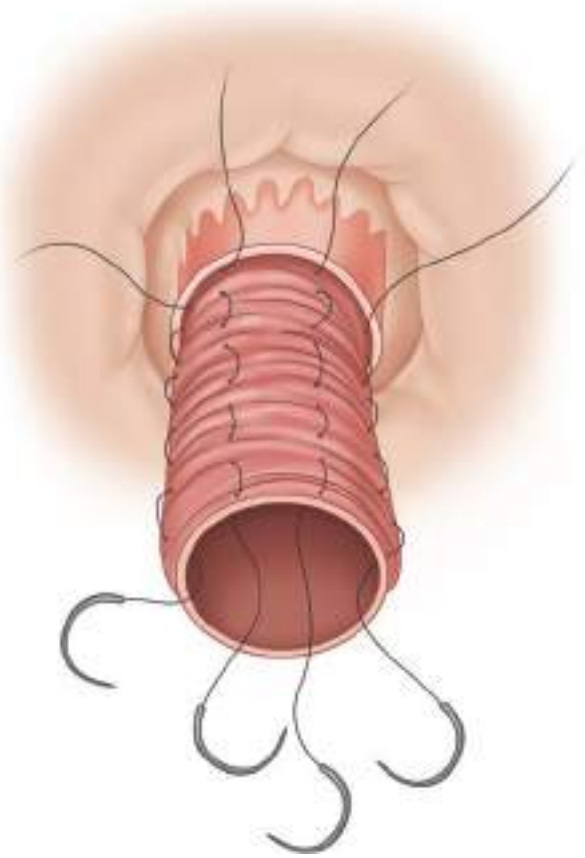

FIGURE 60-4. Delorme procedure. When there is tension at the plane of the mucosal dissection, this is completed. After ensuring that complete hemostasis exists, the muscular layer (the rectal wall) is approximated using sutures starting at the proximal cut mucosal end and including bites of the rectal wall every few centimeters until the other cut edge is reached at the anal region. Placement of these sutures is along the longitudinal axis of the rectal wall and are not full thickness but deep enough to ensure when tied they do not tear through the tissue. As these sutures are placed they compress the wall in an accordion (or concertina) like fashion. Four to six sutures are typically required to stabilize the compressed rectal wall.

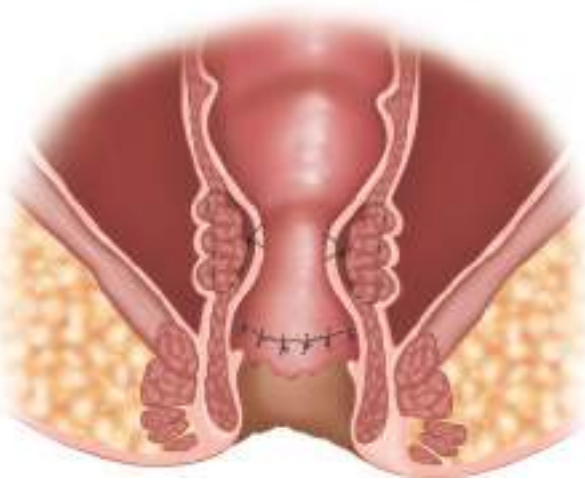

FIGURE 60-5. Delorme procedure. After the sutures that have been placed in the rectal wall are tied down, the two cut ends of the mucosa will be in close proximity. The mucosa is then reapproximated with sutures to create a neo-anastomosis in the anal canal proximal to the dentate line.

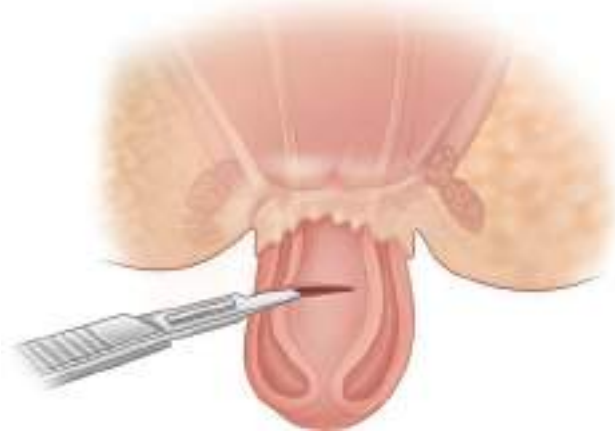

FIGURE 60-6. Altemeier procedure. A circular incision is mapped out approximately 2–5 cm cephalad to the dentate line in the rectal mucosa.

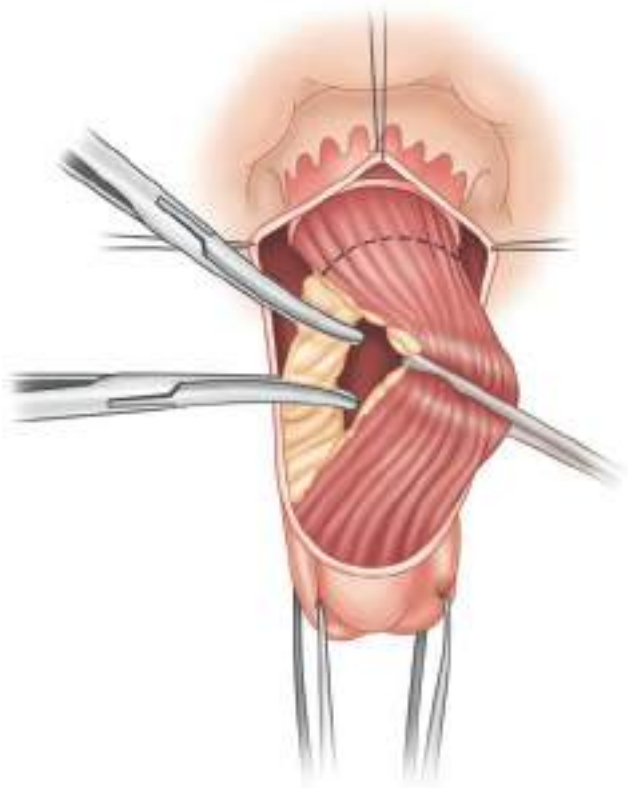

FIGURE 60-7. Altemeier procedure. The incision is deepened and is carried through the entire thickness of the rectal wall. The mesentery to the redundant prolapsed rectum is divided and tied, suture ligated, or cut and sealed using an energy device. Meticulous hemostasis is essential to avoid retracted blood vessels or a mesenteric hematoma.

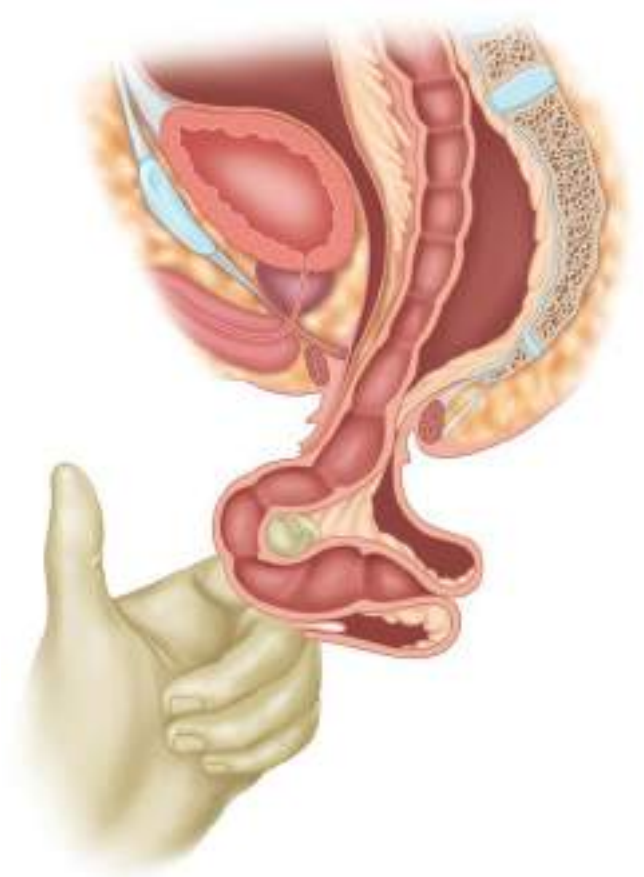

FIGURE 60-8. Altemeier procedure. The rectum is pulled out the anus and the mesentery divided stopping at a point just distal to where the rectum (or sigmoid) no longer easily can be pulled out the anus.

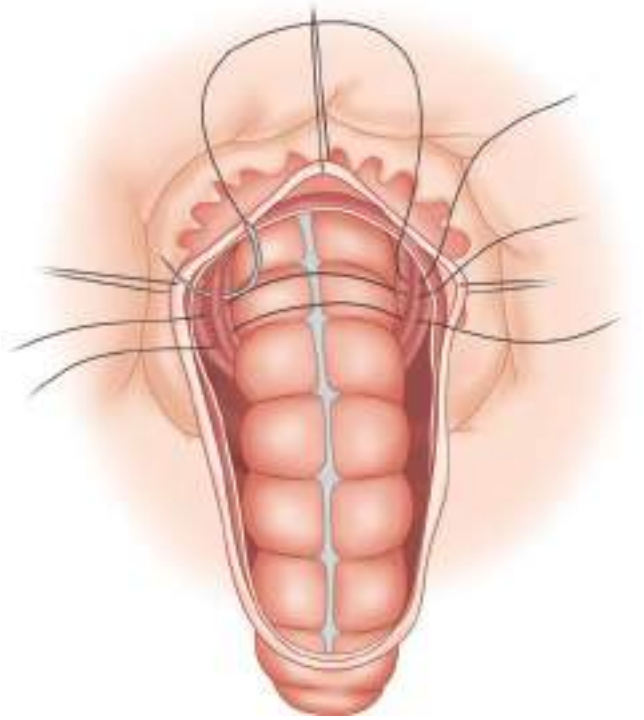

FIGURE 60-9. Altemeier procedure. Anteriorly the levator ani muscles may be approximated with sutures (levatorplasty) which may improve fecal continence.

of the redundant bowel and further fixation of the rectum is anticipated due to the resultant scarring and fibrosis [14]. Prolapse recurrence rates are reported from 0 to 9 % [23–25]. Mobilization of the rectum can vary based on the technique from circumferential to limited posterior and/or anterior and can include unilateral or bilateral division of the lateral rectal ligamentous attachments.

More extensive rectal mobilization and division of lateral stalks is associated with decreased recurrence rates but may precipitate new onset or worsening constipation [26]. New onset constipation after rectopexy is reported in 15 % of patients whereas 50 % described worsening of preoperative constipation [27]. Denervation of the rectum from the neural efferent nerves residing in the lateral ligaments is thought to contribute to worsening function. Unilateral preservation of a lateral stalk and unilateral fastening of the rectal mesentery to the sacrum should be considered to mitigate worsening function [9].

Transabdominal Resection Rectopexy

Sigmoid resection in conjunction with rectopexy was popularized by Frykman and Goldberg in 1969 [28]. It was thought that sigmoidectomy was associated with a lower recurrence rate and improved functional outcome with a minimal

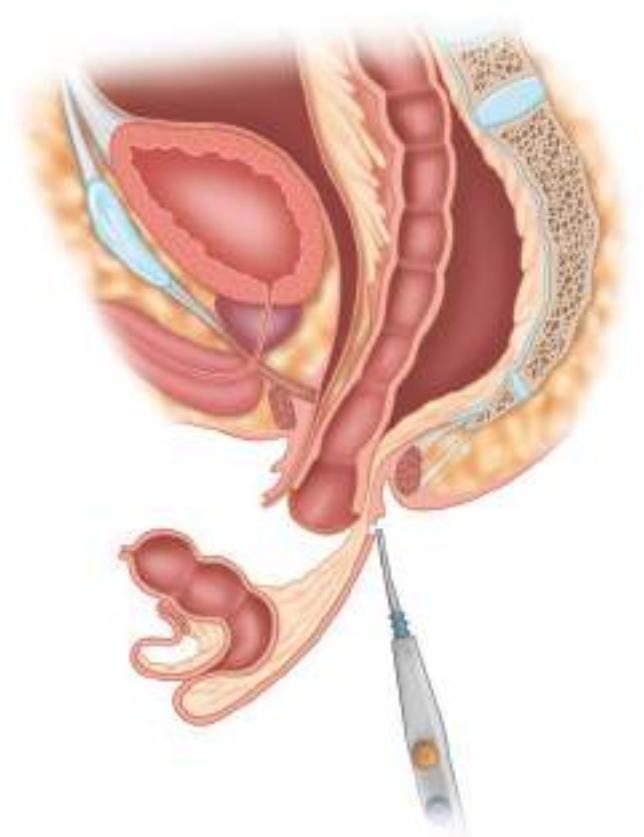

FIGURE 60-10. Altemeier procedure. The redundant rectum and sigmoid colon are excised. It is important to ensure that the proximal bowel has sufficient mesentery to avoid ischemia to this segment.

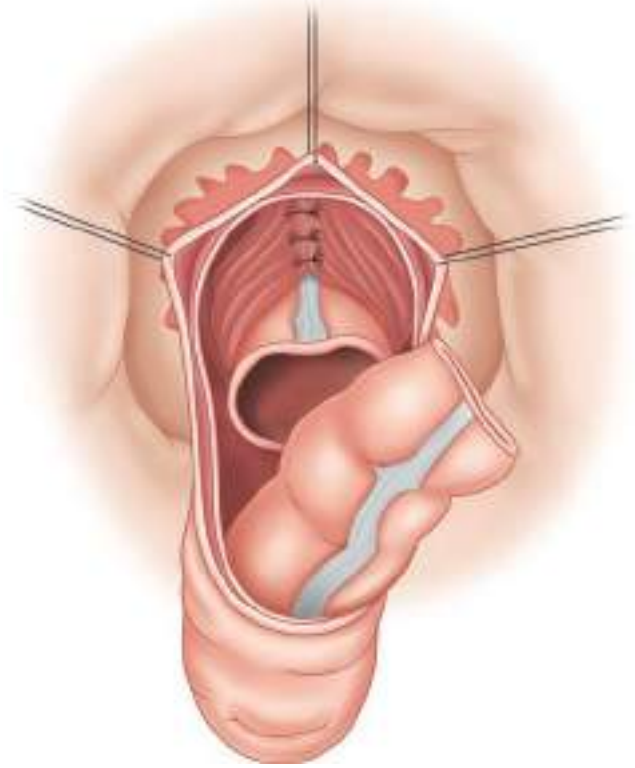

FIGURE 60-11. Altemeier procedure. The redundant rectum and sigmoid colon are excised. It is important to ensure that the proximal bowel has sufficient mesentery to avoid ischemia to this segment. This figure also demonstrates the completed levatorplasty.

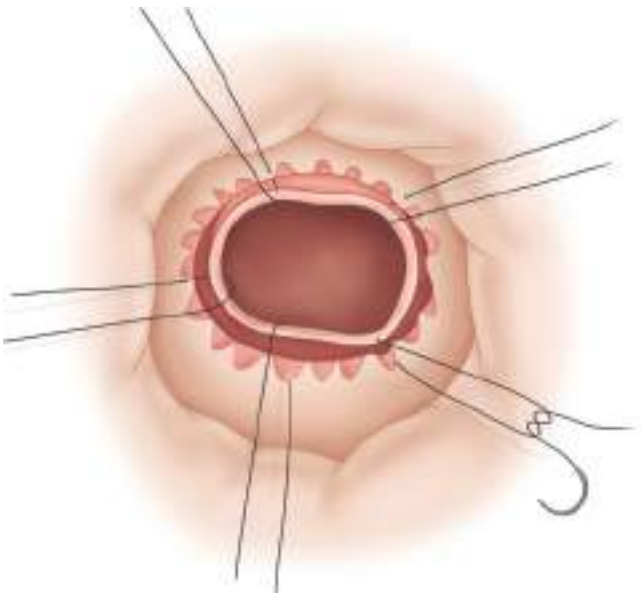

FIGURE 60-12. Altemeier procedure. A tension free end-to-end anastomosis is carried out using sutures (a circular stapled anastomosis also can be done).

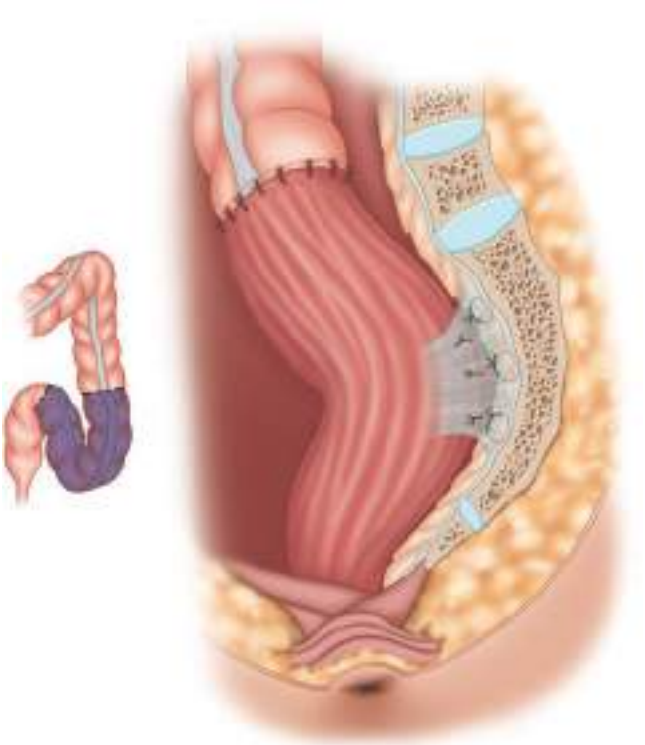

FIGURE 60-13. Resection/rectopexy. The sigmoid colon is excised and an end-to-end anastomosis performed. The rectum is mobilized and non-absorbable sutures are placed in the lateral rectal ligament. The suture is then placed in the anterior sacral ligament (tacks can also be used) to anchor the rectum securely to the sacrum at about the S1 level. It is important to position the needle to enter the sacrum at a right angle. The needle is pushed into the bone and minutely pulled back. Then the curve of the needle is followed when continuing the suture placement at the sacrum. This ensures the suture will be in the anterior sacral ligament. Two sutures on the right are typically placed. Sutures can be placed also on the left side of the rectum, but when tying them down, it is crucial to ensure the rectum is not kinked/occluded.

increase in morbidity [29, 30]. Sigmoid resection may reduce constipation in those who report the symptom preoperatively [31] and resecting the sigmoid may counteract new onset constipation which has been reported after extensive rectal mobilization (Figure 60-13). However, a sigmoid resection is thought to be unnecessary in individuals whose predominant complaint is fecal incontinence [32]. For some patients with confirmed slow colonic motility, sigmoid resection is an inadequate operation and a subtotal colectomy should be considered [33]. The American Society of Colon and Rectal Surgeons in its 2011 Clinical Practice Guideline *Practice Parameters for the Management of Rectal Prolapse* states that "a sigmoid resection may be added to rectopexy in patient with prolapse and preoperative constipation, but it is not necessary in those without constipation" [9].

In the USA, laparoscopic resection rectopexy currently is the most common treatment for full-thickness rectal prolapse [34, 35]. However in European countries, sigmoid resection is infrequently performed and laparoscopic ventral rectopexy is preferred.

Mesh Rectopexy

Fixation materials can vary from simple absorbable or non-absorbable suture to biologic or synthetic mesh. Placement of the mesh can include partial anterior rectal encirclement (Ripstein procedure), partial posterior rectal encirclement (Well's procedure), or partial anterior rectal encirclement (D'Hoore ventral rectopexy) prior to attachment of the mesh to the sacrum.

Ripstein Procedure (Anterior Sling Rectopexy)

Ripstein first described this procedure in 1952 [36]. After complete mobilization of the rectum, an anterior sling of fascia lata or synthetic material was fixed to the anti-mesenteric surface of the rectum and each of the sides then sutured to the sacral promontory. The goal is to restore the normal anatomic position of the rectum. Mortality rates are reported to be from 0 to 2.8 % and recurrence rates between 0 and 13 % [27, 37]. Functional outcomes include a trend towards improvement in continence and a mixed response to constipation [38]. One drawback of the original procedure was the potential of the mesh to obstruct the rectum. To limit the incidence of obstruction the procedure was modified to leave a gap in the mesh to avoid narrowing or kinking of the rectum [39]. Currently people performing this procedure will fix the mid portion of a rectangular piece of mesh to the sacrum and bring each arm around the rectum, suturing the arms to the sides of the rectum, leaving a gap in the anti-mesenteric rectal region. Roberts et al. reviewed their experience with Ripstein and noted a 52 % complication rate with a presacral hematoma reported in 8 % [40]. Recurrence rates in men were three times that in women (24 % vs. 8 %, respectively). They speculated that the difference in recurrence rates was due to technical difficulties in mobilizing the rectum in a narrow male pelvis [40]. The Ripstein procedure (even the modified form) is being used less and less due to the morbidity and potential for new rectal outlet difficulties.

Posterior Mesh Rectopexy

A posterior rectopexy utilizing the Ivalon® sponge was a popular procedure in the past. After nearly full mobilization of the rectum, a rectangular piece of sterilized Ivalon sponge was fixed to the presacral fascia using non-absorbable sutures. The rectum was then drawn upward out of the pelvis and the lateral edges of the sponge wrapped around the rectum to encompass three quarters of the circumference and sewn in place. Major complications included pelvic abscess (2.6–16 %) which required drainage and removal of the sponge. The recurrence rates were low presumably due to fixation from the inflammatory process resulting from the infection. However the infection rates were felt to be prohibitory and this sponge is no longer utilized in repairs.

Currently the posterior mesh rectopexy is fashioned after variations of the Well's procedure. Traditionally the rectum is only mobilized on the right enough posteriorly to allow safe suturing or tacking of a prosthetic material to the periosteum or anterior sacral ligament of the sacral promontory. The mesh is sutured to the rectum on the right side. Mortality rates range from 0 to 3 % and recurrence rates are reported to be 3 % [23, 25, 29].

Laparoscopic Ventral Rectopexy

Ventral rectopexy (VR) described by D'Hoore is based on correcting the descent in women of the posterior and middle compartment by mobilizing the rectovaginal septum down to the pelvic floor between the extraperitoneal rectum and the vagina [41]. The rectovaginal septum is reinforced with (traditionally polypropylene) mesh and the mesh is suspended to the sacrum, thus elevating the pelvic floor (Figure 60-14). VR can correct full-thickness rectal prolapse, rectoceles, and internal rectal prolapse and can be combined with vaginal prolapse procedures, such as sacrocolpopexy, in patients with multi-compartment pelvic floor defects.

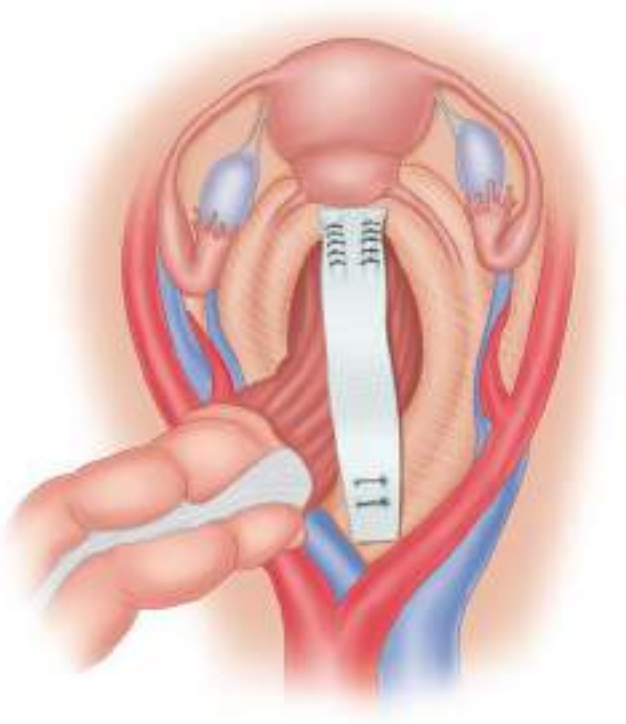

FIGURE 60-14. Ventral rectopexy. The anterior wall of the rectum is mobilized. The mesh (or graft) is attached with sutures to the anterior wall of the rectum. The mesh is then sutured to the anterior sacral ligament or tacked to the sacrum at about the S1 level.

Limiting dissection to the anterior rectum minimizes autonomic nerve damage associated with posterior dissection and division of the lateral stalks. A meta-analysis of 789 patients in 12 published series of laparoscopic VR reports recurrence rates for pelvic organ prolapse at 3.4 % (95 % CI 2.0–4.8) [42]. Complication rates varied between 14 and 47 %. The overall mean decrease in fecal incontinence score was 44.9 % (95 % CI 6.4–22.3) along with a significant decrease in constipation of 23.9 % (95 % CI 6.8–40.9). Laparoscopic VR is the current gold standard for treatment of rectal prolapse in European countries.

Laparoscopic VR is technically demanding and requires a complete ventral dissection of the rectovaginal septum (rectovesical in men) down to the pelvic floor and suturing skills within a confined space that further maximizes the difficulty. Mackenzie and Dixon reported that the proficiency gain learning curve for the relevant clinical and quality-of-life outcomes for laparoscopic VR was between 82 and 105 cases [43]. Proficiency with respect to reduced operating time was reached at 54 cases. Poor technique minimizes the functional benefit and increases the risk for complications. Recurrence after VR may be due to loss of fixation at the sacrum, inadequate mobilization in the rectovaginal space, or incomplete reduction of the prolapse [44].

Adverse outcomes that seem to be unique to VR include mesh complications such as rectal stricture, rectovaginal fistula, pain/dyspareunia, and mesh erosions [45]. Sacral discitis is an uncommon complication that can occur after any type of rectopexy or sacral colpopexy where tacks or sutures are applied to secure the mesh at the site of the sacral promontory [46]. In an analysis of 200 patients undergoing VR, Draaisma et al. noted two patients who experienced mesh infection complicated by discitis at the site of the proximal mesh fixation [47]. Bacterial translocation from the distal rectum to the mesh and ultimately, to the site of fixation at the sacral promontory may explain this complication.

Jonkers et al. retrospectively analyzed laparoscopic resection rectopexy (LRR) and laparoscopic ventral rectopexy (LVR) [48]. A reduction in constipation and incontinence was found in both cohorts but more complications occurred after LRR than LVR. In the absence of more rigorous clinical trials, European surgeons continue to avoid sigmoid resection in favor of VR [49].

Robotic Rectopexy

Robotic procedures offer the advantages of three dimensional visualization, tremor filtering, motion scaling, enhanced dexterity, and superior precision. Developments of robotic surgery have overcome some limitations of conventional laparoscopy such as the difficulties associated with rigid instruments, limited freedom of wrist movement, and technical challenges associated with operating in the confines of a deep pelvis. Disadvantages of robotic surgery include the loss of tactile feedback, the limited range of motion of the robotic arms, increased operative time, and higher equipment costs. Ventral rectopexy is ideally suited for robotic surgery. Robotic rectopexy improves visualization in the deep pelvis and suturing capability and facilitates dissection and mesh placement to the rectovaginal septum. Suturing the mesh to the perineal body, anterior rectum, and lateral rectal attachments is technically easier robotically than laparoscopic suturing. Robotic VR may have a faster learning curve than laparoscopic VR. There have been reports that functional outcomes are improved with robotic VR [50].

Systematic review and meta-analysis comparing the outcomes of robotic rectopexy (RR) versus laparoscopic rectopexy (LR) reveal similar recurrence, conversion, and reoperation rates [51]. The meta-analysis shows that operative time is significantly longer for RR but that RR is associated with a significantly lower blood loss, fewer postoperative complications, and shorter hospital course. However, blood loss was low in both groups (<200 cc) and overall complications were minor.

The cost effectiveness of robotic surgery is debatable. Heemskerk estimated that the cost of robotic compared to laparoscopic surgery exceeds $745 dollars [52]. The experience of the surgical team, learning curve, and surgeon's skill are important aspects that influence operative time and outcomes. Updated systematic analysis of costs could become important to justify increased expense (For a description of robotic rectopexy, please see Video 60.3).

Rectal Prolapse in the Elderly

When considering surgery for rectal prolapse in older patients, the balance between the morbidity of the procedure and overall outcome must be carefully considered. Traditionally age was used as one of the major criteria for deciding the approach (abdominal vs. perineal) for prolapse surgery. The rationale was that perineal procedures can be performed on frail patients with regional anesthesia without the complications and extended recovery associated with abdominal surgery. Fang et al. retrospectively queried the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) database, studying surgeon preference for abdominal (open and laparoscopic) versus perineal procedures as it related to age of the patient [53]. The perineal approach was more commonly performed in patients >80 and those at highest risk. Mortality after perineal procedures was 1.3 % compared to 0.35 % for abdominal procedures. There were no deaths in the laparoscopic group. With the acceptance of laparoscopic surgery for rectal prolapse having lower morbidity, surgeons have taken a closer look at a more durable abdominal procedure in elderly patients. Laparoscopic surgery has been proven to be safe in the elderly and is associated with decreased ileus, less wound infections, and a decreased length of stay [54]. Acceptable morbidity has been reported in the elderly patients who underwent a laparoscopic mesh rectopexy [55]. Robotic rec-

topexy has also been shown to be a safe and effective option in patients older than 75 years [56]. Therefore, with the new era of minimally invasive surgical techniques, an increasing number of elderly patients will be considered for an abdominal procedure to address their rectal prolapse.

Recurrent Rectal Prolapse: What Is the NEXT Operation?

Although many studies have described the management of primary rectal prolapse, there are few reports which address the ideal surgical treatment for recurrent rectal prolapse. Unfortunately, a systematic literature review of the surgical management of recurrent rectal prolapse failed to develop a treatment algorithm due to the use of multiple techniques and low quality studies [57]. Considering single center studies, Steele et al. reported significantly more re-recurrences after reoperation using a perineal procedure compared with an abdominal procedure for their patients with recurrent rectal prolapse ($p=0.03$) [58]. This means that perineal procedures which have a higher incidence of recurrence after the primary procedure have an even greater chance at re-recurrence if utilized again for recurrent rectal prolapse. There is a theoretical risk that a redo perineal rectosigmoidectomy can result in a devascularized segment of rectum [59]. However, Ding et al. reported that redo perineal rectosigmoidectomy is as safe and feasible as primary perineal rectosigmoidectomy as long as the prior anastomosis is included in resected specimen [60]. However, this report also supported the previously mentioned studies regarding a substantially higher recurrence rate if a perineal rectosigmoidectomy is used to treat recurrent rectal prolapse [60].

One note of caution, if the initial repair was a sigmoid resection and rectopexy it is not advisable to perform a perineal rectosigmoidectomy if there is recurrent rectal prolapse. Unless the entire colorectal anastomosis is resected when performing the perineal resection for recurrence a devascularized segment of rectum can remain. Similarly, resection rectopexy following a perineal rectosigmoidectomy should be performed with caution as the distal bowel requires an intact marginal artery for its blood supply. Aggressive mobilization could compromise the artery and lead to distal bowel ischemia.

Recurrent mucosal prolapse after a ventral rectopexy can be ameliorated with a Delorme rectal mucosal resection. If the prolapse is too large to be addressed with a Delorme, the recurrence could be addressed by reattachment of the mesh to the sacrum or reinforcement of the existing mesh. In some situations a suture rectopexy or more extensive rectal dissection and resection/rectopexy may be required. We would not advise trying to excise the mesh that is attached to the rectal wall as this could lead to perforation (Table 60-1).

Combined Vaginal and Rectal Prolapse Procedures

Pelvic floor weakness results in multi-compartment dysfunction. Combined anterior/middle and posterior compartment prolapses and resultant bowel symptoms are common in patients with pelvic floor weakness and prolapse [61]. Failure to appreciate multi-compartment pelvic floor disorders along with a lack of collaboration between surgical specialties has resulted in 10–25 % of women with urogynecologic disorders requiring a second surgery for their colorectal dysfunction

TABLE 60-1. Surgical options for treatment of recurrent rectal prolapse based on the initial procedure

Initial procedure	Redo procedure options	Avoid
Resection rectopexy	1. Repeat resection rectopexy (in setting of constipation) 2. Ventral rectopexy 3. Delorme—patients with mucosal prolapse or limited full-thickness prolapse	Altemeier (perineal proctosigmoidectomy)
Rectopexy	1. Redo rectopexy 2. Resection/rectopexy 3. Ventral rectopexy 4. Altemeier (perineal proctosigmoidectomy) 5. Delorme	
Ventral rectopexy	1. Redo ventral rectopexy (in setting of technical failure) 2. Resection/rectopexy 3. Rectopexy 4. Delorme	Altemeier (perineal proctosigmoidectomy)
Delorme	1. Rectopexy—ventral or sutured 2. Resection/rectopexy 3. Redo Delorme 4. Altemeier (perineal proctosigmoidectomy)	
Altemeier (perineal proctosigmoidectomy)	1. Ventral rectopexy 2. Rectopexy	Resection/rectopexy

[1]. Some units have reported on combined simultaneous treatment of both rectal and genital prolapse [62]. Abdominal sacrocolpopexy with rectopexy for combined middle and posterior compartment prolapse is a safe procedure with a low risk of recurrence and improves bowel function and quality of life [63, 64]. While there could be concern about a bowel resection and mesh placement during the same procedure, one retrospective case series reported no increased risk of complications when a synthetic mesh was utilized for an abdominal sacrocolpopexy was performed in conjunction with a sigmoid resection and anastomosis [65]. A complete history which investigates pelvic floor health, a comprehensive vaginal and rectal examination, and selective advanced testing are crucial to identify and offer optimal treatment when weakness exists in multiple pelvic floor compartments.

Solitary Rectal Ulcer Syndrome

Solitary rectal ulcer syndrome (SRUS) is a disorder of defecation which is often associated with rectal prolapse or internal intussusception. Patients afflicted with this problem present with rectal bleeding, difficult defecation, tenesmus, mucus discharge, and anal pain of unknown etiology. On occasion, the rectal bleeding can be severe enough to require transfusion. On examination there is typically thickened mucosa located anteriorly (Figure 60-15) with ulcers seen in about 23 % of cases and polyps or masses in 74 % [66]. If present, rectal ulcers can be single or multiple shallow ulcers with hyperemic margins and a pale base. Commonly these ulcers occur on the anterior wall just above the sphincter complex but may occur anywhere in the rectal ampulla. This uncommon condition may be misdiagnosed as a polyp or even a cancer because of the alarming appearance seen in some with SRUS. Colitis cystica profunda (CCP) is felt to be a related disorder that produces similar symptoms to SRUS and may have a similar gross appearance. Both are felt to have some element of trauma associated etiology which may be due to intussusception traumatizing the wall as it invaginates downward. This may lead to ischemia which has been speculated to be part of the etiology. Characteristically on biopsy SRUS has fibrotic obliteration of the lamina propria. There can be a thickened muscularis mucosa. Biopsies of CCP demonstrate mucous cysts lined by columnar epithelium deep in the muscularis mucosa. It is conceivable that with trauma from a cephalad prolapsing area of rectum, mucosa could be thrust beneath the surface to produce these mucous cysts. A correct diagnosis of both these conditions is made with accurate pathologic evaluation.

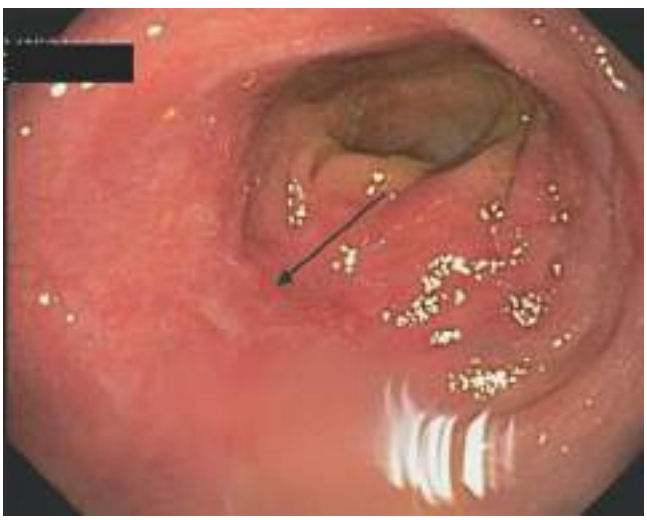

FIGURE 60-15. Solitary rectal ulcer. Inflammation and thickening of the anterior wall of the rectum with early stages of an ulcer.

The workup for both SRUS and CCP includes an in-depth history assessing for straining to defecate, rectal bleeding, and other anal symptoms. Endoscopy with biopsy is essential to make an accurate diagnosis. Treatment of these conditions is challenging and defecography and anal manometry may be useful to guide choices. Interestingly in SRUS, a thickened internal anal sphincter has been reported as a typical finding on endoanal ultrasonography [67].

Treatment is usually directed towards normalizing the defecatory disorder with diet modifications and bowel retraining utilizing pelvic floor physical therapy [68, 69]. Argon plasma coagulation has also been described as a potential treatment modality [70]. In our practice, transanal excision of the lesion is typically not favored as recurrence is particularly high. The Delorme procedure or a proctectomy with a coloanal anastomosis is another option, but again recurrence is high. One specific group of patients that may benefit from surgical intervention are those that have either internal intussusception demonstrated on defecography or overt rectal prolapse. These patients may be offered some form of rectopexy—either suture, mesh, or ventral rectopexy [71–73]. In our experience, anterior dissection may be particularly more challenging is missing the challenging than when dissecting for garden variety rectal prolapse not associated with SRUS or CCP, due to dense anterior fibrosis and inflammation.

In summary, this is a rare but frustrating condition most likely caused by some element of prolapse of the rectum. Conservative treatment is usually the favored approach as surgical intervention that utilizes excision of the lesion seems to have a high recurrence rate.

Conclusion

Surgery should always be considered the treatment of choice for rectal prolapse. The approach (perineal or abdominal) is debatable; however, current trends seem to favor abdominal procedures for all age groups unless the patient is extremely infirmed. Realistic expectations regarding functional outcomes should be reviewed prior to surgical intervention. Fecal incontinence may improve after surgery but full fecal

continence may not be attained. Additional therapy for fecal incontinence may be indicated after surgical healing. Constipation may improve, persist, or worsen after rectal prolapse surgery. Additionally some patients report new problems with constipation after rectal prolapse surgery. Treatment of pelvic floor pathologies should not be compartmentalized. Prolapse or dysfunction of other pelvic floor organs should actively be looked for and surgically addressed in conjunction with appropriate pelvic floor surgeons.

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61
Evaluation and Treatment of FI

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Key Concepts

- A thorough history and physical examination, followed by a trial of conservative measures is the first step to managing FI.
- Preoperative physiology testing may aid in selection of treatment modalities, but does not predict the outcome of treatment.
- Overlapping sphincteroplasty is a successful treatment in patients with complete sphincter disruption.
- Sacral neuromodulation has been demonstrated to be successful in patients with and without a sphincter defect.
- Biomaterial injection and radiofrequency energy delivery appear to provide modest benefit in incontinence scores, but further data is needed to substantiate this.
- The artificial bowel sphincter has demonstrated excellent improvement in incontinence scores, but complications and need for revisions prevent it from being a first line treatment for FI.

Introduction

Fecal incontinence (FI) is defined as the uncontrolled passage of feces or gas [1–4]. It is estimated that at least 18 million adults in the USA suffer from FI, while these figures appear to approach 50 % in institutionalized patients and this is frequently cited as the precipitating reason to transfer to nursing homes [5–7]. Recently, Brown et al. used Neilson data to conduct a survey of >6000 women in the USA older than 45 years with an impressive 86 % response rate [8]. Their results indicated that nearly 20 % of respondents experience episodes of FI at least once per year, while 9.5 % experienced FI at least once per month [8]. This study also demonstrated that patients prefer the term "accidental bowel leakage" rather than fecal incontinence. Prevalence estimates are thought to be conservative since a recent survey indicated that only 28 % of these patients have ever discussed their symptoms with a physician [9]. Of those who did seek care, over 75 % sought care with an internist or family physician, while only 7 % discussed their concerns with a colorectal surgeon [9].

Normal continence is a complex interaction between sensory function, sphincter muscle function, pelvic floor muscle coordination, rectal compliance, and consistency of stool. Failure of any of these mechanisms can lead to impaired continence. The most common historical factor is often prior obstetric trauma in a female [10]. Sphincter disruption from obstetric injury is observed clinically in approximately 10 % of all vaginal deliveries, but occult sphincter damage may be identified in up to 21–35 % of vaginal deliveries. Additionally, other possible causes include sphincter damage from prior anorectal surgery such as fistulotomy, lateral internal sphincterotomy, denervation of the pelvic floor from pudendal nerve injury during childbirth, chronic rectal prolapse, neurologic conditions (spina bifida, or myelomeningocele), or a noncompliant rectum from inflammatory bowel disease, or radiation proctitis [4, 10]. A careful history can be helpful in delineating these precipitating factors.

Focused physical examination includes inspection of the perineal body to look for thinning, or evidence of a prior fourth degree laceration, an assessment of resting sphincter tone and squeeze augmentation, use of accessory muscles, and to rule out other conditions, such as rectal prolapse, anal fistula, or active proctitis. If a rectal prolapse is suspected, straining on the commode may be required to reproduce it. Proctoscopy can rule out the presence of neoplasm, or active proctitis as well.

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Assessment Instruments

It is important to categorize the baseline severity of FI and to track this over time in order to monitor response to either conservative treatment or surgical therapy. The simplest method is a 2-week bowel diary, however a number of grading instruments are commonly used such as the Cleveland Clinic Florida (CCF) Incontinence Score [11], St. Marks Incontinence Score (SMIS) [12], or the Fecal Incontinence Severity Index (FISI) [13]. Other scales, such as the Fecal Incontinence Quality of Life (FIQL) [14] scale, are more reliable measures of quality of life, however, they are cumbersome to use and may be more beneficial in the setting of a research study. There is also emerging evidence that some of the current scoring systems may underestimate response to surgical treatment [15], while very few QOL scales demonstrate internal consistency or predictive validity [16], highlighting the need to develop better validated scales in the future. While we do not endorse one particular system, we do suggest tracking progress with objective measures over time.

Management

The management of fecal incontinence should always begin with attempting conservative measures. Conservative measures can take the form of medical management or lifestyle modification, and in some cases, will include an attempt at biofeedback/physical therapy retraining. Though no one regimen is ideal for every patient, we believe that all patients should at least fail a reasonable attempt at conservative measures prior to proceeding to more aggressive treatment options.

Medications and Lifestyle Modifications

After detailed questioning and review of a bowel diary, the first step is to attempt a medical regimen to control symptoms. If aggravating factors such as lactose, caffeine, or artificial sweeteners appear linked to symptoms, they should be discontinued. Optimizing stool bulk with a fiber supplement is often the easiest step to begin with. If a patient still has loose stools, antidiarrheal medications such as loperamide or diphenoxylate-atropine may be used to slow intestinal motility. A recent Cochrane review examined 16 trials of medical management of FI including 558 participants [17]. The majority of these trials examined FI in the setting of diarrhea and thus, examined the effects of antimotility agents on FI symptoms. The review concluded that most of the studies were small with limited follow-up and were more focused on treating diarrhea than FI [17]. Though the evidence does not conclude that any one regimen is more effective than another, few would argue the merits of a trial of medical measures prior to pursuing more advanced treatment options. In addition to oral medications, select patients experience benefit from scheduled enemas to attempt to control the timing of bowel movements to more socially appropriate times [18].

Biofeedback

Pelvic floor rehabilitation, or biofeedback, may be used in conjunction with medical management. An ideal candidate may be a patient who has some voluntary sphincter contraction rather than extensive or exclusive use of accessory muscles such as the gluteus muscles on examination when asked to squeeze. The literature on this topic is inconsistent with regard to study design and patient follow-up, making it difficult to determine the exact benefit of this modality. Though the designs of the studies vary, studies indicate at least some improvement in 64–89 % of patients [19–22]. However, a Cochrane review in 2006 concluded that no study reported any major difference between the results of biofeedback or any other form of conservative management [23].

Preoperative Testing

While some authors would suggest testing of patients during the first consultation, others tend to reserve testing for patients who may require surgical treatment. Testing most often includes anorectal manometry, ultrasound, and pudendal nerve testing.

Anorectal Physiology Testing

Anorectal physiology testing may be used in the evaluation of patients with FI. Results include resting and squeeze pressures, sphincter length, rectal compliance, and measurement of the rectoanal inhibitory reflex [24, 25]. Interpretation of the results of these tests is dependent upon the equipment used for measurement, and thus, each institution may have different baseline ranges for normal values. Though there is evidence that physiology testing results do not correlate with pre- and post-operative incontinence scores in patients undergoing sphincter repair [26], some authors suggest that results of these tests may help to guide treatment decisions [25, 26]. The ultimate goal would be to correlate the results of testing modalities to objectively select the best treatment option for an individual patient. However, further studies will be needed to fill this important gap in our current knowledge.

A point of further controversy is the value of pudendal nerve terminal motor latency (PNTML) testing. There is evidence that the pudendal nerves may be injured, most commonly in association with vaginal childbirth [27]. However, there is controversy as to whether PNTML testing is a useful adjunct in choosing a treatment algorithm. There appears to be no association of PNTML testing results with

response to sacral neuromodulation [28] and though some studies suggest a decreased efficacy of sphincter repair in the setting of pudendal neuropathy [29, 30], others have failed to corroborate this finding [31, 32].

Ultrasound

Ultrasound is a useful technique to document the presence of an internal or external sphincter injury. Thus, it may be an important adjunct to the workup of patients with a prior history of vaginal childbirth, or prior anorectal surgery. Ultrasound has been demonstrated to correlate with anal resting pressures, but does not correlate directly with objective incontinence scores such as the FISI [33]. Though there is a degree of inter-observer variability in diagnostic accuracy of endoanal ultrasound, the technique appears more reliable than transvaginal or transperineal ultrasound in detecting sphincter defects [34]. Whether or not to use ultrasound testing depends upon the treatment that is planned. While the presence of an ultrasound defined sphincter defect does not correlate with patient outcomes using sacral neuromodulation [28, 35], and studies of biomaterial injection have excluded patients with a sphincter defect [36, 37], preoperative ultrasound is a critical element in the planning of a sphincteroplasty operation [38].

Surgical Techniques

General Considerations

When conservative measures fail, patients should be carefully evaluated for appropriate testing such as anorectal physiology testing or endoanal ultrasound. When all of the above tests are normal, a defecography may be considered. Patients found to have rectal prolapse or full thickness intra-anal intussusception on exam and/or defecography should be considered for a surgical treatment of their prolapse (see Chap. 60). Others should undergo a rational sequence of treatments balancing the severity of their symptoms against the morbidity and the expected success rates of various surgical interventions. While data comparing the success of different treatment modalities for FI is not robust, a rational algorithm on how to sequence these treatments can still be derived (see Figure 61-1).

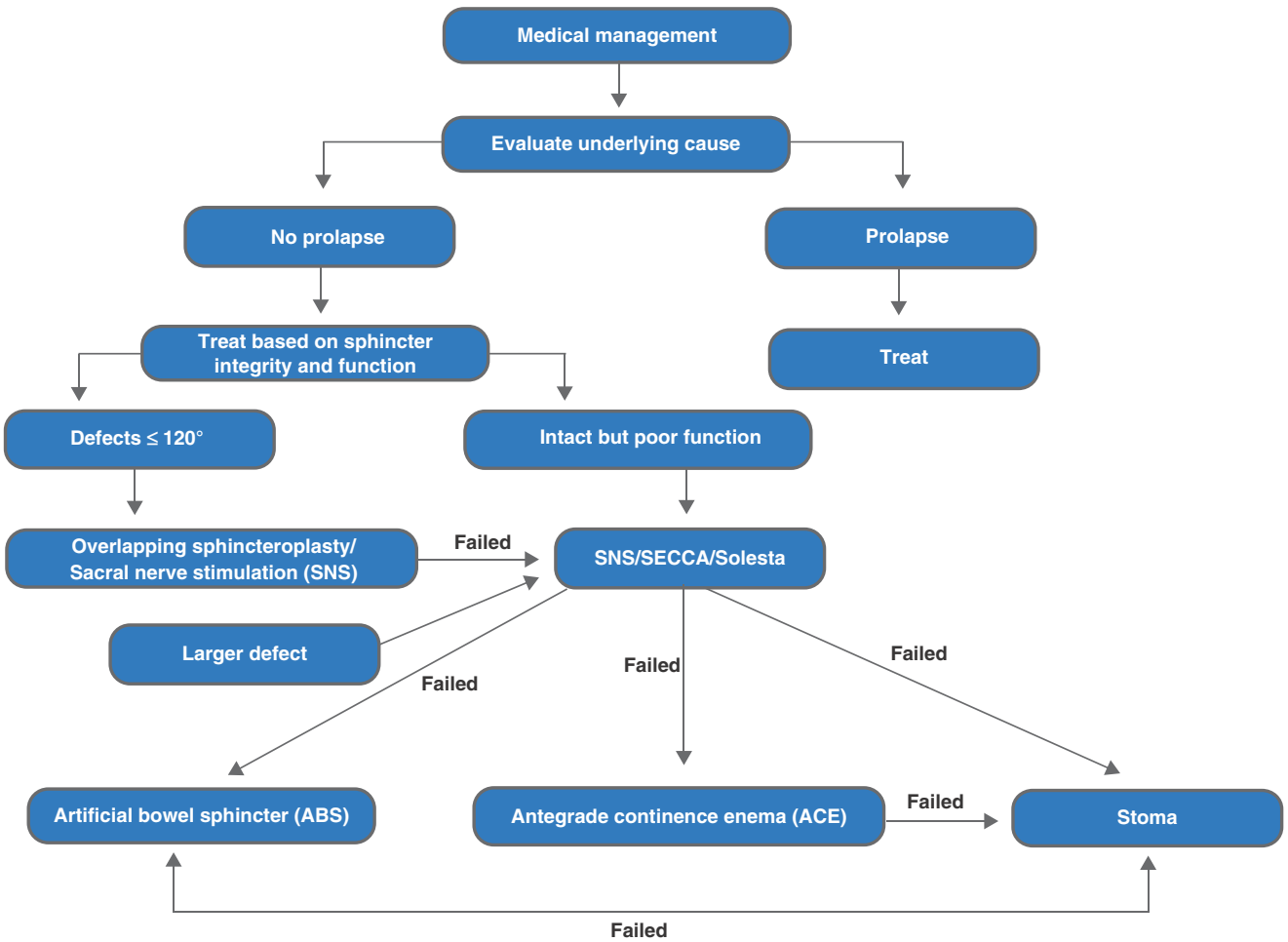

FIGURE 61-1. Step-wise algorithm aimed at managing patients presenting with fecal incontinence.

In the remainder of this chapter we will describe these treatments in further detail, limiting our discussion to the surgical approaches that are currently available in the USA.

Overlapping Sphincteroplasty

This procedure remains the gold standard for the treatment of fecal incontinence in young women with obstetric sphincter injury [39], which is usually confirmed by an anal ultrasound (Figure 61-2). It is also indicated in older women with severe FI and an external sphincter defect not larger than 120° on anal ultrasound. Though its efficacy in treating incontinence may decrease with increasing patient age and in the patients with coexisting pudendal neuropathy, both issues of age and relevance of pudendal neuropathy are still debated and decisions need to be made [40] on a case-by-case basis [30, 31]. Prior to offering this procedure, patients must be counseled regarding its efficacy in the short and long term. Patients should be advised that approximately 80 % of women can expect reasonable function (though not full continence) short term [41]. Patients should also understand that the efficacy of this repair deteriorates with time: by 10 years most women who undergo sphincteroplasty do become incontinent again [42–44]. There is some data suggesting that biofeedback after surgery may decrease or slow down the rate of this deterioration, but this study has not been reproduced [45].

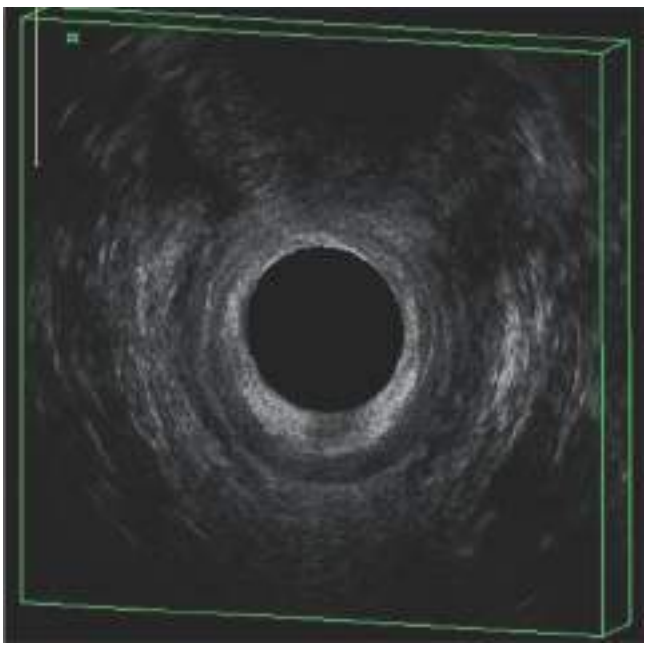

FIGURE 61-2. Three-dimensional ultrasound demonstrating the anterior sphincter defect. The internal sphincter appears hypoechoic (*dark*) and the external sphincter appears hyperechoic (*white*), with the incomplete ring anteriorly (*top*), indicating the sphincter defect.

Sphincteroplasty is performed following a full bowel preparation, under general or regional anesthesia, in either lithotomy or the prone jack-knife position (Video 61.1). A curvilinear incision is made on the perineal body, with the goal of separating the anus from the vagina (Figure 61-3). The injured external sphincter and the perineal body scar due to this injury is carefully separated from the skin, the ischiorectal fat, the anal mucosa/internal anal sphincter complex, and the vagina (Figure 61-4). In the patients with a coexisting internal anal sphincter injury the dissection around the anus is carried in the submucosal plane. Care must be taken not to buttonhole the vagina or the anus during this dissection. Separation of internal and external sphincters and individual repairs can be considered if the two are clearly identified. Otherwise the repair should be made en bloc. To repair the injury, the anterior scar is divided (Figure 61-5). Mobilization of the scar-sphincter complex should continue circumferentially around the anus, with the goal of ultimately overlapping the scar anteriorly [46]. Care should be taken not to extend the dissection beyond 180°, to avoid injury to the pudendal nerves that are coming in laterally to innervate the anus

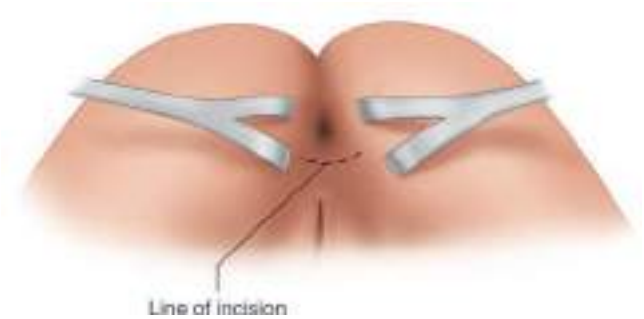

FIGURE 61-3. Overlapping sphincteroplasty: a curvilinear incision is made on the perineal body.

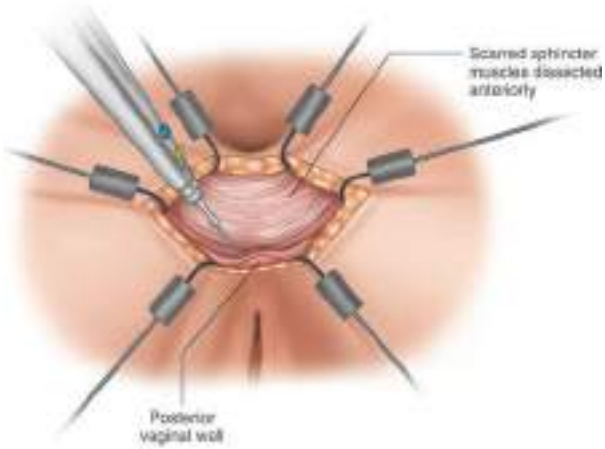

FIGURE 61-4. Overlapping sphincteroplasty: scar with attached retracted sphincter muscles are dissected anteriorly.

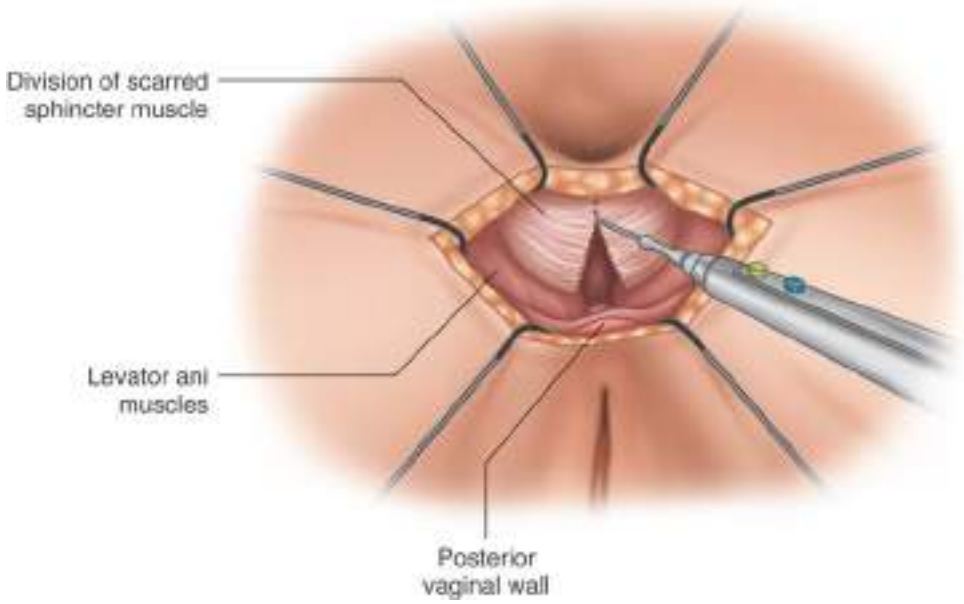

FIGURE 61-5. Overlapping sphincteroplasty: anterior scan/sphincter complex is divided.

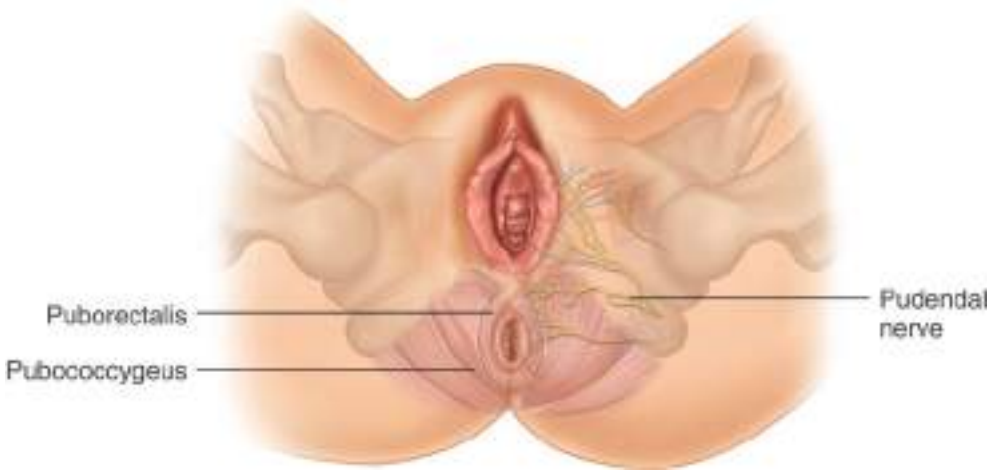

FIGURE 61-6. Overlapping sphincteroplasty: surgeons must be aware of the course of the pudendal nerve and aim to minimize pudendal nerve injuries at the sphincter of sphincter repair by avoiding dissection beyond more than 180-degrees anteriorly.

(Figure 61-6). Once dissection is completed, an anterior levatorplasty can be performed with absorbable sutures (Figure 61-7a). Following this, the sphincter-scar complex is overlapped and sutured in place with two or three non-absorbable (or very slowly absorbable) vertical mattress sutures able to withstand and hold together despite a predictable low level wound sepsis (Figure 61-7b) [47]. (After wound irrigation, the wound is closed as a "T" to decrease tension on skin, and the center of the incision is left open to facilitate drainage. A Penrose drain can be left in the opening. As with any perineal wound, the healing following this repair is slow and partial wound separation is common).

In patients with recurrent fecal incontinence after a repair, a repeat ultrasound can be considered to assess success of repair. Some argue that reintervention with a repeat repair can be offered [48], though data regarding success following repeat sphincteroplasty is slim and other options, such as sacral neuromodulation, may be more appropriate.

Sacral Neuromodulation

Sacral neuromodulation (SNM) is an FDA approved treatment for both fecal incontinence and overactive bladder. It works by modulating nerve impulses to the S3 nerve root.

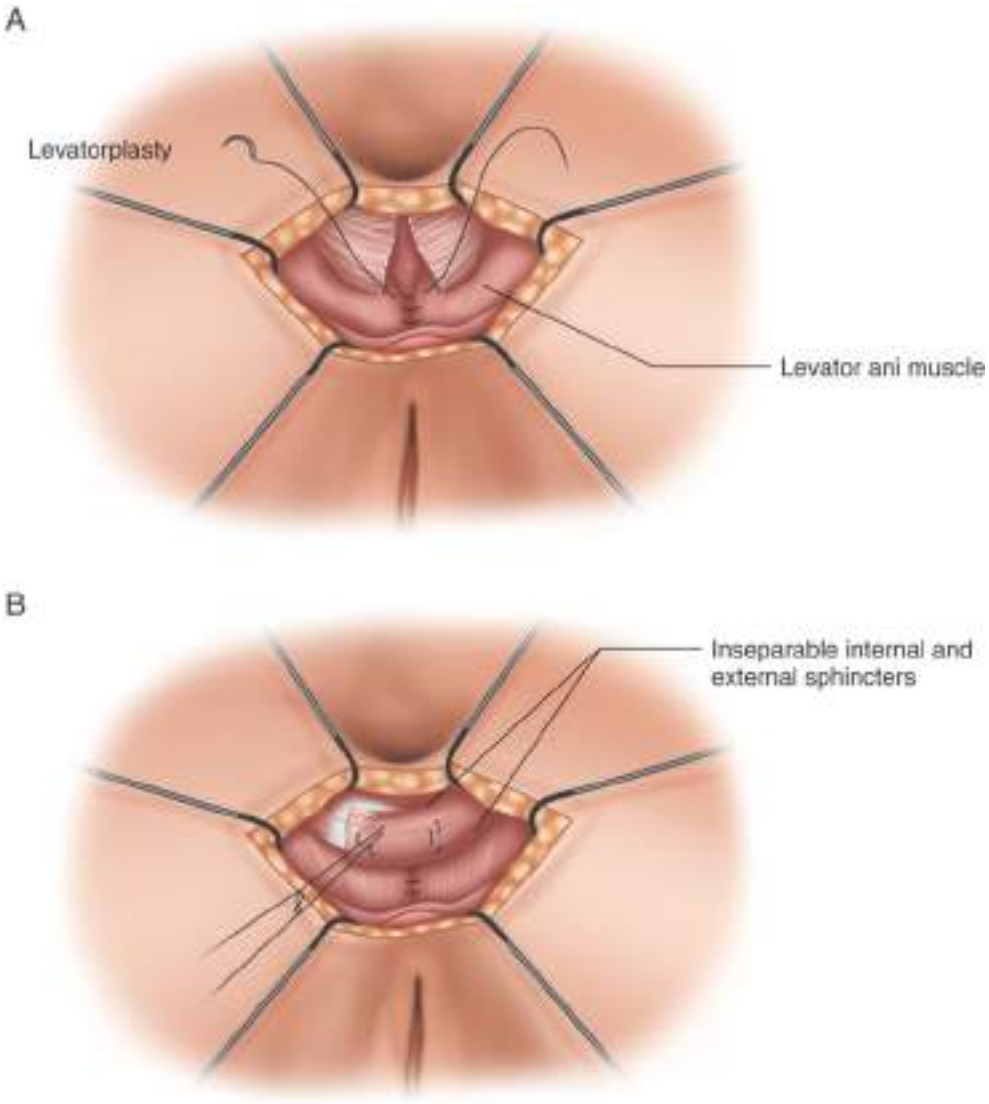

FIGURE 61-7. Overlapping sphincteroplasty: (**a**) levatorplasty is performed when appropriate, (**b**) scar-sphincter complex is overlapped to allow the ends of the retracted muscles to be realigned as close as possible to each other.

SNM appears to even be effective in patients with a disrupted sphincter complex on ultrasound, as studies have shown excellent efficacy in defects up to 120° [35, 49]. It also does not seem to work by directly augmenting sphincter function as measured by anorectal manometry [50]. It has been postulated that sacral neuromodulation promotes antegrade neuromodulation of the cerebral cortex—as seen in elegant brain MRI studies of patients with and without SNM [51].

Similarly, SNM may alter colorectal transport and motility [52]. Even more intriguing, other forms of neuromodulation such as percutaneous tibial nerve stimulation (PTNS) via a needle or a gel pad to the medial malleolus may also be effective in the treatment of fecal incontinence. Though as of now only SNM is FDA approved in the USA for the treatment of fecal incontinence, studies are being conducted worldwide to evaluate other methods of stimulation such as PTNS.

Though the full mechanism of action leading to an improvement in fecal continence following neuromodulation with SNM is still poorly understood, the beneficial effect of this treatment on fecal continence has been documented and replicated in several well-conducted studies both in the USA and all over the world [49]. SNM has been shown to result in a reduction in the severity and the frequency of fecal incontinence episodes, with 69–83 % of patients experiencing more than a 50 % improvement in weekly episodes of incontinence both short and long term [53–55]. Furthermore, 35–40 % may achieve full continence [49].

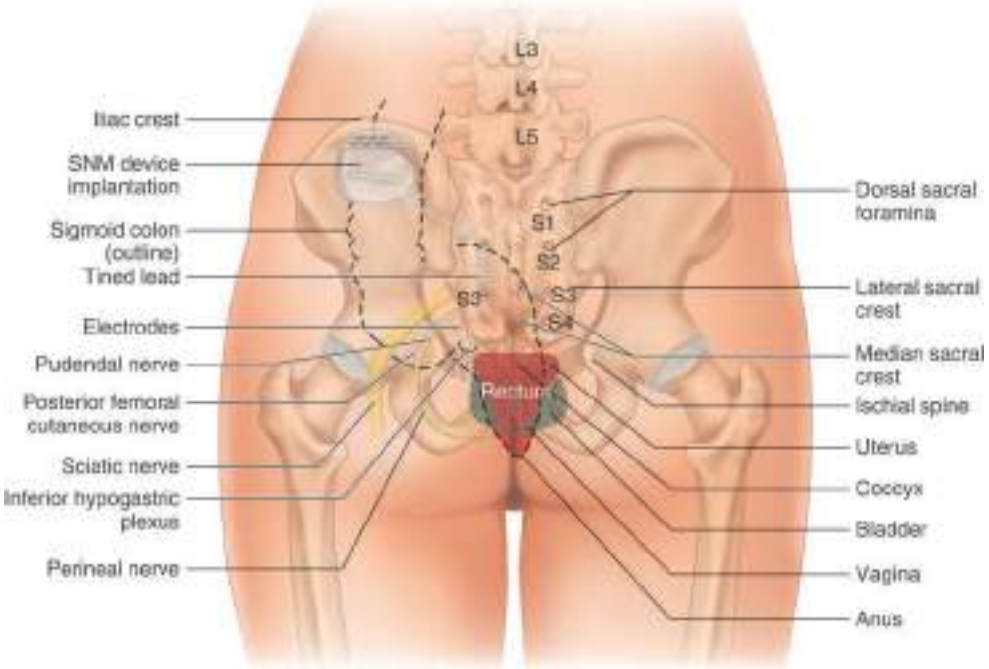

FIGURE 61-8. Sacral nerve modulation: the lead is placed through the S3 foramen and the implantable pulse generator is placed below the iliac crest and lateral to the sacrum.

Sacral neuromodulation is performed in two stages (Video 61.2). Fluoroscopy is used to identify the S3 sacral foramen, which is then accessed percutaneously by a needle. Once the needle location is confirmed radiographically, proximity of the S3 sacral nerve root is also assessed by gently stimulating the needle with a low electrical voltage. If the needle is appropriately placed, the surgeon is expected to observe a slight downward flexion of the patient's toes on the ipsilateral side as the needle, and the "bellows reflex"—a slight tightening of the gluteal and anal muscles. Once the needle is appropriately placed, a tined wire is passed through the needle and deployed in the same location (Figure 61-8). The wire is then tunneled under the skin to prevent infection and is connected to an external lead in its new location. The external lead is then tunneled one more time to yet another skin site prior to being connected to an external neurostimulator, which is then used to provide low voltage stimulation to the S3 root for a 1–2 weeks efficacy trial. Up to 90 % of patients report at least a 50 % reduction in fecal incontinence episodes and are then offered a second surgery, which involves the implantation of a more permanent hidden subcutaneous neurostimulator. This second procedure is again performed under local anesthesia, with mild sedation. The pocket hiding the coupling of the tined lead to the external neurostimulator wires is reopened. The external wires are discarded and a permanent neurostimulator is connected to the tined lead.

The first stage can also be done by placing a temporary wire rather than the tined lead. This is termed percutaneous nerve evaluation (PNE). In this procedure, the patient is placed in the prone position in the office. After a sterile prep and drape, a distance of 9 cm is measured cephalad from the tip of the coccyx and marked. The initial puncture sites are 2 cm lateral to this point. After instillation of local anesthetic, a finder needle is passed through the S3 foramen. When the patient is awake, it is not possible to turn the amplitude high enough to elicit a bellows response. Instead, the surgeon relies on sensory response to test stimulation. An S3 response is confirmed by sensation in the rectum, perineum, or vagina. Bilateral non-tined temporary leads are then placed. The patient then proceeds to keep a diary at home and the temporary leads are removed in the office in 1 week. If the test has been successful, the stage 2 procedure involves placement of the entire system in one setting. The benefit for this approach is to avoid one trip to the operating room, however, it is best suited for patients with daily incontinence, or more severe symptoms because the test period is only 1 week. This procedure may be performed with or without fluoroscopic guidance.

Despite the two-step approach currently used to place SNM, the procedures are well tolerated, and the infection rate is about 11 % [56, 57]. Long-term, the main drawback of the treatment is the need for revisions and replacements of the neurostimulator due to lead migration, infections or loss of battery power [49]. In addition, at this point the device is contraindicated in the patients needing body MRIs for other conditions (though MRI of the head and neck are approved).

Sphincter Augmentation Procedures

Several sphincter augmentation procedures have emerged as an alternative to sphincter repair, with varying success rates and complication profiles. These treatments include biomaterial injection and radiofrequency energy delivery. It is important to note that radiofrequency energy delivery is contraindicated if the patient has previously had a biomaterial injection.

Radiofrequency Energy Delivery

Radiofrequency energy delivery is performed under mild sedation, either in the operating room or the endoscopy suite. The treatment is administered via a patented anoscope (SECCA®). This anoscope allows insertion of four nickel-titanium curved needles at 5 mm intervals, for four separate levels from distal to proximal within the anal canal. These needles contain electrodes that administer radiofrequency energy to raise the temperature of the internal sphincter to 85°. Each electrode within the needle has thermocouples, measuring tissue and mucosal temperatures during energy delivery. In addition, the device assures that the mucosa is being cooled by chilled water to the base of each needle. Studies looking at the efficacy of this technique reported modest improvements in continence scores short and long term, though very few patients reported full resolution of symptoms [58–62]. Many studies reveal decrease of CCF score from a baseline of approximately 14 to a postoperative score around 10 [63]. Furthermore, long-term follow-up is very limited, though it appears that the short-term results are sustained in the long term [63].

The procedure is performed under moderate sedation in the jack-knife prone position. The dentate line is clearly identified. The needles are deployed in three or four quadrants at four levels within the upper anal canal, being careful about the anterior quadrant in females to avoid needle penetration into the vagina (Figure 61-9a). Once deployed, radiofrequency energy

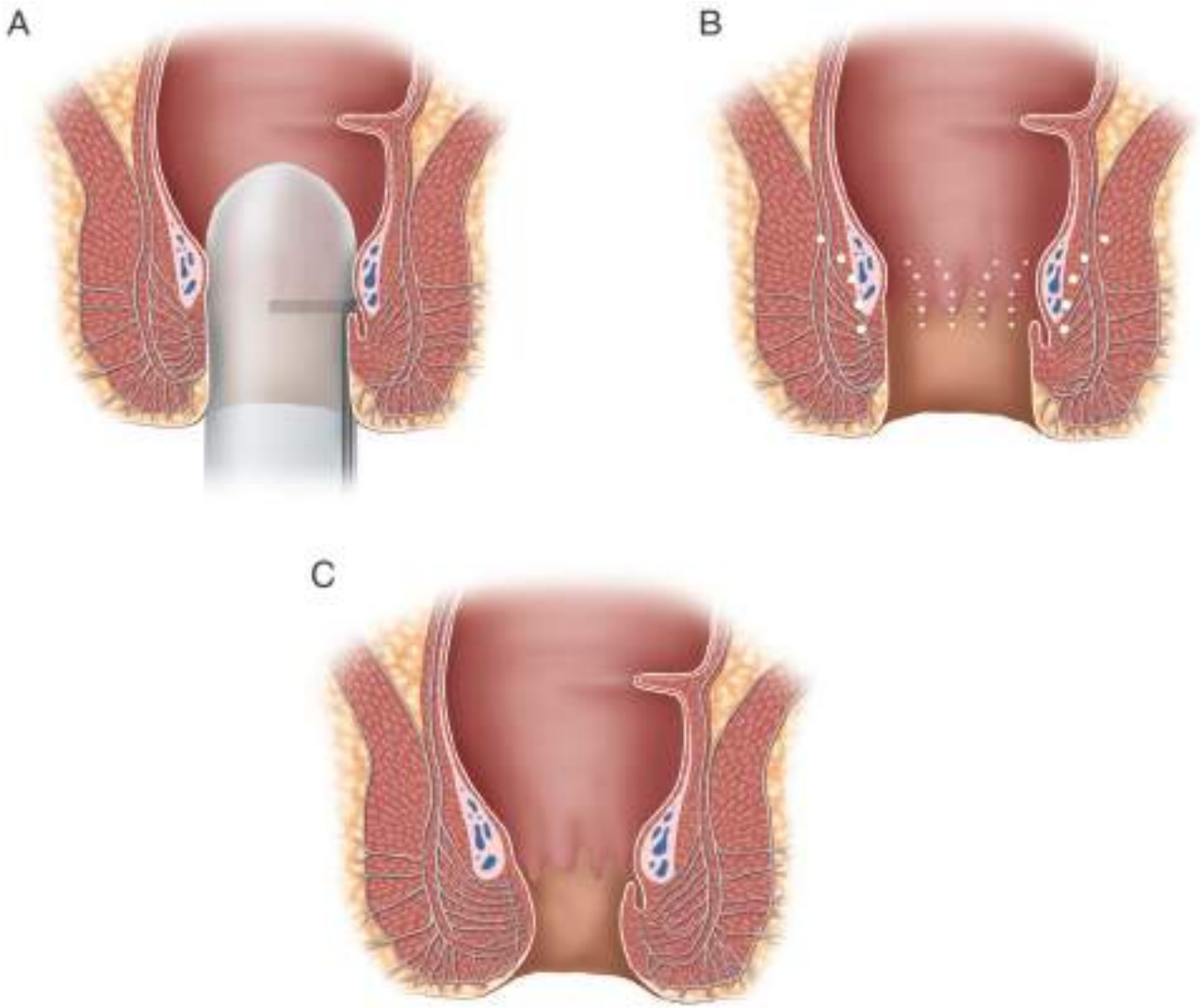

FIGURE 61-9. Secca procedure. (**a**) Anoscope wires are deployed in 3–4 quadrants circumferentially and are meant to enter the internal anal sphincter. (**b**) Radiofrequency treatment is performed at four levels within anal canal, both above and below the dentate line. (**c**) Procedure leads to internal anal sphincter thickening.

is administered to the internal anal sphincter where the device needles have penetrated the tissue. It is thought that the treatment results in a thickening of the internal sphincter complex via an increase in the thickness of the muscularis propria, a change in collagen cell composition and a decrease in the interstitial cells of Cajal [64] (Figure 61-9b, c). Common side effects include pain, infection, excessive scarring of the anus and, rarely, rectovaginal fistula formation [63].

Biomaterial Injection

Currently, NASHA Dx (Solesta®) is the only injectable agent approved by the FDA for the treatment of fecal incontinence in the USA. This substance is a stable, non-degrading dextranomer stabilized in hyaluronic acid. Its effect on the patients with FI was studied in a randomized controlled trial comparing Solesta to a sham injection. The trial showed that injection of Solesta® in the submucosal space in the upper anal canal led to a 50 % reduction in the severity of fecal incontinence in 52 % of patients as compared to the 30 % rate observed in the patients receiving placebo [37]. Most studies have offered patients a repeat injection and at least one study identified a higher degree of improvement in patients receiving a repeat injection [65].

Injections are performed with or without a local anesthetic, in a sterile fashion. The gel is injected between the mucosa and the internal sphincter, with or without ultrasound guidance (Figure 61-10). Care must be taken to place the gel above the dentate line. Complications are rare, though anal abscess and fistula can occur. The compound is contraindicated in patients with active inflammatory bowel disease, rectocele, previous pelvic radiation, full thickness rectal prolapse, and anorectal malformations [66]. Overall, Solesta injections are most effective for mild incontinence or seepage. Its role in the setting of a sphincter defect, when a second injection should be offered, and long-term efficacy need to be determined.

Sphincter Replacement Strategies

Most patients with persistent severe fecal incontinence despite all treatments listed above will benefit from a stoma or mini stoma alternatives described below. Few patients are considered for an artificial bowel sphincter. They must be motivated, without major medical comorbidities, and have sufficient healthy tissue surrounding their anal canal. A sufficient volume of healthy tissue surrounding the anus is

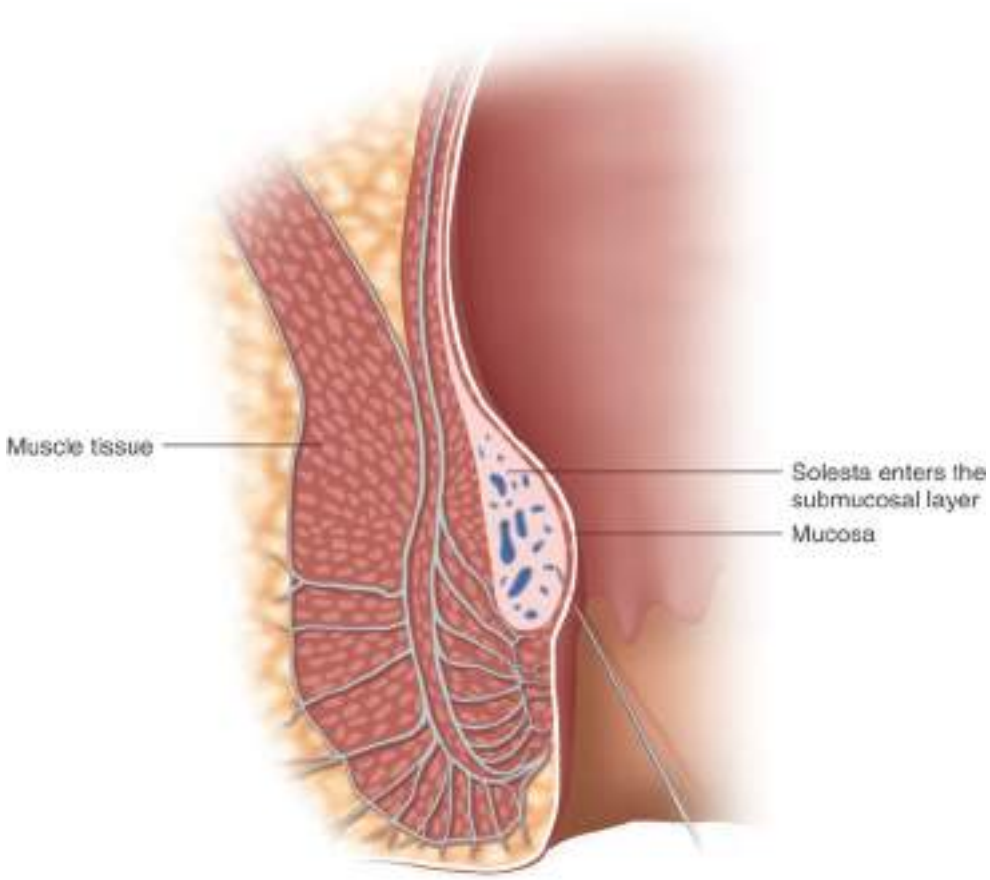

FIGURE 61-10. Biomaterial injection is performed by inserting the needle above the dentate line and into the submucosa.

necessary to provide implant coverage. The tissue also must also be healthy enough to allow wound healing without implant infection following placement. Thus, patients with a prior history of pelvic radiation, inflammatory bowel disease, diabetes, or immunosuppression are generally excluded. While the devices can be implanted under stoma coverage, most surgeons report reasonable outcomes without utilizing a stoma.

There are currently two artificial bowel sphincter devices, one of which (ABS) has been FDA approved for compassionate use for over 20 years. ABS is a fluid filled cuff that is placed around the anal sphincter through a perineal body incision or two incisions on either side of the anus. Thin plastic tubing is tunneled subcutaneously from the cuff to the scrotum (in the male) or the labia (in the female). This is connected to a pump that has a button that allows active deflation and passive re-inflation of the cuff. When the pump is compressed 8–10 times, this leads to the cuff deflating and fecal evacuation can occur (Figure 61-11). During deflation of the cuff by compressing the pump, fluid within the cuff is actively transferred through the pump into a storage balloon that is placed in the space of Retzius. The balloon is connected to the entire apparatus via another set of tunneled tubing. Then over the next 8–10 minutes the fluid is passively transferred back to the cuff via a one way valve in the pump. This in turn reinflates the cuff and closes the anus.

Since this device is a foreign body placed via an incision around the anus in a patient who is incontinent, it is not surprising that implantation of an ABS can be associated with major infections. Additionally, as many as 20 % of patients require revisions and removal of their device due to infection, erosion or device malfunction [67–69]. Ultimately only 50–80 % of patients have a remaining functional implant [67–72]. However, those who do keep their ABS in the long run report excellent fecal control of solid stool. Some retrospective series report normal continence in 65 % of patients and continence to solid stool in 98 %. In fact, some patients with new control of their fecal leakage may forget to open their devices on a regular basis and could develop fecal impaction [73, 74]. Even with regular device activation, new problems with rectal evacuation of stool and/or fecal impaction are commonly encountered in previously incontinent patients. These patients may respond to laxative or enema therapy but some ultimately have the device removed due to inability to satisfactorily moderate the evacuation difficulty. Long term all patients with an ABS remain at a high risk of requiring additional device revisions due to fluid leakage or delayed malfunction of the cuff itself, the tubing connecting the cuff to the manual control button, or the balloon reservoir in the space of Retzius. Yet another common cause for revisions is scar creation around the balloon in the space of Retzius. This in turn leads to poor anal cuff deflation and subsequent outlet obstruction [67–72]. Alternately, the scar can have calcifications which may puncture the balloon and also lead to device malfunction.

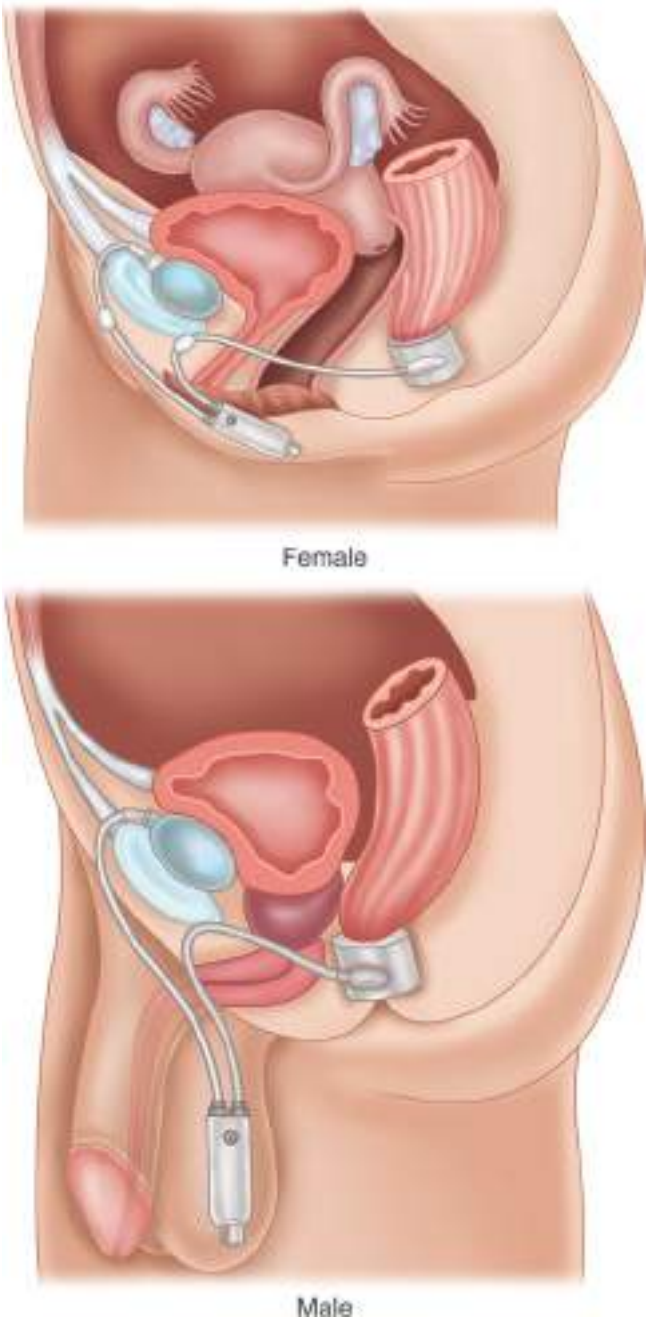

Figure 61-11. Artificial bowel sphincter placement in males and females. The cuff is placed to encircle the anus, while the balloon is located in the space of Retzius. The button is placed in the labia in females and in the scrotum in males.

An alternative device, the magnetic artificial sphincter (MAS), is currently under FDA review. The device contains small magnets on a flexible string. These magnets are placed on a string that surrounds the anal sphincter similar to the cuff of an ABS (Video 61.3). The device is carefully placed as high as possible around the anal sphincter, preferably just below the puborectalis muscle. The surgeon measures and then chooses the number of magnets needed to provide com-

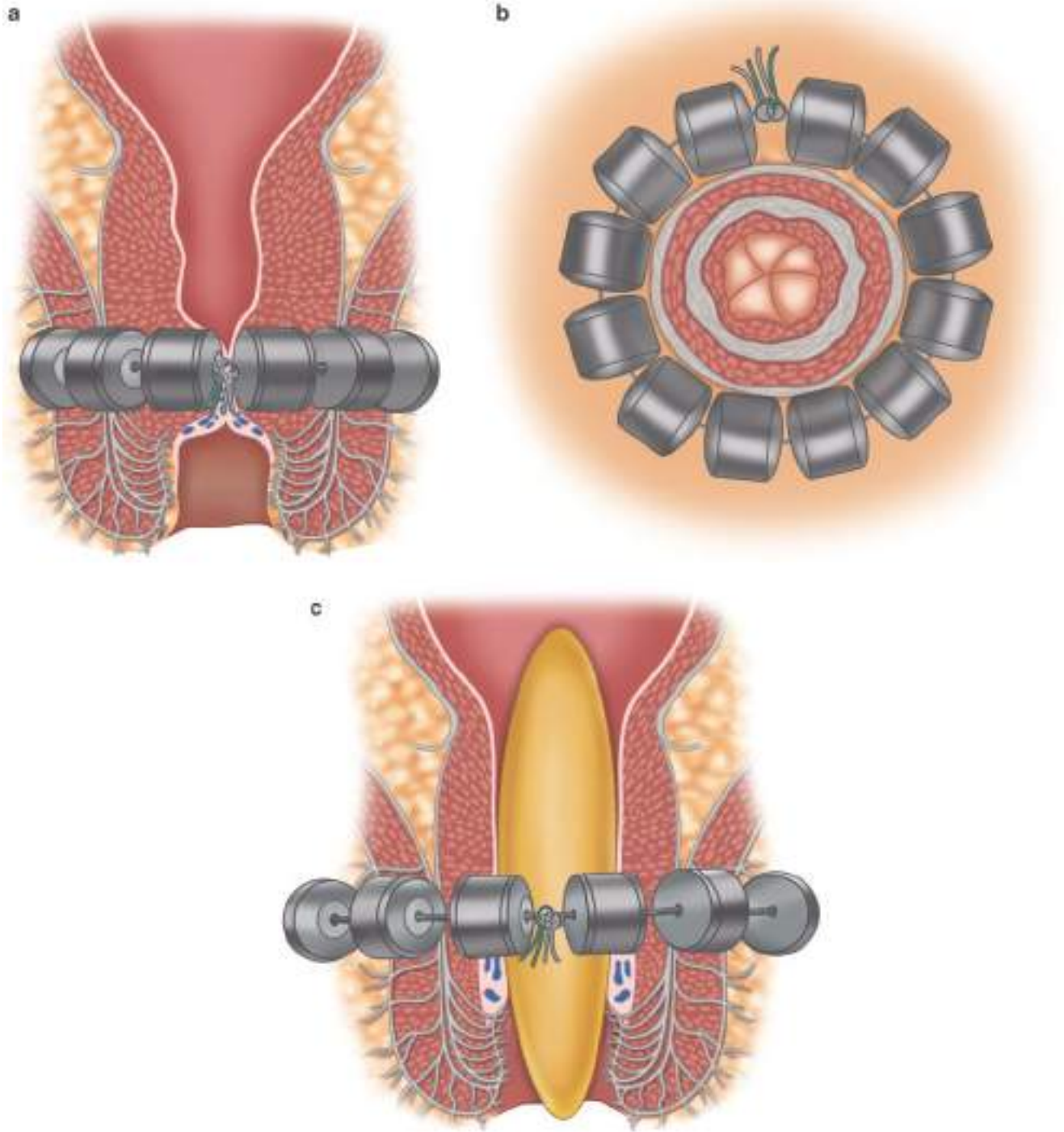

FIGURE 61-12. Magnetic anal sphincter. (**a**) In the resting state the magnets keep the anal canal closed. (**b**) Axial view to demonstrate placement of the magnetic sphincter outside the sphincter complex. (**c**) With bowel movements and Valsalva, the magnets expand to allow passage of stool.

plete occlusion of the anal canal when the magnets clump together (Figure 61-12a, b). During defecation, the magnets are forced apart by defecation and the device is allowed to expand in an "open position." Therefore, the string that contains these magnets has some redundancy to accommodate the fecal bolus and expand to the open position (Figure 61-12c). Thus, the natural position of the magnets leads to a closure of the anus which prevents anal leakage. Original studies describing MAS efficacy reported a promising improvement in patient continence as measured by a decrease in the Wexner Fecal Incontinence Severity Score and the Fecal Incontinence Quality of Life Scores [75, 76]. Complications at the time of

implantation appear comparable to those noted when placing the previously discussed fluid filled artificial bowel sphincter, with 29 % of patients reporting postoperative pain, temporary swelling and erythema in both gluteal regions after the implantation from low grade infections. Ultimately as many as 15 % require device explantation [75, 76]. A small randomized controlled study comparing initial 30 days complication rates and revision/explantation rates of MAS to ABS showed the two devices to be comparable in the short term, with comparable functional outcomes [77]. It is hoped, however, that this new device may require fewer long-term revisions following a successful implantation. While this is a reasonable supposition, long-term data on device function and device retention is still not available and a study reporting the satisfaction rates in the first 23 women in the world implanted with this device from 2008 to 2012 suggests the satisfaction rates may decrease over time [78]. As of this writing the company is in the process of obtaining FDA approval that allows this device to be implanted in patients who fail SNM therapy.

Stoma and Stoma Alternatives

Stoma creation remains a valid alternative for patients suffering from fecal incontinence. If all other treatments fail, patients receiving a well-constructed ostomy can expect an improved quality of life with a resumption of normal activities. When questioned, 84 % of patients undergoing ostomy creation to address fecal incontinence state that they would choose to have the stoma created again [79]. This being said, the observed quality of life is mainly in the domain of social functioning, while other quality of life domains measured by the SF-36 such as vitality, emotional health, etc. remain suppressed [80]. Furthermore, patients with a stoma are at risk for a separate set of stoma-related complications such as stricture, prolapse, peristomal inflammation, and retraction, among others (see Chap. 55). Therefore, given the numerous treatments available to ameliorate fecal incontinence severity, stoma creation should be an option of last resort.

In a small number of patients who failed other interventions and are seeking an alternative to a traditional stoma, a reverse appendicostomy [81] or a cecostomy tube placement can be considered. This provides a small opening from the skin into the colon for administration of an antegrade colonic enema (ACE) consisting of water, laxatives, or a combination of the two to clear the colon in a predictable fashion. The goal is to allow a patient to leave the house without fearing a major fecal accident. Patients interested in the ACE procedure are counseled to expect spending at least 1 hour emptying their bowels after each irrigation. Furthermore, many can expect persistent leakage of mucus and stool, skin difficulties from fluid leakage near the cecostomy tube or mini stoma, and in cases of native tissue conduits such as appendicostomies—stoma stenosis and stoma revisions. Furthermore, the majority of the data regarding short- and long-term efficacy of this approach is in children [82, 83], while the data in adults is mostly anecdotal.

Though other surgical options have been described such as injection of alternative bulking agents [66, 84–106], graciloplasty (stimulated and unstimulated) [107–115], pudendal nerve stimulation [116, 117], etc., these options are not available currently in the USA. For a full discussion of these options, please see the ASCRS FI task force review of all available options [118].

Conclusions

Fecal incontinence is a common, yet under recognized condition. Since the vast minority of patients seek medical care due to embarrassment, colorectal surgeons should feel comfortable in asking patients if they suffer from this debilitating problem. Recently many new treatment modalities with the potential to improve quality of life and symptoms have become available. Direct comparisons of these modalities with regard to cost and efficacy will help shape the treatment algorithms of the future.

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62
Functional Bowel Disorders for the Colorectal Surgeon

Jennifer M. Ayscue and Anjali S. Kumar

Key Concepts

- Irritable bowel syndrome (IBS) may arise from motility disorders, visceral hypersensitivity, and/or dyssynergy of the brain-gut relationship.
- Treatment for IBS often involves a combination of diet and medications.
- Chronic pelvic pain has multiple names, causes, anatomic and physiologic features. Similarly treatment options are numerous, but algorithms can be followed.

Introduction

Functional syndromes like IBS and chronic pelvic pain are a set of disorders that have roots in physiologic causes, but often include a strong psychological component. Chronic conditions like these are labeled "functional" when organic or anatomic causes have been ruled out. Most syndromes like these are poorly understood by gastroenterologists and colorectal surgeons who are generally more comfortable treating visible disease with specific procedural interventions. It is paramount that colorectal surgeons understand the symptoms, diagnostic criteria, and treatment strategies of these disorders, especially with respect to the role of medical management and physical therapy. These conditions can be vague and unremitting, causing frustration for the provider to definitively treat and for the patient to find relief permanence.

Irritable Bowel Syndrome

Epidemiology

Although IBS is the most commonly diagnosed gastrointestinal (GI) disorder, most colorectal surgeons do not have a good grasp of the intricacies associated with this common problem. It affects approximately 3–22 % of the population [1–3] depending on which criteria is used for measurement. IBS is diagnosed based on clinical symptomatology and is 1.5–2 times more prevalent in women versus men with women having more complaints of abdominal pain and constipation and men complaining more of diarrhea [4].

Pathophysiology

The pathophysiology of IBS is not well understood. It was initially thought to correlate with psychiatric illnesses, but since that time, other potential relationships have emerged. These include motility disorders, visceral hypersensitivity, and the notion of the brain-gut syndrome. More recently, other concepts like immune activation, genetic predisposition, altered intestinal permeability, history of acute gastrointestinal infection, and the human microbiome have been potentially implicated in the cause of IBS [5, 6]. It is interesting to note that more than 60 % of the human fecal load consists of bacteria, and alterations in the body's bacteria quantitatively or qualitatively may either lead to or treat the symptoms of IBS. The natural history of IBS is generally one of a chronic, relapsing disease. A mere 2–5 % of patients are ultimately diagnosed with alternative organic GI disorders and only 12–38 % of cases improve over time [5]. However, it has been noted that in patients who develop symptoms of IBS after a gastrointestinal infection, their symptoms usually resolve after only 5–6 years [7]. It is most likely that IBS is caused by a combination of factors and may require a blend of therapeutic options.

Diagnosis and Symptoms

Patients with IBS are diagnosed using clinical symptoms after exclusion of specific organic causes. The first diagnostic criteria were provided by Manning et al. in 1979 [8], but these were subsequently revised by multinational groups into the Rome I, Rome II, and the most recent Rome III criteria [9]. The Rome III criteria includes recurrent abdominal pain or discomfort at least 3 days per month for the past 3

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months, with symptom onset >6 months before diagnosis, associated with two or more of the following:

(1) *improvement with defecation*,
(2) *onset associated with a change in frequency of stool*,
(3) *onset associated with a change in stool form/appearance*.

In addition, guidelines published by the American College of Gastroenterology IBS Task Force recommend no additional testing with the possible exception of serum serology for celiac sprue, colonoscopy for patients over the age of 50 or in patients with specific alarm features which include rectal bleeding, unintended weight loss, iron deficiency anemia, nocturnal symptoms, and a family history of selected organic disease such as colorectal cancer, inflammatory bowel disease, and celiac sprue [10]. Celiac disease may be indistinguishable from IBS with abdominal pain, gas or bloating, and diarrhea, constipation, or both. It is an enteropathy resulting from an immune-mediated response to deamidated gliadin and is diagnosed by small intestinal biopsy demonstrating villous atrophy, crypt hyperplasia, and inflammation of the lamina propria or by serum test for specific elevated antibodies. In fact, 38 % of patients with celiac disease have been shown to have symptoms of IBS compared to control patients in a meta-analysis of four case–control studies [11]. Of the antibody tests, elevated Immunoglobulin A (IgA) anti-tissue transglutaminase antibody is the most diagnostic, followed by elevation of IgA endomysial and anti-tissue transglutaminase antibodies, and to a lesser degree, anti-gliadin antibody levels which are useful in monitoring the response to treatment of celiac disease. Other differential diagnoses for IBS include microscopic colitis, gastrointestinal infection, lactose maldigestion, inflammatory bowel disease, thyroid dysfunction, chronic constipation, and small intestinal bacterial overgrowth (SIBO) [12]. Although patients with IBS may present with symptoms of chronic constipation, IBS patients have abdominal pain or discomfort as a significant related symptom.

IBS may be classified into diarrhea-predominant (IBS-D) in which ≥25 % of bowel movements are classified as loose (not related to laxatives) according to the Bristol Stool Form Scale [13] or constipation-predominant (IBS-C) where ≥25 % of bowel movements are classified as hard or lumpy. Patients who have alternating features of at least 25 % of each type of stool are called IBS-mixed (IBS-M) [6]. Placing patients into these categories is important because many treatment strategies and recommendations are symptom-based (Table 62-1).

Treatment

Diets have long been implicated in the pathogenesis and symptomatology of IBS. Even though only about 1–10 % of Western society populations have true food allergies [14], patients with IBS often complain that the ingestion of food is a frequent precipitant of their symptoms with foods high in carbohydrates or fat being the most commonly implicated [15]. The relationship may represent a food intolerance, but many IBS patients commence dietary modifications occasionally leading to inadequate nutrition [16]. Recommended first line therapies have focused on specific dietary alterations such as gluten restriction. This may improve symptoms in patients with IBS, especially those who are diarrhea-predominant, according to controlled trials [17, 18]. However, a study by Biesiekierski et al. reported even better symptom relief in IBS patients with a diet restricting poorly absorbed carbohydrates unrelated to gluten intake [19]. A randomized, controlled trial by Halmos et al. demonstrated that reducing the intake of poorly absorbed short-chain carbohydrates, otherwise known as fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs), significantly improved the severity of symptoms of IBS [20]. Dietary FODMAPs are (1) fructose (fruits, honey, high fructose corn syrup (HFCS)), (2) lactose (dairy), (3) fructans (wheat, garlic, onion, inulin, etc.), (4) galactans (legumes), and (5) polyols (sweeteners, stone fruits). Examples of varying levels of FODMAP diets (low, moderate, high) are detailed in Table 62-2. A subsequent study by Staudacher et al. randomized 41 patients to either a FODMAP diet or their regular diet, and they noted that 68 % (13/19) of patients in the FODMAP diet reported adequate control of their symptoms as opposed to only 23 % (5/22) of patients eating their regular diet [21].

Fiber has long been recommended as first-line therapy for IBS, especially IBS-C, but overall results have been disappointing. A randomized, controlled trial of 275 patients showed that psyllium and soluble fiber improved symptoms of IBS over insoluble fiber (bran), followed by placebo. They reported early dropout of some patients due to reported worsening of symptoms especially in the bran group [22]. In a 2014 meta-analysis, a modest benefit for soluble fiber, but not for insoluble fiber was also noted in patients with IBS [23]. Thus, the American College of Gastroenterology Functional Bowel Disorders Task Force has recommended psyllium in the treatment of IBS [24]. However, use of insoluble fiber should be discouraged, especially in IBS-C patients. Table 62-3 details characteristics and examples of soluble and insoluble dietary fibers.

IBS has been shown to occur subsequent to episodes of bacterial gastroenteritis, leading to the implication that the gut biome may substantially relate to the pathogenesis of IBS [25]. SIBO has been studied as a possible cause of IBS. Unfortunately, definitive evidence that patients with IBS also have SIBO is variable, but it appears to be more common in IBS-D predominant patients [26–29]. Rifaximin is a poorly absorbed, broad spectrum antibiotic used for SIBO and is not

TABLE 62-1. Treatment options in irritable bowel syndrome

	Mixed IBS	Diarrhea-predominant IBS	Constipation-predominant IBS
Dietary modifications	Lactose free, gluten restriction, low FODMAP	Lactose free, gluten restriction, low FODMAP	Lactose free, gluten restriction
Fiber supplement	Trial (psyllium)	Trial (psyllium)	Trial (psyllium)
Antibiotic, probiotics	Consider trial of antibiotics if has SIBO, probiotics	Consider trial of antibiotics if has SIBO, probiotics	Consider trial of probiotics
Peppermint oil	Consider trial	Consider trial	Consider trial
Antidiarrheals/ Antispasmodics	Consider loperamide, diphenoxylate atropine	Consider loperamide, diphenoxylate atropine, hyoscyamine	Not recommended
Antidepressants	Consider trial of TCAs, SSRIs	Consider trial of TCAs, SSRIs	Consider SSRIs
Psychological therapies	May consider	May consider	May consider
5-HT3 antagonists	Alosetron (restricted)	Alosetron (restricted)	Not recommended
Prosecretory agents	Not recommended	Not recommended	Trial of linaclotide, lubiprostone
Osmotic laxatives	Not recommended	Not recommended	Trial of PEG, other non-stimulant laxatives

TABLE 62-2. Examples of foods by varying levels of FODMAP (Fermentable Oligo-Di-Monosaccharides and Polyols)

Food group	Low FODMAPs	Moderate FODMAPs (limit)	High FODMAPs (avoid)
Eggs, meats, poultry, fish	Meats, eggs, fish, shellfish		
Dairy	Lactose low dairy: cream cheese, half and half, hard cheeses (cheddar, colby, parmesan, swiss, etc.), soft cheeses (brie, feta, mozzarella, etc.), sherbet, yogurt (greek), whipped cream		High lactose dairy: buttermilk, chocolate, creamy/cheesy sauces, custard, ice cream, milk (cow's, goat's, sheep's, condensed, evaporated), soft cheeses (cottage, ricotta, etc.), sour cream
Meat, non-dairy alternatives	Non-dairy milks, nuts (walnut, macadamia, peanut, pecan, pine), nut butters, tempeh, tofu	<10 almonds <10 hazelnuts	Cashews, beans, black eyed peas, bulgur, lentils, miso, pistachios, soybeans, soybean milk
Grains	Made with gluten free/spelt grains		Made with wheat/barley/rye when it's the major ingredient
Fruits	Bananas, blueberries, cantaloupe, cranberries, grapes, honeydew, kiwi, lemon, lime, mandarin, orange, pineapple, raspberries, strawberries	¼ avocado, <3 cherries, ½ grapefruit, ½ pomegranate, <¼ cup shredded coconut, <10 dried banana chips	Apples, applesauce, apricots, blackberries, canned fruit, dates, dried fruits, mango, nectarines, papaya, peaches, pears, plums, prunes, watermelon, avocado
Vegetables	Alfalfa/bean sprouts, bell peppers, carrots, cabbage, cucumbers, eggplant, green beans, kale, lettuce, potatoes, radishes, spinach, squash, tomatoes, zucchini	¼ cup canned artichoke hearts, <3 asparagus spears, 4 beet slices, <½ cup broccoli, <½ cup brussel sprouts, <1 cup savoy cabbage, 1 celery stick, <½ cup green peas, 3 okra pods, <10 pods snow peas, ½ corn cob, <½ cup sweet potato	Artichokes, cauliflower, mushrooms, sugar snap peas
Beverages	Coffee, tea		Made with HFCS, fortified wines (sherry, port)
Seasonings, condiments	Jam/jelly/pickle/relish/salsa/sauce/maple syrup without HFCS, most spices and herbs, homemade broth, butter, chives, cooking oils, mustard, pepper, margarine, mayonnaise, green onion, olives, pesto, salt, seeds, sugar, soy sauce, vinegar		Products with HFCS, agave, garlic, garlic salt/powders, honey, hummus, molasses, onions (not green), onion salt/powders, tomato paste, artificial sweeteners (isomalt, mannitol, sorbitol, xylitol)

TABLE 62-3. Characteristics of soluble and insoluble fibers and dietary sources of each

Fiber type	Mechanism	Dietary sources
Soluble	1) retains water and turns to gel during digestion 2) slows digestion and nutrient absorption from the stomach and intestine	Oat bran, barley, nuts, seeds, beans, lentils, peas, and some fruits (citrus, apples, strawberries) Many vegetables
Insoluble	Speeds the passage of foods through the stomach and intestines and adds bulk to the stool	Wheat bran, vegetables and whole grains

specifically Food and Drug Administration (FDA) approved for IBS, but in a recent meta-analysis of five randomized trials, it was shown to improve symptoms in predominantly non-constipated IBS patients [30]. Probiotics, which contain live bacteria, have shown some potential in improving global symptoms such as bloating and flatulence in IBS [21]. In particular, preparations with a combination of probiotics may have the most overall effect on symptom improvement. Prebiotics, which are nutrients taken to encourage the growth of probiotic bacteria, and synbiotics, which are a combination of probiotics and prebiotics, have also been considered as potential added or alternative therapy. However, to date, studies on probiotics, prebiotics, and synbiotics are insufficient to make adequate recommendations on their use.

Other therapies, including exercise, psychological therapies and acupuncture may have variable benefit. Regular exercise has been shown to improve symptoms in IBS with a statistically significant difference in the IBS symptom severity score [31]. The effect of psychological therapies was evaluated in a recent meta-analysis of 32 varying trials on different psychological therapies including hypnotherapy. They reported overall improvement in IBS symptoms relative to control therapies [32], but access to therapists experienced in the management in patients with IBS may be challenging. In a controlled study of acupuncture, there was no demonstrated benefit in IBS patients compared to sham acupuncture [33].

Diarrhea-Predominant IBS (IBS-D)

Antispasmodics such as hyoscine, dicyclomine, otilonium, cimetropium, and pinaverium have been tried with some degree of success in IBS-D. A 2011 Cochrane review reported improvement in abdominal pain and global IBS symptoms over placebo [34], but use may be best for postprandial abdominal cramping and loose stools [5]. Anticholinergic side effects such as constipation, fatigue, dry mouth, dizziness, and blurred vision may limit use of antispasmodics, especially in the elderly.

Peppermint oil has also been used and may be effective through diminished visceral hypersensitivity and effect of pain sensation in the gut. A meta-analysis of nine studies showed a statistically significant improvement of global IBS symptoms with few side effects such as reflux [35].

Tricyclic antidepressants (TCA) and selective serotonin reuptake inhibitors (SSRIs) have also shown promising results for global symptom improvement and reduction of pain in IBS, although the side effect profile may limit patient tolerance [21]. Thus, these medications should be selected carefully with close physician follow-up. TCAs were studied as a part of a meta-analysis of 17 randomized controlled trials including 1084 patients [29]. Patients receiving TCAs were statistically less likely to remain symptomatic versus placebo. TCA side effects include dose-dependent constipation, drowsiness, weight gain, dry eyes and mouth, and QT-prolongation.

Serotonergic agents affect gastrointestinal secretion, motility, and sensation. Serotonin subtype 3 (5-HT_3) receptors affect visceral pain, and 5-HT_3 antagonists decrease painful gut sensations and slow intestinal transit [36]. Alosetron, a selective 5-HT_3 antagonist has shown efficacy in IBS-D [37]. However, reports of severe constipation and ischemic colitis initially led to its withdrawal by the United States FDA in 2001. It was subsequently reintroduced in 2002 under a risk management program, restricting its use to treatment only for women with severe IBS-D. Ondansetron, a less potent 5-HT_3 antagonist has been shown to significantly improve stool consistency, nausea, stool urgency and frequency, bloating, and global IBS symptoms [38].

Although loperamide is an effective antidiarrheal, it has not been shown to be effective and is not recommended in the treatment of symptoms of IBS except to decrease the frequency and increase the consistency of stool [21].

Constipation-Predominant IBS (IBS-C)

Tegaserod, a partial serotonin subtype 4 (5-HT4) receptor agonist, increases intestinal secretion, augments the peristaltic reflex, and accelerates gastrointestinal transit [39]. It was granted FDA approval for IBS-C patients in 2002 but was withdrawn by the FDA in 2007 for possible cardiovascular adverse effects and is not currently available in the USA. Prucalopride, another 5-HT4 agonist, is available in Canada and Europe, but data is lacking.

SSRIs have similar effects in the bowel as serotonin receptor agonists. As an antidepressant, SSRIs were also studied as part of the meta-analysis by Ford et al. and were noted to have similar results with significant improvement in symptoms of IBS over placebo [29]. However, side effects of this medication include sexual dysfunction, nausea, drowsiness, agitation, and diarrhea, so they are more appropriately considered for use in IBS-C patients.

Prosecretory agents have also shown promise in the treatment of IBS-C. Linaclotide is a hormone in the guanylin peptide family that activates guanylate cyclase-C receptors in the intestinal lumen. This leads to a cascade of events causing sodium and water secretion as well as modulation of afferent pain sensors [40]. In a 2013 meta-analysis of three controlled trials in patients with IBS-C, a statistically significant improvement of symptoms was noted with 290 μ linaclotide compared with placebo [41]. Lubiprostone, another prosecretory agent, works by activating chloride channels in the intestine, resulting in chloride and water secretion and faster intestinal transit. In two randomized controlled trials, lubiprostone was also shown to improve symptoms in 1171 IBS-C patients compared to placebo with a relatively low incidence of nausea and diarrhea [42].

Laxatives have also been tried in the treatment of IBS-C patients. PEG formulations have been studied, but overall results have been disappointing. Chapman et al. reported on the use of PEG in 139 patients noting an increase in the number of bowel movements to at least four per week with an increase of at least two or more from baseline, but there was no improvement in abdominal discomfort or pain [43]. No other known randomized controlled trials have been performed for other laxatives, and use has been limited due to cramping and increased pain concerns.

Chronic Functional Pelvic Pain

Like IBS, chronic functional anal pain is a set of disorders that has roots in physiologic causes, but can often have a strong psychological component. Chronic pain in the anal canal, rectum, or pelvis is labeled "functional pain" when organic or anatomic causes have been ruled out. Like IBS, these pain syndromes are typically poorly understood by gastroenterologists and colorectal surgeons who are generally more comfortable treating visible disease with specific procedural interventions. In addition, there is a paucity of research evidence available to guide the diagnosis and treatment of these conditions. Therefore, like IBS, chronic functional pelvic pain can be frustrating for the provider to definitely treat.

Chronic pelvic pain syndromes affect up to 7 % of the population, but are brought to the physician's attention in only a third of these cases. Patients often report significant impairment in quality of life, work absenteeism, and psychological distress due to chronic pelvic pain.

A challenge in caring for patients with anorectal and pelvic pain is that a number of structural and inflammatory etiologies must be considered. Absence of a visible anorectal abnormality as evidenced by anoscopy or proctoscopy is useful in completing this evaluation. The provider should keep an eye out for cryptitis, fissure, abscess, hemorrhoids, solitary rectal ulcer, inflammatory bowel disease, and rectal ischemia. Chronic prostatitis and pelvic endometriosis should also be considered as potential contributors to chronic pelvic pain. These disorders are difficult to elicit on physical exam, but symptoms of these disorders may be elicited in the history.

A limitation in achieving success in these patients is that there is little consensus on the usefulness of the various diagnostic modalities (imaging studies, defecography, manometry, pudendal nerve terminal motor latency, endoscopy, endoscopic ultrasound) used in evaluating such patients. There are also a wide variety of therapeutic options (including massage, dietary modifications, laxatives, antispasmodics, antidepressants, anxiolytics, topical agents, local anesthetic injections, steroid injections, botox injection, and surgery). Studies testing the effectiveness of these therapeutic modalities are difficult to conduct as many of these disorders are multifactorial and difficult to stratify. Typically, pelvic pain disorders are grouped into the following disease descriptions: chronic proctalgia, coccygodynia, and pudendal neuralgia.

Chronic Proctalgia

To improve consistency in the diagnosis of anorectal pain syndromes, the Rome III criteria has defined chronic proctalgia as: "chronic or recurrent rectal pain or aching lasting at least 20 min, in the absence of structural or systemic disease explanations for these symptoms." Duration of pain >20 min is a distinguishing feature, since shorter episodes of pain are classified as proctalgia fugax. Proctalgia fugax is sudden, severe pain in the anorectal region which lasts <20 min, and is usually described as disappearing completely, just as suddenly as its onset. Although proctalgia fugax can recur, the number of episodes is relatively few and is therefore not considered a chronic pain syndrome.

Chronic proctalgia is further divided by the Rome III criteria into two subtypes: (1) levator ani syndrome (LAS) is termed when traction on the pelvic floor produces tenderness and (2) unspecified functional anorectal pain where painful sensations are absent when the levator muscle is palpated during digital rectal examination.

Inflammation of the levator or arcus tendon of the levator ani muscle has been suggested as a cause of chronic proctalgia, since tenderness on palpation is most commonly found on the left side where the muscle inserts into the pubic ramus of the pelvis. This etiology has been called into question by investigators who have unsuccessfully attempted to relieve symptoms with local steroid injections to decrease inflammation [44, 45]. In addition to psychosocial factors such as anxiety disorders, depression, and stress, history of spinal surgery and childbirth are common features in patients presenting with this syndrome.

Anorectal physiology and imaging studies (defecography) are often undertaken but found to have little diagnostic or prognostic value. Increased anal canal resting pressures on anorectal manometry are inconsistently reported.

Treatment considerations include biofeedback, digital massage of the levator muscles, trigger point injection with a steroid or botulinum toxin, and electrogalvanic stimulation (EGS) (Figure 62-1).

In a prospective, randomized trial of 157 patients, Chiarioni et al. found that among patients meeting Rome III criteria for chronic proctalgia, those with dyssynergic defecation were more likely to report successful outcomes after pelvic floor rehabilitative therapy. The authors suggest that a simple balloon evacuation test performed in the office with a disposable Foley catheter filled with 50 mL of water enables providers to select patients that will be more likely to benefit from biofeedback [46].

Caudal block steroid injection and/or pelvic tender point injection with a mixture of triamcinolone acetonide and lidocaine resulted in no improvement of rectal pain, which discredits the inflammatory etiology of these syndromes [44, 45]. Temporary paralysis of the muscle has also been tested by injection of Botulinum Toxin A and resulted in prolonged balloon expulsion but no differences in rectal pain [47].

Digital massage of the puborectalis sling (Figure 62-2) can be undertaken with the intention of relaxing the tensed

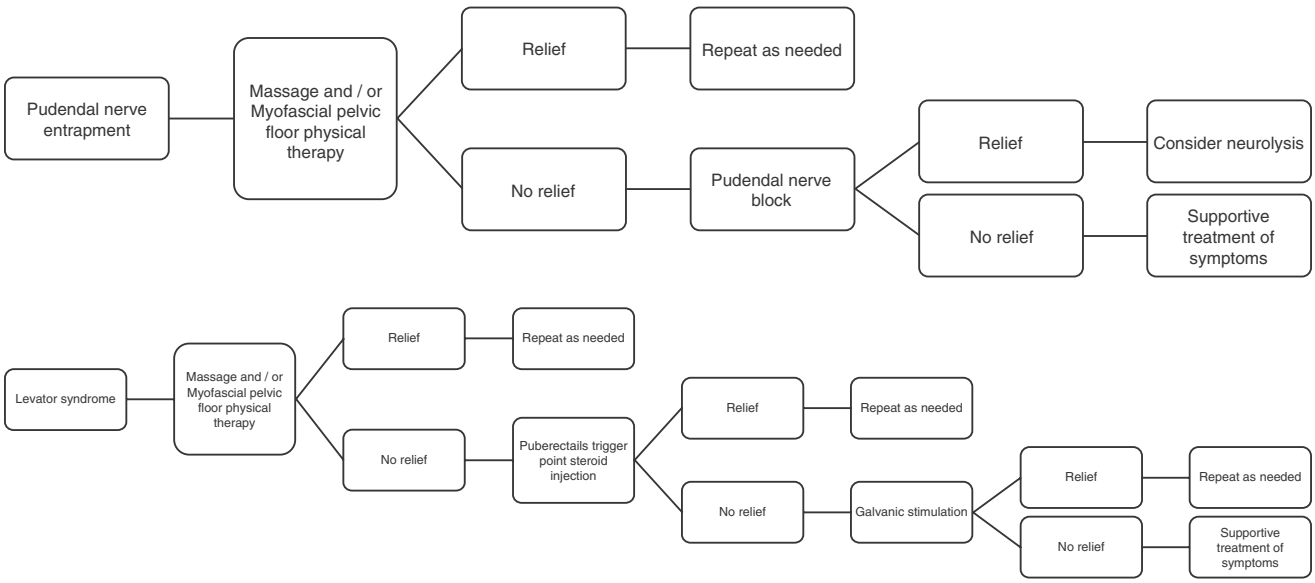


FIGURE 62-1. Algorithm for management of chronic proctalgia.

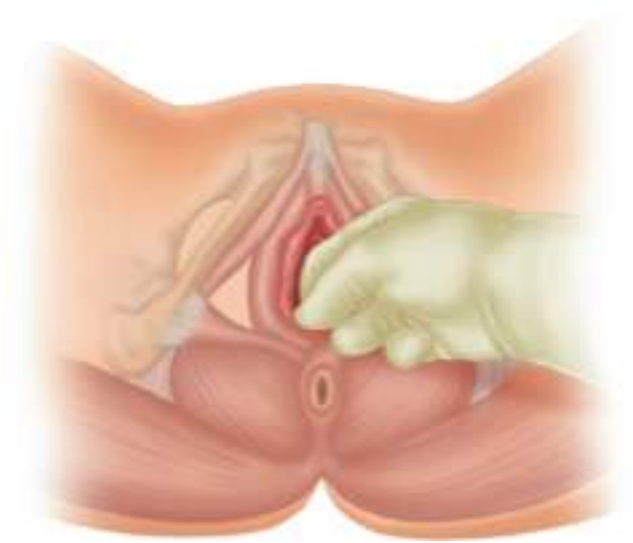


FIGURE 62-2. Massage with myofascial release via a vaginal approach.

muscles [48]. Therapists advise that massage should be performed firmly and repetitively (affected side massaged up to 50 times). Many believe that if the massage does not cause discomfort, it may not be effective [48]. It is important to note that massage of the levator ani muscle is seldom prescribed as sole therapy, and is often employed in conjunction with hot sitz baths or a short-term course of oral Diazepam, both of which are assumed to have myorelaxant properties. Success was as high as 68 % in a study of 316 chronic proctalgia patients [49].

As illustrated in the management algorithm (Figure 62-1), EGS can be considered when conservative measures have failed. In delivering EGS, a low frequency oscillating current (80 cycles per second) is applied to the pelvic floor muscles through an anal probe. This induces fasciculation which will cause prolonged fatigue. It is thought that this fatigue breaks the spastic cycle in order to provide sustained symptom relief. It is important to counsel patients that the side effect most commonly reported is mild worsening of pain on the first days of treatment. Studies have reported a success rate of 25–91 %. Sohn et al. reported the highest success rates among their 80 patients. They delivered EGS at gradually increasing voltages (0–300 V, per patient tolerance) for 1 h per day for three sessions in a 10-day period. These results were not able to be reproduced by other investigators who attempted the same protocols [50].

Coccygodynia

Pain arising in or around the coccyx is termed coccygodynia. It can be exacerbated by prolonged sitting on hard surfaces. When the pain lasts more than 2 months, it is considered chronic. Chronic spasm of the pelvic floor which exerts tension on a stiff coccyx may be an etiologic factor, with accidental trauma acting as a trigger. Traumatic childbirth and repetitive trauma (such in the case of truck drivers or horseback riders) can also factor into its cause. Lumbar disc degeneration, history of epidural injection, and previous spinal or rectal surgery are also commonly reported in the history of patients complaining of this condition.

Obesity and female gender may predispose patient to this condition, accounting for pelvic rotation which exposes the coccyx and makes it more vulnerable to traumatic injury. One study found that coccyx instability, defined as intermittent

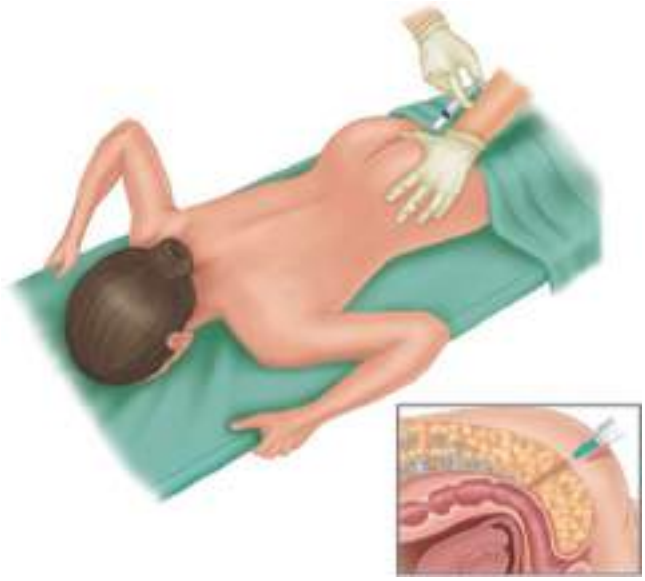


FIG. 62.3. Patient positioning for coccygodynia injection (*top*). Sagittal view of intended tract and bony landmarks for injections for coccygodynea (*inset*).

subluxation or hypermobility seen on lateral dynamic radiographs when sitting, was associated with a high prevalence of symptom reporting [51]. Pre-existing spinal alterations may play a role in those complaining of post-traumatic coccygodynia [52]. Spicule (bone spur) or bursitis (inflammation of structures in close proximity to the coccyx) may also cause pain. Though magnetic resonance imaging (MRI) may be helpful to exclude tumors, disc disease, and identify anatomic risk factors, many believe that they do not add significant insight into the diagnosis of coccygodynia [53]. Depression and anxiety disorder have also been reported to amplify coccygeal pain symptoms in the absence of anatomic findings [54].

Trigger point injection with steroid (Figure 62-3) can be considered for transient relief of pain. Coccyx manipulation (Figure 62-4) has been found in a recent prospective, randomized, controlled study to be beneficial (22 % of patients in the manipulation group reported a significant pain decrement compared to only 12 % of patients in the placebo group) [55].

As outlined in the treatment algorithm (Figure 62-5), in selected patients with severe and unresponsive coccygodynia, surgery may be considered [56]. Wray et al. randomize a group of 120 patients between treatment with injections of methylprednisolone and bupivacaine alone or injections and manipulation of the coccyx under general anesthesia. Injections alone were successful in 60 % and injections plus manipulation was successful in 85 % of the patients in that arm of the study. The 23 patients who failed either of these two treatments came to coccygectomy. Nearly all had a good result, suggesting that this operation may be appropriate in those patients who have failed a trial of less invasive therapy [57].

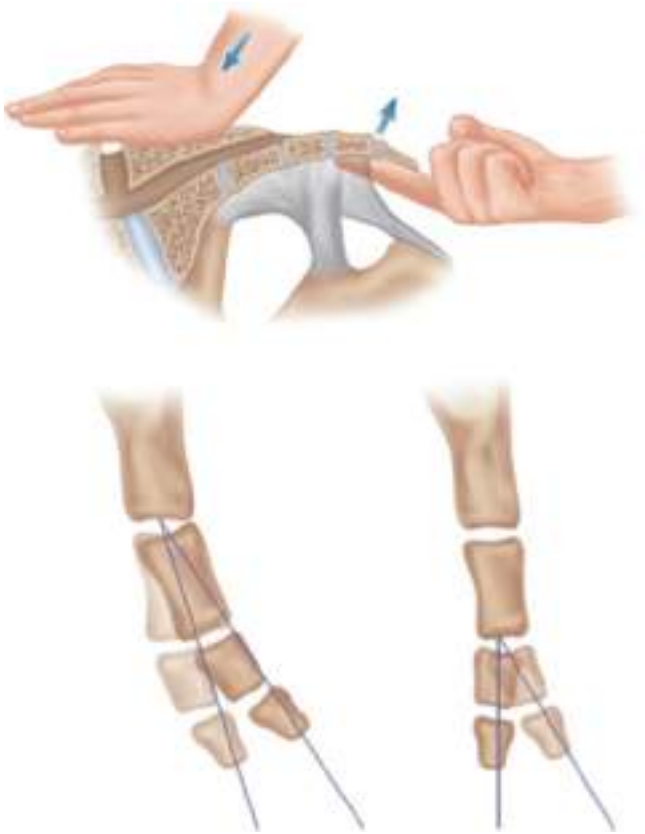


FIGURE 62-4. Operative manipulation for chronic coccygeal pain. The *top figure* demonstrated digitation via the anus with the patient in the prone position. The *bottom illustration* demonstrates (from a sagittal view) the intended overall effect of changing the angle of the coccygeal structures.

Pudendal Neuralgia

Pudendal neuralgia is also called Alcock's canal syndrome, or pudendal canal syndrome. When chronic pain is reported in the perineal area in the absence of organic diseases that may explain this symptom, the provider could consider entrapment injury. The pudendal nerve travels through a musculo-osteo-aponeurotic tunnel between the sacrotuberal and sacrospinal ligaments as illustrated in Figure 62-6 (lateral view).

The pudendal nerve arises from S2, S3, and S4 of the sacral plexus. The nerve leaves the pelvis beneath the piriformis muscle through the greater sciatic foramen. It then passes on to the sacrospinous ligament medial to the ischial spine and reenters the pelvic cavity. While beneath the levator ani muscles, it runs ventrally through Alcock's canal, a thickening of the obturator internus fascia. In the ischiorectal fossa, it gives off an inferior rectal and a perineal branch. The two documented sites of pudendal nerve entrapment are between the sacrotuberous and sacrospinous ligament and in the pudendal (Alcock's) canal.

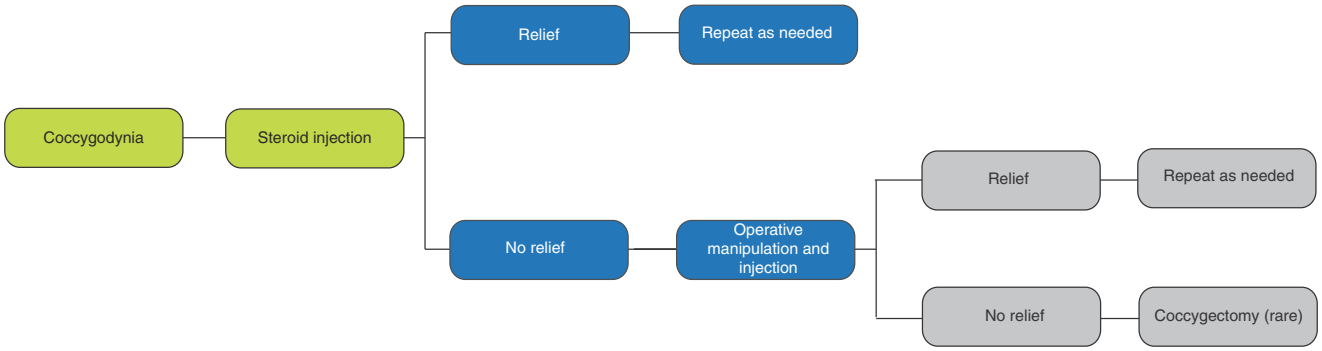


FIGURE 62-5. Algorithm for management of coccygodynia.

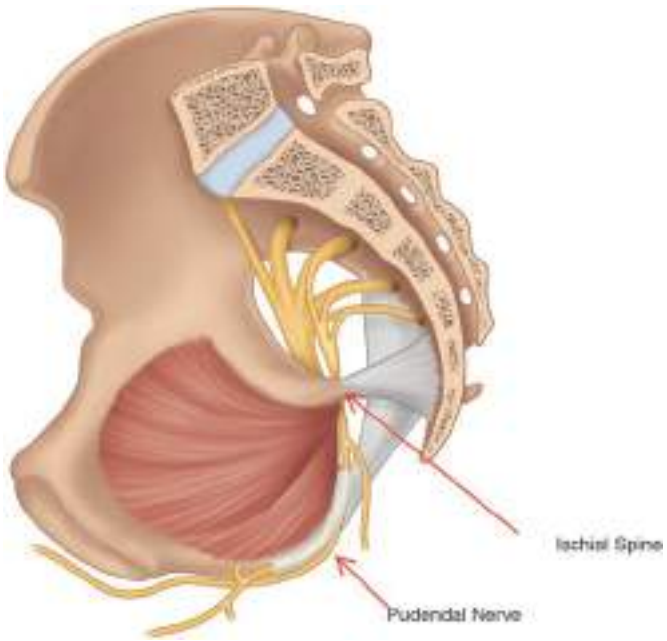


FIGURE 62-6. Demonstration of the anatomical course of the pudendal nerve from a posterolateral view of the bony and ligamentous structures.

Many patients with chronic pain have induced hypertrophy of the pelvic muscles caused by athletic activities in their youth, which has in turn caused remodeling of the ischial spine and rotation of the sacrospinous ligament and nerve compression.

Colorectal surgeons should keep in mind that although entrapment is the most common etiology, herpetic neuropathy, stretch neuropathy, and post-radiotherapy neuropathy can also be risk factors elicited by a careful history [58].

In 2006, a multidisciplinary working group on pudendal neuralgia held in Nantes, France [59], identified five requirements of essential diagnostic criteria for pudendal neuralgia:

(1) *Pain should be limited to the innervation territory of the pudendal nerve. This excludes any pain that is limited to the coccygeal, pelvic, or gluteal areas*;
(2) *Pain is predominantly experienced while sitting, in accordance with the nerve compression etiology hypothesis. In long-standing pudendal neuralgia, pain may become continuous, but it is still worsened by the sitting position*;
(3) *The pain rarely awakens the patient at night*;
(4) *On clinical examination, no objective sensory impairment can be found even in the presence of paresthesia. The presence of a sensory defect should prompt investigations to exclude diseases of the sacral nerve roots and the cauda equina; and*
(5) *Pain should be relieved by anesthetic infiltration of the pudendal nerve. This is an essential criterion, but it lacks specificity as pain related to any perineal disease may be relieved by pudendal nerve block.*

The experts cautioned that a negative block does not exclude pudendal neuralgia, as the block may have been confounded by technical errors.

The experts also listed the following as exclusion criteria for the condition: (a) pain in a territory unrelated to the pudendal nerve, (b) symptomatic pruritus instead of paresthesia, (c) exclusively paroxysmal pain, and (d) imaging abnormalities that could explain the symptom.

There are a number of treatment options that have been described in recent literature, ranging from operative or image-guided nerve injections, neuromodulation, and operative augmentation of the entrapment (i.e., release) (Figure 62-7).

Nerve Injection

Operatively, colorectal surgeons may consider taking the patient for an anal exam under anesthesia and either transanally or transvaginally, attempt to palpate the pudendal nerve for a directed block (Figure 62-8). Success rates are variable [60]. Therefore, image-guided therapy may be more precise than this blind approach.

Mamlouk et al. reported 52 CT-guided pudendal nerve blocks of anesthesia and steroid performed in 31 patients who suffered from chronic pelvic pain with a presumed diagnosis of pudendal neuralgia.

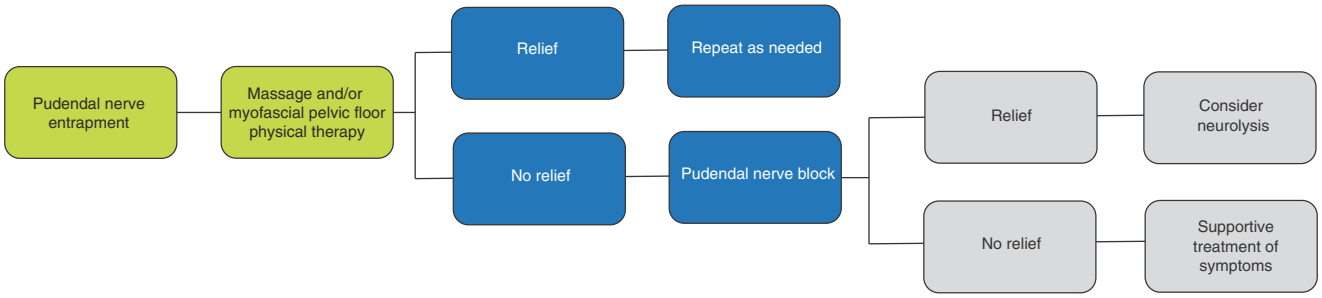
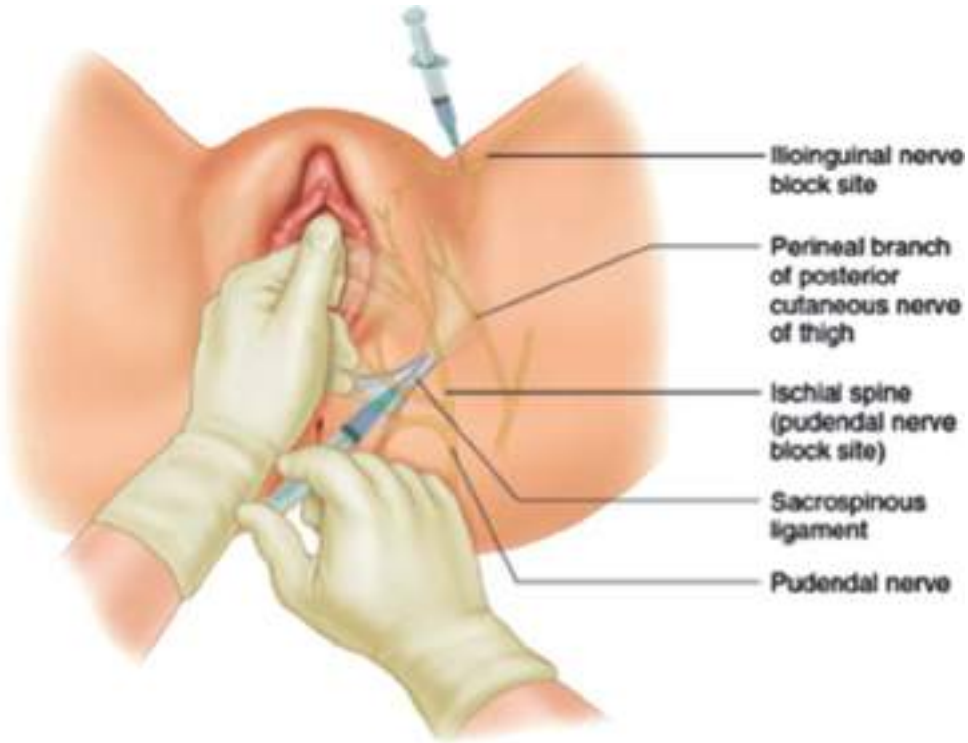


FIGURE 62-7. Algorithm for management of pudendal nerve entrapment.

FIGURE 62-8. Demonstration of the administration of a pudendal nerve block with the patient in lithotomy position. Note that digitation for landmarks in this illustration is via the vagina, however, a transanal rectal approach can also be considered.



All procedures were successful technically, which was defined as contrast material filling the pudendal canal on CT. Of the 31 patients, two had long-term relief with pudendal nerve blocks alone. Fourteen had subsequent surgery based on initial improvement with block(s), and all 14 patients improved after surgical nerve release. The authors concluded that CT-guided pudendal nerve blocks were more valuable diagnostically than therapeutically [61].

Schelhorn et al. describe a case report of an MR guided perineural injection procedure in an athletic, young adult. A 20-guage MRI Chiba needle (100 mm, Somatex, Medical, Teltow, Germany) was advanced transgluteally and obliquely, aiming the needle position almost parallel to the obturator fascia. The needle tip was placed within the pudendal canal and position was verified with initial saline injection. Then a mixture of triamcinilone and bupicivaine was injected. The pain improved, but returned after 6 days post procedure, therefore the procedure was repeated until the patient reported complete relief. A total of six injections were undertaken in this manner over a period of 2 months, ultimately resulting in complete relief [62].

Neuromodulation

A neurosurgery group published a case report of a male patient with pudendal neuralgia who underwent lead placement with a 16-contact surgical lead at the level of conus medullaris which allowed for multicolumn stimulation. Using transverse combinations, these surgeons were able to obtain 100 % paresthesia over the perineal area without

unwanted dorsal root stimulation. They reported that this patient's perineal and radicular pain was successfully relieved for 12 months with an improvement in all quality of life domains and a reduction in drug consumption [63].

Sacral nerve stimulation (SNS) is a technique that many colorectal surgeons have experience with in the treatment of fecal incontinence. A case report by Valovska et al. suggested that SNS may prove to be beneficial in pudendal entrapment, although the device is not FDA approved for this indication. The authors showed improvement in a patient's symptoms after Interstim (Medtronic, Minneapolis, MN, USA) lead placement. The patient suffered from chronic pelvic pain due to a nerve injury as a result of hysterectomy. Initial implantation with test leads resulted in pain improvement, and a permanent implant was placed (4 tined Interstim leads, individually placed into the bilateral S3 and S4 foramina). The patient was followed for 4 years with good results [64].

Nerve Ablation

Destroying the nerve can result in symptom relief. This can be done by operative division as described below, or by image-guided techniques. Prologo et al. reported a case series of 11 patients with pudendal nerve entrapment who underwent CT-guided cryoablation of the nerve within Alcock's canal. They used a 17-gauge cryoablation probe (Ice Sphere, Galil Medical, Arden Hills, MN), and undertook two 8-minute-5-minute freeze–thaw cycles. The patients showed a significant reduction in their pain scales ($p < 0.005$) [65].

Operative Approaches

In terms of neurolysis, there are four described approaches to surgical decompression of the pudendal nerve. All surgical methods involve neurolysis to eliminate the possible source of compression: transperineal, transgluteal, transischiorectal, and laparoscopic. We have also included recent reports of other operative approaches to alter the anatomy of the canal.

Transperineal

With patients positioned in lithotomy position, a semicircular incision is undertaken on the side of the anus on which the nerve is affected. Identification of the inferior rectal nerve is performed and this nerve is followed blindly with a finger until the pudendal nerve is reached. Adhesions around the pudendal nerve are then bluntly reduced. The approach allows access to the rectal branch and should be limited to patients with only rectal involvement of pudendal neuralgia. However, it is a blind procedure that does not allow for extensive dissection of the nerve beyond the distal Alcock's canal.

Transgluteal

With the patient positioned in prone jackknife a transgluteal incision is made overlying the sacrotuberous ligament. When the ligament is reached, it is transected at its narrowest portion and edges of the ligament are reflected open. The pudendal nerve is found immediately below the ligament together with the pudendal vein and artery. In this manner, the nerve can be visualized from the subpiriformis fossa to the distal Alcock's canal. Neurolysis is performed and the sacrospinous ligament is transected. The nerve is then transposed anteriorly to decrease tension. Surgery is concluded by the closure of the subcutaneous fat and overlying skin.

Persistent nerve entrapment even after neurolysis procedures can be approached in a way described by Hibner et al. [66]. They recommend a transgluteal incision, identification of the nerve via a nerve monitoring system, followed by adhesiolysis from the piriformis muscle to the distal Alcock canal (a surgical microscope was employed). They enclosed the nerve in a NeuraWrap Nerve Protector (Integra, Plainsboro, NJ, USA) and coated it with an activated platelet-rich plasma. An ON-Q PainBuster (Halyard Health, Alpharetta, GA, USA) catheter was placed along the nerve into the Alcock canal, and 0.5 % bupivacaine was infused at 2 mL/h. The sacrotuberous ligament was repaired using an Achilles or gracilis cadaver ligament. The overlying subcutaneous tissue and skin were then closed. Eight of the nine patients followed reported global improvement, and using an 11-point numerical pain scale, scores improved from a mean of 7.2–4.0 ($p = 0.02$).

Transischiorectal

In this technique, an incision is made in the lateral wall of the vagina in women and between the rectum and the scrotum in men. Dissection is then directed to the ischiorectal fossa on the affected side. Electromyogram is used to direct the surgeon to the area of compression to limit the need of extensive dissection. Similarly to the transperinal approach, access to the pudendal nerve is limited. Recovery is difficult in men with painful incisions between the scrotum and rectum that are prone to infection.

Laparoscopic

This approach does not require transection of the sacrotuberous ligament and provides good visualization of the nerve's course, but long-term success rates have been poor. Perhaps with robotic surgery, which allows greater visualization and precision, this approach will be further improved.

Another option is to decompress the pudendal nerve, as described by Erdogru et al. (Figures 62-9 and 62-10) They undertook 27 laparoscopic pudendal nerve decompression/transposition procedures (Istanbul technique) and protected their release with an omental flap in an effort to prevent

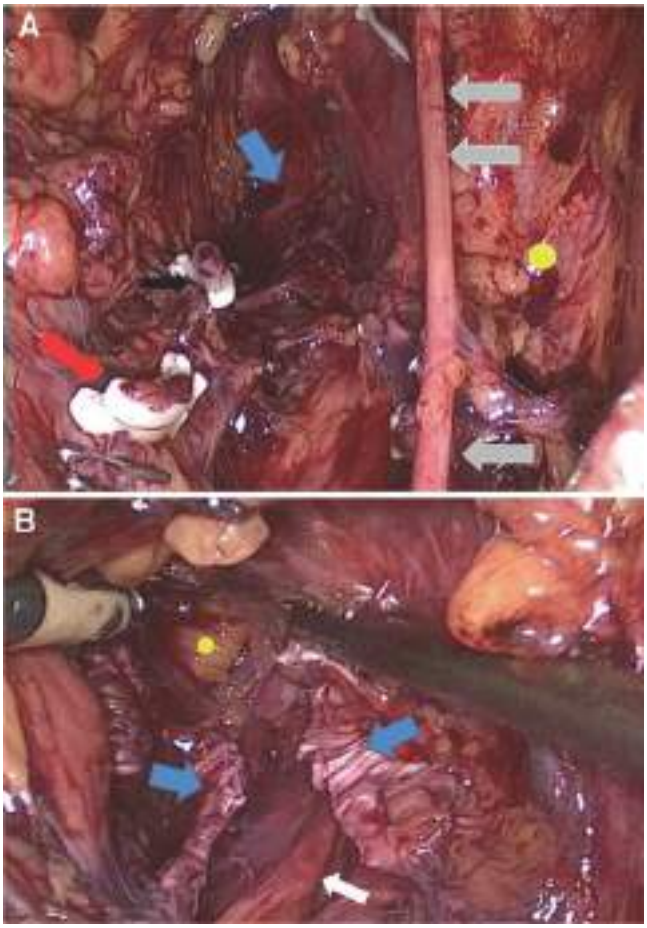


FIGURE 62-9. (**a**) Exposure of the sacrospinous ligament (SSL) from an internal perspective and the lateral deep pelvic topographic anatomy. *Blue arrow* the right SSL. *Black arrow* divided right obturator vein. *Red arrow* divided medial umbilical ligament. *Gray arrows* right obturator nerve. (**b**) With division of SSL, pudendal nerve clearly identified beneath the ligament and the fatty tissue in front of Alcock's canal entrance. *Blue arrows* divided right SSL. *White arrow* the right pudendal nerve. *Yellow dot* the fatty tissue in front of Alcock's canal entrance. *With permission from Erdogru T, Avci E, Akand M. Laparoscopic pudendal nerve decompression and transposition combined with omental flap protection of the nerve (Istanbul technique): technical description and feasibility analysis. Surg Endosc. 2014 Mar;28(3):925–32. (68) © Springer.*

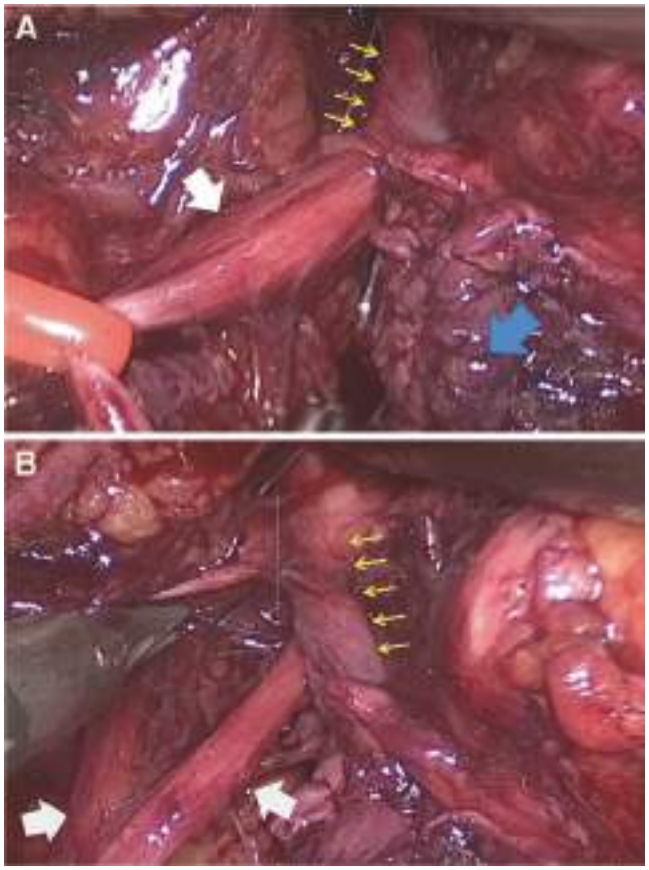


FIGURE 62-10. (**a**) The entrance of the right pudendal nerve into Alcock's canal with the view of medial side of the aponeurosis of internal obturator muscle as the inside wall of Alcock's canal. *White arrow* right pudendal nerve. *Blue arrow* incised right sacrospinous ligament (SSL). *Yellow arrows* inside wall of Alcock's canal as the aponeurosis of internal obturator muscle. (**b**) After incision of proximal part of Alcock's canal, the right deep perineal branch of the pudendal nerve has been identified. *White arrow* right pudendal nerve. *Yellow arrows* inside wall of Alcock's canal as the aponeurosis of internal obturator muscle. *With permission from Erdogru T, Avci E, Akand M. Laparoscopic pudendal nerve decompression and transposition combined with omental flap protection of the nerve (Istanbul technique): technical description and feasibility analysis. Surg Endosc. 2014 Mar;28(3):925–32. (68) © Springer.*

refibrosis around the nerve long-term. The technique involves complete division of the sacrospinous ligament and splitting of the inner (caudal) side of the levator ani muscles until the fatty tissue in front of the entrance to Alcock's canal is reached. The aponeurosis of the internal obturator muscle is opened, thus opening the canal. With a 6-month follow-up, a >80 % reduction in the visual analog pain scale was noted in over 80 % of the patients [67]. Quality of life scores also improved and were maintained during the 12-month follow-up.

Augmentation of the Canal

Venturi et al. studied patients who underwent Alcock's canal augmentation via transperineal injections of autologous adipose tissue with stem cells along the canal to increase space for the nerve to travel and decrease compression. This was a pilot study undertaken in 15 women and initial results were promising. They followed pudendal nerve motor terminal latency (PNMTL) and there was a trend to better conduction, and improved pain scores in the short term [68].

Conclusion

In summary, although IBS and chronic functional pelvic pain represent a spectrum of disease entities that are difficult to diagnose, manage, and treat, a systematic approach with a multidisciplinary team is essential. While surgery is only occasionally necessary, the colorectal surgeon must remain knowledgeable about these life-altering problems.

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63
Middle and Anterior Compartment: Issues for the Colorectal Surgeon

Cecile A. Unger and Marie Fidela R. Paraiso

Key Concepts

- Multi-compartment pelvic floor disorders are common and require a multi-disciplinary team approach to evaluation and management.
- The levator ani muscles and connective tissue structures of the pelvis provide the main supports to the pelvic floor and pelvic organs.
- Transvaginal repair of pelvic organ prolapse is commonly performed at the time of transperineal repair of rectal intussusception or prolapse.
- The most commonly performed abdominal procedure for pelvic organ prolapse is the sacral colpopexy, which can be performed concomitantly with ventral or other types of rectopexy.
- A transvaginal or transanal approach can be taken to repair a rectocele, but the transvaginal approach is more common and seems to have better outcomes with less morbidity.

Introduction

Many patients who complain of descensus in a single pelvic compartment may be affected by prolapse in multiple pelvic compartments [1] and several publications have described coexistence of rectal and pelvic organ prolapse [2–9]. In addition, there is a high incidence of anorectal dysfunction in women with genital prolapse. As a result, multi-compartment pelvic floor disorders are now increasingly being evaluated and managed together by female pelvic medicine and reconstructive surgery (FPMRS) surgeons and colorectal surgeons [10, 11].

It is imperative for specialists to recognize when consultation with the one another is indicated, as joint management may significantly improve patient outcomes. For instance, defecatory symptoms may not improve with transvaginal rectocele repair alone [12], as obstructive symptoms may be related to more extensive posterior compartment dysfunction. For example, studies have shown that an enterocele is not an uncommon finding in patients presenting with a rectocele, and may occur in up to 42 % of patients [13], and rectal intussusception may occur in up to 68 % of patients undergoing defecography for symptomatic rectocele [14].

The other posterior compartment conditions that may occur with anterior and middle compartment prolapse include sigmoidocele, anismus, perineal descent, and/or rectal prolapse. Peters et al. [15] showed that in 55 patients evaluated with rectal prolapse, 52 of the patients had other pelvic floor defects, and 39 were found to have occult rectal prolapse that simulated a rectocele or enterocele. Patients with the above-mentioned posterior defects often require radiographic evaluation for accurate diagnosis, as well as a multi-disciplinary team approach to management [16, 17].

In this chapter, we review the anatomy of the pelvic floor and the important relationships between its compartments, we describe the FPMRS surgeon's approach to the evaluation and management of pelvic organ prolapse, we provide an overview of the transvaginal and abdominal approaches to apical prolapse procedures that can be performed concomitantly with colorectal procedures, and we describe and compare the different approaches to the rectocele repair.

Anatomy of the Pelvic Floor

The levator ani muscles (puborectalis, iliococcygeus, and pubococcygeus) contribute to the main support of the pelvic organs and play an important role in the pelvic floor (Fig. 63-1). [18]. In their normal state, the levators maintain constant tone, which helps support the pelvic organs against fluctuating changes in intraabdominal pressures, and also keeps the urogenital hiatus closed, drawing the distal urethra, vagina and rectum up toward the pubic bone [19]. The muscles can also be voluntarily contracted (performance of a Kegel exercise) but can also be lengthened and relaxed, which is important for micturition and defecation.

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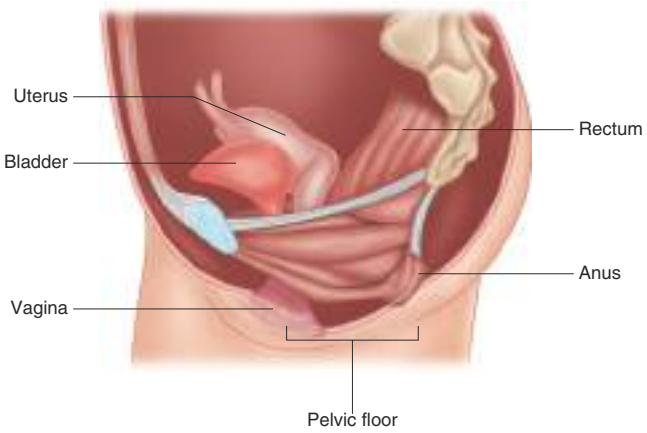

FIGURE 63-1. Interaction between the levator ani muscles and the pelvic organs. The levator ani muscles (puborectalis, iliococcygeus, and pubococcygeus) contribute to the main support of the pelvic organs and play an important role in the pelvic floor.

The *puborectalis* originates from the each side of the pubic bone and forms a U-shaped sling that courses above the external sphincter muscle and around the anorectal junction [19]. The *iliococcygeus* is the least bulky of the levator ani muscles and is located posteriorly, arising from the ischial spines and the *arcus tendineus levator ani* with its fibers meeting in the midline and inserting into the coccyx. The *iliococcygeal raphe* forms as a result of the converging iliococcygeal muscle fibers, and forms the *levator plate*, an anatomic shelf on which the rectum, proximal vagina, and uterus rest. In a woman with normal support, the levator plate lies almost parallel to the horizontal plane in the standing position [20]. The *pubococcygeus* originates from the inner surface of the pubic bone and contains three divisions that are named according to the attachments of the muscle fibers [21]. The *pubovaginalis* inserts into the lateral walls of the vagina and helps to maintain para-vaginal and urethral support and plays a role in urinary continence [22]. The pubococcygeus muscle fibers that attach to the perineal body are termed the *puboperinealis*, and in its contracted state, the muscle draws the perineal body toward the pubis. The *puboanalis* is comprised of muscle attachments to the anus at the level of the intersphincteric groove, and along with the puborectalis muscle, this muscle helps to elevate the anus, which also keeps the urogenital hiatus closed [23].

The *perineal membrane* (also referred to as the *urogenital membrane*) spans the opening of the ventral pelvic outlet [24] and is continuous with the *arcus tendineus fascia pelvis*, attaching the distal vagina and urethra to the distal pelvis, while the dorsal outlet is made up of dense connective tissue that attaches to the ischiopubic rami as well as the distal vagina and perineal body [23]. The *perineal body* is located between (and attaches to) the distal third of the posterior vagina and the external sphincter of the anus and is made up of a portion of the *bulbospongiosus* and *superficial transverse perineal muscles* as well as dense connective tissue [25]. This muscular structure supports the distal vagina and rectum, and these attachments can easily be disrupted during childbirth, necessitating proper reattachment and repair after delivery in order to restore the proper distal pelvic floor supports.

There are important relationships between the levator ani muscles and the connective tissue structures that attach the uterus, cervix, vagina, and rectum to the pelvic walls, and these interactions are also responsible for structural support in the pelvis. The supporting or *endopelvic fascia* is a more complex and controversial structure than the levator ani. Located between the visceral peritoneum and parietal fascia of the levator ani is fibroareolar tissue containing neurovascular bundles, smooth muscles, collagen, and elastin, which is often called the endopelvic or endovisceral fascia [26]. This structure fans out to envelop the pelvic organs and anchors them to the surrounding pelvic sidewall structures. DeLancey calls the endopelvic fascia the *viscero-fascial layer* because it is a combination of the pelvic viscera and endopelvic fascia and plays a key role in the support of the vagina and uterus [27, 28]. Norton [29] has described the interaction between levator ani and endopelvic fascia as the "boat in the dry dock." The levator ani is like the water in a dry dock that floats the boat, and the ligaments are like the mooring that holds the boat in place. When the water in the dock begins to recede, the moorings are strained to hold the boat in place. The term "ligament" is commonly used to describe pelvic floor connective tissue structures; however, it is important to recognize that these structures do not really meet the true definition of the term. In fact, there is great variation in the composition and function of these structures. Some consist of dense connective tissue bands that connect portions of the bony pelvis and are responsible for pelvic stability. These "ligaments" are often used as anchoring sites in pelvic organ prolapse surgery, and examples include the sacrospinous ligaments, uterosacral ligaments, and the anterior longitudinal ligament of the sacrum. Smooth muscle, fibrous, and areolar tissue also make up some of these connective tissue structures, and are more likely to play a role in the orientation and support of the pelvic organs inside the pelvis. Examples of these structures include the round and broad ligaments of the uterus.

The rectovaginal septum is a condensation of tissue that extends approximately 3 cm proximal to the perineal body but is not present above the rectovaginal pouch [30] and it is attached to the pelvic sidewalls by the *arcus tendineus fascia rectovaginalis* [31]. Surgically and histologically, it is hard to delineate this layer of tissue between the vagina and rectum, and the same has been described for the layers of tissue between the vagina and bladder in the anterior compartment [32]. These tissues have previously been referred to as the pubocervicovesical (anterior) and rectovaginal (posterior) fascial layers; however, histological studies cast doubt over the "fascial" nature of these layers [28], and surgically, the layer that can be separated between

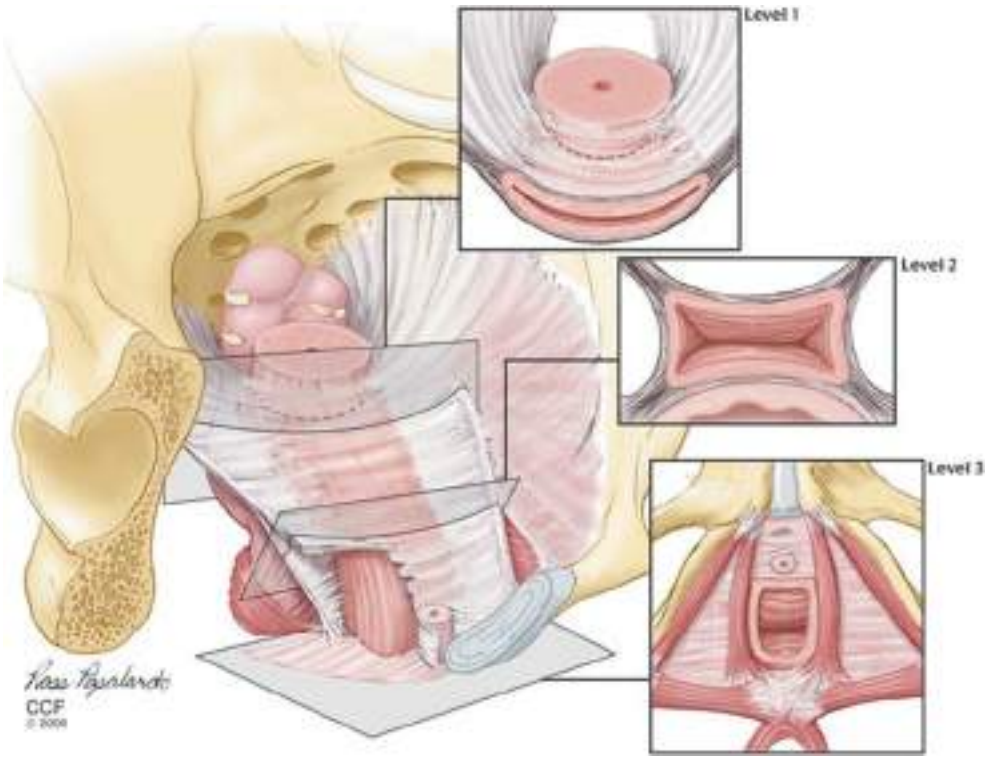

FIGURE 63-2. Illustration of the endopelvic fascia and the levels of support to the vagina. From Lee PYH. Pelvic Floor Disorders. In: Beck, D.E., Roberts, P.L., Saclarides, T.J., Senagore, A.J., Stamos, M.J., Nasseri, Y. (Eds.) ASCRS Textbook of Colon and Rectal Surgery, 2nd ed. Springer, New York, 2011. Meurette Reprinted with permission Ó Cleveland Clinic Center for Medical Art and Photography 2004–2009.

the vagina and the rectum and the vagina and the bladder appears to predominantly be made of vaginal muscularis. Therefore, when we describe repair of a cystocele and/or rectocele, we commonly refer to plication of the muscularis layer, rather than a separate fascial layer between the two structures.

DeLancey [33] has described three levels of vaginal connective tissue support that help us understand how and why pelvic floor support defects occur (Fig. 63-2). The parametria are the lateral supports to the uterus and cervix and are made up of perivascular connective tissue that contains the uterosacral and cardinal ligaments. These structures are known as Level I support and provide the apical support of the vagina to the pelvic sidewalls, keeping the vagina suspended vertically over the pelvic floor. Women with Level I support defects present with either uterine/cervical or post-hysterectomy vaginal apex prolapse. The mid portion of the vagina is suspended to the pelvic sidewalls via lateral connective tissue attachments to either the arcus tendineus fascia pelvis or the medial aspect of the levator ani muscles. These attachments are important for anterior vaginal wall and bladder neck support. Defects in these supports can manifest as anterior vaginal wall prolapse (a cystocele) or stress urinary incontinence symptoms. As previously mentioned, the distal vagina attaches to the perineal body posteriorly, and these attachments contribute to Level III support. Defects in these structures can present as distal posterior vaginal wall prolapse (a rectocele) as well as perineal detachment and descent.

The etiology of pelvic organ dysfunction is multifactorial but appreciating the relationships between the above-mentioned anatomic structures is an important part of understanding how pelvic floor dysfunction occurs. For example, mechanical disruption of the connective tissues or neuromuscular injury of the pelvic floor can lead to anatomic changes such as lengthening or widening of the genital hiatus as well as a change in the incline of the levator plate [34]. If the axis of the vagina becomes more vertical, the pelvic organs can become oriented directly over the larger hiatal opening, which can lead to descensus of the pelvic organs through the hiatus [35]. We also believe that there may be a genetic component to pelvic floor disorders. Recent histologic studies have demonstrated that the elastin and collagen content in the vaginal walls of women with pelvic organ prolapse and incontinence differs from women who do not suffer from these conditions [36]. It is not completely clear whether these women have a genetic predisposition to changes in collagen and elastin homeostasis, placing them at risk for pelvic floor dysfunction over time, whether the distension and mechanical disruption caused by the prolapse is responsible for the histologic changes reported, or if a combination of these factors are at play. There is currently

ongoing research examining these questions, but what remains clear is that the underlying etiology of pelvic floor disorders is complicated and likely involves multiple factors.

Evaluation of Pelvic Organ Prolapse

The diagnosis of pelvic organ prolapse is made using a combination of history and physical examination. Patients with symptomatic prolapse usually describe vaginal bulge, pressure, discomfort, as well as functional symptoms such as difficulty voiding or defecating, and sexual dysfunction. The physical examination for prolapse includes a general gynecology examination and should be conducted with the patient in the dorsal lithotomy position. If physical findings do not correspond with symptoms, or if the maximum extent of prolapse cannot be confirmed, the woman can be reexamined in the standing position.

The pelvic organ prolapse quantification (POP-Q) examination is a validated tool that is used to measure and report prolapse [37]. Using the hymen as a reference point, the POP-Q measures the genital hiatus length, the perineal body length, the total vaginal length, the amount of cervical or vaginal apex prolapse, and the presence/extent of prolapse of the anterior and posterior vaginal walls. All measurements are taken while the patient is performing a Valsalva maneuver with the exception of total vaginal length. The maximal amount of prolapse noted is used to assign a stage to the prolapse (Table 63-1).

Many women with pelvic organ prolapse also have urinary incontinence. Women who do not have symptoms of incontinence are at risk for de novo stress urinary incontinence when their prolapse is corrected because the previously obstructed urethrovesical junction is straightened by elevating the vaginal apex and anterior vaginal wall [38]. Adding an anti-incontinence procedure at the time of prolapse repair significantly reduces the incidence of stress urinary incontinence [39, 40], and as a result, it is important to screen patients for incontinence symptoms at the time of evaluation, and also to evaluate patients for occult incontinence before proceeding with surgery. During the pelvic examination, if the patient has a full bladder, she may be asked to cough or Valsalva, and her urethra is examined for leakage of urine. Alternatively, simple cystometry can be performed with placement of a catheter attached to a 60 cc syringe with the plunger removed placed approximately 15 cm above the level of the pubic symphysis. The bladder is filled with normal saline and the patient is then asked to cough, and the urethra is observed for any degree of leakage of urine. Otherwise, urodynamic testing is performed, and an overview of this office procedure is described below.

Based on current evidence, there is no role for routine imaging in the evaluation of pelvic organ prolapse, but it may be useful for diagnosis and management when rectal intussusception, occult rectal prolapse, sigmoidocele, or enterocele is suspected as the underlying cause of a patient's defecatory symptoms. For example, rectal prolapse frequently coexists with other pelvic floor defects and internal rectal prolapse may simulate a rectocele or enterocele and requires defecography to establish the diagnosis [15]. Anal manometry, defecating proctogram, dynamic MRI, and endoanal ultrasound may also have an important adjunctive role in assessing obstructive defecatory symptoms and/or fecal incontinence in patients presenting with pelvic floor disorders, and are often ordered and/or performed by the colorectal surgeon to help with assessment and treatment planning. Indications and interpretation of these tests has already been discussed in previous chapters, and not within the scope of this chapter.

Overview of Urodynamics

Urodynamic testing is an office-based procedure that is used to evaluate the function of the lower urinary tract system. Pelvic floor surgeons rely on urodynamic testing for several different indications; however, there are no agreed upon guidelines for when to perform the procedure, and testing is often based upon clinical history, presenting symptoms, previous pelvic floor surgeries, and upcoming planned procedures [41]. Table 63-2 lists common indications for urodynamic testing used by most FPMRS surgeons.

Urodynamics evaluates the pressures at which the detrusor muscle of the bladder is able to accommodate during bladder filling, how well a patient is able to suppress micturition at

Table 63-1. Pelvic organ prolapse stages

Stage 0	No prolapse; apex descends within 2 cm of the total vaginal length
Stage 1	Most distal portion of the prolapse descends to a point greater than 1 cm above the hymen
Stage 2	Most distal portion of the prolapse descends within 1 cm of the hymen (above or below)
Stage 3	Prolapse extends more than 1 cm beyond the hymen but no more than within 2 cm of total vaginal length
Stage 4	Complete eversion; extension within 2 cm of the total vaginal length

Table 63-2. Indications for urodynamics

Complicated lower urinary symptoms history
Pre-operative evaluation of stress incontinence
Urgency incontinence refractory to medical therapy
Recurrent urinary incontinence after anti-incontinence surgery
Frequency, urgency, and pain syndromes unresponsive to therapy
Nocturnal enuresis
Lower urinary tract dysfunction after pelvic radiation or radical pelvic surgery
Neurologic disorders
Continuous incontinence
Voiding dysfunction

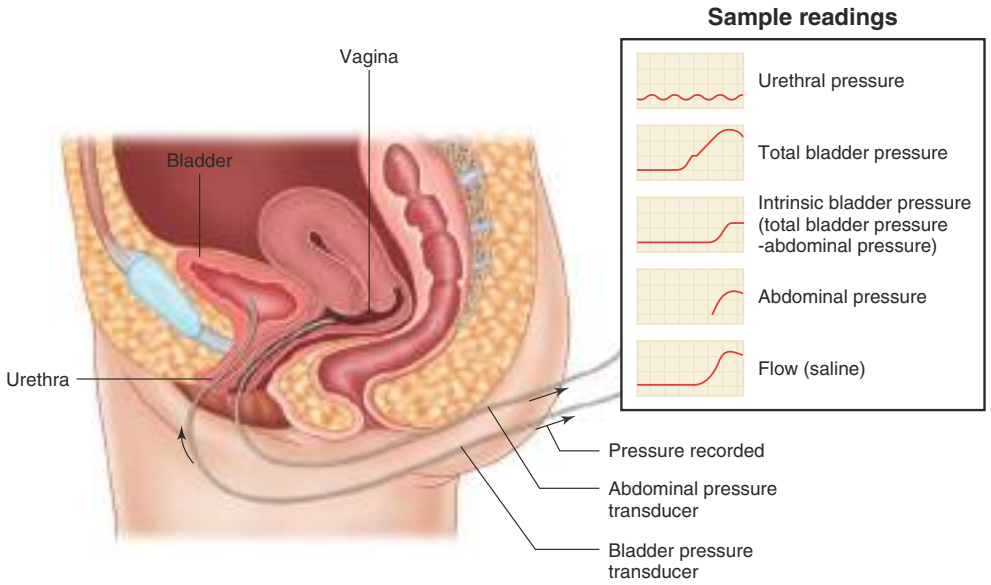

FIGURE 63-3. Set-up and catheter placement for multi-channel urodynamics. A catheter is placed inside of the bladder and measures *vesical pressures* (P_{ves}) and a catheter is placed inside of either the rectum or vagina and measures *abdominal pressures* (P_{abd}).

various volumes, and how well the patient is able to initiate voiding which requires adequate detrusor muscle contraction with simultaneous relaxation of the urethra. The procedure is performed and recorded in a standard fashion in order to facilitate clear communication between providers, and the terminology used to report urodynamic findings is based on published guidelines by the International Continence Society (ICS). Figure 63-3 depicts the set-up and catheter placement for multi-channel urodynamics, which is the method most commonly used by practitioners. Patients are positioned comfortably on a urodynamics chair and disposable micro-transducer catheters are used. A catheter is placed inside of the bladder and measures *vesical pressures* (P_{ves}) and a catheter is placed inside of either the rectum or vagina and measures *abdominal pressures* (P_{abd}). *Detrusor pressure* (P_{det}) is determined by subtracting the abdominal and vesical pressures ($P_{abd} - P_{ves} = P_{det}$).

The first stage of urodynamics is referred to *filling cystometry*, which assesses the relationship between volume and detrusor pressure during bladder filling, also known as the *storage phase*. The bladder is then filled with normal saline and the patient is asked about bladder sensations: first sensation of filling, first desire to void, strong desire to void, symptoms of urge, and pain. The bladder is filled until *cystometric capacity* is reached and this volume is recorded. Detrusor contractions are also recorded during filling and are defined by rises in P_{det}, which represent *detrusor overactivity*, an abnormal finding on urodynamics that is indicative of overactive bladder disorder. Bladder *compliance* can be calculated by dividing the volume change by the change in P_{det}, which should remain low and constant during filling. Rises in P_{det} not associated with a detrusor contractions are a sign of poor bladder compliance and can be associated with neurogenic bladder disorders. In order to assess ability to suppress micturition during filling, patients are asked to perform provocative measures (Valsalva, cough, jumping) to simulate stresses on the bladder, and episodes of leakage with these maneuvers are indicative of stress urinary incontinence. Under normal physiologic conditions, as the bladder fills, urethral resistance should generate enough pressure to compensate for any abdominal or detrusor pressure that is experienced during normal activities. The *leak point pressure* measures the urethra's ability to prevent involuntary leakage of urine, and is defined as the lowest P_{det} or P_{ves} at which urine is expelled through the urethra. *Abdominal leak point pressure* is most commonly used to assess stress urinary incontinence as it assesses the ability of the urethra to resist increased abdominal pressure. This information is sometimes helpful to assess the severity of stress urinary incontinence.

The second stage of urodynamics is *uroflowmetry* and it involves assessment of bladder emptying, known as the *voiding phase*. After they undergo filling during the first phase of the study, patients are asked to void into an electronic volume detector and a graphical representation, or flow pattern, of the weight of the urine over time is created. Conditions that alter the uroflowmetric parameters include bladder neck obstruction, urethral resistance, and detrusor contractility. In addition to urine flow, post-void residual (PVR) is also assessed after passive or active filling of the bladder. Techniques to determine PVR include ultrasonographic assessment as well as catheterization.

Surgical Management of Middle and Anterior Compartment

Women presenting with bothersome pelvic organ prolapse have a number of treatment options, including observation, conservative treatment with a pessary and/or pelvic muscle exercises, and surgery [42]. Surgical management should be chosen after careful counseling, and if the patient no longer is improved by or does not desire conservative therapies. Surgical management should aim to address all of the segments of the vagina that are involved in the prolapse and an attempt should be made to improve related visceral function of the lower urinary tract, vagina, and anorectum [38].

There are important considerations to review with the patient before proceeding with prolapse surgery. These discussion points often help the surgeon and patient make a decision about appropriate route and approach to the surgery, and these important factors are listed in Table 63-3.

Transvaginal Repair

Transvaginal repair of pelvic organ prolapse is commonly performed at the time of transperineal repair of rectal intussusception or prolapse. In most cases, the FPMRS surgeon first performs the transvaginal prolapse repair, in order to operate in a clean-contaminated field, and the colorectal surgeon follows and performs his or her transperineal repair after the vaginal repair has been completed. However, the order of surgery can be coordinated based on surgeon preference and availability. Below we provide a brief overview of the surgeries performed.

Anterior compartment prolapse refers to prolapse of the bladder due to defects in the anterior vagina and is called a *cystocele*. This can be repaired performing a native tissue repair (anterior colporrhaphy) or with placement of a biologic or mesh graft. Cystocele repair is commonly performed at the time of transvaginal apical repair and confers very little additional morbidity to the overall procedure. The overall rate of anterior compartment recurrence has been estimated to be as high as 55 % [43], but depends on definitions used for recurrence. The rate of recurrence also appears to be higher in native tissue groups compared to mesh or graft augmentation groups: RR 1.39 (95 %CI 1.02–1.90) with a polyglactin mesh inlay and RR 2.72 (95 %CI 1.20–6.14) with a porcine dermis mesh inlay [44]. While the recurrence rate is higher after native tissue repair, it remains unclear if the higher adverse event rates associated with mesh augmentation (i.e., mesh erosion rate ~10 %) for repair of the anterior compartment outweigh the risk of recurrence, and at this time, most surgeons would argue that it does not.

Table 63-3. Preoperative considerations

Is hysterectomy indicated? Does the patient desire uterine preservation?
Is the patient sexually active? Does she desire to maintain sexual function?
Through which route should the surgery be performed—vaginally, abdominally, laparoscopically, robotically?
Should a native tissue repair be performed or is graft augmentation necessary?
Is the patient undergoing a concomitant colorectal procedure, and which route is best for that procedure?
Should a concomitant anti-incontinence procedure be performed, and if so, which one?

Middle compartment prolapse refers to apical prolapse and includes post-hysterectomy vaginal apex prolapse as well as uterovaginal prolapse. Uterine-sparing techniques, namely hysteropexy, exist for the repair of apical prolapse in patients who desire uterine preservation. In other patients, vaginal hysterectomy with apical suspension or post-hysterectomy apical suspension, are commonly performed procedures. Apical suspension can be performed through an extra or intraperitoneal approach. Intraperitoneal bilateral uterosacral colpopexy is often performed at the time of vaginal hysterectomy and is a popular surgery in the USA. It is most commonly performed vaginally, but can also be done abdominally or laparoscopically, with or without robotic assistance. Its biggest advantage is that it suspends the vaginal apex in such a way that it maintains the normal axis of the vagina [38]. During this procedure, the uterosacral ligaments are exposed bilaterally and two to three delayed absorbable and/or permanent sutures are placed through the ligament 1–2 cm above the level of the ischial spines. These sutures are then passed through the vaginal cuff, suspending the apex of the vagina to the ligaments once the sutures are tied down. Studies have shown that success rates after uterosacral colpopexy are high. In a systematic review by Margulies et al. [45] the pool rates for anatomic success by compartment (anterior, apical, posterior) were 81.2 %, 98.3 %, and 87.4 %, respectively. Interestingly, patients with more severe prolapse had significantly worse cure rates, which has been reported in other studies as well [46].

Extraperitoneal suspensions are usually performed for post-hysterectomy vaginal vault prolapse, but can also be done after hysterectomy once the peritoneum is closed. The vaginal apex can be suspended unilaterally to the sacrospinous ligament for moderate-to-severe prolapse, or to the bilateral iliococcygeus fascia just below the ischial spines, in cases of minor apical prolapse or if the vagina is not long enough to reach the sacrospinous ligament. A sacrospinous suspension can be performed via an anterior, apical, or posterior approach and requires careful extraperitoneal dissection of the pararectal space down to the ischial spine and the sacrospinous ligament. Suspension sutures made of either delayed absorbable and/or permanent material are then placed through the ligament with care taken to avoid the pudendal neurovascular structures through direct visualization using a standard needle driver, or through specialized ligature carrier instrument such as the Deschamps or the Miya hook. The Capio™ (Boston Scientific, Inc., Natick, MA) is a suture-carrier device that was developed in the last decade and is also commonly used by surgeons to perform this

procedure. Once two to four suspension sutures are placed through the ligament, the sutures are passed through the vagina, suspending the apex to the ligament once the sutures are tied down. Studies have shown that the sacrospinous colpopexy is effective in treating apical prolapse with recurrence rates as low as 8 %; however, anterior compartment recurrence is more common after sacrospinous suspension, with rates as high as 37 % 6–15 years after surgery [47]. The sacrospinous ligament suspension remains a popular approach for post-hysterectomy prolapse and concomitant cystocele repair at the time of suspension is recommended.

If patients are older and no longer desire sexual activity, a vaginal obliterative procedure can be performed instead of a reconstructive procedure. This is commonly performed at the time of transperineal colorectal procedures when patients present with concomitant advanced stage pelvic organ and rectal prolapse, especially if they are older and frailer and are determined to not be good candidates for a transabdominal repair. Obliterative procedures can be performed for post-hysterectomy vaginal prolapse as well as for uterovaginal prolapse, in which case either the uterus is left in situ (a Lefort procedure), or a vaginal hysterectomy is performed followed by a colpectomy and obliteration of the vagina (colpocleisis). The major advantage of the obliterative procedure is that is associated with a quick operative time and low morbidity, but most importantly, these procedures are associated with the lowest rates of recurrence and very high patient satisfaction [48].

Abdominal Repair

The most commonly performed abdominal procedure for pelvic organ prolapse is the sacral colpopexy, which can be performed through a laparotomy or by laparoscopy or robot-assisted laparoscopy. The procedure involves suspension of the vaginal apex to the anterior longitudinal ligament of the sacrum using a bridging synthetic or biologic graft. Synthetic grafts that have been used in the past include polypropylene mesh, polyester fiber mesh, polytetrafluoroethylene mesh, Dacron mesh, and silastic silicone rubber. Large-pore, light-weight polypropylene mesh is currently the most common type of synthetic mesh used, and we recommend using this mesh over the others, as it is associated with the least amount of complications. Biologic materials that have used for this procedure include fascia lata, rectus fascia, dura mater, porcine dermis, and porcine small intestinal submucosa. The data that exist comparing synthetic mesh and biologic materials have shown that anatomic outcomes with biologic materials such as fascia lata are inferior to those when synthetic mesh is used [49, 50]. We prefer to use mesh for routine sacral colpopexy procedures; however, we recommend using biologic materials, and most often use cadaveric fascia lata, for combined ventral rectopexy procedures when a sigmoid resection is performed. This recommendation is based on the theory that infection resulting from anastomotic leak would necessitate removal of the implanted prosthesis. The data supporting this recommendation are sparse.

To perform the procedure, the patient should be positioned in dorsal supine low lithotomy position. The bladder is drained continuously with a Foley catheter. A sponge stick or end-to-end anastomosis (EEA) sizers can be placed in the vagina and rectum for manipulation of the vaginal apex and delineation of the rectovaginal septum. A laparotomy is performed, or intraperitoneal access is gained laparoscopically with or without robotic assistance. The patient is positioned in steep Trendelenberg and the small bowel is placed or packed into the upper abdomen, and the sigmoid colon is deviated to the left pelvis as much as possible. Pertinent anatomy is identified, including the bilateral ureters, the bifurcation of the aorta, and the iliac vessels. A longitudinal incision is made in the peritoneum over the sacral promontory and the anterior longitudinal ligament is exposed. Care must be taken here to avoid injury to the presacral venous plexus and middle sacral artery. Next, either a subperitoneal tunnel is created or the peritoneum is opened from the sacrum down to the posterior cul-de-sac in order to cover the graft with peritoneum after it is attached to the sacrum. The vaginal EEA sizer or alternate probe is then used to elevate the vagina and the peritoneum over the anterior vagina is dissected sharply in order to create a 4 cm pocket between the vagina and bladder. The same technique is used posteriorly: the rectovaginal septum is identified by separating the vaginal and rectal EEA sizers, and the peritoneum is incised sharply so that a posterior 4–6 cm pocket can be created. The mesh is then secured to the anterior and posterior vagina in a "Y" configuration using 0 or 2-0 suture (our preference is monofilament delayed absorbable suture) and with the vagina placed in the right pararectal space, the stem of the mesh is secured to the sacrum using 0 or 2-0 suture (our preference is monofilament permanent). The peritoneum is then closed over the mesh with absorbable suture.

Sacral colpopexy or colpoperineopexy can also be performed in conjunction with ventral or other rectopexy and requires a multi-disciplinary team approach to the surgery (Fig. 63-4a, b). During the peritoneal dissection, the colorectal surgeon mobilizes the sigmoid and rectum and either the FPMRS surgeon or colorectal surgeon performs the posterior dissection of the rectovaginal septum down to the level of the perineum (in the case of perineopexy) so that the posterior mesh may be attached as caudal as possible. This is especially important for patients with outlet defecatory dysfunction and/or a perineocele on examination. As mentioned in the chapter on rectal prolapse, in cases of redundant sigmoid colon suspected on defecography or other preoperative studies and confirmed intraoperatively, the colorectal surgeon may choose to perform a partial sigmoid resection with EEA in conjunction with the prolapse repair. If this is the case, as we previously mentioned, we advocate for biologic graft placement to avoid the need for removal if postoperative

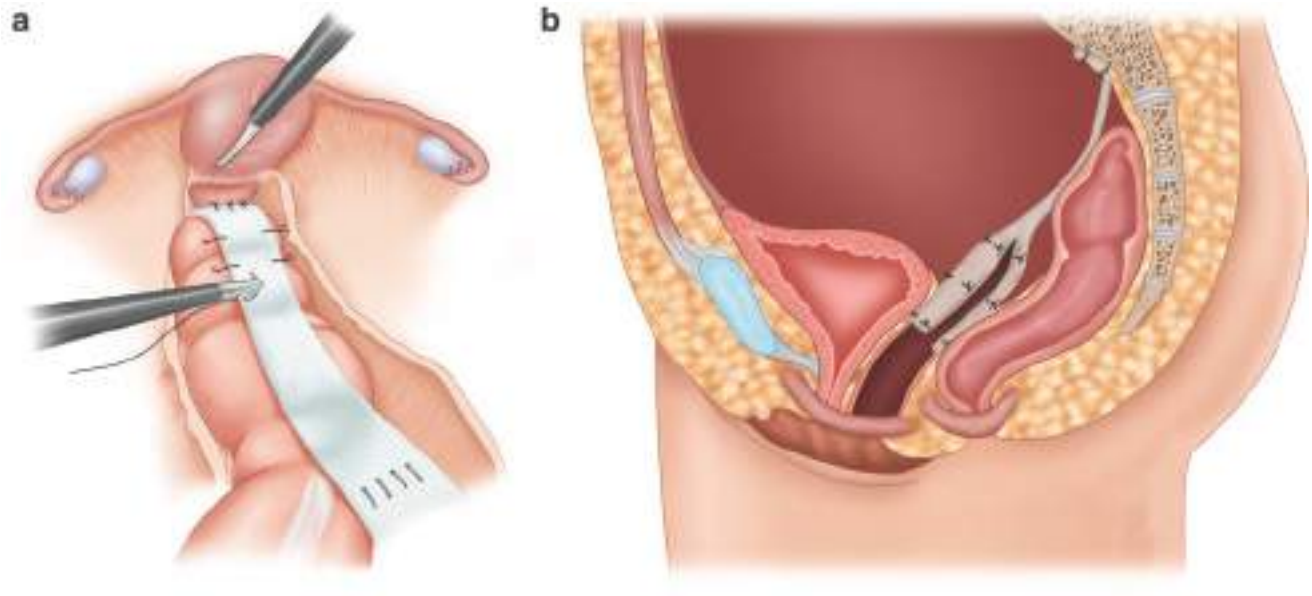

FIGURE 63-4. Combined sacro-colpo-rectopexy procedure. (**a**) The graft is secured to the anterior rectum. (**b**) Sagittal view of the procedure showing suspension of the vagina and rectum to the sacrum using a graft.

anastomotic leak occurs. In our practice, we use porcine small intestinal submucosa (6 or 8 ply) for this portion of the procedure. Instead of posterior vaginal placement, the posterior graft is attached to the fascia of the pubococcygeus and iliococcygeus muscles laterally, to the distal rectum, lateral rectal attachments, and to the perineum distally. The mesh is then secured to the sacrum by one of the surgeons while the other confirms that there is adequate suspension without too much tension of both the rectum and vagina. Restoration of normal anatomy is key during this portion of the surgery.

Pooled data show that sacral colpopexy has superior outcomes to a variety of vaginal procedures including sacrospinous colpopexy, uterosacral colpopexy, and transvaginal mesh [44]. However, the procedure is associated with longer operating time, longer time to return to daily activities of living, and increased cost if the open abdominal approach is performed. Therefore, care should be taken in choosing the appropriate patients for the procedure, and the risks and benefits of the procedure versus the other approaches should be discussed.

With regard to combined rectopexy and sacral colpopexy procedures, there are many published reports of successful outcomes showing that a multi-disciplinary transabdominal approach is both safe and effective with good symptomatic improvement for patients with combined genital and rectal prolapse [17, 51–58]. Review of the literature also reveals that adverse events related to combined rectopexy with sacral colpopexy appear to be low, and there does not seem to be significant added morbidity to performing the procedures together. In a single institution retrospective analysis, VanderPas et al. [59] looked at 133 patients who underwent sacral colpopexy alone, suture rectopexy alone with sigmoid resection, or combined sacral colpopexy with suture rectopexy with and without sigmoid resection. The authors found that the only difference in perioperative adverse events between the groups was the rate of postoperative ileus: the rate was much higher in the rectopexy alone group compared to the two sacral colpopexy groups (22.2 % vs. 3.8 % vs. 5.9 %, $p=0.004$). Otherwise, they reported that concomitant sacral colpopexy at the time of rectopexy did not increase the rate of intra- or postoperative complications.

The main concern is for spondylodiscitis, a condition that includes a spectrum of spinal infections such as discitis, osteomyelitis, epidural abscess, meningitis, subdural empyema, and spinal cord abscess [60]. Implanted prosthetic materials pose an ongoing risk during surgery and post-operatively because of the direct inoculation of bacteria at the time of graft and suture placement and because of the continued presence of a foreign body. As sacral colpopexy involves placement of a graft material over the sacrum, it represents a unique risk for spondylodiscitis, and there are reported case reports after this procedure [61, 62]. There are also reported cases of spondylodiscitis after combined rectopexy cases with and without sigmoid resection [63, 64]. More importantly, our group has found a significant increase in the risk of pelvic abscess formation after combined ventral rectopexy cases compared to sacral colpopexy alone (11.1 % vs. 0.8 %, $p<0.001$). In this cohort of patients, resection of the bowel did not seem to contribute to this increased risk, and rectopexy alone was sufficient for abscess formation.

Extra caution must be taken during these procedures to place the sacral sutures in the anterior longitudinal ligament of the sacrum and not inadvertently in the vertebral disc space, as this may increase the risk of bacterial inoculation

into the space, especially when the graft has been attached to the rectum. While there are documented reports of favorable outcomes using synthetic mesh, even with sigmoid resection is performed [59], our group attempts to minimize the risk of infection of prosthetic synthetic material by using a biologic graft when a bowel resection is indicated and by always using monofilament delayed absorbable sutures on the rectum and vagina and monofilament permanent sutures on the sacrum. We also have a low threshold to evaluate postoperative patients with either a CT scan or an MRI who complain of malaise and/or lower back pain or who have ongoing nondescript symptoms that cannot be explained by another cause of infection.

Surgical Management of the Posterior Compartment: Approach to the Rectocele Repair

Symptoms associated with a rectocele can often be managed effectively without surgery. Conservative management includes the initiation of a routine bowel regimen in order to avoid constipation and straining with bowel movements. A good regimen usually includes a high fiber diet, adequate water intake, and an over-the-counter stool softener. Pelvic floor physical therapy with or without biofeedback is also a conservative management strategy that can be offered to patients who are noted to have dysfunction of the pelvic floor muscles on examination. In addition, rectoceles protruding into the middle and upper vagina may also benefit from pessary placement.

Surgical management is an option for patients who fail conservative management. Surgeons differ in their opinion regarding when surgical management is indicated. Some surgeons (many colorectal surgeons) believe that dysfunctional fecal evacuation alone is not an indication and that patients should complain of needing to splint to defecate, or have vaginal protrusion of the rectocele beyond the hymen. In our urogynecology practice, we offer patients surgical treatment if they fail conservative measures, have any emptying/evacuation complaints and/or vaginal bulge or protrusion symptoms. Surgical management and planning are done after a thorough pelvic floor examination as mentioned above. Prolapse of the posterior vaginal wall can be isolated or can occur in conjunction with prolapse of the other compartments, and surgical planning is done accordingly. Concomitant enterocele and sigmoidocele can also be present with a rectocele, but there are no data describing how often this occurs, and whether or not the presence of one of these conditions affects surgical outcomes after rectocele repair.

Before proceeding with surgical management, an important thing to always consider is that constipation symptoms may be related to underlying physiologic dysfunction [65], and not the rectocele itself. In addition, while posterior compartment prolapse is commonly associated with symptoms of bowel dysfunction, it is unclear how related they are to the presence or severity of prolapse [66], which can make the decision to proceed with surgical management a challenge. There are data, however, that show significant improvement in anatomy of the posterior compartment as well as defectaory symptoms after rectocele repair [67], and therefore, there is reason to believe that posterior repair is beneficial for some patients. Patients should be well counseled about the possibility of persistent constipation or defecatory symptoms after rectocele repair, and conservative management of these symptoms may still be needed after surgery. Several approaches to rectocele repair exist. The transvaginal techniques used by pelvic floor surgeons will be discussed here. The transanal techniques will be discussed in Chap. 59.

Transvaginal Repair

Transvaginal repair is currently the most common approach to rectocele repair, and two techniques for transvaginal repair exist. The “traditional” or “midline plication” technique involves plication of the vaginal muscularis and rectovaginal tissues with or without the underlying levator muscles in the midline. A “site-specific” repair entails repair of discrete defects in the vaginal muscularis and rectovaginal tissues without plication of the levator muscles, usually with a finger inside of the rectum to discern repair of the defects.

Figure 63-5 provides an overview of how the transvaginal rectocele repair is performed. Patients are positioned in the dorsal lithotomy position. The posterior vaginal wall is injected with a local anesthetic with dilute epinephrine (our preference is 0.5 % lidocaine with 1:200,000 units epinephrine) and then incised in the midline from the most dependent portion of the rectocele proximally, (easily identified on rectovaginal examination), to the hymen. If there is detachment of the rectovaginal septum from the perineum, a gaping genital hiatus, and/or a perineocele, a perineorrhaphy should also be performed, and the perineal epithelium should also be incised. Once incision is made, clamps are placed on the incised vaginal epithelial edges, gentle traction is applied, and the fibromuscular layer of the vagina is dissected off of the epithelium, creating bilateral epithelial flaps. If an enterocele sac is encountered, it is usually opened, the small bowel contents are reduced and the sac is purse-stringed shut with either permanent or delayed absorbable No. 0 or 2-0 suture. Next, plication is performed either in the midline, or in a site-specific manner using either No. 0 or 2-0 absorbable or delayed absorbable suture until the rectocele is completely reduced. If a perineorrhaphy is performed, a 0 absorbable suture is used to reconstruct the perineum by plicating the inferior portion of the bulbospongiosus muscles and the superficial transverse perianal muscles and reattaching this complex to the rectovaginal septum if indicated. The epithelial edges are then trimmed bilaterally and reapproximated with 2-0 absorbable suture.

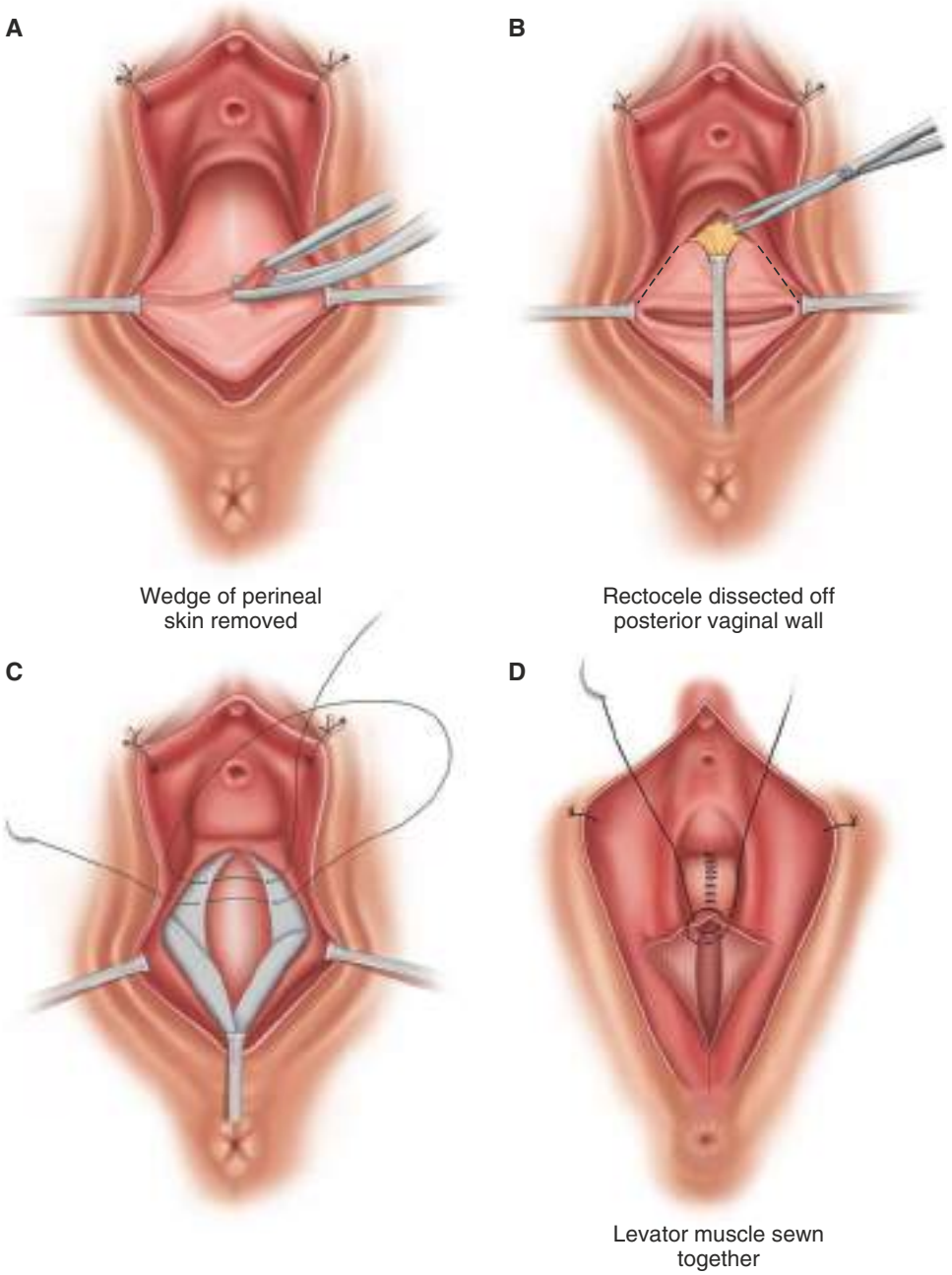

FIGURE 63-5. Transvaginal rectocele repair. (**a**) The posterior vagina and perineum are incised. (**b**) The epithelium is dissected off of the underlying vagina muscularis. (**c**) The muscularis and rectovaginal tissues with or without the underlying levator ani muscles are plicated. (**d**) The posterior vaginal epithelium is reapproximated.

The transvaginal rectocele repair can be further modified by augmenting the repair with either a synthetic or biologic graft. Synthetic graft materials can be either absorbable or permanent and are commonly made out of polyglactin or polypropylene, and the most commonly used biologic grafts are dermal or intestinal and are bovine or porcine in nature. The data that exist on posterior compartment repair with graft augmentation do not show significant benefit from its use. Altman et al. [68] prospectively looked at augmentation with a porcine dermal graft and reported a 40 % anatomic recurrence at 3 years and less than 50 % of patients had improvement in their defecatory symptoms. Sand et al. [69] compared rectocele repair with and without placement of a polyglactin mesh and found that recurrence was similar between the two groups.

In a review of posterior vaginal wall prolapse by Maher and Karram [70], midline plication and site-specific repair were found to both have a mean reported anatomic success

rate of 83 %. The authors also found that of the patients undergoing midline repair, 18 % complained of postoperative dyspareunia and 26 % complained of defecatory dysfunction with need to perform vaginal digitation to defecate, compared to 18 % for both problems in the site-specific groups. In their retrospective analysis, Abramov et al. [71] found that patients undergoing site-specific repair were more likely to experience recurrent rectocele compared to their midline plication cohort (32 % vs. 13 %, $p=0.015$). In a randomized trial by Paraiso et al. [72], patients with a stage II or greater rectocele were randomized to one of three rectocele repair arms: midline plication, site-specific repair, and augmented repair with porcine small intestinal submucosa graft. At 1 year, anatomic failure was found to be highest in the augmented group, followed by the site-specific repair group (46 % vs. 22 % v. 14 %, $p=0.02$). Interestingly, there was no statistical difference in defecatory and dyspareunia symptoms between the three groups. In a multicenter randomized trial, Sung et al. [73] also found no statistical difference in postoperative dyspareunia and resolution of defecatory symptoms in patients undergoing any type of native tissue repair (midline plication and site-specific) compared to a porcine small intestinal submucosa graft augmented repair; however, contrary to the above-mentioned studies, the authors also did not find a difference in objective and subjective success rates between the two groups.

Transanal Repair

In 1967, Marks [74] described the transanal rectocele repair procedure. While less commonly performed (compared to the transvaginal approach), it is still performed by some colorectal surgeons (see Chap. 59).

Several trials exist comparing the transvaginal and transanal approaches to rectocele repair. Kahn and Stanton [75] looked at women with symptomatic rectoceles with and without defecatory dysfunction who had impaired rectal evacuation on defecography but normal anorectal compliance on anal manometry. Transvaginal repair involved midline and levator plication and was performed by FPMRS surgeon, while the transanal colorectal surgeons performed a transanal repair. Nieminen et al. [76] performed a trial with broader inclusion criteria and included all women with symptomatic isolated rectoceles and intact anal sphincter function who did not respond to conservative management. Transvaginal repair was performed by FPMRS surgeons and involved midline plication only without levator plication and transanal repair was performed by colorectal surgeons. Both trials reported significant alleviation of symptoms by both operative techniques, but the transanal approach seemed to be associated with more clinically diagnosed rectocele recurrences and decreased incidence of dyspareunia.

In general, the transvaginal approach seems to be the more commonly performed operation for symptomatic rectocele particularly by FPMRS. The anatomic outcomes seem to be better, and it may be associated with less morbidity. However, the procedure is associated with higher rates of postoperative dyspareunia, especially if levator plication is performed, and it does not always resolve all defecatory symptoms.

Conclusions

Pelvic floor disorders are mostly a continuum of a disease process resulting from the loss of pelvic floor support. It is not uncommon to have multi-compartmental dysfunction, often requiring a multi-disciplinary team approach to evaluation and management. FPMRS surgeons and colorectal surgeons must strive to work together to offer their patients treatment strategies that are associated with the best outcomes but also with the lowest risk of morbidity. Understanding the anatomic relationships of the pelvic floor is the first step in achieving this. Second, is having a good grasp of each specialist's evaluation and management strategies, and working together to offer patients a comprehensive plan of care.

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Part VI
Miscellaneous

64
Pediatric Colorectal Disorders

Daniel H. Teitelbaum and Peter F. Ehrlich

Key Concepts

- **Cloacal anomalies**: These are among the most complex of pediatric colorectal conditions. Careful anatomic assessment must be done prior to surgical correction. Long-term follow-up is essential as future gynecological and genitourinary problems may arise that also need corrective action.
- **Anorectal atresias:** Imperforate anal anomalies are commonly associated with both genitourinary and spinal anomalies; both of which may complicate the long-term management and care of such patients. Life-long incontinence may be seen in up to 50 % of such patients.
- **Hirschsprung disease:** While surgical correction will result in a good stooling pattern. Many patients may suffer from recurrent enterocolitis after a pull-through, which requires immediate attention by a surgeon experienced in dealing with this secondary disorder. Children may also occasionally suffer from anorectal incontinence. In general, they need to be followed long-term for similar potential problems.
- **Necrotizing enterocolitis (NEC):** NEC may lead to full-thickness intestinal necrosis, resulting in the loss of a considerable amount of small and/or large intestine. Even without intestinal loss, an ischemic-associated stricture may occur, which is typically in the splenic flexure region, and may require dilation or resection of this portion of the colon.
- **Inflammatory bowel disease:** Diagnosis and the treatment are quite similar to adults. A key consideration is the need to ensure adequate growth and maturation through adolescence. Often this plays directly into the timing and decision for surgery.
- **Constipation:** Constipation can be challenging and typically can be initially approached with medical management. It is important to rule out Hirschsprung disease and anatomic obstruction. For the most intransigent of cases, some will benefit from an appendicostomy.

Introduction

Pediatric colorectal disease processes range from complex congenital developmental disorders to a wide range of acquired disorders. This chapter, while not trying to be a comprehensive review, will discuss some of the key colorectal disorders that are commonly cared for in childhood, and often carry with them life-long issues that colorectal surgeons may often encounter. Thus, familiarization with both of these types of disorders, and the management of potential complications, is paramount.

Congenital Anomalies

Cloacal Anomalies

Cloacal anomalies are the most severe and complex form of anorectal malformation (ARM) and occur in ~1:20,000 live-births [1]. Embryologically, the cloaca is a transient organ that becomes divided to separate the gastrointestinal tract from the genitourinary tract [1].

Clinically, a cloaca describes the condition in which the urethra, vagina, and rectum empty into a single channel with a single perineal orifice, located on the anterior perineum at the expected site of the urethra [2] (Figure 64-1). Typically, this is associated with a hypoplastic formation of the labial structures, and the perineal opening may be so small that adequate removal of secretions may be inhibited. This may lead to associated significant abdominal distension due to reflux of urine into the vaginal cavity, or excess secretions of the uterus due to maternal hormonal stimulation. This distension may worsen as the infant is unable to pass meconium and may require urgent decompression via a vaginostomy tube placement as well as colostomy (see section "Current Therapy").

Various cloacal malformations may present with similar prenatal imaging features, including dilation of the vaginal cavity [1]. The exact anatomic delineation will require

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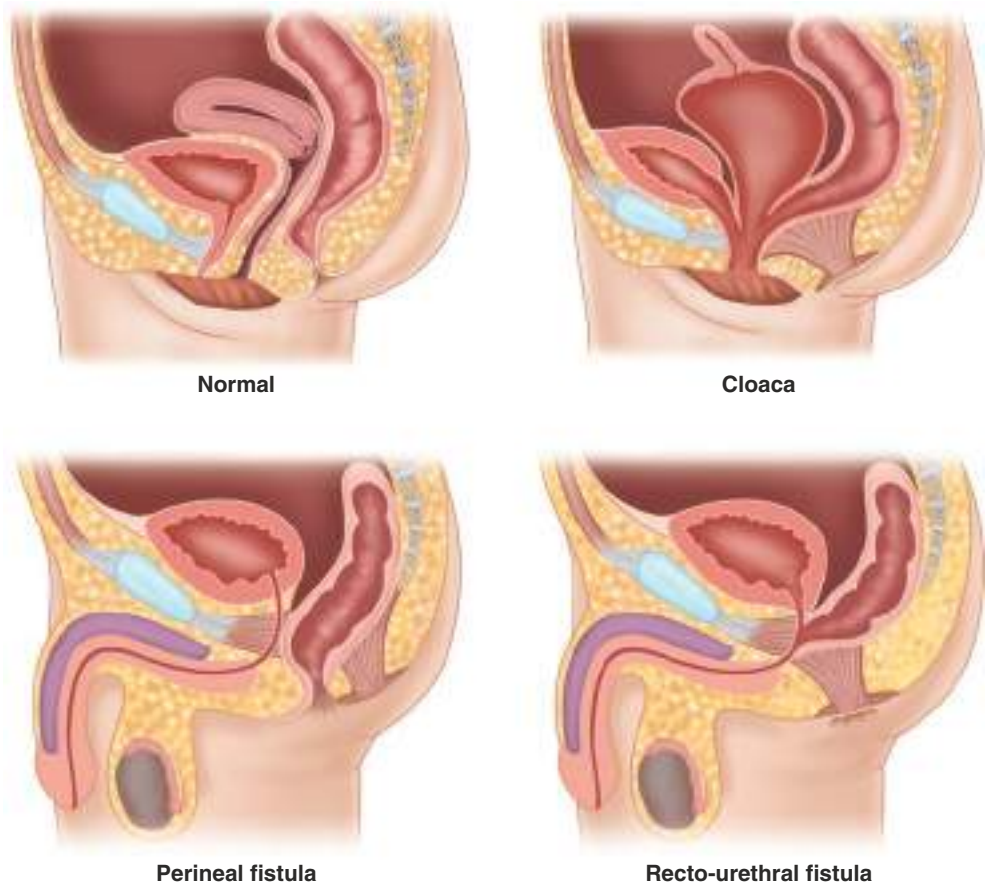

FIGURE 64-1. Classification of anorectal atresias. *Top left panel* Normal cross-sectional appearance of female anatomy. *Bottom left panel* Male with low imperforate anus (perineal fistula). Rectum is located within most of sphincter mechanism. *Top right panel* Female with cloaca. Note rectum, vagina, and urinary tract fuse into a single common channel. *Bottom right panel* Male with high imperforate anus (recto-urethral fistula). There is no plane of dissection between the rectum and urethra.

endoscopy and extensive radiologic work-up. One variant of cloacal malformation is a urogenital sinus, in which only the urethra and vagina form a common channel; the rectum is separate and in the appropriate anatomic location.

Mechanisms Underlying Cloacal Anomalies

Normally present in the 4–5-week old embryo, the cloaca is a derivative of hindgut endoderm [3]. A urorectal septum forms at the cranial aspect of the cloaca to divide it into the urogenital sinus ventrally and the anorectum dorsally [4]. Once the urorectal septum reaches the perineum, the cloacal membrane dissipates to open the urogenital sinus and, separately, the posterior anorectum. The urogenital sinus will mature to become the urinary bladder and urethra with a portion incorporated into the vagina and hymen [5].

The subtypes of ARM observed result from the timing of developmental arrest. The actual causes of the various stages of arrest are not known, but molecular models implicate Homeobox, bone morphogenetic proteins (BMPs), and Sonic hedgehog (SHH) signaling [6]. In addition, changes in sex hormone concentrations have been implicated, as evidenced by the association of urogenital sinus malformation variants with female virilization in congenital adrenal hyperplasia [1].

Current Therapy

The current therapy for cloacal anomalies is surgical. An initial prenatal work-up should determine the presence or absence of hydrocolpos (distended vagina filled with fluid). Failure to recognize and manage hydrocolpos can lead to serious complications, including vaginal rupture, hydronephrosis (distended and dilated kidney), and sepsis [7]. These complications are prevented with early vaginal decompression and drain placement when the colostomy is formed. We have recently described a minimally invasive approach via combined cystoscopy and vaginoscopy [8]. Occasionally, perforation of either the vagina or uterus may occur in utero; and this will be associated with significant abdominal distension, gastrointestinal dysfunction, and respiratory distress. In these latter cases, initial surgery will be considerably more challenging, and typically an open abdominal approach may be needed.

Definitive surgery is undertaken once the anatomy has been mapped out using radiologic imaging and endoscopy. Recent uses of 3-dimensional imaging using either fluoroscopy or MRI scanning requires the instillation of contrast into the vagina, bladder, and rectum, but dramatically increases the accuracy of the preoperative imaging [9]. The length of the common channel is a major factor when choosing a definitive surgery [10]. Short common channels (<3 cm) can be repaired with a perineal incision and have less associated morbidities [11]. Long common channels (>3 cm) require a more complicated repair with abdominal and perineal incisions [10]. Long-term outcomes depend upon associated anomalies. Measurement of the channel length is typically assessed with cystoscopy and vaginoscopy just prior to the definitive surgery.

Surgical management will require separation of the rectum from the cloacal channel, with implantation in the center of the remaining sphincter complex. The introital structures (i.e., vaginal and urethral) are then mobilized as a single unit and brought down to the perineal skin. For long channel anomalies, greater degrees of mobilization may be required, or a combined intra-abdominal and perineal mobilization may be needed. In almost half of the cases, a Didelphus system is found including vaginal septum or in more extensive cases, two complete hemi-uterine structures. These should be identified at the time of the initial surgery with some attempts to unify the two vaginal cavities.

Long-term follow-up is critical, as many of these children will have life-long urological and gynecological problems. Additionally, as with all patients with imperforate anus, the incidence of anorectal incontinence is at least 50 % (see below).

A distinct entity, cloacal exstrophy (i.e., bladder and cecum open onto the external abdominal wall), is associated with an omphalocele, imperforate anus, and ambiguous genitalia (typically absence of a phallus in males). In one review, 96 % of cloacal exstrophy patients had foreshortened colons and 13 % had short bowel syndrome, resulting in prolonged hospitalization and intravenous nutrition [12].

Anorectal Atresia

Anorectal atresia, or imperforate anus, is caused by abnormalities in hindgut development [10] that result in ectopic positioning of the anal opening in the cloaca due to anatomical and/or genetic factors. The extent of ARM directly relates to the degree of development in the posterior aspect of the cloaca (Figs. 64-1 and 64-2). Smaller defects have a more posterior phenotype, such as an anocutaneous fistula; while more extensive defects will lead to more anterior abnormalities, such as a recto-urethral fistula occurring above the levator muscular complex, and in very severe cases manifesting as a cloaca [13, 14].

Underlying Mechanisms

Animal models suggest that a disruption in endoderm development results in ARM. A mutation of fibroblast growth factor receptor 2IIIb (*Fgfr2IIIb*) or the gene encoding its ligand, fibroblast growth factor 10 (Fgf10), results in both colonic and duodenal atresias, suggesting a similar mechanism causes both defects [15]. *Fgfr2IIIb* encodes a membrane-bound tyrosine kinase receptor thought to be expressed only in the endoderm of the developing intestine [16]. Fgf10 is expressed in the rectum when anorectal continuity is established in mice [17]. Mutation of *Fgfr2IIIb* or Fgf10 [18], Hedgehog signaling [15, 19], Wnt5a [20], and *caudal type homeobox 2* (*Cdx2*) mutations have all been associated with ARM phenotype in mice [21]. Recent literature suggests familial inheritance patterns. For patients with a rectovestibular or rectoperineal fistula, almost 15 % had a positive family history for ARM [22]. Thus, genetic consultation is important.

ARMs are associated with the VACTERL complex, which encompasses: Vertebral defects (e.g., sacral anomalies or hemi-vertebra), Anal atresia, Cardiac defects (most commonly atrial septal or ventriculoseptal defects), Tracheo-Esophageal fistula, Renal anomalies, and Limb dysplasias (e.g., typically a

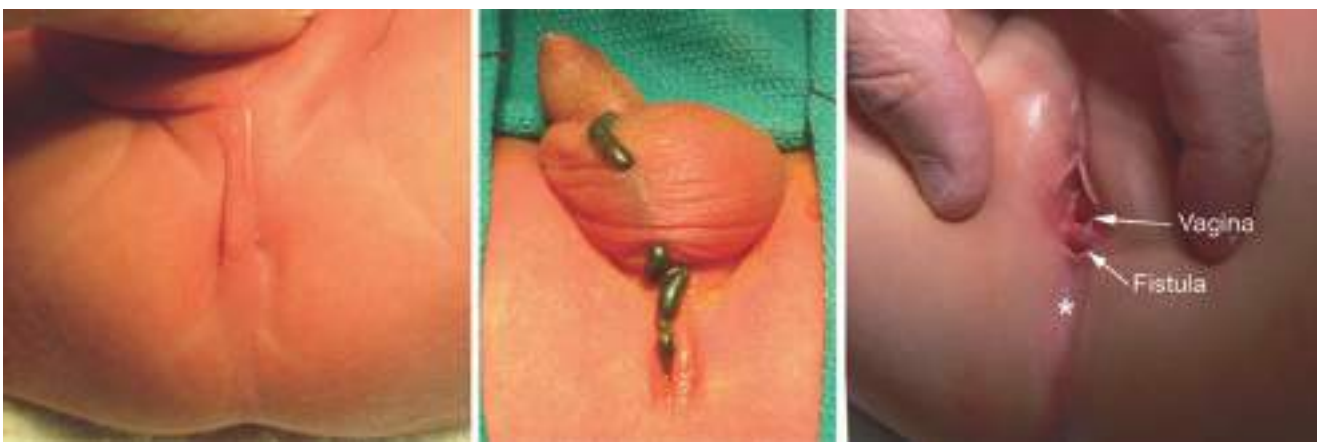

FIGURE 64-2. External appearance of perineum in various forms of imperforate anus.

poorly formed radial bone and/or absent thumb). The incidence is estimated to be 1:10,000–1:40,000 live-births [23].

Prior to surgical interventions a work-up for each of these anomalies should be undertaken. In general, this would include the following: plain films of the vertebral column (cervical to coccyx), ultrasound of spinal cord to rule out a tethered cord, cardiac echo—as the most common defects are atrial septal defects and/or ventricular septal defects, assurance that a decompressing tube may be passed from the mouth to the gastric lumen to help rule out most types of trachea-esophageal anomalies, and an ultrasonographic exam of the genitourinary system.

Current Therapies

The initial decision is whether to perform a primary repair or colostomy. To assist in this decision, the child should have a post-24-h prone lateral radiograph to visualize the terminal location of the rectum, which may be facilitated with ultrasonography. A primary pull-through is feasible if the rectum has descended below the pubo-coccygeal muscle complex. However, a colostomy should be performed if there is any question of rectal position or when atresias terminate above the pubo-coccygeal muscle complex. Placement of the ostomy should be as proximal as possible in the descending colon. This allows sufficient distal rectum to pull-through to the perineum.

Anatomic uncertainty increases the risk of injury to adjacent tissues [24]. Furthermore, the recto-urethral fistula often connects through the child's prostate or sphincter complex of the urinary bladder. To better define these connections, a radiologic contrast study through the colostomy should be performed [2].

The classic procedure is the posterior sagittal anorectoplasty [25]. In this procedure, a large midline incision is made on the perineum. The rectum is identified (typically just above the levator complex), and is opened to allow the identification of the recto-urethral fistula. Careful dissection of the fistula using a submucosal dissection is performed, followed by ligation of the fistula, and mobilization of the rectum to allow a pull-through without excess tension. Using a Pena muscle stimulator, careful placement of the rectum through the residual sphincter complex can be performed (Figure 64-3). More recently, a laparoscopic approach to the pull-through procedure has been advocated, which allows a far less extensive perineal dissection, with ligation of the recto-urethral fistula from above via the laparoscopic approach [26].

Long-Term Considerations

Children with anorectal atresia require long-term follow-up, as most will continue to have problems well into adulthood. In the few months following surgery, the child will require dilations of the anal canal. In general, a 12-month-old child will necessitate the easy passage of a #14 Hegar dilator before the protective colostomy may be closed.

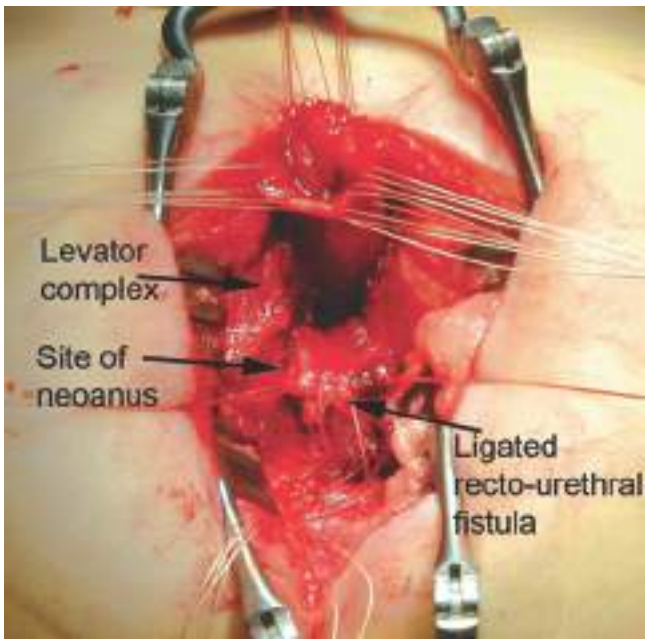

FIGURE 64-3. Intraoperative appearance of a posterior sagittal anorectoplasty (PSARP).

The most common long-term issues relate to the evacuation of a bowel movement. Functional outcomes are dependent upon the height of the fistula Lower lesions typically have issues with constipation, while higher fistulas have issues with incontinence [10]. Another strong predictor of anorectal continence is the integrity of the sacrum. Infants having more than three intact sacral vertebral bodies will typically have a reasonable chance for continence. For children with imperforate anus with a perineal fistula, the greatest issue is long-term constipation. Most of these children will require daily laxative therapy. In general, polyethylene glycol is the most commonly used agent initially, and can result in long-term success.

For infants with poorly formed sacral elements and/or imperforate anal anomalies with a more proximal fistula, incontinence may be at 50 % or higher. Strategies to deal with incontinence are dealt with below in this chapter.

Hirschsprung Disease

Hirschsprung disease (HD) is characterized by the absence of colonic ganglion cells, typically in the distal colon. The lack of a functional myenteric nervous system leads to a derangement of motility necessary for propagation of enteric contents, resulting in obstruction [27]. HD is estimated to occur at 1:5000 live-births with a male-to-female preponderance of 4:1 [28], except in total colonic aganglionosis, which has a stronger association with female patients.

Presentation and Underlying Mechanisms

Infants present with delayed passage of their first bowel movement (meconium), which typically occurs in the first 24 h of life. The diagnosis should also be considered in children suffering from difficult bowel movements, poor feeding, poor weight gain, and progressive abdominal distension. Figure 64-4 shows the most likely pathogenesis of aganglionosis. The aganglionic area lacks nitric oxide synthase (NOS) and cannot produce the smooth muscle relaxant nitric oxide, thus leading to colonic constriction. This is worsened by an increased number of stimulatory parasympathetic fibers that increase the constriction of the distal colon. A contrast enema will show a constricted distal rectum (Figure 64-5) with a more dilated proximal colon. It is important to again note that the dilated part is the *normal* segment of bowel. While this may demonstrate the transition zone, the extent of aganglionosis may be difficult to predict with accuracy on enema alone, particularly in newborns. Suction rectal biopsy (typically at the bedside), or full-thickness rectal biopsy in the operating room for older children, should be performed to detect hypertrophic nerve trunks and the absence of ganglion cells in the colonic submucosa to confirm the diagnosis.

The pathogenesis of HD is uncertain, but may involve failure of either neural crest cell migration or survival [29]. Multiple genetic markers have been identified as playing a crucial role in HD [28]. While less than half of HD cases have been traced to a specific genetic cause, mutations in the *RET* proto-oncogene pathway compromise nearly half of all familial cases and a smaller fraction of sporadic cases. At this time, it is unclear how

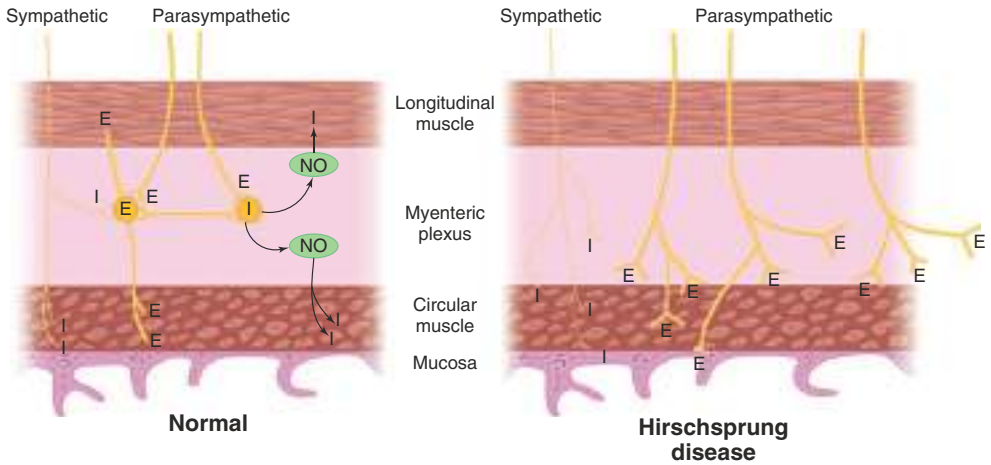

FIGURE 64-4. Diagram showing the pathophysiologic processes which drives functional obstruction in Hirschsprung disease. Note in Hirschsprung patients there is predominance of excitatory parasympathetic fibers (causing an increase histologically of hypertrophic nerves) with a loss of intrinsic ganglion cells and a loss of nitric oxide, which is critical for the relaxation of smooth muscle. E: excitatory; I: inhibitory; NO: nitric oxide

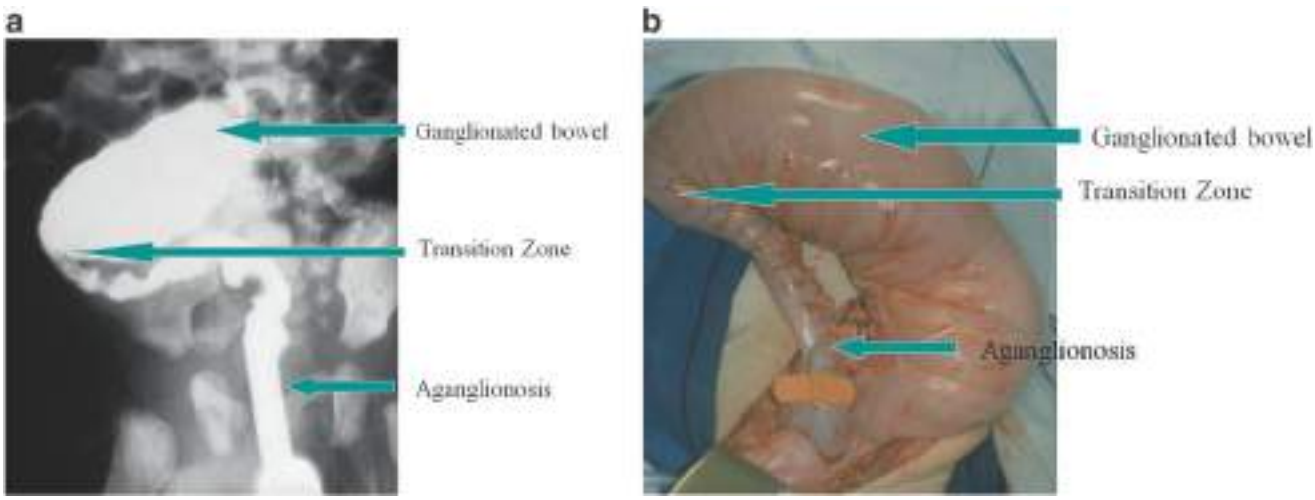

FIGURE 64-5. (**a**): Radiographic contrast enema in infant with Hirschsprung disease. Note constricted distal colon representing the aganglionic segment, with a transition zone and proximal, dilated ganglionated colon. (**b**): Operative image of same patient. Note constriction of aganglionic segment and dilation of proximal colon with a hypertrophy of the longitudinal muscle layer.

these mutations translate to aganglionosis, especially since not all family members of patients with HD who carry the same *RET* mutations will show a HD phenotype [30]. Loss of ganglion cells results in an absolute loss of NOS with resultant depletion of nitric oxide in the aganglionic portions of the bowel and failure of the smooth muscle to relax [31].

Molecular Markers

Over 30 genetic mutations have been identified in patients with HD, including mutations in *RET*, *EDN3*, or *EDNRB*. However, such mutations can also be found in non-affected family members. In addition, largely due to incomplete penetrance and variable expressivity, it is not possible to perform accurate prenatal diagnosis of HD at this time [30]. As specific genetic mutations are associated with other anomalies, however, genetic screening may still be valuable in these patients. For example, certain *RET* mutations can lead to medullary thyroid cancer, and genetic screening offers the ability to identify these mutations and prophylactically remove the thyroid prior to malignancy development.

Current Therapies

Swenson performed the successful surgical treatment of HD in 1948, consisting of a full-thickness perineal resection and colo-anal anastomosis, though there have been several advancements since then [32]. Today, the most common techniques involve an open, laparoscopic, or transanal approach with a retrorectal pull-through (Figure 64-5b) [33]. The Soave procedure involves a mucosal/submucosal resection distally and a full-thickness resection proximally of the diseased segment, followed by a pull-through procedure within the muscular cuff. Finally, the Duhamel procedure involves a resection of the proximal diseased bowel with a retrorectal mobilization (leaving the diseased rectum in-situ) and performing a retro-rectal anastomosis with the rectum and normally innervated bowel. Regardless of the approach, the concept is to remove or bypass the aganglionic segment with an anastomosis of proximal, ganglionic bowel. Many studies have attempted to tease out which technique is superior without a clear consensus [34–36], and most children do well regardless of the type of procedure [37–39].

After surgery, children may experience long-term postoperative complications including soiling/incontinence, constipation, and recurrent enterocolitis [40, 41]. This latter complication, enterocolitis, is a GI inflammatory condition that can lead to diarrhea and systemic septicemia, and has been reported in up to 40 % of children after a pull-through procedure. While the etiology is unknown, it may be a complex interaction between intestinal microbiome and still undefined abnormalities within the ganglionic intestinal segment. Medical management including broad spectrum antibiotics and/or minor procedures can aid in many situations to alleviate enterocolitis [42, 43].

Long-term incontinence has been reported in approximately 5 % of children after a pull-through [44]; however, a larger number may have a delay in successful toilet training or persistent stooling problems for several years after their pull-through. Although uncommon, an occasional patient with a successful pull-through may develop secondary problems including strictures, recurrent enterocolitis, or secondary loss of ganglion cells. These more uncommon conditions may require reoperation, including a posterior myomectomy (in the case of recurrent enterocolitis) [45], or redo-pull-through for strictures or aganglionic segments [46].

Acquired Diseases

Necrotizing Enterocolitis

NEC is an acquired disease affecting the intestine of newborns and is a leading cause of infant morbidity and mortality in neonatal intensive care units (NICUs). NEC is currently the most common premature newborn surgical emergency [47]. Infants born with a birth weight of <1000 g and/or <28 weeks gestation are at the greatest risk. The presence of pneumatosis intestinalis on radiographs or intraoperatively will be seen in most advanced cases; and at times this air may extend into the portal tree (Figure 64-6).

Underlying Mechanisms

Empiric and experimental data suggest that NEC occurs in a vulnerable host who has become further compromised at the level of the gastrointestinal tract, and whose main purposes of barrier function and immune modulation are disturbed or immature. This initiates an ischemic cascade that becomes unbalanced, resulting in loss of epithelial barrier function with subsequent progressive enteric mucosal and then full-thickness injury [47].

Gut colonization has been documented to involve both environmental and genetic factors, and bacterial colonization may be abnormal in infants with NEC [48]. The process appears to be driven by abnormal bacteria/TLR4 signaling pathway, leading to diminished nitric oxide production, decreased intestinal motility with subsequent bacterial overgrowth, and breakdown of barrier function [49].

Current Therapies

Prevention of NEC should be considered the primary treatment. Breast milk has been shown to significantly decrease the incidence of NEC [50]. This is believed to be due to the high concentrations of epidermal growth factor (EGF) and IgA in human breast milk [51]. As well, human milk provides a rich source of oligosaccharides which, while indigestible by humans, serves as a nutritional substrate for lactobacillus and other favorable strains of Firmacutes within the microbiome [52].

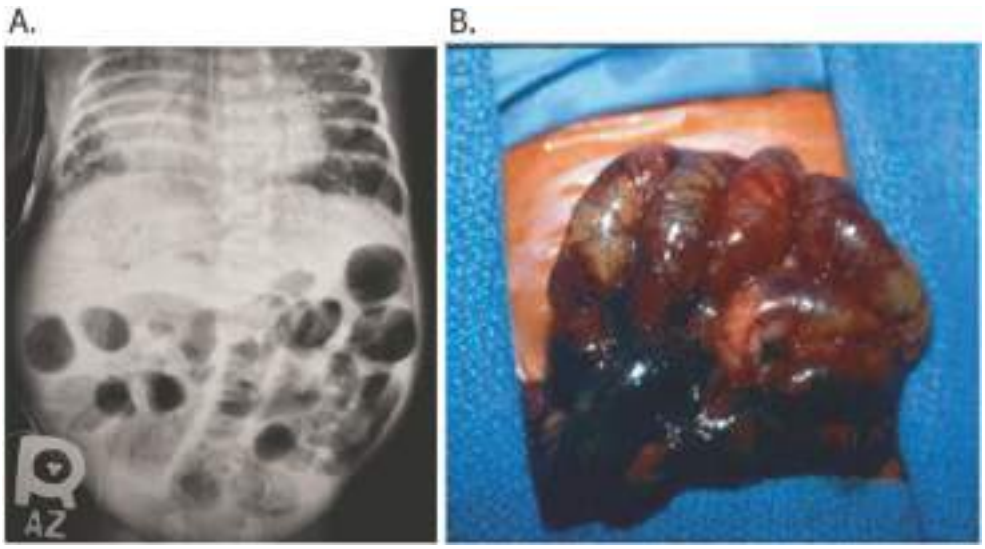

FIGURE 64-6. (**a**) Radiograph of a premature neonate with necrotizing enterocolitis. Note diffuse pneumotosis intestinalis, and air in the biliary tree. (**b**): Intraoperative appearance of the same neonate showing pneumotosis intestinalis and patchy ischemia/necrosis to the small bowel.

In the absence of a surgical emergency, supportive care is the basis of treatment. This consists of discontinuing enteral feedings, GI tract decompression, and administration of intravenous fluids/nutrition. Broad spectrum antibiotics should also be given [47]. Frequent abdominal examinations and radiographs are performed to monitor for disease progression/regression.

In general, surgery is indicated for clinical signs of perforation (e.g., pneumoperitoneum) or clinical deterioration despite maximum medical treatment. The goal of operative treatment is to remove necrotic intestine while preserving bowel length. Unfortunately, almost 50 % of neonates undergoing surgery do not survive, emphasizing the severity of NEC. Furthermore, infants may suffer from considerable loss of small and large bowel with resultant short bowel syndrome. As many neonates may be hemodynamically unstable, and may not tolerate a full laparotomy, performing a percutaneous drainage of the abdomen via a small right lower quadrant incision is an option for very small premature infants an alternative to surgery. Outcomes between open laparotomy and drainage have been shown to have somewhat equivalent outcomes [53].

Constipation and Anorectal Incontinence

Childhood constipation is a common problem, especially in Western societies [54]. Persistent constipation can lead to fecal retention, impaction, and overflow incontinence. Constipation can be classified as either organic or functional. Most children pass meconium in the first 48 h of life [55]. In the neonatal period, a child with "constipation" should be considered to have an organic cause of their constipation or a bowel obstruction until proven otherwise. In children outside of the neonatal time period, the vast majority of their constipation is functional [56]. Functional constipation is defined as constipation not associated with a congenital anomaly, acquired disease or medications. The Rome III criteria is considered the best method to make an accurate diagnosis of functional constipation [57, 58]. Management of functional constipation in childhood includes education especially around toilet training, dietary changes, and oral medications. The most commonly used medications are polyethylene glycol, or in more resistant cases, senna glycosides (sennosides). Our first step in all the children we evaluate with chronic constipation is to empty the colon of stool and begin a bowel management program. In children who have or should have been toilet trained, we have found behavioral pediatric therapy as a useful adjunct, although the evidence supporting this approach is mixed in the literature [59, 60]. Those children that are refractory to initial treatment need further work-up to rule out an organic cause. Motility assessment, colonic transit, and manometry are useful in guiding future therapy, especially if considering a more invasive intervention. In the few studies to date reporting long-term outcomes, cure rates for chronic constipation are reported between 50 and 70 % [61, 62]. Other non-surgical treatments that have been reported include abdominal wall transcutaneous electrical stimulation [63, 64], and more recently, the PERISTEEN™ (Coloplast, UK) enema program has also reported good results in some children with functional chronic constipation [65].

Surgical Treatment for Chronic Functional Constipation

In spite of the prevalence, the majority of children with functional chronic constipation can be managed without surgery. A few, however, fail and more aggressive interventions are needed. There are no controlled trials of surgical therapy for children with chronic functional constipation. Common

FIGURE 64-7. Example of a Chait tube showing the pigtail end which secures it in the cecum.

procedures used include the Malone anterograde continent enema (MACE) [66–68], or other anterograde continent enema procedures such as a cecostomy typically via a Chait® tube (Cook Medical Co.) [69, 70] (Figure 64-7). One advantage of these procedures are that they are reversible. Resection of a megarectum or colon in children has been reported with mixed results, as has a colostomy [71]. Perhaps the most recent approach to children with intractable constipation has been the use of sacral nerve stimulation (SNS). To date, when used in children with chronic constipation and or fecal incontinence, SNS has shown promising preliminary results [72–75], with series demonstrating up to an 80 % success. One limitation to the use of SNS is that in the USA the use is limited to children over 15 years; thus, its usage in younger patients is considered off-label.

Figure 64-8 shows a decision and management tree in the msanagement of functional constipation.

Constipation and Fecal Incontinence in Children with Hirschsprung Disease (HD) or Anorectal Malformations (ARM)

Constipation and/or fecal incontinence are considerably more challenging to treat in children with HD or ARM. In HD, bowel dysfunction has been reported by parents in up to 65 % of children [76]. Problems are more common in younger children and can have a significant impact on their social interactions and overall quality of life. While such problems may improve in adolescence, in some patients problems can be life-long [77]. In one long-term study, 42 % of patients reported occasional soiling, 12 % had frequent soiling, 46 % had no soiling, and constipation occurred in 9 % [78]. If a child has HD with an associated syndrome, the risk of bowel problems was significantly higher. The etiology of constipation or fecal incontinence in children with HD includes: enterocolitis, anastomotic issues (including stricture), sphincter dysfunction, and a retained/acquired aganglionic segment. As stated early, enterocolitis is one of the most devastating complications of Hirschsprung disease. Symptoms can occur acutely, be recurrent and low grade or chronic [40]. In either situation, this requires prompt treatment with rectal decompression of air and fecal contents, antibiotics, and if needed, intravenous fluids [79].

Strictures at the anastomotic site (often due to ischemia) may respond to dilatations, however, persistent strictures will require a repeat pull-through [80]. Sphincter dysfunction may also be due to excessive stretch of the sphincter complex or retention of an aganglionic rectal cuff, the latter of which may lead to obstructive symptoms due to a high-pressure zone in the anal canal after endorectal pull-through [45]. Constipation can also be the result of a retained or long aganglionic segment [80]. This latter problem may be due to the retention of a small segment of aganglionic bowel at the initial operation at the level of the sphincters to help with continence. As the child grows, this aganglionic segment may also grow, therefore creating a functional obstruction. Findings of an aganglionic segment may also be due to an anastomosis at the transition zone where there are fewer ganglion cells and some larger nerves.

Children with these disorders lack adequate sphincter complex musculature or innervation. Thus, constipation and fecal incontinence are even more prevalent in children with ARM [81–83]. Only one-third will have voluntary bowel movements and complete evacuation, while the remaining will require some interventions. ARMs comprise a wide variety of lesions and bowel problems that depend on the anatomic defect (i.e., where there are pelvic muscles and nerves), the quality of the surgical repair, and early aggressive treatment to avoid the development of a megacolon. With the use of a focused bowel management program, the majority can be expected to achieve social continence and improved quality of life [84].

Diagnostic Work-Up and Therapy

In children with HD and bowel dysfunction, a digital examination, contrast enema, stool studies, and endoscopy with biopsies (at 2, 4 and 6 cm) above the anastomosis are all critically important. The combined results will help determine if there is transitional zone or aganglionic tissue. In cases where it is uncertain as to whether there is fecal incontinence, anorectal manometry may prove useful. Defecography and motility studies may also be helpful. For enterocolitis, oral antibiotics (typically metronidazole, or intravenous if the child is sick) and a rectal decompression are the first-line treatment options [40, 85]. For sphincter dysfunction or aganglionic segments, the initial therapy is a bowel management program (see below). If those treatments

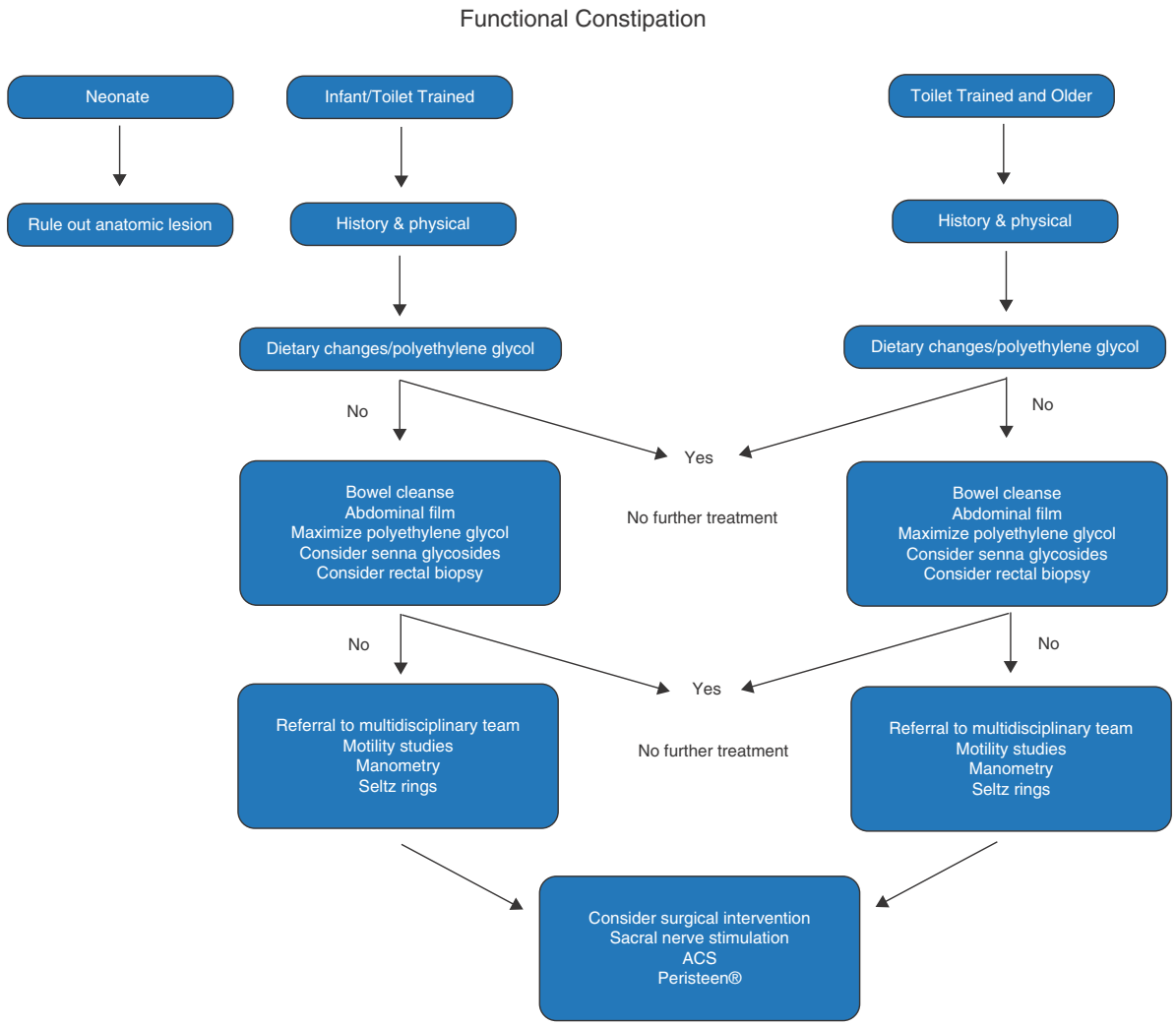

FIGURE 64-8. Decision tree in the management of functional constipation. Abbreviations: *ACE* antegrade continent enema.

fail, internal anal sphincter botulinum toxin injections can result in good long-term outcomes in up to 50 % of children who suffer from an outflow obstructive symptoms [86, 87]. Surgical therapy includes posterior myotomy, ACE procedures, and in cases that have failed other treatments, re-do pull-through [45, 80].

For constipation and fecal incontinence in children with ARM, it is important to realize that the loss of a sphincteric complex may result in both of these symptoms. As such, the initial investigations should also include a contrast enema to rule out retention of stool with overflow incontinence. Similar to HD motility studies, defecography and manometry can be helpful. In either case, the first-line of therapy consists of a bowel management program. While most often not necessary, surgical therapy includes an ACE procedures, or for severe cases, a colostomy. SNS in children with HD and ARM has been performed, but the data is preliminary, and no conclusions can be made whether incontinence is improved by this modality.

Inflammatory Bowel Disease in Children

Crohn's and Ulcerative Colitis (UC) are the most common forms of IBD encountered in childhood [88, 89]. In many aspects, both the medical and surgical therapy are similar to the adults and are detailed in other chapters. In children, Crohn's and UC can occur at any age, but the peak incidence is in late adolescence to early adulthood. In addition, there is a slight female predominance. Children with IBD tend to present differently than adults, as there is often a more prolonged course prior to definitive diagnosis. The initial symptoms are often systemic in nature without focal gastrointestinal manifestations. These include: fever of unknown origin, arthritis, and chronic microcytic anemia. Approximately 35 % of children present with delayed growth or development, which can precede the development of any other overt symptoms by months or even years, and for Crohn's patients in particular, significantly delay the recognition of disease [88, 89].

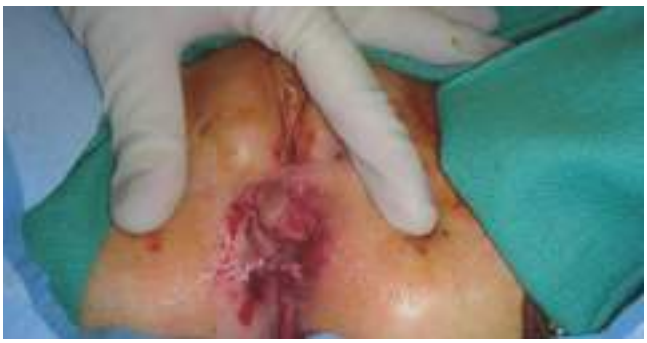

FIGURE 64-9. Pediatric perianal Crohn's disease.

Presentation

In Crohn's disease the most frequent distributions are the following: 33 % are limited to the small bowel alone, 45 % involve both the ileum and colon, 20 % have isolated colonic Crohn's, and 1/3 of patients have perianal disease (Figure 64-9), though this is rarely the sole location. Most patients have oral lesions, yet they are rarely severe [88, 89].

Ulcerative Colitis

Children with UC may present with extra-intestinal manifestations. The most common is a polyarthritis, involving large joints, but without joint destruction. In UC, the severity of inflammation largely parallels the severity of the intestinal component. Therefore, a colectomy is curative not only of the colitis, but also most other extra-intestinal manifestations—although (similar to adults) bile duct pathology is not prevented [88, 89].

Molecular Basis

With the exception of very early-onset IBD occurring before the age of 2 years, no overt differences in genetic susceptibility have been identified in children as compared to adults. In contrast, very early-onset IBD seems to be a genetic disease with defects in the IL-10 signaling pathway likely being involved [90].

Investigations

In children, the endoscopic appearance of the bowel is the same as in adults, as is the histopathology. Radiographically, magnetic resonance enterography is preferred to CT scan, especially with the concerns of radiation from repeated computed tomography scans CT over time [91, 92].

Medical Treatment

The drug choices to treat both Crohn's and UC in children are identical to adults. However, a unique consideration in the medical management of children with IBD is the long-term impact of treatment on growth, bone health and social development [88, 93]. On one hand, medical therapy exposes the child to years of toxic therapy. This should be compared to uncontrolled inflammation and the risk of disease-associated complications, such as fibrosis, fistulas, and cancer. Infliximab use has reduced the need for surgery in children for both Crohn's disease and UC [94]. For Crohn's disease, the multicenter REACH trial and the Scottish trial found that overall response rate was 88 %, and the 8-week remission rate was 59 % (REACH trial) and 47 % (Scottish trial), respectively [95–97]. For UC, infliximab induced a response in 73.3 % of patients and the overall remission rate at week 54 was 28.6 %.

Surgical Indications

The surgical indications in the pediatric population are similar to adults, with the exception of growth retardation. For children with Crohn's disease, acute indications include exsanguinating hemorrhage, perforation, suspected cancer, unresponsive disease, growth retardation, systemic complications, and steroid dependency. In children with UC, they classically include toxic megacolon, perforation, uncontrolled bleeding, and obstruction. On a more chronic basis, indications include refractive disease, steroid dependency, failure to thrive, and impaired psychosocial development. The principles of surgery for children with IBD are identical to those in adults. For CD, it is important to remember that only the diseased segment is removed, as the need for future surgery is high.

In patients with UC, when a restorative total proctocolectomy is required, most surgeons are performing the ileal pouch-anal anastomosis (i.e., J-pouch). A recent review from the Cleveland Clinic compared outcomes in children and adults in children who underwent a restorative proctocolectomy. Although patients who had the surgery at a pediatric age tended to have a higher incidence of postoperative pouch complications, the long-term rates of pouch retention were comparable [98]. Interestingly, a multicenter review between straight and J-pouch reconstructions demonstrated less frequency of bowel movements in the J-pouch group, but this benefit was lost by 3 years of age, suggesting that both approaches may be quite successful in children [99].

Summary

While in many pa0rts of the world, pediatric patients are managed by pediatric specialists including pediatric surgeons. Yet, common colorectal problems will still be referred to general surgeons and colorectal surgeons. As such, it is important that surgeons of all backgrounds have a generalized awareness for the more common clinical conditions that are encountered, their treatment, and what may require modification in this population to account for growth, development, or a different natural history of disease in this population.

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65
Considerations for Geriatric Patients Undergoing Colorectal Surgery

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Key Concepts

- The geriatric population is diverse, with varying levels of health status including physiologic reserve and cognitive function. As such, chronological age is a poor marker of functional, physical, and cognitive decline in the elderly.
- Fit elderly patients, those without significant comorbidities or cognitive decline, can be managed similar to that of younger patients. Frail patients are associated with higher morbidity and mortality in both elective and emergent operations.
- Elderly patients undergoing emergent procedures are at high risk (17–31 %) for post-operative mortality.
- Minimally invasive surgery is safe and appropriate in the elderly population, allowing them to benefit from decreased post-operative morbidity, faster return of bowel function, decreased length of stay, and less pain.
- While some assessment models identify age as an independent risk factor for adverse outcomes, a focus on chronologic age substantially limits effective management of the geriatric patient.
- Frailty is used to represent a global limited reserve in the elder population. As such, abnormalities in frailty domains are a potentially useful tool for predicting poor outcomes.

Introduction

Today's elderly population is steadily growing, due in part to improvements in general medical care, enhanced screening protocols, and advances in anesthesia. In fact, the average life expectancy for a 75-year-old man and woman is now 10.7 and 12.8 years, respectively [1]. Life expectancy is further predicated on level of fitness (Figure 65-1). Recent projections suggest over half of all current operations in the USA are performed on patients older than 65 years of age, with estimates of surgical volume increasing from 14 to 47 % between 2000 and 2020, due to more elderly patients [2]. This steadily increasing volume of elderly patients underscores the importance of defining, and applying appropriate treatment in this population.

Unfortunately, considerable evidence suggests elderly patients with cancer are less likely to be offered standard of care treatment. This is particularly evident in clinical cancer trials, where elders comprise only 25 % of participants [3]. Exclusion of older patients is not limited to clinical trials, but also extends to chemotherapy, radiation therapy, and surgical intervention [4, 5]. For decades, advanced chronological age has been considered the main factor for determining surgical intervention in older patients. Non-operative bias stems from outdated reports demonstrating higher risk of mortality and morbidity. Recent, but inconsistent, data suggests elective surgery may be safe in the elderly with mortality rates as low as 4.7 % [6–10]. However, post-operative mortality and morbidity in the older population remain variable, with post-operative morbidity reported as high as 60 % [6, 9, 10]. The discrepancy in data may reflect the absence of a consistent definition of "elderly" in the literature, as well as incomplete information concerning common risk factors unique to the elder population.

Several studies have attempted to identify risk factors predictive of adverse peri-operative outcomes in the elderly (e.g., emergency surgery, ASA, pre-operative comorbidities, and advancing age); however, the evidence is inconsistent and surgical decision algorithms remain unclear [11]. Current risk stratification models, such as Colorectal Physiologic and Operative Severity Score for enumeration or Mortality and Morbidity (CR-POSSUM) [12, 13] and National Surgery Quality Improvement Program (NSQIP) Morbidity and Mortality Risk Calculator [14], employ chronological age as a variant predictor of adverse peri-operative outcomes. Despite this, chronologic age does not accurately reflect functional, physical, and cognitive decline.

In this chapter, we will elucidate current outcomes in the geriatric population, highlighting standard and alternative endpoints across a range of diagnoses treated electively and

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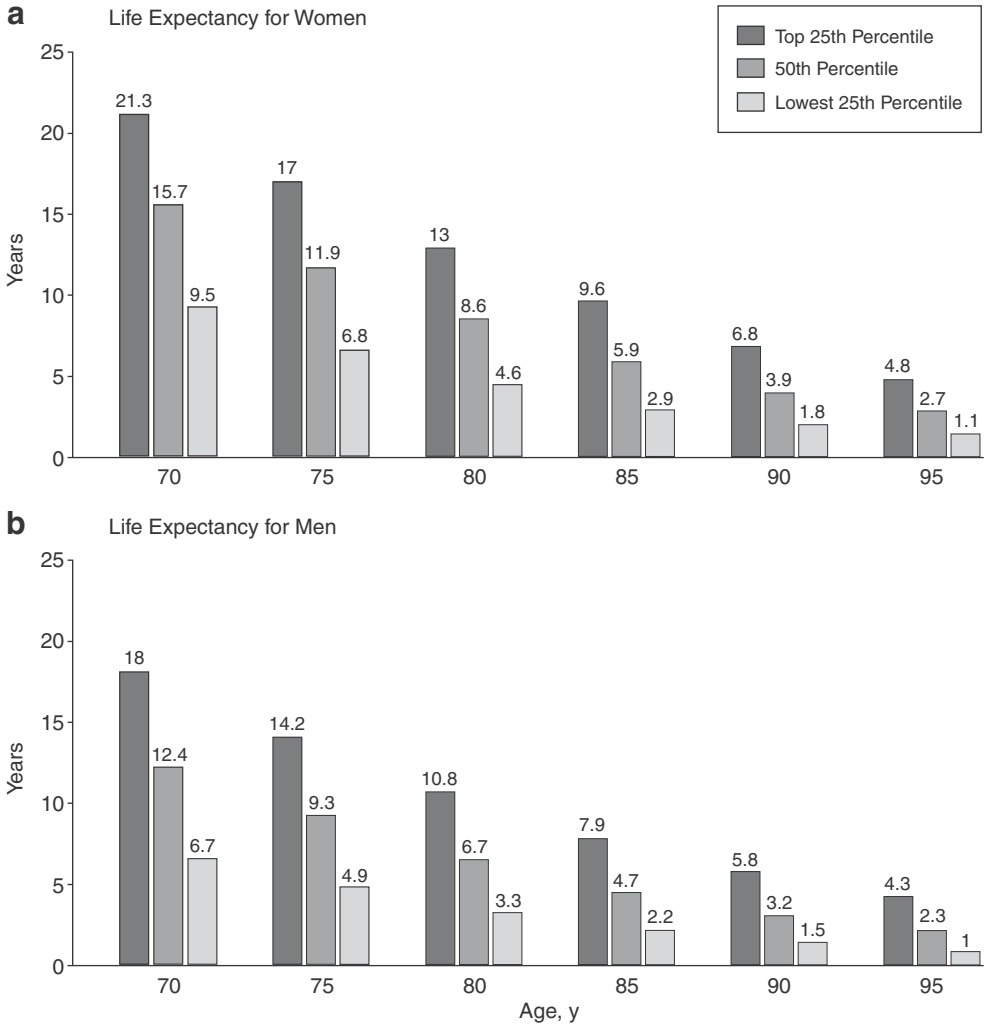

FIGURE 65-1. Life expectancy of elderly based upon age, gender, and fitness level. Life expectancy for those greater than age 70. Although it will vary with current health status, the majority of people are living longer. With permission: Walter LC, Kovinsk KE. Cancer Screening in Elderly Patients: A Framework for Individualized Decision Making. JAMA 2001 2001;285(21):2750–6 [131].

emergently. We will also review the importance of a thorough pre-operative evaluation in elder patients with a focus on current and future risk assessment models to help predict outcomes. Recognition of pre-operative markers depicting the unique variability of the geriatric patient may provide additional insight in predicting poor outcomes, and thus aide pre-operative decision-making.

Current Outcomes in the Geriatric Population

The challenge with evaluating and comparing outcomes among the elderly is population heterogeneity due to diverse health status. The elderly exhibit significantly higher rates of comorbidities ranging from cardiovascular disease to cognitive decline. Congestive heart failure, hypertension, and other chronic comorbidities are relatively higher in elderly cohorts, with those over 85 years significantly worse off than their 71- to 75-year-old counterparts [15, 16]. Similarly, cognitive impairment affects 6 % of patients in the 75–79 age cohort, increasing to 10 % in 80–84 year olds, and more than 18 % in patients 85–89 [16].

The incidence of colorectal pathology is seemingly linked to increasing age, and as such, elderly individuals are increasingly evaluated for surgical care of cancer, bowel obstruction, rectal prolapse, and volvulus [17]. The difficulty for a surgeon lies in determination of appropriate treatment options, each guided by underlying comorbidities and desired patient endpoints. To assist in patient education, the surgeon should understand how different pathologic states and presentations lead to wide-ranging outcomes in this unique population.

Mortality

Key Point: Elderly colorectal patients undergoing emergent procedures are high risk for post-operative mortality, ranging between 14 and 31 %.

Modern health care continues to favor longevity as a central outcome measure. As such, in-hospital and 30-day mortality statistics are the most universally reported surgical outcomes in elderly colorectal patients. Historically, a 29–33 % overall mortality was reported for patients over 75 and 80 years undergoing colorectal surgery from 1955 to 1982, respectively. This has steadily declined over the ensuing years. Patients above 80 demonstrated a 16.2 % overall mortality (14.2 % emergent; 2.1 % elective) in 1985–1991. For patients older than 70, overall 30-day mortality decreased from 29.7 % during 1955–1982, to 18.2 % in 1977–1987, 9.8 % in 1988–1990, and 6.2 % in 1997–2004 [6]. Other studies show similar acceptable mortality rates in the geriatric population, including a 9.6 % 30-day mortality in POSSUM-matched patients over aged 75 [18], and 8.7 % in-hospital mortality in octogenarians undergoing lower gastrointestinal procedures [17].

Emergency surgery poses less favorable outcomes for patients of all ages. The elder population is no different. In fact, mortality rates may diverge by a factor of 7 between elective and emergent procedures. In studies of octogenarians undergoing lower gastrointestinal procedures, in-hospital mortality was reported to be at least 28–32.3 % following emergent cases, compared with 1.7–4.7 % in elective cases [17, 19]. On multivariate analysis, an emergent procedure was independently associated with increased mortality [17]. When all emergent colon resections by age group were analyzed between 2001 and 2008 in the NHS system, overall 30-day mortality for patients older than 70 was 24.1 %. When divided by age cohort, mortality was 17 % in those aged 70–75, 23.3 % in 76–80, and 31 % in those over 80 years of age [20]. Thus, elderly colorectal patients undergoing emergent procedures are high-risk for post-operative mortality.

Mortality rates are also higher in patients admitted from a long-term care facility or nursing home (47.6 %) [19]. The elevated rates are likely related to an increasing number of synchronous comorbidities and lower performance status for this particular subset of the elderly. Moreover, patients discharged to institutions following surgery demonstrated 6-month mortality rates of 40 %, compared to 17 % of those who were discharged home [19]. Additionally, elderly patients with DNR orders undergoing emergent exploration also demonstrated higher mortality rates. Those undergoing surgery for bowel obstruction demonstrated a 30-day mortality of 30 %. Further analysis suggested mortality of 40 % when the patient sustained a post-operative complication, versus 20 % without a complication. As DNR was independently associated with mortality, it is possible DNR patients receive less intensive post-operative care when a complication occurs, thereby leading to worsened outcomes [21]. Thus, physicians caring for an elder in the emergent setting should carefully discuss goals and expectations of treatment with patients and their family members as expected outcomes after surgery may not be fully realized.

Given these poor results, the utility of 30-day and in-hospital mortality time points in the elderly has been questioned. The physiologic reserve of the elderly is clearly less than that of the younger population; therefore, it is not surprising to see a greater impact on their long-term post-discharge survival. Several groups have begun studying longitudinal time points including 90-day, 180-day, and 1-year post-operative mortality. Predictably, 90-day outcomes for patients over 80 years are worse, demonstrating mortality of 13–19 % [22]. In elderly colorectal patients, those aged 70–75 showed 34.7 % 1-year mortality, versus 41.6 % in 76–80 year olds, and 51.2 % in those over 80. Overall, a 15–20 times higher rate of death was seen in each cohort when compared to age-matched general population [20]. Similarly, an analysis of NHS colorectal procedures involving 29,000 patients aged 75 and older undergoing elective colectomy demonstrated a 30-day in-hospital mortality of 5.4 %. One-year mortality ranged from 15.6 % in 75–79 to 18.8 % in 80–84 and 23.3 % in 85–89 age groups [22]. Differences in short- and long-term outcomes suggest a focus on the wrong endpoints in the elderly.

Morbidity

Key Point: Understanding the relationship between age and comorbidity allows surgeons to stratify appropriate surgical intervention without relying on age alone.

The elderly experience increased complication rates following surgery. It is unclear whether age itself serves as a risk factor, or simply a marker of higher morbidity patients. A NSQIP analysis of surgical patients over 70 years old demonstrated a linear relationship between age and complications, increasing 0.71 % per year of age [6]. Octogenarians undergoing lower GI procedures demonstrated a 53.5 % overall rate of morbidity, with 38.4 % requiring post-operative surgical intensive care unit (SICU) admission. Common major complications included pneumonia (25 %), respiratory failure (15 %), and MI (13 %), followed by ileus and delayed extubation as common minor complications. Not surprisingly, pulmonary comorbidities have been linked with an increased risk of complications [17, 23].

As one would expect, increased complication rates parallel increased rates of mortality in elder patients undergoing emergent operations. In fact, certain analyses have shown a 17 times higher risk of complication following emergent surgery in the elderly, whereby 87.9 % of emergent elderly patients demonstrated a complication, of which 62 % were major. Furthermore, patients undergoing emergent procedures are rarely sent home independently (6.5 %), especially compared to elderly patients undergoing elective procedures (69.2 %) [17].

In addition to specific organ-based complications, elders are prone to delays in functional recovery. The return to functional baseline status is often prolonged and may occur as follows: mental status (3 weeks), timed up and go (6 weeks), activities of daily living (ADL) (6–12 weeks), and grip strength (>24 weeks). For clarification, "Timed up and Go" is a simple test used to measure an individual's mobility which requires the individual to rise from a chair, walk a small distance, turn around, and sit back down. Interestingly, the majority of patients over age 60 years may not return to functional baseline for at least 6 months post-operatively, signifying the potential impact of surgery on this patient population. Considering this data represents patients without post-operative complications, it's no surprise that recovery times further worsen in patients experiencing complications [24].

Disease-Specific Outcomes

Mortality and morbidity rates vary with elective and emergent operations, as well as with various procedures and pathologic states. This section reviews outcomes associated with several procedures and pathologies commonly encountered in the geriatric.

Ostomy Closure

Key Point: Age alone should not preclude one's decision to restore intestinal continuity. Creation of a stoma is not without risk and may be more detrimental in the elderly population.

Colostomy closure is a high-risk procedure in most patients regardless of age and comorbidity. Consequently, often it is not offered to elderly patients due to concern over poor outcomes. With historical mortality rates ranging between 0 and 4.5 %, and morbidity rates as high as 50 %, surgical trepidation is understandable. Yet, data suggests elderly patients may tolerate stoma reversal just fine with no differences in complications rates, despite increased comorbidities. In an analysis of surgical outcomes, Bosshardt et al. demonstrated a reversal rate of 78.6 %, with a 6.1 % morbidity and no mortality among patients greater than 70 years [25]. In a study of 84 colostomy closures from 1987 to 1993, those patients older than 70 years demonstrated no difference in complication rates when compared to younger patients, despite having significantly higher ASA scores [26].

Creating a stoma avoids certain peri-operative risk, in particular that associated with anastomotic leak, which is notorious for substantial mortality and morbidity in the elderly population [27, 28]. In fact, studies show the elderly are more likely to undergo stoma formation even when fit for restoring intestinal continuity. In a retrospective analysis from 1992 to 2002 of patients over 70 years old ($n=103$) compared to younger patients ($n=280$), rates of stoma formation and overall outcomes were evaluated. Elderly patients were more likely to undergo stoma formation for cancer (75 % vs. 45 %) and obstruction (6.8 % vs. 2.9 %), but less likely in IBD cases (2.9 % vs. 28.9 %) and diverticulitis (11.7 % vs. 16.1 %). Furthermore, elderly patients were less likely to undergo closure of stoma even when considered fit for surgery (78.6 % vs. 95.2 %) [25].

Nevertheless, creating a stoma is not without its own misfortune. Quality of life and social impairments associated with an ostomy must be considered. Older patients have difficulties in properly managing a stoma bag, and the bag affects their psychological well-being. Independent maintenance of the stoma may not be attainable [28]. In addition, several studies have demonstrated older age (>65) to be linked independently to major stoma complications [25, 29].

Given the potential for higher rates of complications from stoma formation, difficulties related to long-term stoma management in elderly, and the lower likelihood of closure for this population, primary anastomosis should be considered. The risk associated with restoring intestinal continuity should be weighed against the patient's underlying pre-disposing risks factors; however, for elderly patients desiring closure of a stoma, age alone should not rule out performance of this procedure.

Fecal Incontinence

Key Point: Treatment of fecal incontinence greatly improves quality of life in elderly patients, and often is successful with management of constipation and biofeedback.

Rates of fecal incontinence in elderly patients are high, especially within an institutional environment, so early diagnosis and management may benefit a large number of colorectal patients. Prevalence of fecal incontinence is currently estimated between 2 and 5 % in patients over 65 years of age, increasing to 3–17 % in patients over 85 years old. Non-institutionalized patients over 65 years old are 5-times more likely to have gross incontinence compared to younger patients. This leads to embarrassment, depression, and reclusivity. Fecal impaction was noted as the most common predisposing process to fecal incontinence, reported in up to 42 % of geriatric patients in treatment units [30]. Constipation often leads to fecal incontinence in the elderly population, with heavy laxative use producing liquid stool and subsequent overflow incontinence around partial or complete impaction [31]. Other factors independently associated with fecal incontinence include prior bowel resection, prior hemorrhoidectomy, loose/liquid stool, and constant fecal urgency [32]. Fecal incontinence is increasingly prevalent in institutionalized elders with rates reported over 50 %. Risk factors in institutionalized patients include neurologic disease, psychiatric disease, poor mobility, age over 70 years, and dementia [30].

Successful management of fecal incontinence depends upon underlying etiology. For constipation, appropriate bowel regimens are highly successful. Other etiologies require appropriate workup with defecography, anal manometry, and endorectal ultrasound to determine management options. Biofeedback is a well-described conservative management option for fecal incontinence, with high rates of success in elderly patients [33, 34].

Diverticulosis/Diverticulitis

Key Point: Management in the elderly remains controversial, with worse outcomes following elective surgery providing support for non-operative management in patients without complicated disease. In those requiring surgery, early intervention is advocated.

Diverticular disease is quite common among the elderly population, with incidence steadily increasing with age. In fact, greater than 65 % of patients 80 years or older demonstrate some degree of diverticulosis, and 10–25 % of patients develop symptoms consistent with diverticulitis. Unfortunately, significantly higher rates of comorbidities may preclude the elder population from standard surgical treatment, including restoration of intestinal continuity. A study specifically comparing management and outcomes of young patients vs. elderly (over 70 years) treated for perforated diverticulitis demonstrated elderly patients underwent fewer primary anastomoses (25 % vs. 46 %). Worse, only 43 % of Hartmann's procedures were subsequently closed, disproportionately impacting the elderly population. Although 30-day mortality was significantly higher in elderly patients (14 % vs. 4 %), there was no difference in rate of complications (32 % vs. 33 %), and no factors were independently associated with worsened outcomes [35]. Other studies have identified certain factors placing the elderly population at particularly high risk for increased complications risk in the setting of diverticulitis. Specifically worth mentioning is end-stage renal disease (ESRD). In an analysis of elderly patients (>65 years) with ESRD undergoing surgical management of diverticulitis, ESRD was associated with more emergent surgery, higher rates of complications, and increased ostomy creation [36].

Several other studies have demonstrated worse outcomes in elder patients undergoing emergent operations for diverticulitis, with mortality rates of 10.4–12.4 % in emergent and 2.4–3.1 % in elective cases [37, 38]. A study utilizing the Medicare Provider Analysis and Review (MEDPAR) inpatient file evaluated in hospital mortality of over 23,000 patients older than 65 years with a primary admission diagnosis of diverticulitis. The study demonstrated an increase in the adjusted odds of in-hospital mortality with age: OR 1.3 (70–74 years), OR 2 (75–79 years), OR 3 (80–84 years), and OR 5.4 (85 years and up). Additionally, in-hospital mortality was higher in emergently treated patients (8 % vs. 1.4 %), and in particular those older than 85 years (15 %). In fact, emergently treated patients older than 85 years had a 5-times increased risk of mortality compared with 65- to 69-year-old patients [39].

Similarly, a study utilizing ACS-NSQIP from 2005 to 2009 demonstrated mortality increased with age with rates as high as 18 % in patients greater than 70 years old undergoing emergent management of diverticulitis [40]. Despite these findings, the likelihood of requiring emergent operation for diverticulitis is low in the elderly. Furthermore, various studies have shown the probability of perforation decreases with age, even in patients with repeated attacks [40, 41]. In fact, more than half of emergently treated patients are younger than age 65, while only 15 % are over 79 years of age [40].

Thus, although diverticulitis is commonly encountered in the elderly population and appears to have a lower risk of perforation in this age group, this must be balanced against the potential impact and higher mortality associated with emergency surgery and sepsis on this population. As such, early intervention should be considered in certain circumstances given the significant rise in complications associated with urgent/emergent procedures in the elderly population.

Rectal Prolapse

Key Point: Surgical management is safe, effective, and indicated in the elderly to prevent suffering and reduced quality of life.

Rectal prolapse can be quite debilitating at any age, causing a significant decline in quality of life. For this reason, surgery should be considered in most cases. The choice of operation will depend upon goals of care, patient comorbidities, and surgeon comfort with treatment options. Outcomes for both transabdominal and perineal approaches have been shown similar among young and old groups. In an 18-year retrospective study from the University of Minnesota, patients undergoing perineal proctectomy for rectal prolapse were grouped into the following age cohorts: <70 years, 70–79 years, 80–89 years, >89 years. There were no differences between groups in post-operative length of stay, early complications, or late complications. The overall complication rate was 5.6 %, with an acceptable 8.3 % rate in patients >89 years old. Interestingly, late complications decreased as patient age increased, possibly due to death from other causes or patients not seeking care due to age. Overall recurrence rate was calculated at 22.6 %, with the lowest rate seen in eldest adults [42].

Historically, transabdominal approaches have been avoided in the elderly patients due to concern for patient comorbidities and inability to tolerate general anesthesia. More recent data suggests otherwise, demonstrating improved outcomes with transabdominal repair. The shift toward a transabdominal repair may in part be related to a

shift in technique with minimally invasive approaches gaining favor over the past two decades. A recent study using the ACS-NSQIP 2006–2009 dataset compared laparoscopic, open, and perineal procedures for rectal prolapse. When grouped by age, 33 % of patients were 70–79 years, 53 % 80–89 years, and 15 % >89 years old. From a demographic standpoint, higher ASA level and mean age of patients were seen in perineal procedures, but no other significant differences occurred between groups. Laparoscopic procedures demonstrated the lowest complication rate at 2.2 %, compared with 8.7 % perineal and 12.3 % open. On adjusted analysis, undergoing open procedure was the only independently associated risk factor for complication development (OR 6.3). Overall mortality was quite low at 1.7 %, with no difference between treatment groups. While similar hospital length of stay was shown between perineal and laparoscopic procedures, open rectopexy patients spent an average of 2 days longer in the hospital. Interestingly, although most surgeons choose perineal procedures due to concern for patient comorbidities and inability to tolerate general anesthesia, this study demonstrated over 83 % of patients underwent general anesthesia, regardless of procedure, ASA, or underlying comorbidities [43].

It is not the goal of this chapter to compare outcomes of minimally invasive and perineal techniques. Nonetheless, it should be stated that current data suggest minimally invasive approaches are safe and effective in the elder population, with lower complication rates, a potentially more durable repair and mortality similar to that of a perineal repair. As such, surgeons should consider laparoscopic or robotic-assisted rectopexy [44] for elderly patients with or without underlying comorbidities.

Colonic Volvulus

Colonic volvulus is more common in the geriatric patient. While cecal volvulus usually presents in the 5th and 6th decades of life, sigmoid volvulus has a mean age at presentation of 68 years and a peak incidence in the 8th decade. Historically, mortality rates are less than 12 % in urgent cases with viable bowel and 30 % in urgent cases with non-viable bowel [45, 46]. Spontaneous reduction of cecal volvulus occurs in less than 2 % of patients and is not considered a viable treatment option. More than 90 % of sigmoid volvulus patients are successfully decompressed with endoscopy. Management almost exclusively involves resection due to the low risk of this procedure in most settings, and high risk of recurrence when non-resectional procedures are performed. Surgical management of sigmoid volvulus is suggested within 2–5 days of decompression.

Data shows elderly patients more likely to undergo Hartmann's procedure for management of sigmoid volvulus. The surgeon should consider the higher 30-day mortality in elderly patients undergoing Hartmann's resection (25–50 %) compared with primary anastomosis (8–13 %) [47–49]. Additionally, consider laparoscopic resection when possible to further decrease risk of complications. In patients not fit for operative intervention, percutaneous endoscopic colonic (PEC) tube placement is associated with 75 % decompression. However, a 4 % mortality and 30 % complication rate limit its use in all but the most comorbid patients. For a disease almost exclusively confined to the elderly, data supports resection and anastomosis in most patients following endoscopic reduction.

Inflammatory Bowel Disease

Key Point: Restorative proctocolectomy may be safe in select elders; however, careful consideration should be given to the risk of fecal incontinence and decline in quality of life.

Inflammatory bowel disease (IBD) is often felt to be a disease of younger patients; however, it has a second mode of incidence at 55–70 years. Reports suggest IBD in the elderly carries an altered phenotype from younger patients, including involvement of different gastrointestinal sections, poorer response to therapy, higher complications, and higher mortality. However, worsened outcomes may simply be related to misdiagnosis and mismanagement in older patients. A retrospective evaluation of all IBD patients surgically treated from 1989 to 1999 compared elderly patients over age 60 years to a younger cohort using 30 total matched clusters in an SAS statistical algorithm. As seen in other disease processes, elderly patients underwent significantly higher percentage of emergent procedures. Despite this, no difference in 30-day mortality was seen between groups. Complication rates were significantly higher in the elderly cohort (47 % vs. 20 %), with subsequent adjusted analysis demonstrating OR 3.5 for age alone in development of a post-operative complication [50].

When operating on the elderly in an elective fashion for IBD, controversy exists regarding performance of high-risk procedures such as ileo-pouch anal anastomosis (IPAA). Despite the obvious unease in regards to higher morbidity and mortality associated with a restorative proctocolectomy in the elder population, the majority of concern lies with the risk for fecal incontinence and decline in quality of life. Remarkably, the majority of the literature supports similar rates of morbidity (29.4 %) and mortality (5.9 %) in patients younger and older than 65 years of age, except for higher rates of dehydration from ileostomy in elderly patients [51–53]. While some degree of incontinence is also not unexpected in the elderly population, anal sphincter function can be severely impaired after undergoing IPAA, producing a significant impact on one's QoL. That being said, current data suggest that select elderly patients can achieve adequate function after an IPAA. At the Cleveland Clinic, 17 of 1911 patients undergoing IPAA for ulcerative colitis (UC) were over 70 years of age at time of surgery. Thirty-eight percent reported complete

continence, 12 % reported rare incontinence, and 50 % reported some incontinence. Using quality of life instruments, 82 % of elderly patients stated they would undergo pouch surgery again, and 89 % recommended it to others [53].

Pellino and colleagues reported similar results in 27 patients over 70 years of age undergoing IPAA for UC. When compared to 81 younger controls, long-term follow up showed similar outcomes between groups in bowel control and health-related quality of life at 1 and 3 years post-ileostomy closure, but elderly patents still had higher rates of partial incontinence. Further, elderly were more likely to be taking anti-diarrheals at 1 year, with no difference between groups at 3 years [54]. Similar results were seen following IPAA in patients older than 80 years for UC. At 6 months, elderly patients reported higher rates of nocturnal seepage and use of anti-diarrheals. At 12 months, only nocturnal seepage was different between groups. Despite these long-term difficulties, 100 % of patients were happy with IPAA and would undergo surgery again [55].

Despite multiple factors contributing to pouch failure rates, age has not been implicated. In a study by the Mayo Clinic looking at patients over 55 years, a 1.6 % pouch failure rate was determined at 10 years for patients older than 70 with a mean follow-up of 8 years. While incontinence was reported more often in elderly patients, no difference was demonstrated in post-operative complications (e.g., pouchitis, stricture, fistula, obstruction), quality of life, or pouch failure rates between young and old cohorts. On average, elderly patients had two nightly stools compared with 0–1 for younger patients. Rates of severe sexual restriction were more common in elderly patients, measured as 15 % incidence at 5 years and 22 % at 10 years [56].

As with any patient, multiple factors should be considered when discussing surgery for IBD. Data suggests no difference in patient need for surgical resection based upon age at presentation, and no difference in rates of surgery for hospitalized IBD patients [57]. As such, surgical management of IBD is safe for elderly patients and should be considered in select individuals but not in the absence of serious thought for the risk of fecal incontinence and decline in quality of life.

Colon Cancer

Key Point: Although chronologic age alone should not be an exclusion criterion, more work is needed to establish an optimal and efficient strategy for choosing who would benefit most from not only surgical resection but potential adjuvant therapy after surgical intervention.

Colon cancer is largely a disease of old age, disproportionately affecting the elderly, with prevalence and incidence increasing significantly into the 8th decade of life (Figure. 65-2) [58]. In those older than 75, colon cancer is the most common primary neoplasm [59]. Unfortunately, clear guidelines for the management of elderly patients are lacking due to exclusion of this population from most studies of colon cancer. Inclusion of the elderly in outcomes studies produces mixed results due to confounding variables such as underlying comorbidities and different rates of emergent operations compared to younger patients. Additionally, published outcomes may demonstrate selection bias linked to global location and time period of diagnosis [60].

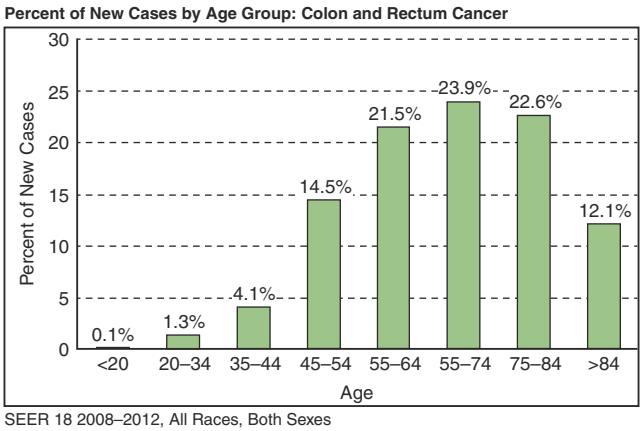

FIGURE 65-2. Colon cancer is largely a disease of old age with prevalence and incidence increasing significantly into the 8th decade of life. Colon and rectum cancer represents 8.0 % of all new cancer cases in the USA [58]. Available at http://seer.cancer.gov/statfacts/html/colorect.html.

The skepticism regarding oncologic resection in the elderly is not entirely unsubstantiated. When matched for stage and histology, numerous studies have demonstrated higher 30-day mortality rates of 8–22 %, along with higher complications rates that are almost double that seen in younger populations [60–62]. As you would expect, mortality and post-operative complication rates were increased after oncologic resection in elders undergoing emergent resection. Reported mortality rates for patients over 70 undergoing emergent colectomy are between 6.1 and 38 % [60, 63]. In a mult-icenter German trial of colectomy for cancer, overall complication rates increased from 32 % for elective procedures in the elderly to 50 % in emergent cases. Of note, while numerous studies have demonstrated increases in peri-operative complication rates among elders, anastomotic leak rates have not been among them [60, 61].

Numerous studies have demonstrated that select elders will benefit from standard oncologic treatment including surgical resection with or without adjuvant chemotherapy. Neuman and colleagues utilized the SEER database from 1992 to 2005 to evaluate patients over 80 years of age who underwent colectomy for stages I–III colon cancer. Ninety-day mortality was reported at 6.6 % and 1-year mortality at 14.3 % [15]. Sixteen percent of patients over age 80 years demonstrated metastatic disease at surgery. When broken out by stage of disease: Stage I median survival calculated as 69 months, with a 5-year survival of 77 %; Stage II median surgical calculated as 54 months, with a 5-year survival of

35 %; Stage III median survival calculated as 33 months, with a 24 % 5-year survival; and Stage IV median survival was 24 months, with a 0 % 5-year survival [64]. In fact, based on available data, if elderly patients survive initial post-operative period and any complications, 5-year survival has been shown to be similar to younger patients [60].

Likewise, older persons with Stage III disease have been shown to derive the same benefit from adjuvant therapy as their younger counterparts. In a systematic review of Stage III patients from 4 randomized controlled trials (XELOXA, AVANT, X-ACT, NSABP C-08), oxaliplatin demonstrated improved disease free survival (DFS) in all study groups and all ages. While effect was attenuated in patients over age 70, adjusted analysis did not show age as independently associated with DFS [65]. These findings are consistent with reports of patients over 75 years demonstrating no difference in cancer-specific survival (CSS) when compared to younger patients [66].

Reluctance to treat elders with colorectal cancer is not limited to surgical resection. Numerous studies demonstrate the exclusion of patients over 75 from participating in oncologic clinical trials. As a result, a disparity persists in the administration of standard adjuvant therapy between younger and older patients despite a meaningful survival advantage for most patients. In fact, recent studies suggest only 14 % of all patients over age 80 diagnosed with colon cancer received chemotherapy [15], with less than 20 and 60 % receiving chemotherapy for Stages II and III disease, respectively [64]. The discrepancy in management is, in part, related to concern the elderly cannot tolerate chemotherapy. However, based on current literature, this is not the case. Pooled analyses of adjuvant chemotherapy trials have not reported increased side effects in older patients except for myelosuppression [67, 68] and fatigue [68].

In a systematic review of Stage III patients from 4 RCTs, higher rates of grades III and IV toxicity were noted in elderly patients receiving oxaliplatin, although neuropathy was no different between groups [65]. The MOSAIC trial, which compared the use of adjuvant 5-FU-based chemotherapy with and without oxaliplatin (Eloxatin), also demonstrated no difference in dose intensity between patients younger than 70 and ≥70 years old for either 5-FU or oxaliplatin. Nonetheless, fewer than 5 % of elder patients completed all 12 cycles compared with the younger group, but the study also excluded patients over 75 years old, which suggests the elderly may have been underrepresented in this trial [69].

FOLFOX is well tolerated by the elderly. However, they may not see the same survival benefits of FOLFOX compared to younger patients, so consider infusional 5-FU or capecitabine alone. It is important to note that patients over 80 years had more minor complications from capecitabine, but adjusted analysis did not demonstrate an association with age [70]. This treatment plan is usually beneficial for the elderly, as they are more susceptible to toxicity from oxaliplatin. Palliative chemotherapy is controversial due to limited data, as most studies excluded patients older than 65 years of age from treatment. Recent work demonstrates little benefit of palliative therapy on overall survival in the elder population. Yet as discussed above, select elders will tolerate therapy similar to that of a younger population. In a recent single-institution study looking at patients over 70, no difference in response rate to palliative therapy was found versus younger patients (24 % vs. 21 %). However, there was a significant increase in median OS from 8 to 11.7 months when elderly received chemotherapy. Additionally, progression-free survival doubled from 4 to 10 months. When comparing regimens, fewer side effects were seen with capecitabine compared to 5-FU, and bolus 5-FU produced more side effects than infusional therapy. Of note, in patients over 65 receiving bevacizumab, higher rates of arterial thrombotic events were seen. Based on these findings, the authors recommended continuing with standard regiments for both curative and palliative protocols for all patients, regardless of age, with continued tailoring based upon toxicity and response to regimen [71, 72].

Rectal Cancer

Key Points:

- *For the elderly population, the surgeon should be particularly aware of pre-operative fecal incontinence and decreased mobility as restoration of an intestinal continuity with a low anastomosis may worsen the predisposing condition leading to a debilitating and degraded quality of life.*
- *In the elderly patient population with rectal cancer, fit elders have been shown to tolerate chemoradiotherapy (CRT) similar to that of younger patients.*

Advancements in the treatment of rectal cancer including minimally invasive techniques, developments in organ-sparing procedures with local treatment, sphincter-sparing techniques, neoadjuvant CRT, and adjuvant chemotherapy regiments have all benefited patients. However, determining the optimal treatment for rectal cancer for patients at any age requires a complex decision-making process. As colorectal surgeons, it is our responsibility to understand and coordinate the wide variety of modalities available to optimize survival, minimize morbidity, and maximize quality of life. Although always critical, strong considerations should be given to intent of surgery, possible functional outcomes, and preservation of anal continence and genitourinary function when treating rectal cancer in the elderly population.

As in other disease processes, elders with rectal cancer present with an increased number of comorbidities [73]. As such, numerous studies demonstrate a direct correlation

between comorbidity and surgical complication rates. This is certainly not surprising given the increased morbidity associated with a pelvic dissection. Remarkably, despite the increased morbidity with a pelvic dissection, operative mortality has not been shown to be significantly different among older and younger populations. In patients over 75 years of age treated at a tertiary referral center for cancer, operative mortality was under 2 % for both groups [73]. In a similar study of open cases for rectal cancer in patients over 75 years old, higher rates of emergency procedures (5 % vs. 3 %) and multiple comorbidities (26 % vs. 13 %) were seen in the elderly; however, overall post-operative mortality was similar between the two groups (3.5 % in elderly vs. 0.5 % in younger individuals) [74].

Consistent with findings in colon cancer, overall survival for older patients with rectal cancer is worse. This is to be expected given the added complexity associated with the increasing comorbidities of the elderly population. Nonetheless, as was also demonstrated in colon cancer, disease-specific survival has not been shown to be worse in elder patients [73, 74]. The study from Memorial Sloan-Kettering Institute in 2000 collected prospective data on 157 patients over the age of 75 undergoing pelvic surgery. Overall survival was significantly lower in elderly patients (51 % vs. 66 %) while disease-specific survival was identical, especially when compared stage for stage [73]. Additionally, in an analysis of the DOD military database and central tumor registry, a lower 5-year survival rate occurred following curative resection in elderly (43 % vs. 65 %), but cancer-specific survival was no different between elderly (60 %) and younger patients (70 %). DFS was also similar at 60 % vs. 69 % in elderly and young, respectively [74].

Common to all generations, functional outcomes following pelvic surgery remain of utmost importance. For the elderly population, the surgeon should be particularly aware of pre-operative fecal incontinence and decreased mobility as restoration of an intestinal continuity with a low anastomosis may worsen the predisposing condition, leading to a debilitating and degraded quality of life. When a linked Medicare dataset was analyzed for functional outcomes in elderly patients over 80 years old from nursing facilities who underwent sphincter-sparing procedure or stoma creation, no differences were seen in demographics, pre-operative incontinence (23 % vs. 28 %), or operative mortality (13 % vs. 18 %). On multivariate analysis, pre-operative incontinence was a risk factor for post-operative incontinence [75].

Low anterior syndrome results in increased bowel function, erratic bowel movements, urgency, obstructed defecation, and minor fecal leakage. Following LAR, complete recovery of bowel function to a "new normal" typically occurs at 6–7 months, although some patients may spontaneously improve at 12–18 months. Surprisingly, current data suggest no difference in functional outcomes among elderly patients. Almost 85 % of elderly patients report minor, or no, issues with incontinence [76]. Hida and colleagues evaluated a 107 patients undergoing low anterior resection (LAR) with colonic pouch anastomosis within 4 cm of the anal verge. The cohort was grouped in three categories: age <60, 60–74, and >74 years old. Functional outcomes were no different amongst groups and, as expected, improved in all groups when the anastomosis was 5–8 cm from the anal verge (Table 65-1) [77]. Thus, in well-selected patients with intact sphincter mechanisms, procedures that spare a stoma are perfectly reasonable in the elderly.

Table 65-1. Outcomes by age cohort in rectal cancer following ultra-low colon J-pouch reconstruction [77]

Outcome	<60 years old (%)	60–74 years old (%)	>74 years old (%)
Urgency	10	14	20
Incomplete evacuation	3.3	7	0
Anti-diarrheals	77	71	80
Garment soiling	30	36	20
Protective pad	57	57	40
Gross incontinence	13	7	20
Fear releasing flatus	50	43	60
Avoid social activity	50	57	60
Dissatisfaction with function	27	29	0

Functional outcomes after low anterior resection were no different amongst the elderly when compared to younger candidates; thus procedures that spare a stoma are perfectly reasonable in select elderly

In contrast to colon cancer, neoadjuvant CRT is often employed to down-size and perhaps even down-stage a rectal cancer. In the revised Dutch TME trial, the effects of pre-operative radiotherapy (5×5Gy) were compared in those 75 or older with rectal cancer to those younger. The proportion of patients receiving pre-operative radiotherapy in the TME study did not differ between the young and elderly (50 % vs. 49 %, $p=0.70$). Although peri-operative complications had a greater impact on the elderly with a mortality of 50 % vs. 7.1 % in younger patients, radiotherapy was not an independent risk factor leading to more complications. In fact, elder patients appeared to respond better to therapy than younger patients. Those receiving pre-operative radiotherapy not only demonstrated lower recurrence rates (5.4 % vs. 14 %), but distant metastases survival (81 % vs. 69 %) and cancer-free survival (81 % vs. 66 %) were both greater; a phenomena not seen in the younger population [78].

Multi-modality neoadjuvant therapy with the addition of capecitabine also appears to be well tolerated by select elderly. In a recent multicenter retrospective analysis, 125 elders between 70 and 90 years of age underwent neoadjuvant CRT. Of those patients, adverse effects ≥grade 2 were observed in 32 % of the patients while only 15 % observed adverse effects ≥ grade 3. Dose reduction for toxicity was only performed in 18 % of the patients and CRT discontinuation was necessary in just 9 % of patients [79]. These results are comparable to younger patients as reported in a recent RCT with grade 2 adverse events observed in 22–38 % of participants, and grade 3 or 4 in 14–29 % [80–82].

Some data have revealed increased toxicity with the addition of chemotherapy to radiotherapy. A retrospective study in 2013 looked at 126 patients aged 70 or older who underwent RT or CRT for rectal cancer. The overall rate of grade 3 toxicity was 34.9 %; with a rate of 8.7 % in RT only group and 26.2 % in the CRT group (P=0.004) [83]. Although toxicities may be slightly more frequent in the elderly, data show patients can tolerate chemotherapy and radiation with limited modifications of the planning treatment. Older patients with rectal cancer of varied stages can be safely treated with careful monitoring and frequent modification of treatment.

Amongst colon, breast, and lung cancer, recruitment of elderly patients in clinical trials for rectal cancer is sparse [73]. As a consequence, our judgment of the appropriateness of therapeutic strategy is severely inadequate. Modern oncologic principles may require tailoring for elderly patients. Radical surgery for rectal cancer is not always the best option, and should be compared against risk of mortality and patient goals for functional life. To illustrate this, Neuman et al. utilized a Markov analysis to demonstrate non-operative "watch and wait" management of rectal cancer as superior to operative management with radical surgery. The study demonstrated that observation was preferred to surgery if the ability to correctly identify patients with true complete responses exceeded 58 %, if quality of life after surgery was poor (utility <0.81), or if the relative reduction in recurrence risk with surgery was <43 % when compared with observation. Overall, the conclusion was surgery benefits the average healthy 65-year-old patient [84].

The impact of surgery extends beyond the peri-operative 30-day period. Long-term consequences on a patient's overall health status, quality of life, and survival must be considered, especially in the elderly. Given the lack of adequate management algorithms in the elderly population, oncologic management of the elderly should be tailored to the individual with an adequate understanding of the patient's underlying functional, physical, or cognitive impairments.

Laparoscopic Surgery in the Elderly

Key Concept: Minimally invasive surgery is safe and appropriate in the elderly.

The benefits of laparoscopy are well established with decreased pain, better cosmesis, early return of bowel function and shorter hospitalization. These benefits extend to the elder population in both benign and oncologic disease with numerous studies validating the benefit of minimally invasive surgery in this group. In one of the largest studies comparing open and laparoscopic colorectal surgery, Frasson and colleagues looked at a cohort of 535 patients, 37.6 % of which were over the age of 70 [85]. Laparoscopy was shown to reduce post-operative morbidity in the laparoscopic group when compared to open resections (20.2 % vs. 37.5 %) as well as length of stay (9.5 vs 13 days). Additionally, the impact of laparoscopy was more pronounced in the older cohort when the two groups were compared highlighting the potential advantage in this population. Other studies have shown similar results demonstrating that laparoscopic is safe in the elderly and its benefits are not exclusive to the younger [86].

Reoperative Evaluation in the Geriatric Patient

There is a consistent data throughout the literature suggesting 30-day mortality significantly increases for each decade through age over 90 years [6, 87]. Yet it is clear that one's age is a poor representation of physiologic reserve and multiple other factors play a significant role in the assessment of an elder individual. In fact, a patient's physiologic age, rather than one's chronological age has been shown to be a more precise indicator of one's ability to tolerate surgery. Because elderly patients are more susceptible to surgical complications, the surgeon must optimize modifiable risk factors when possible. For instance, it has been estimated that the prevalence of cardiovascular disease in women is 12 and 19 % of men 75–84 years old. That risk may be mitigated by following established management guidelines in the administration of appropriate aspirin, statins, and beta-blockade in the peri-operative period. Unfortunately, adherence is notoriously poor, despite data indicating that 3-year mortality may be decreased in peri-operative patients. Thus, it is mandatory for the surgeon to properly assess the patient in the pre-operative setting to improve peri-operative outcomes and patient safety (Table 65-2).

In general, surgical risk groups are based on type of surgery and defined as "low," "medium," and "high-risk," with 30-day cardiac event rates (MI and death) of <1, 1–5, and >5 %, respectively. All abdominal procedures involving the colon and rectum are included within the "medium" risk group (at a minimum). Laparoscopic cases are treated similarly to open cases regarding cardiac risk. In addition, functional capacity is utilized for pre-operative risk assessment. It is estimated based on patient daily activity, or measured with exercise testing. As a reference, 1 metabolic equivalent of task (MET) is an expended metabolic equivalent at rest, 4 METs is equivalent to climbing 2 flights of stairs, and 10 METs represents strenuous sports activities (Table 65-3). Anything less than 4 METs is considered poor functional capacity, but is not strongly associated with worsened cardiac outcomes in abdominal surgery. That being said, current guidelines recommend patients with poor functional capacity to undergo further cardiac evaluation and risk-benefit analysis. Patients with greater than 4 METs do not require further cardiac workup, regardless of risk factors [88, 89]. Use of functional capacity, or other cardiac risk indices such as the Lee index, identify patients requiring further pre-operative cardiac testing.

Table 65-2. Preoperative workup for geriatric patients undergoing colorectal surgery

Cardiac assessment
1. Patients with active cardiac conditions require cardiology assessment and workup
2. Patients with over two clinical risk factors require heart rate management, but do not need cardiac testing unless results will change operative management
3. Patients undergoing low risk surgery, more than 3 METs, or fewer than 3 clinical risk factors may proceed with surgery
Pulmonary assessment
4. Encourage smoking patients to quit more than 8 weeks pre-op, although 4 weeks may be long enough in some studies
5. Aggressive management of COPD and asthma
6. Routine CXR and PFTs not indicated
Diabetes and glucose assessment
7. Obtain baseline glucose level
8. Obtain baseline BUN and creatinine
Nutritional assessment
9. Patients with BMI <18 or unintentional weight loss over 10 % in 6 months require evaluation by a registered dietician
10. Pre-operative nutritional assessment labs not otherwise indicated
Anemia and hematologic assessment
11. Obtain baseline hemoglobin and hematocrit
Cognitive assessment
– All patients require adequate history from patient and family member
– All patients require cognitive assessment (Mini-Cog)
– All patients require anxiety/depression assessment
– All patients require assessment of alcohol use, identification of possible abuse
– All patients require evaluation of decision-making capacity to ensure informed consent
– Any new findings, or worsening of existing findings, requires further evaluation by appropriate geriatrician or mental health care provider
Laboratory and non-invasive testing
– Unless previously indicated above, routine CBC, BMP, PT/PTT, EKG, CXR are not required

Adapted from Chow et al. [118]

Table 65-3. Metabolic equivalents of task—table derived using values from Tudor-Locke C et al. website companion, http://appliedresearch.cancer.gov/atus-met/ (*Source*: 19564664)

Activity performed	METs
Low intensity activities	*<3*
– Sleeping	0.9
– Reading/writing	1.6
– Washing, dressing, grooming self; grocery shopping	2.1
– Bowling	3.0
Moderate intensity activities	*3–6*
– Walking (3.0 mph)	3.3
– Home exercise, light to moderate effort	3.5
– Bicycling, leisure, light effort	4.0
– Dancing	4.5
– Playing volleyball, softball	5.5
High intensity activities	*>6*
– Hiking, fencing, wrestling	6.0
– Soccer, snowboarding	7.0
– Basketball, jogging	8.0
– Tennis, racket sports	8.5
– Jumping rope	10.0

Metabolic equivalents are used to measure functional capacity and are often utilized for pre-operative risk assessment in surgical candidates of all ages

Cardiac Evaluation

Keynote: Overall, the risk of a peri-operative cardiac event for patients undergoing a procedure of 'medium" risk is less than 1 % compared to a 4 % risk in patients with known CAD.

Current studies advocate that the risk of a cardiac event or death in the elder population is no greater than younger patients; hence the application of recommendations is universal. Overall, the risk of a peri-operative cardiac event for patients undergoing a procedure of 'medium" risk, which includes all intra-abdominal cases, is less than 1 % compared to a 4 % risk in patients with known CAD. Clinical cardiac risk factors include angina, prior MI, heart failure, stroke/TIA, renal dysfunction, and IDDM. Additionally, exercise tolerance, ambulatory EKG changes, echo changes demonstrating prior MI, valvular disease or left ventricular diastolic dysfunction, and positive stress test have also been associated with increased risk of peri-operative cardiac event [90]. As such, an EKG is required for patients with presence of cardiac risk factors prior to any surgical intervention. Patients undergoing medium risk surgery (i.e., abdominal) without risk factors should be considered for at minimum an EKG evaluation. Echocardiography is not required in patients free of cardiac symptoms, but should be considered in patients undergoing high-risk surgery [89, 90]. Interestingly, there is minimal evidence to suggest pre-operative revascularization reduces risk in non-cardiac surgery. Instead of cardiac catheterization, beta-blockade, and statins pre- and peri-operatively are strongly recommended [90]. For patients with recent MI, risk of recurrent MI in all comers is over 30 % when surgery performed within first month. Thirty-day mortality related to surgery is 14 % during first month, dropping to 10 % after 3 months, and to normal risk when more than 6 months from date of MI [91]. The take-home point is that unless surgical

intervention is urgent or emergent, patients with recent myocardial infarction should be delayed at least 6 months.

Pulmonary Evaluation

Key Points:

- *Chronic obstructive pulmonary disease (COPD) is the single most important risk factor for development of post-operative pulmonary failure.*
- *In patients with history of tobacco abuse, smoking cessation for more than 6–8 weeks is recommended.*

Studies of post-operative complications in elderly colorectal patients have consistently demonstrated higher risk of respiratory failure, pneumonia, and failure to extubate. The surgeon should identify patients with pre-existing lung conditions and recent functional decline. In such patients, it is prudent to refer to pulmonary specialists for optimization through inhalers, incentive spirometry, mobilization, and other indicated treatments [90]. Risk factors requiring further work up include abnormal CXR, high ASA, abnormal respiratory exam, elevated Goldman Cardiac Risk Index [92] (Figure 65-3), and elevated Charlson comorbidity index [93]. (Table 65-4) Interestingly, obesity is not a pertinent risk factor [89]. In contrast, COPD is the single most important risk factor for development of post-operative pulmonary failure. Up to 25 % of elderly patients with COPD have an operative pulmonary complication, with mortality approaching 7 % [89]. In patients with history of tobacco abuse, smoking cessation for more than 6–8 weeks is recommended [90]. If patients pursue smoking cessation, duration needs to be greater than 2 months, otherwise risk of pulmonary complications is significantly increased. This includes patients who cut down before surgery, with relative risk 6.7 for individuals undergoing major non-cardiac surgery [94].

Surgical site is the most significant non-modifiable risk factor for pulmonary complication, with risk increasing as surgical site moves closer to diaphragm. This is illustrated by rates of upper and lower abdominal complication between 13–33 % and 0–16 %, respectively. Minimally invasive surgery greatly mitigates the risk of pulmonary complication based on surgical site. Anesthesia type also plays a role, with rigorous systematic review demonstrating epidural anesthesia superior to general anesthesia, producing lower mortality (3.1 % vs. 2.1 %), rates of pneumonia, and rates of respiratory depression. As such, some strongly advocate for spinal/epidural anesthesia in patients at high risk for post-operative pulmonary complications [94]. Unfortunately, there are no general pulmonary guidelines or recommendations for surgical optimization in the elderly [89]. Therefore, routine consultation with the anesthesia team, or pulmonary medicine, will greatly enhance management.

Goldman Cardiac Risk Index (9 risks)	Points
1. Age > 70 years	5
2. Cardiac History	
Preoperative MI < 6 months	10
3-4. Physical Examination	
3. S_3 Gallop or HJR > 12 cm H_2O	11
4. Significant aortic stenosis	3
5-6. Electrocardiogram	
5. Rhythm other than NSR or atrial ectopy	7
6. VPBs > 5/min	7
7. General Medical Status: one or more of these factors	3
a. pO_2 < 60 or pCO_2 > 50 mmHg	
b. Serum K < 3.0 or HCO_3 < 20 meg/mL	
c. BUN > 50 or creatinine > 3.0 mg/dL	
d. Chronic liver disease or delibitation	
8-9. Type of Surgery	
8. Intrathoracic, intraperitoneal, or aorta	3
9. Emergency	4
Possible total points and complications rate	**53**
Class I: 0.7% cardiac complications & 0.2% mortality	0–5
Class II: 5% cardiac complications & 2% mortality	6–12
Class III: 11% cardiac complications & 2% mortality	13–25
Class IV: 78% cardiac complications & 56% mortality	≥ 26

FIGURE 65-3. Goldman cardiac risk index is a tool used to estimate a patient's risk of peri-operative cardiac complications. With permission from Goldman L, Caldera DL, Nussbaum SR, et al. Multifactorial index of cardiac risk in noncardiac surgical procedures. *N Engl J Med.* Oct 1977;297(16):845–850 [92].

Diabetes and Glucose Management

Key Point: Current research indicates that elderly patients may greatly benefit from strict control of glucose levels below 180 mg/dL.

Surgical stress is associated with insulin resistance, and this effect has been shown to be more pronounced in elderly patients. As such, reducing insulin resistance is of potential benefit in improving peri-operative outcomes. Multiple studies have advocated drinking a high carbohydrate drink 2 h before surgical intervention to help prevent insulin resistance. Reduction in resistance might lead to decreased infectious complications, decreased ileus, less anxiety, and less peri-operative discomfort and hunger [95]. Without these drinks, 66.7 % of non-diabetic patients had at least one episode of hyperglycemia within 72 h of surgical intervention. On adjusted analysis, hyperglycemia was independently associated with increased rates of sepsis, surgical site infection, reoperation, and increased LOS [96]. Allowing clear liquids

TABLE 65-4. Charlson comorbidity index—summation of score for given patient provides index

Clinical comorbidity	Item score
Myocardial infarct	1
Congestive heart disease	
Peripheral vascular disease	
Dementia	
Cerebrovascular disease	
Chronic pulmonary disease	
Connective tissue disorder	
Diabetes, without complications	
Peptic ulcer disease	
Chronic liver disease (no portal hypertension)	
Each decade over 40 years	
Hemiplegia	2
Moderate, severe renal disease	
Diabetes, with complications	
Solid organ tumors, cancer	
Leukemia	
Lymphoma	
Moderate/severe liver disease, cirrhosis	3
Malignant tumor with metastases	6
AIDS	

Charlson comorbidity index is the most widely used comorbidity index which was developed to predict the 1-year mortality. Adapted from Charlson 1987 [93]

until 2 h before a procedure, then providing a carbohydrate drink, has been associated with reducing the risk of insulin resistance, decreasing the likelihood of complications from hyperglycemia, and limiting significant fluid shifts that are so prevalent in dehydrated elderly colorectal patients [90].

Strict glucose management has been well established to improve peri-operative outcomes in surgical patients. It is particularly important in the elderly population when you consider that over 27 % of patients older than 65 carry the diagnosis of diabetes, and another 50 % are at risk for development [97]. In fact, poor glycemic control (defined as any episode >150 mg/dL) has been independently associated with worsened mortality (OR 11.5) and increased risk of surgical site infections in elderly patients over 70 years undergoing abdominal surgery [98]. Recent studies have shown that elderly patients may greatly benefit from strict control of glucose levels below 200 mg/dL [96, 97, 99]. Caveats include an increased risk of hypoglycemia in elderly patients attributable to impaired counter-regulatory mechanisms, renal insufficiency, or delay in diagnosis related to delirium and altered mental status which are common in the elder population [96, 97].

Nutritional Assessment

Keynote: Malnourishment in the elderly has been shown to increase the risk of peri-operative complications by 6-fold. Optimization of nutritional status is highly recommended including the employment of registered dieticians or nutritionists.

Malnourishment affects between 2 and 32 % of elderly, and that's among the "healthy" geriatric population. In hospitalized elderly patients, prevalence of malnourishment is between 1 and 83 % [100, 101]. There is a sixfold increased risk of complications in malnourished elderly patients [89]. Further, poor pre-operative nutritional status was independently associated with post-operative delirium and mortality in elderly patients. Therefore, optimization of nutritional status and enhancement of protein metabolism is paramount [98]. In fact, enlisting the assistance of a registered dietician or nutritionist increases the rate of improving pre-operative nutritional status [90].

Using BMI or albumin alone to evaluate elderly patients is neither robust nor accurate, and is a poor indicator in clinically ill patients [90]. Prealbumin, transferrin, and retinol-binding protein provide a more accurate picture of patient nutrition. Abnormal vitamin A, B, or C levels indicate a high-risk for complications post-operatively. Clinically, obtain any history of recent weight loss, any chewing/swallow difficulties, any physical limitation/disability, underlying mental confusion, or ethanol consumption. If time permits, screening tools include Subjective global assessment (SGA) or Mini nutritional assessment (MNA) are also helpful and may provide further insight. [100] Evaluation and proactive management of malnutrition in the elderly improves surgical outcomes and should be performed on at-risk patients.

Anemia and Hematologic Disorder Evaluation

Key Point: For patients over age 65, pre-operative transfusion to treat hematocrit levels <24 % is associated with decreased 30-day mortality.

Anemia prevalence increases with age. Over 20 % of patients >85 years carrying the diagnosis, while 16 % of men and 10 % of women over age 75 are anemic. Underlying causes of anemia are split in thirds between malnutrition (iron deficiency accounts for 50 %), renal dysfunction, and unexplained anemia. Anemia in the elderly is subtle, with less than 3 % of patients having a hemoglobin level below 11 g/dL. However, it should not go overlooked, as it is associated with worsened mortality, morbidity, and functional status [102]. A NSQIP study evaluating anemia demonstrated a 0.8 % increased risk of 30-day surgical mortality for every 1 % point below "normal," defined as hematocrit of 39 [103]. In a propensity-score matched analysis of NSQIP patients over age 65, pre-operative transfusion for hematocrit levels <24 % was associated with decreased 30-day mortality. In patients with HCT >30 %, transfusion was associated with decreased mortality only when blood loss was significant (500–999 ml) [104].

A pre-operative CBC provides a baseline and allows the surgeon and anesthesiologist to discuss triggers for operative

blood transfusion. Because of anemia's correlation with nutrition, testing can be completed simultaneously [105]. For major elective surgeries, consider treatment with iron supplementation, folate supplementation, erythropoietin, or transfusion. Discussions regarding immunosuppressive effects and transfusion-related acute lung injury (TRALI) should be thoroughly covered during the informed consent process [103].

Dementia and Mental Status Evaluation

Cognitive dysfunction is common in elderly patients, with rates between 5 and 15 % in the general population and increasing to >60 % in high-risk groups. Although delirium and dementia in the elderly surgical patient have been shown to be significant risk factors for adverse outcomes, it is rare for a surgeon to perform an in-depth cognitive assessment either due to lack of time or knowledge base. In either case, pre-operative cognitive assessment may prove invaluable in improving peri-operative outcomes in the elderly population.

Delirium is the one of the most common post-operative complications in the elderly. It has been defined as a documented change in mental status characterized by reduced environmental awareness and attention disturbance. In a prospective analysis of patients aged over 70, undergoing abdominal surgery, the overall incidence of delirium was 60 % with a 30-day mortality of 20 % in those patients. In fact, 40 % of patients had 3 or 4 risk factors for delirium [98]. Recent studies have implicated dementia as the single biggest risk factor for post-operative delirium, although multiple additional factors have also been implicated (Table 65-5).

Table 65-5. Risk factors for delirium

Pre-operative
Dementia
Age [90]
Malnutrition [98]
Cognitive impairment [101]
Visual impairment [101]
Dehydration [90]
Immobilization [90]
Polypharmacy [90]
Severe illness [101]
Peri-operative
Poor fluid status [98]
Poor glycemic control >150 mg/dL
Metabolic derangements [90, 98]
Uncontrolled pain (PCA necessary to improve delirium in elderly patients [101])
Addition of more than four new medications [98]
Bladder catheters [98]
Serum urea nitrogen to creatinine ratio >17 [101]
Prolonged bed rest
Physical restraints [98]

Pre-operative prevention is possible in patients, with studies showing simple geriatric consultation decreases post-operative delirium. In the Hospital Elder Life Program, focus and management of six factors reduced delirium: visual and hearing impairment, cognitive impairment, sleep deprivation, immobility, and dehydration. Treatment should not utilize medications as first-line therapy. Instead, avoidance of triggers, reorientation, massage, relaxing music, 1 on 1 care with family are recommended. If medication is required, haldol should be initially considered and the clinician should refrain from restraints except in the most severe cases [106].

Current Risk Assessment

Commonly used predictors of post-operative complications are, for the most part, not tailored to the geriatric population. For example, the popular American Society of Anesthesiology is determined by a subjective estimate of organ system disease and likelihood of survival while the Lee and Eagle Criteria account for cardiac function only. Even recent pre-operative risk models such as the CR–possum take only age into account. As we've discussed, chronological age is a poor marker of functional, physical, and cognitive decline in the elderly. Several risk models have attempted to include markers for physiologic status such as the National Surgical Quality Improvement Program (NSQIP). Among other physiologic variables, the model includes age (<65, 65–74,75–84, 85 or greater) and functional health status (defined as independent, partially dependent, and totally dependent), both of which may help account for elder patients who are frail and reside in nursing homes or assisted living facilities. While these models identify age as an independent risk factor and are validated estimates of pre-operative risk, they are substantially limited in the evaluation of the geriatric patient. They fail to pre-operatively discriminate between the geriatric patients who should be considered for surgery, to identify those unfit individuals who should be excluded from radical therapy, and most importantly, those patients with modifiable health risks which can be optimized peri-operatively and perhaps improve outcome.

Frailty

The older population is a heterogeneous group with varying levels of health status. The current models for predicting peri-operative risk do not account for the diverse levels of physiologic reserves in the older surgical patients. The term "frailty" has been increasingly recognized as a surrogate for decreased physiologic reserve in the elder population. It has been described as a phenotype associated with the dysregulation of multiple physiologic systems such as the immune, adrenal, hormonal, and cardiovascular systems [107] In 2001, Fried et al. characterized frailty as an age-associated decline in five domains (Table 65-6): shrinking, weakness,

Table 65-6. Frailty score

Domain	Definition
Shrinking	Unintentional weight loss ≥10 pounds in the last year
Decreased grip strength	Patient squeezed a hand-held dynamometer (strength measurement was adjusted for BMI and gender)
Exhaustion	Response to questions about effort and motivation
Low physical activity	Survey about leisure time activities
Slowed walking speed	Speed at which patient could walk 15 ft.

Chart adapted from Makary 2010 [10]
Frailty score has been described as an age-associated decline in 5 domains: shrinking, weakness, exhaustion, low physical activity, and slow walking speed [107]

Table 65-7. Geriatric assessment domains

Domain	Measures
Functional status	1. Activities of daily living (Subscale of MOS Physical Health) [119] 2. Instrumental activities of daily living (Subscale of the OARS) [120] 3. Karnofsky Performance [121] 4. Timed Up and Go [122] 5. Number of Falls in Last 6 Months [123]
Comorbidity	Physical health section (OARS Subscale) [120]
Cognition	Blessed orientation-memory-concentration test [124]
Psychological	Hospital Anxiety and Depression Scale [125–127]
Social functioning	MOS social activity limitations measure [119]
Social support	MOS social support survey: Emotional/information and tangible subscales [119, 128]
Nutrition	1. Body mass index [128] 2. % Unintentional weight loss in last 6 months [129, 130]

A comprehensive geriatric assessment (CGA) should be a key part of the treatment approach for all older cancer patients [108, 109]

exhaustion, low physical activity, and slow walking speed. The definition was instrumental in providing the framework to help define this challenging population. In nonsurgical patients, frailty has been shown to identify those patients at risk for increase falls, disability, hospitalizations, institutionalization, and mortality [107].

In 2010, Makary and colleagues used the Fried criteria to establish the Hopkins' Frailty Score, which demonstrated that the frailty was a potentially useful tool in predicting poor outcomes in the elderly surgical population. Frailty was prospectively measured in 594 patents (aged 65 years or older who presented for elective major and minor surgery). Patients scoring 4–5 were classified as frail, 2–3 were intermediately frail, and 0–1 were non-frail. Utilizing multiple logistic regression, frailty was shown to be independently associated with the development of post-operative complications (OR 2.54; 95% CI 1.12-5.77), length of stay (OR 1.69; 95 % CI 1.28-2.23), and discharge to a skilled or assisted living facility after previously living at home (20.48; 95 % CI 5.54-75.68). In addition, when combined with other current risk assessment models such as ASA, Lee and Eagle scores, assessing frailty improved their predictive power [10].

The proposed standardized definition of the frailty score is a step in the right direction, laying the framework for decision-making algorithms in this challenging population. Yet the proposed five characteristics of the Fried frailty are still only several pieces of the puzzle. The term frailty is used to represent a global limited reserve in the elder population and as such other abnormalities in frailty domains have been used to describe or define frailty. Numerous studies have linked nutrition, cognition, and geriatric syndromes to poor outcomes in the elderly population—none of which are components of current surgical risk models.

Comprehensive Geriatric Assessment (CGA)

According to the National Cancer Comprehensive Network guidelines, a multidimensional comprehensive geriatric assessment (CGA) should be a key part of the treatment approach for all older patients [108, 109]. The CGA generally includes a compilation of validated tools to assess comorbidity, functional status (including ability to live at home), physical performance, cognitive impairment, psychological status, nutritional status, medication review, and social support (Table 65-7). In general, the benefits of geriatric assessment in older patients include prolongation of life and prevention of hospitalizations and admissions to adult living facilities [1, 110–112], prevention of geriatric syndromes such as delirium and falls [113, 114], prevention of cognitive decline [115], and detection of unsuspected conditions that may affect cancer treatment in more than 50 % of patients aged 70 or over [116].

To date, only a few studies have incorporated CGA as a pre-operative assessment tool, although it has been found useful in predicting morbidity and mortality. In the European Pre-operative Assessment of Cancer in the Elderly (PACE) pilot study [9], elements from CGA were found to be associated with an increased risk of poor surgical outcomes and increased length of stay. The study included 460 patients greater than 70 years of age undergoing elective cancer surgery for solid tumors, of which 32 % were gastrointestinal in origin. The presence of dependent instrumental activities of daily living (IADL), abnormal performance status, or a moderate-to-severe brief fatigue inventory (BFI) score prior to surgery was associated with a 50 % increase in the risk of post-operative complications. In a recent Norway study by Kristjansson et al. [7], the CGA was predictive of surgical morbidity in 178 elderly colorectal cancer patients with a median age of 80. This study is consistent with previous work identifying frailty as a predictor of surgical outcomes [10, 117]. More recently, Robinson and colleagues used seven frailty characteristics (Time Up and Go, Katz score, Mini-Cog, Charleston Index, anemia, poor nutrition, and the geriatric syndrome of falls) to define frail, pre-frail, and non-frail individuals. Of 201 patients who underwent

Table 65-8. 2012 American College of Surgeons NSQIP and American Geriatric Society proposed checklist

In addition to conducting a complete history and physical examination of the patient, the following assessments are strongly recommended:
Assess the patient's **cognitive ability** and **capacity** to understand the anticipated surgery.
Screen the patient for **depression**.
Identify the patient's risk factors for developing post-operative **delirium**.
Screen for **alcohol** and other **substance abuse/dependence**.
Perform a pre-operative **cardiac** evaluation according to the American College of Cardiology/American Heart Association algorithm for patients undergoing non-cardiac surgery.
Identify the patient's risk factors for post-operative **pulmonary** complications and implement appropriate strategies for prevention.
Document **functional status** and history of **falls.**
Determine baseline **frailty** score.
Assess patient's **nutritional status** and consider pre-operative interventions if the patient is at severe nutritional risk.
Take an accurate and detailed **medication history** and consider appropriate peri-operative adjustments. Monitor for **polypharmacy**.
Determine the patient's **treatment goals** and **expectations** in the context of the possible treatment outcomes.
Determine patient's **family** and **social support system**.
Order appropriate pre-operative **diagnostic tests** focused on elderly patients.

Adapted from Chow et al. [118]
American College of Surgeons 2012 best practices guidelines for the peri-operative care of the geriatric surgical patient

major cardiac or colorectal procedures, frailty was independently associated with increased post-operative complications, prolonged hospital stay, and higher 30-day readmission rates [117].

Current Recommendations

In 2012, the American College of Surgeons NSQIP and American Geriatric Society collaborated to create best practices guidelines for the peri-operative care of the geriatric surgical patient. In addition to conducting a complete history and physical, the authors recommended evaluations of pre-operative domains which included problems specific to elderly individuals. These domains are very similar if not the same domains included in the CGA discussed above and include cognitive impairment, frailty, poly-pharmacy, risk of malnutrition, and lack of family or social support. A proposed checklist was drafted for surgeons across all specialties to utilize in the evaluation of a surgical geriatric patient (Table 65-8) [118].

Improving Outcomes

Defining the elderly is the first step in improving outcomes and the frailty score has laid the foundation. Given the multiple domains involved in defining this complex population, it is not surprising that a multidisciplinary approach is likely required to improve outcomes. Pre-operative assessments should be designed at early detection and treatment of surgical and medical complications, in addition to early mobilization, pain management, and discharge planning. Assessments pre- and post-operatively should be performed by a team of providers including a consultant geriatrician, nurse specialist in geriatrics, occupational therapist, physiotherapist, and social worker in order to help identify discharge needs as well as education in optimizing post-operative recovery. Several orthopedic geriatric units have successfully incorporated pre-operative CGA to identify at-risk individuals and apply targeted therapy to help reduce post-operative adverse outcomes, as well as length of stay. The use of CGA may provide a systematic approach to identifying elders classified as frail and the opportunity to optimize these patients peri-operatively. When a specific multidisciplinary system was implemented for the management of demographic and POSSUM-matched patients over 75 years undergoing major colorectal resection, post-operative major complications were reduced to 17.2 % from 30.8 %. This lead to reduced costs, shorter hospital length of stay, and better quality of life for patients who returned home instead of being placed in a nursing home [18].

Conclusion

In summary, as a result of the growing population of frail older persons with chronic disease courses, surgeons will increasingly be faced with the challenge of managing various disease states in this population. Because surgery in the elderly is traditionally circumvented, it is a crucial first step to develop valid tools within surgery to assess comorbid illness, disability, and geriatric syndromes, and to understand how patterns of care and surgical outcomes of elderly persons relate to these underlying conditions. Once these steps are taken, evaluation of interventions to improve overall outcomes can focus not only on survival, but also to maintain function, improve quality of life, and prevent geriatric syndromes in the context of post-operative care for elders.

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66
Health Care Economics

Guy R. Orangio

Abbreviations

ACA	Patient Protection and Affordable Care Act 2010
ACO	Accountable Care Organizations
ACS	American College of Surgeons
AMA	American Medical Association
APM	Alternate payment models
BBA	Budget Balanced Act 1997
BPCI	Bundled Payment for Care Improvement
CEA	Council of Economic Advisers
CER	Comparative effectiveness research
CF	Conversion factor
CMMI	Center for Medicare and Medicaid Innovation
CMS	Center for Medicare and Medicaid
COBRA	The Consolidated Omnibus Budget Reconciliation Act 1985
COBRA	The Consolidated Omnibus Budget Reconciliation Act 1986
CPR	Customary, prevailing, reasonable charges
CPT	Current Procedural Terminology
DSH	Disproportionate Share Hospitals/Safety Net Hospitals
FFS	Fee-for-service
FFV	Fee-For-Value Model
GCP	Geisinger compensation plan
GDP	Gross domestic product
GHS	Geisinger Health System of Pennsylvania
HCFA	The Health Care Financing Administration
HHS	The Department of Health and Human Services
HMO	Health Maintenance Organization
MGPO	Massachusetts General Physicians Organization
MVPS	Medicare volume performance standards
NHI	National health insurance
NHR	National healthcare reform
NQS	National strategy for quality improvement in health care
OBRA	The Omnibus Budget Reconciliation Act 1989
Part A	Medicare Part A hospital payment
Part B	Medicare Part B physician payment
PCHI	Partners Community Healthcare Inc.
PEAC	Practice Expense Advisory Committee
PERVUs	Practice expense relative value units
PFS	Medicare physician fee schedule
PLI	Practice liability insurance
PPRC	Physician Payment Review Commission
RBRVS	Resourced-based relative value scale
RUC	American Medical Association Speciality Society Relative Value Scale Update Committee
RVS	Relative value scale
SGR	Sustainable Growth Rate
SSTA	Social Security Tax Act of 1935
TPC	Total physician compensation
UAF	Updated adjustment factor
UCR	Usual customary, reasonable charges
VBM	Value-based modifier
wRVU	Work-relative value unit

Key Concepts

- In 1965 President Lyndon B. Johnson signed Medicare and Medicaid Amendments (Titles XVIII and XIX) in to law.
- In 1987 the Resource-Based Relative Value Scale was instituted as the basis for Medicare Physician-Fee-Schedule.
- All congressional attempts at controlling the rising cost of health care in America failed.
- The Patient Protection and Affordable Care Act of 2010 mandated Alternative Payment Models.
- These alternative payment models require clinical integration to be successful in decreasing costs, increasing efficiency and quality in the delivery of health care to patients.

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- Surgeons will have to understand these new alternative payment models in order to continue to deliver quality cost-effective care to their patients.
- The Resource-Based Relative Value Scale in combination with Quality Metrics will be the foundation of total compensation for surgeons within these new alternative payment models.

Introduction

Health Care Reform has become one of the most important social movements since Franklin Delano Roosevelt signed the Social Security Tax Act (SSTA) of 1935. He was the first President to advocate federal assistance to the elderly; the SSTA was a social welfare legislative act. It included insurance for older aged individuals (Title I), unemployment compensation (Title III), aid to families with dependent children (Title IV), maternal and child health (Title V), public health services (Title VI), and aid to the blind (Title X) [1]. President Roosevelt wanted to include national health insurance (NHI) in the bill, however his advisors at the time of development of the bill were concerned that attaching NHI as an amendment to the bill would prevent passage of the act [2]. President Roosevelt was under tremendous pressure from the American Medical Association (AMA) not to include NHI in his Tax Act, and he ultimately did yield to that pressure [1, 2].

Over the next 30 years there were continued federal discussions on the development of some form of NHI. President Harry Truman was a staunch supporter of NHI, but he did not have the political support in Congress to pass such a bill while he was President. It wasn't until July 30th, 1965 when President Lyndon B. Johnson signed Medicare and Medicaid Amendments (Titles XVIII and XIX) of the Social Security Act that instituted a national health program in the USA [3]. At the signing ceremony in 1965, President Johnson's speech was dedicated to past President Truman (who was in attendance), thanking him for his efforts and influence during the development and the passage of these amendments. The reality of the cost of Medicare became evident very quickly: first year Medicare costs were $2.4 billion for hospital payments and $640 million for physician payments. Since 1965 the cost of Medicare and Medicaid has continued to rise and to this date has never been reformed.

Today the cost of health care in America is staggering. A 2014 headline on the *Forbes* website exclaimed, **"Annual U.S. Healthcare Spending Hits $3.8 Trillion"—**the title of an article written by Dan Munro and appeared in Pharma & Healthcare 2014 [4]. Health care expenditures in the USA are currently about 18 % of the Gross Domestic Product (GDP) and it is projected to rise sharply. If health care costs continue to grow at the current "historical" rates by 2040 it will be 34 % of the GDP, while Medicare and Medicaid spending will rise to 15 % of the GDP. So today, it's no surprise that the American people, federal and state governments, and commercial payers are pushing for Health Care Reform.

President Barack Obama had "National Healthcare Reform (NHR)" as part of his electorate campaign for President in 2006, and on March 23rd, 2010, he signed into law the Patient Protection and Affordable Care Act [5].

Health Care Reform in America is "happening now" and it is moving at an unprecedented speed. Health Care Reform is not a new topic, but the previous paragraphs point out a very important premise: that the Delivery of Health Care in America is expensive and this cost cannot continue at the current rate of increase. One of the main targets of Health Care Reform is the current method of physician reimbursement, Fee-For-Service.

Physician Reimbursement

Fee-For-Service: Resource-Based Relative Value Scale

> Fee-For-Service (FFS) *is defined as payment to a provider, usually a physician, who receives a set fee for a particular service-such as performing a physical exam or administering an inoculation-either directly from the patient or from an insurer or other payer. Fee-for-service thus generates payments driven by the volume of services performed.* [6]

After passage in 1965, the Medicare and Medicaid Amendment to the Social Tax Act deemed that physician payments from 1966 to 1992 were based on a system of "customary, prevailing and reasonable" (CPR) charges. This was based on the "usual, customary and reasonable" (UCR) system used by the private health insurers. The CPR method of reimbursement was included in the original amendments in 1965. The UCR system was suppose to achieve two goals: (1) to limit doctors' fees within the fiscal capacity of an organized and tax-supported insurance scheme; and (2) to allow each doctor to continue his or her unique pattern of charging, without a standardized fee schedule [7].

Physicians submitted claims to Medicare with the charges they would "like" to collect. The reimbursement was based on each physician's profile of median charges (customary or usual) for all procedures, which were generated by a computation from the claims submitted the year prior. The prevailing charge was calculated each year for each procedure, by computer screening among all individual doctors' as "customary" charges in a particular region. Medicare would then pay the doctor the actual charge on the current bill that was based on the "customary" charge over the past year or the local medical profession's "prevailing" charge over the past year, whichever was the lowest [8]. Even physicians didn't know what the reimbursement would be after submission of the bill. By the 1980s it was clear that the UCR payment system was not working and was becoming more contentious over time.

The government tried to limit costs by means of economic controls, which were a mixture of inducements and price ceilings. They also tried to protect patients from the excessive balanced billing, which at that time was permitted. It was becoming clear that reform in physician payments was necessary and that a standard fee schedule may be required. The Department of Health and Human Services (HHS) and the Health Care Financing Administration (HCFA) at that time were devoted to free competition and market forces as a means of controlling the cost of physician services, including Medicare.

They were hopeful that the Medicare beneficiary, and other people would join Health Maintenance Organizations (HMOs) there by inducing the market to become dispersed to HMOs and individual patient doctor transactions. HCFA and HHS were very supportive of independent practitioners and did not want to suppress the "free enterprise" that existed in the medical profession. At that time the medical profession in general had tremendous impact in Washington. Unfortunately because of the rising costs in health care and inaction of HHS and HCFA, the task of physician payment reform became the problem of Congress. In 1985, Congress created the Physician Payment Review Commission (PPRC) with the intent of reforming Medicare physician reimbursement. At the same time Congress commissioned a research project to develop a Relative Value Scale (RVS) as the best basis for a new payment system. A research team at the Harvard School of Public Health was given a large grant in 1985 to devise a resource-based RVS for Congress to enact in the future.

With the threat of Congress instituting a completely unacceptable method of reimbursement for physicians, the AMA and several specialty societies agreed to supply expert advice to a Harvard research team. The Harvard team had been designing relative value scales for over a decade, attempting to reward work and other inputs of resources, and correcting biases from historical charges.

The Harvard team did produce an RVS in 1979 that was based on that research project [9]. The American College of Surgeons (ACS) at first would not cooperate with the Harvard project and created a rival research staff in order to develop its own fee schedule. The Harvard team tried to develop a uniform methodology, identifying the dimensions of complexity based on judgment, skill, physical effort, and stress due to risk of the service. The team inferred the roles of each of these in dozens of procedures from interviews with doctors, and then developed a relative weight of each of these dimensions for each procedure and time by means of a psychometric method.

To this day the methodology is questioned for reasons including the fact that it benefits cognitive over the surgical (procedural) specialties [8]. Originally, the Harvard team used telephone interview surveys of a small sample of physicians in order to gather their judgments on the relative amount of time required for different procedure (intraservice time). Then the Harvard team had the data and conclusions evaluated by committees of medical specialists (specialty panel) [10].

The criticism of the "original" methodology is that it was felt to be impossible to accumulate complete and reliable data to construct a stable measure of relative "resource-based" weights among procedures based, in large part, solely on "telephone" interviews and physicians' attitudes to this type of survey (physician compliance, and the thousands of procedures to be surveyed).

By 1987 the Resource-Based Relative Value Scale (RBRVS) was recognized as an alternative basis for establishing a payment rate for services and procedures of physicians in the medical and surgical specialties. The RBRVS would be measured by

(1) Time of procedure
(2) Pre- and post-service times
(3) Intensity of the procedure
(4) Practice costs, including malpractice premiums, and
(5) The cost of specialty training

The time and intensity would be based on a national survey of physicians who performed these procedures. A panel of multiple stakeholders would then be convened, including members of the medical profession, third-party payers, consumers, and other interested parties to evaluate and construct recommendations for policy purposes [11].

After several years and several new research grants, Congress was assured that a scientifically designed RBRVS would be phased in by 1993. The finished RBRVS was incorporated into new Medicare legislation by several acts of Congress: The Consolidated Omnibus Budget Reconciliation Act (COBRA) of 1985, which specified delivery by 1987; and the Omnibus Budget Reconciliation Act (OBRA) of 1986, which delayed the completion date until July 1, 1989 and specified implementation by December 31, 1989.

Part of the problem was due to the fact that since the enactment in 1965 of Medicare, Part B (physician payment) contained no administrative structure or cost controls. The reason for the lack of control of Part B was Washington was more concerned with Part A (hospital payment), and Part B was at that time voluntary for physicians. Washington was also concerned if there were strong cost containment controls it would have triggered protests from the medical profession and physicians would not support Medicare Part B.

The federal government attempted to control the increasing costs of the Medicare program by instituting "budget neutrality" and "expenditure caps." In the 1980s, the federal government mandated that if there was to be any restructuring of Medicare reimbursement policy it would not result in higher total costs (i.e., budget neutrality). In addition, spending would be "capped" at a particular level, for example, Medicare Volume Performance Standards (MVPS) (please see the next section Fee-for-Service). These two methods of controlling costs were controversial and also did not change

the continued increasing cost of the Medicare program. The federal government eventually decided to develop a "fee schedule" based on a conversion factor that was decided by Congress. *Washington realized then that with "the creation, monitoring, and updating of such a fee schedule it would require the full participation-and even the leadership-of the medical profession*" [8].

So the development of Joint committees, a permanent confederation of the AMA, specialty societies, and economic representatives who specialize in contracts and reimbursement, along with national negotiators who would develop agreements on the fee schedule and pass them on to Congress for review and approval.

In 1991, the initial meeting of the AMA Specialty Society Relative Value Update Committee (RUC) took place. The RUC is an expert panel of physicians that makes recommendations to the government on the resources required to provide medical services and maintain each service's "relativity" to a family of codes and to the entire RBRVS.

Charter documents were constructed, and the formation of three committees was outlined to help in this venture: RUC Research Committee, RUC Advisory Committee, and the Health Care Professionals Advisory Committee. Finally, in January 1992 the Medicare RBRVS was implemented. By May of 1992, the RUC had considered the first relative value recommendation from the American College of Obstetricians and Gynecologists (CPT code 58435: Transcervical introduction of fallopian tube catheter), and HCFA accepted the first RUC recommendation [12].

In July of 1992, the RUC submitted the first set of recommendations to HCFA for 253 new and revised CPT 1993 codes. This progressed relatively rapidly over the next few years, and by January 1997, the RUC had performed the first 5-Year-Review of the RBRVS, and there were already over 1000 CPT codes. At that time HCFA accepted 95 % of the RUC's recommendation. Shortly thereafter, two very important additions occurred; first, in January 1998, the Practice Expense Advisory Committee (PEAC) was created, which developed values for physician practice expense and were now resource based rather than a percentage of the wRVU (ultimately in 2003, the RUC submitted recommendations for the PEAC on direct practice expense). Second, in January 2000, the implementation of Resource-Based Professional Liability Insurance (PLI) was formed. Neither of these issues were part of the early original determination of the CPT codes. To put this all into perspective, to date there are over 8000 CPT codes listed in the Current Procedural Terminology (CPT) manual.

Today the RUC represents the entire medical profession; however, voting members of the RUC Committee are appointed by their national medical specialty societies, and usually represent those recognized by the American Board of Medical Specialties or are those that represent a large percentage of physicians in patient care and those that account for a high percentage of Medicare expenditures.

Table 66-1. Composition of the AMA RVS update committee (RUC) 2015–2017

RUC representative/society member	Appointment approval by
Chairperson currently cardiothoracic surgeon	AMA board of trustees
AMA representative	AMA appointee
American osteopathic association	Approved by AMA board of trustees
Health care professionals advisory committee (HCPAC)	
Practice expense review committee (chairperson)	AMA board of trustees
Society members	Recommended by specialty and approved by AMA board of trustees all society members
Anesthesiology	
Cardiology	
Dermatology	
Emergency medicine	
Family medicine	
General surgery	
Geriatric medicine	
Infectious disease[a]	
Internal medicine	
Neurology	
Neurosurgery	
Obstetrics/Gynecology	
Oncology/Hematology[a]	
Ophthalmology	
Orthopedic surgery	
Otolaryngology	
Pathology	
Pediatrics	
Colon and rectal surgery[a]	
Radiology	
Thoracic surgery	
Urology	

[a]Indicates a rotating seat

Four seats rotate on a 2-year basis, with two reserved for internal medicine subspecialty, one for primary care and another for any other specialty. Currently, there are 29 voting members of the RUC and over 100 medical specialties are represented at the three meetings per year [12]. Table 66-1 indicates the current composition of the RUC panel.

The methodology used to evaluate the services (CPT codes) presently is the online survey, and while it is much more sophisticated than the "phone surveys" used by Hsiao in the 1980s, it still does include many of his early recommendations [9]. These surveys are sent to practicing physicians or the specialty society who are the predominant providers of the procedure or family of procedures. An expert panel of the providers, which in many cases is composed of multiple specialty representatives, discusses the results of the survey, the new or revised "CPT Code" is then presented to the RUC, and finally the Work-Relative Value Unit (wRVU) is determined. There is a lot of discussion among the RUC voting members prior to arriving at the wRVU, assuring that the principles of the RBRVS are maintained.

The PEACs review the practice expense for each of the codes and sends its recommendation to the RUC for approval. Next, the wRVUs and the Practice Expense RVUs (PE-RVUs) for each code are submitted to the Center for Medicare and Medicaid (CMS). CMS then may accept the given RUC value or modify the value. That wRVU value is then published in the Federal Registrar, released annually in November, as the Final Rule. CMS then takes in to consideration regional variations of cost and the final total value is presented:

$$\begin{aligned}&\text{The General Formula :}\\&\text{Total RVU} = (\text{work RVU} \times \text{work GPCI})\\&\quad + (\text{practice expense RVU} \times \text{practice expense GPCI})\\&\quad + (\text{malpractice RVU} \times \text{malpractice GPCI}).\\&\quad \text{Payment Total RVU} \times \text{Conversion Factor}\\&\quad (\text{current value } 35.8013)\end{aligned}$$

The Conversion Factor (CF) calculation is a scaling factor that converts the geographically adjusted number of RVUs for each service in the Medicare physician fee schedule into a dollar payment amount. The CF is based on the (1) Medical Economic Index, which measures the weighted average annual price changes in the inputs needed to produce physician services; (2) the Sustainable Growth Rate (SGR); and (3) the updated adjustment factor (UAF). Table 66-2 has examples of three common CPT codes utilized by colon and rectal surgeons with all components and approximate reimbursement utilizing the current conversion factor.

This can also be looked at by the percentage of RVS value of the CPT code. For a typical CPT code, the average breakdown is as follows:

(a) Physician work, 50.9 %
(b) Practice expense, 44.8 %
(c) Professional liability insurance, 4.3 %

While this may seem a bit confusing, it really boils down into a few key aspects. Since 1992, the RBRVS has been the main payment system for Part B and is the basis for the Medicare Physician Fee Schedule. Second, the principle of the Physician Fee Schedule (PFS) is that Medicare will pay a standardized "approved amount" for each service regardless of the physician's fee for the service. Third, the CMS physician fee schedule remains the basis for commercial insurance company fee schedules throughout America. Finally, the work-RVU is the current value method of reimbursement for most "employed" physicians today. We will discuss this in much more depth later on in this chapter. It is quite evident that the Medicare PFS is the economic engine that runs the health care reimbursement and delivery of medical care in the USA.

Fee-For-Service: Why Did It Fail?

William R. Roper MD, CMS Administrator 1988

> …We face substantial problems in controlling the overall growth in expenditures for physicians. A fee schedule based on a relative value scale, no matter how carefully constructed, cannot be expected to address the growth in the volume and intensity of services. Whatever their merits, fee-for-service systems do not provide physicians with incentives to control this growth.

This is a quote from Dr. William R. Roper MD, who was the administrator of HCFA in the mid-1980s during the development of the Resourced Based Relative Value System [13].

As I mentioned in the previous section, the federal government attempted "expenditure caps" to try and control the rising Medicare costs. One example was the Omnibus Budget Reconciliation Act of 1989 (OBRA-89) that established the MVPS, which began in 1990. Under the MVPS policy, payment update for physicians' fees depended on the difference between the actual rate of growth in expenditures for physicians' services and a performance standard established for the year [14]. In reality, OBRA-89 also failed to slow rising Medicare costs. In response, the federal government passed the most controversial method of adjusting physicians' fee schedule based on the comparison of actual expenditures to target expenditures: the SGR. While the SGR is now of historical discussion, until April 2015 it was the most hotly contested approach of adjusting the physician's fee schedule. For that reason I will discuss the evolution and eventual repeal of the SGR method of controlling the rising costs of Medicare PFS.

On August 5th, 1997, the Balanced Budget Act (BBA) was enacted, and Section 1848(f) of the Act, as amended by section 4503, replaced the Medicare Volume Performance Standard (MVPS) with the SGR provision. Section 1848(f)(2) specified a formula for establishing SGR targets for physicians' services under Medicare [14]. Under the MVPS policy, payment update for physicians' fees depended on the

Table 66-2. Common current procedural terminology (CPT) codes billed by colon and rectal surgeons

CPT code	Descriptor	W RVU[a]	PE RVU[b]	PLI RVU[c]	Total RVU	Medicare payment $
44140	Colectomy partial with anastomosis	22.59	12.42	4.64	39.65	1370.58
44204	Laparoscopy, surgical; colectomy, partial, with anastomosis	26.42	12.59	5.53	44.54	1592.51
46260	Hemorrhoidectomy, internal, external, 2 or more columns/groups;	6.73	5.65	1.33	13.71	490.20

[a]Work-RVU
[b]Practice expense RVU
[c]Practice liability insurance RVU

difference between the actual rate of growth in expenditures for physicians' services and a performance standard established for the year [15].

The formula to calculate the SGR was based on an estimate of percentage change in each of four factors:

1. Fees for physicians' services
2. The average number of Medicare fee-for-service beneficiaries
3. The 10-year average annual percentage change in the real GDP per capita
4. Expenditures due to changes in law or regulations

The SGR was a failed mechanism intended to constrain Medicare PFS (Part B) spending by adjusting annual physician fee updates. The mechanism has been criticized as both ineffective and inequitable. Since 2003, Congress has averted formula-adjusted physician fee cuts by overriding the SGR. Every time Congress had to override the SGR there was a cost—one that required payment, except Congress could not find the funds due to budget restrictions. In a "catch-22" proposition, each year the scheduled cuts to Medicare PFS reimbursements were listed at or above 20 %. While this may lower federal expenditures, such large Medicare cuts would actually jeopardize beneficiaries' access to physicians because many physicians would stop seeing Medicare beneficiaries [16].

This all led to the Medicare Provider Payment Modernization Act of 2014 (H.R. 4015 and S. 2000), also called the "2014 SGR fix." This bill actually had bipartisan and bicameral support, except the legislation never left the congressional committee stage because Republicans and Democrats could not agree on how to pay for it. The Congressional Budget Office estimates the cost in 2015 as $174.5 billion [17, 18]. Since 2003, Congress had been trying to repair and/or repeal the SGR in order to stop the rising costs of Medicare spending and all have failed to change the trend. The 2014 SGR fix presented for the first time the Eligible Professionals (EP) definition, which includes physicians (73 %), physician assistants, nurse practitioners, clinical nurse specialist, and therapists with two payment pathways: one Fee-for-Service reimbursement and one for physicians involved in value-based alternative payment models: including the Accountable Care Organizations (ACO), bundled payments, and patient-centered medical homes [17, 18]. The proposed fee cut was scheduled to take effect on April 1, 2015, and would have instituted a 21.1 % decrease in physician fees. However, with overwhelming bipartisan and bicameral support, on April 15, 2015, Congress passed the Medicare Access and Children Health Insurance Payment Reauthorization Act, which repealed the SGR payment formula and guaranteed the Medicare PFS a 0.5 % increase in reimbursements to physician through 2019. President Barack Obama signed the Medicare Access and Children's Health Insurance Program (CHIP) Reauthorization Act of 2015 into law on Thursday, April 16th, 2015.

Since the inception of the PFS and the continued increase in health care costs, Congress, and CMS have focused on disassembling the current fee-for-service system and replacing it with Alternate Payment Models (APM). The Patient Protection and Affordable Care Act of 2010 mandated many of these changes in the delivery of health care in America. I will discuss some of the key portions of the law that will influence how physicians are reimbursed and deliver care.

The Patient Protection and Affordable Care Act of 2010 (P.L. 111–148)

In June 2009, the Executive Report of the President by the Council of Economic Advisers (CEA) entitled *The Economic Case for Health Care Reform* was released. This was one of the most influential "white papers" that stimulated health care reform, in general, and ultimately played a large part in development of the Affordable Care Act of 2010. At its roots, the report stated that the American health care system had substantial inefficiencies that have contributed to the spiraling health care costs.

The CEA pointed to key elements as the cause of these inefficiencies in the health care system:

1. Tremendous variation across states in Medicare spending per enrollee, with no evidence of corresponding variations in either medical needs or outcomes
2. Payment systems that reward medical inputs rather than outcomes
3. High administrative costs
4. Inadequate focus on disease prevention.

The CEA also implicated market imperfections in the health insurance market that create incentives for socially inefficient levels of coverage [5]. The CEA focused on two key components for health care reform:

1. Containment of the growth rate of healthcare costs, and
2. The expansion of insurance coverage.

As a very brief summary of the ACA 2010, it is an approach to expanding access to health care coverage and it;

> Requires most U.S. citizens and legal residents to have health insurance. Creates state-based American Health Benefit Exchanges through which individuals can purchase coverage, with premium and cost-sharing credits available to individuals/families with income between 133-400 % of Federal Poverty Level (FPL) ($19,530 for a family of three) and in (2013) creates separate Exchanges through which small businesses can purchase coverage. Require employers to pay penalties for employees who receive tax credits for health insurance through an Exchange, with exceptions for small employers. Impose new regulations on health plans in the Exchanges and in the individual and small group markets. Expand Medicaid to 133 % of the FPL. [19]

The ACA 2010 is about individual mandates, employer requirements, expanding public programs such as Medicaid and the CHIP, premium and cost-sharing subsidies to individuals and employers, tax changes related to health insurance or financing health reform, instituting health insurance exchanges, developing benefit guidelines, influencing private insurance with rules and regulations to increase participation with all levels of insured patients, mandating the "role" of states in insurance market regulations, administration of health plans and cost containment, and mandating quality improvement and health system performance measures that include prevention, wellness, and long-term care. It is the most inclusive and comprehensive reform in the history of the USA. This law affects all Americans, but the areas that are or will "directly affect" our participation and reimbursement in the health care delivery system are under the categories of Cost Containment, and Improving Quality/Improving Health System Performance. I will expand on these two areas of the law with a series of tables and discussion points.

ACA: Cost Containment Changes

Under the category of Cost Containment the law mandates many "Administrative" changes to health insurance companies: i.e., commercial payers must enact certain provisions in order to simplify delivery and relieve obstructions to the care to their beneficiaries (Table 66-3). The law also institutes sweeping changes within Medicare, which mandate the restructuring of payments to all providers (Tables 66-4 and 66-5). Medicaid is also affected by restricting payments for drugs. Of more concern, it dramatically decreases funding to Disproportionate Share Hospitals (DSH/Safety Net Hospitals) by $17.6 billion (2014–2020), and changing the methodology for distributing the "reductions" to these critical hospitals (Table 66-6). Of note, the vast majority of these DHS are major academic teaching centers, and this could negatively affect residency programs throughout the USA.

The final section of Cost Containment is Waste, Fraud and Abuse—where the overriding principle involves decreasing the cost of fraud by expanding over site, increasing the penalties for submitting false claims and augmenting funding for anti-fraud activities (Table 66-7). It is estimated by the Federal Bureau of Investigation that 3–10 % of all healthcare billings are fraudulent. To put this in context, every year Medicare pays over $566 billion for more than 50 million beneficiaries and Medicaid pays $428 billion for 70 million people [20].

Improving Quality/Health System Performance

Under the heading of Improving Quality/Health System Performance the law affects several areas that are important to physicians: Comparative Effectiveness Research (CER), Medical Malpractice, Medicare, Medicaid, and National Quality Strategy.

Table 66-3. Cost containment of ACA 2010: administrative simplification

Simplify health insurance administration by	Rules adoption date	Effective date
A single set of rules for eligibility verification & claims status	July 1, 2011	January 1, 2013
Simpler electronic funds transfer, health care payment & remittance	July 1, 2012	January 1, 2014
Simpler health claims/equivalent encounter information, enrollment & disenrollment in health plan premium payments, referral certification & authorization	July 1, 2012	January 1, 2016
Health plans must document compliance with these standards ($1 penalty per covered life)		April 1, 2014

Table 66-4. Cost containment: Medicare advantage (MA) plans restructure payments

MA	Restructure payments based on % of FFS[a] those with high % of FFS decrease their payments and increase those with a lower % of FFS	Phase in revised payments over 3 years beginning in 2011 for most areas For some areas phase in over 4–6 years beginning in 2011
MA	Bonus for those plans receiving four or more stars based on the current five star quality rating system for MA as much as a double bonus	Beginning 2012
MA	Modify rebate system based on quality rating	Phased in by 2019
MA	Phase in adjustments to plan payments or coding practices related to health status of enrollees (equaling 5.7 %)	Phased in by 2019
MA	Require MA plans to submit to Secretary of Health partial payments if ML ratio is less than 85 %	2014
MA	Require Secretary to suspend enrollment to MA plan if ML ratio[b] is less than 85 % for 2 consecutive years or terminate plan contract if ML ratio is less than 85 % for 5 consecutive years	2014
MA	Cap total payments, including bonuses at current payment levels	2014

[a]Medicare fee-for-service
[b]Medical loss ratio

Table 66-5. Cost containment: Medicare

Change	Effective date
Reduce annual market basket updates to inpatient hospital, home health, skilled nursing facility, hospice & other Medicare providers & adjust for productivity	Effective varying dates
Freeze the threshold for income-related Medicare Part B premiums	For 2011 through 2019
Establish a Payment Advisory Board of 15 members (no physicians) to submit legislative proposals containing recommendations to reduce the per capita rate of growth in Medicare spending if spending exceeds a target growth rate	Beginning in April 2013
Reduce Medicare Disproportionate Share Hospital (DSH)[a] payments initially by 75 % then subsequently increase payments based on % of uninsured population and the amount of uncompensated care	Effective January 1, 2015
Eliminate Medicare improvement fund	Effective upon enactment
Allow ACOs that voluntarily meet quality thresholds to share in cost savings they achieve for the Medicare program.	January 1, 2012
Create an Innovation Center (with in CMS) to test, evaluate, and expand Medicare, Medicaid, and CHIP (different payment structures & methodologies to decrease expenditures and/or improve quality)	January 1, 2011
Reduce payments by specified percentages to account for preventable readmissions	Effective October 1, 2012
Reduce payments to certain hospitals-acquired conditions by 1 %	Effective fiscal year 2015

[a]DSH—Hospitals that treat indigent patients receive at least partial compensation

Table 66-6. Cost containment: Medicaid

Change	Effective date
Increase Medicaid rebate for drugs: brand name 23.1 %, multiple source drugs 13 % on average manufacture average price	Effective on enactment
Reduce aggregate Medicaid DSH allotments	$0.5 billion 2014 $0.6 billion 2015 $0.6 billion 2016 $1.8 billion 2017 $5.0 billion 2018 $5.6 billion 2019 $4.0 billion 2012 $17.6 billion total reductions
Reduce aggregate Medicaid to DSH[a] allotments by developing a methodology to distribute the DSH reductions in a manner that imposes the largest reduction in DSH allotments for states with the lowest percentage of uninsured or those that do not target DSH payments, imposes smaller reductions for low-DSH states and accounts DSH allotments for 1115 Waivers[b]	Effective October 1, 2015
Prohibit federal payments to states for Medicaid services related to healthcare acquired conditions	Effective July 1, 2011

[a]DSH—Disproportionate Share Hospitals "safety net hospitals"

[b]1115 Waiver Section 1115 of the Social Security Act that gives the Secretary of Health and Human Services authority to approve experimental, pilot, or demonstration projects that promote objective of the Medicaid and CHIP programs. As long as these programs: expand eligibility, provide services not typically covered, or use innovative service delivery systems that improve care, increase efficiency, and reduce costs for Medicaid or CHIP programs

Table 66-7. Cost containment: waste fraud and abuse reduction

Change	Effective date
Provider screening	Dates vary
Enhanced oversight periods for new providers and suppliers initial claims (including enhanced oversight for 90 days)	Dates vary
Moratorium in areas identified as being at elevated risk of fraud in all public programs	Dates vary
Require Medicare & Medicaid providers and suppliers to establish compliance programs	Dates vary
Develop a data base to capture and share data across federal and state programs	Dates vary
Increase penalties for submitting false claims	Dates vary
Increase funding for anti-fraud activities	Dates vary

The ACA of 2010 supports CER by establishing a non-Profit Patient-Centered Outcomes Research Institute to conduct research that compares clinical effectiveness of medical treatments. This institute will be overseen by an appointed multi-stakeholder Board of Governors and with assistance of expert advisory panels. The law does state that the CER findings may not be construed as mandates, guidelines, or recommendations for payment, coverage, or treatment or used to deny coverage. The funding for this project was available at the beginning of the fiscal year 2010. The law mandates the funding by imposing a "fee" on issuers of specified health insurance policies and sponsors of self-insured health plans. It is a once-a-year fee based on the average number of lives covered under the policy or plan.

The law also mandates that medical malpractice "reform" is an important issue and awards 5-year "grants" to states in

order to develop, implement, and evaluate alternatives to current tort litigations, only if the proposals are likely to enhance patient safety by reducing medical errors and adverse events that are likely to improve access to liability insurance (5-year-funding began in fiscal year 2011). Unfortunately, I don't believe this is what physicians have in mind for Medical Malpractice Reform.

The Improving Quality/Health System Performance reference to Medicare for alternative payment models to providers is shown in Table 66-8. These changes to Medicare reimbursement are definitely one of the most important issues facing physicians today. This indicates the direction of the ACA of 2010 is toward the elimination of the fee-for-service method of payments to physicians. This method *is and will* continue to force physicians into Clinically Integrated Networks, and in addition, places some of the economic risks on the providers. The changes to Medicaid payments are just as onerous and are reviewed in Table 66-9.

National Quality Strategy

The National Quality Strategy was a mandate to "define quality" and also to incorporate quality measures into physician payments as incentives or penalties (Table 66-10). From this aspect, multiple "quality measures" have developed and are utilized today.

This brief overview suggests that the ACA of 2010 is forcing the initiation of alternative payment models and the formation of health care networks, which in turn forces physicians into clinically integrated networks. There are several methods of "physician integration" such as employment by the integrated network, physician hospital organizations, or independent practitioner organizations, or join a multispecialty practice. Whichever mechanism of integration the surgeon decides, one the following Alternative Payment Models or a combination of them will be the method of reimbursement.

TABLE 66-8. Improving quality/health system performance: Medicare

Change	Effective date
Establish a national Medicare pilot program to develop and evaluate paying a "Bundled Payment" for acute inpatient hospital/outpatient services, physician services, and post-acute-care services for an episode of care that begins 3 days prior to hospitalization and spans 30 days following discharge.	Establish pilot program by January 1, 2013 and expand program, if appropriate, by January 1, 2016
Create home demonstration program to provide high-need Medicare beneficiaries with primary care services in their home and allow health professional to share in any savings if they: reduce preventable hospitalizations, prevent hospital readmissions, improve health outcomes, improve the efficiency of care, reduce the cost of health care services, and achieve patient satisfaction	Effective January 1, 2012
Establish a hospital Value-Based Purchasing Program in Medicare to pay hospitals on performance on quality measures. Also extend physician quality reporting initiative beyond 2010	Effective October 1, 2012
Develop plans to implement Value-Based Purchasing Programs for skilled nursing facilities, home health agencies, and ambulatory surgical centers	Report to Congress due January 1, 2011

TABLE 66-9. Improving quality/health system performance: Medicaid

Change	Effective Date
Demonstrations projects in Medicaid to pay "Bundled Payments" for episodes of care that include hospitalizations	January 1, 2012 through December 31, 2016
Global capitated payments to safety net hospital systems	Effective fiscal years 2010 through 2012
Organize ACOs[a] for pediatric medical providers and allow them to share in cost savings	Effective January 1, 2012 through December 31, 2016

[a]Accountable care organizations

TABLE 66-10. Improving quality/health system performance: national quality strategy

Change	Effective date
Develop a National Quality Improvement Strategy (NQIS) that includes improving the delivery of health care services, patient health outcomes, and population health	Due to Congress by January 1, 2011
Create processes for development of quality measures involving input from multiple stakeholders for selecting quality measures to be used in reporting to and payment under federal health programs	Due to Congress by January 1, 2011

Alternative Payment Models

As mentioned in the previous section, the ACA of 2010 created the Center for Medicare and Medicaid Innovation (CMMI) and provided it with $11 billion for developing pilot projects and demonstration programs, all of which are currently underway, and each with the goal of developing different ways to organize and/or reimburse physicians other than the current fee-for-service method [21].

The Patient-Centered Medical Home

Medical home projects focus on providing comprehensive primary care that is patient-centric through better coordination of the care patients receive from all providers. This model may include a single payer or multiple payers, and may include Medicare beneficiaries as well. It is based on a risk-adjusted comprehensive per member per month payment or initially the private payers pay an enhanced fee-for-service evaluation and management payment to physicians who add processes of care. These include tools that organize clinical information or adoption of evidenced-based guidelines, as well a bonus payment for improved outcomes such as a decrease in hospital bed admissions or emergency department visits. Of note, the payment is still based on the fee-for-service model under the umbrella of the Medical Home Model.

These Medical Home pilot projects have demonstrated very modest savings up until now. UnitedHealthcare reported savings of about 4 % over a 2-year period and WellPoint reported 3 % in its first year in New Hampshire [21, 22]. Both systems continue to pay physicians on an FFS basis, along with some incentives for coordination of care.

The Michigan Blue Cross Blue Shield (BCBS) Medical Home pilot is utilizing an FFS model, but physicians receive higher fees for certain evaluation and management office codes and preventive care visits. The higher fees are based on quality measures adopted, the performance achieved, and also reflect the outcome results of all patients in the area, not just those who are BCBS of Michigan. In 2012 and 2013, BCBS of Michigan included added payments to specialists for the use of evaluation and management codes. In 2014, specialists received added payment based on the quality and efficiency of care provided to the population [23].

Accountable Care Organizations

The ACO model is authorized in Title III, section 3022 of the ACA and is under the Medicare Shared Savings Program. The ACOs comprise of groups of physicians, other health care professionals, and facilities that agree to work together to provide high-quality, coordinated care to their patients at measureable levels of savings. This model reimburses physicians on an FFS basis, but in order to control the increase in volume, they pay more to physicians who coordinate care and employ information technologies. The CMMI developed an alternative model, the Pioneer ACO, which is for organizations that have experience in offering high-quality, coordinated care to patients. These organizations must be willing to share losses and savings with CMS as long as they generate a minimum of 2 % savings. The ACO must have at least 5000 patients, have no enrollment process, but instead is based on where patients receive their primary care. The initial results of the Pioneer ACOs, reported in 2013, were not impressive, as all 32 met quality performance metrics, but only 13 produced savings large enough to share with CMS. The outcomes resulted in nine leaving the program, seven going onto regular Medicare Savings Programs, and two ceasing to function as an ACO [23].

Bundled Payment Pilot Projects

The CMS Innovation also developed the Bundled Payment for Care Improvement (BPCI) initiative, which was launched in January 2013. The BPCI is a new payment model that allows participating hospitals to enroll in bundled payment agreements with CMS for up to 48 predefined clinical conditions aggregated from Medicare Severity Diagnosis-Related Groups (MS-DRGs). While there are four different models of bundling, the *hospital* is the focal point of the bundle, and the bundle is based on an episode of care. The bundle includes physician services, post-acute providers, related readmissions, and any ancillary services provided during this episode of care. The providers indicate which conditions they want to bundle and propose a discounted price to CMS, based on historical reimbursements for a similar set of services [21].

These three payment models described above are *primary care driven* and *specialists* have historically shown little interest in trying or supporting alterative payment models because of the current FFS model. However, CMS and Congress are actively working to force specialists into alternative payment and delivery models.

Some of the early results of these models have been variable, including a recent independent study of the Michigan Blue Cross Blue Shield Physician Group Incentive Program that does support the FFS method of payment, but is now evolving into Fee-For-Value (FFV) model. They looked at the impact on quality and spending from 2008 to 2011 for over 3 million beneficiaries in over 11,000 physician practices. This statewide model has been evolving over a decade and includes independent practice associations, physician hospital organizations, and large multispecialty group practices. These groups provide clinical leadership, administrative structure, and technical infrastructure. Overall, there are more than 19,000 physicians, involving 68 % of active primary care physicians and 49 % of all active specialists. These physician organizations serve as intermediaries between BCBS of

TABLE 66-11. Center for Medicare and Medicaid Innovation: bundled payments for care improvements (BPCI) payment models

Model	Description	Phase 1	Phase 2	Payment type
1	Involves hospital payments for inpatient stays for most Medicare FFS discharges	Nonrisk bearing	Risk bearing	Retrospective
2	Includes all Medicare Parts A and B payments for the 48 selected clinical conditions	Nonrisk bearing	Risk bearing	Retrospective
3	Includes payments only for post-acute claims for participating skilled nursing facility, inpatient rehabilitation facility, long-term care hospital, home health agency, or physician practices	Nonrisk bearing	Risk bearing	Retrospective
4	Initial hospitalization, health care provider fees during the hospitalization, and payments for readmission	Nonrisk bearing	Risk bearing	Prospective "lump sum" payment to the participating hospital, which then pays the physicians and other provider groups

Michigan and practices participating in the Physician Group Incentive Program. These physician practices have established over 1400 patient-centered medical homes. Since it is primary care-based, the physicians who participate are eligible for up to a 20 % increase in reimbursement in their office evaluation and management fees. They may also bill for care coordination and care management services provided by ancillary providers. They also have an opportunity to earn an additional 15 % on evaluation and management fees for high performance on quality measures. The study did show that participation in the incentive program was associated with an ~1.1 % lower total spending for adults and 5.1 % lower spending for children, along with improved performance in 11 of 14 quality measures over time [24].

Unfortunately, the Patient-Centered Medical Home model, when utilized with the Medicaid population, found little to no impact on acute care use and only modest support for reduced costs and primary care use among patients with higher proportions of chronically ill patients [25].

Basically, the principle of the bundled payment model provides a payment for all of the care a patient needs over the course of a defined clinical episode of care. Its intent is to decrease healthcare spending and improve quality by financial incentives for providers for the elimination of services that are clinically ineffective or duplicative. Also, a shared payment encourages the coordination of care by holding multiple providers jointly accountable, and is designed to decrease the cost of the bundle of services.

In 2008, the PROMETHEUS Bundled Payment model was developed. This experiment was based on multiple services that were anticipated to be required under a particular episode of care: for a patient diagnosed with a specific medical condition or receiving a specific medical procedure. The payment rates are called "evidence-informed case rates." It is a risk-stratified model based on both the probability risk and technical risk. Probability risk is the classic risk used by insurance companies to predict the event will or won't happen, and the technical risk is related to "care production." The providers are expected to control technical risk or potentially avoidable complications through planning and training. So the PROMETHEUS model is designed to transfer the financial responsibility/risk for events related to technical risk (i.e., the providers), and the insurers retain the risk for probability. Three pilot sites were originally included: two chose chronic medical conditions and one chose a procedure.

Yet multiple challenges existed in implementing a bundle, including: defining the bundles, defining the payment method, implementing quality measurement, determining accountability, engaging the providers, and redesigning the care. As of May 2011, none of the pilot sites had been able to utilize PROMETHEUS as a payment method or had executed bundled payment contracts between payers and providers. However, even with the early poor results the participants did see promise and value in the bundled payment model [26].

Without a definitive way forward, the CMMI/BPCI initiatives for Medicare beneficiaries developed four models of payment (Table 66-11). Some highlights include:

The Risk-Bearing Phase (Model 2) has been the main type of bundle payment utilized because it represents the most comprehensive bundled payment by including all services following an index hospitalization. What was found was that the hospitals that enrolled in the BPCI initiative were large, nonprofit, teaching hospitals in the Northeast that have existing affiliations with post-acute-care providers. The few that enrolled in the risk-bearing model chose to focus on three or fewer conditions. The study did find that the most opportunity for savings was in the post-acute-care services such as skilled nursing facilities, rehabilitation facilities, and home health agencies. These services accounted for the highest amount of the variation in total episode-based care spending and are thus targets to reduce healthcare spending [27].

The reality of this section is that multiple stakeholders, especially CMS and the commercial payers, are spending a lot of money on alternative payment models. Much of the data discussed is weak, but what we are seeing today is that the "fee-for-service" method of reimbursement as is known today is going to be re-invented or discarded.

An important point to consider, as it pertains to the payment reform models as discussed in the previous sections, is that the current FFS method will be replaced "broadly" by new incentives that will reward appropriate quality care and value.

Even with payment reform, clinically integrated organizations such as ACOs will pay physicians a substantial amount by the FFS payment model. The hybrid FFS method of payment will include volume (wRVU), quality, and efficiency metrics for the provider who delivers care within these integrated delivery systems. The FFS payment model will remain the basis for determining the bundled payment (i.e., episode of care) amount and the method of reimbursement to the providers who deliver the care under the bundle. So at least for now the "Relative Value Scales," which is the measure of physician inputs by time and intensity of effort, will remain an integral part of payment reform.

Any reform to the Medicare PFS has broader provider payment reform because it directly influences private third-party payer's method of physician reimbursement. The Affordable Care Act section 3007 created a type of payment reform, a "Value-Based Modifier" (VBM) under the Medicare PFS. As required by law Medicare is "budget neutral"; however, the VBM will increase or decrease payment rates to each physician on the basis of CMS' assessment of value, which is based on various indicators of quality and efficiency [6, 28].

Clinical Integration

These alternative payment models ultimately rely on Clinical Integration, and there are many factors that are driving established physicians and physicians coming out of residency into integrated networks. Physicians are migrating to employment because of both healthcare market dynamics and physician's preferences. There is continued concern about the long-term economic effects of healthcare reform and decreasing reimbursement. Many small and medium-sized private practices are having difficulty managing their overhead costs. They also can't compete against the larger organizations, so they give in and or become absorbed/purchased by some of these integrated networks. Young physicians finishing residency are more interested in daily practice than on operating a business, especially because the economics of traditional private practice are so uncertain.

Hospitals and Health Care Networks are hiring physicians for several reasons: better clinical alignment with physicians to reduce the variation in care; increase in cost; and because government and commercial payers are pushing for better outcomes and reduced costs or face financial penalties. Since ACOs are mostly *hospital-centered*, hiring physicians can assist them accrue more patients more rapidly and these networks may influence the care delivered to the community. Integration of physicians into health care networks can have ongoing programs to evaluate and modify individual practice patterns because of the high degree of interdependence and cooperation among the physicians within the networks, which in turn will control costs and ensure quality.

Clinical integration facilitates the coordination of patient care across the "Continuum of Care" in order to achieve Quality Care; these integrated networks must include six goals of integration. The integrated system must be

1. Patient-focused
2. Safe
3. Timely
4. Effective
5. Efficient
6. Equitable

Physician payment reform must achieve a change in physician behavior by their delivery of care to patients within the clinically integrated networks. The current method of modification of physician behavior is through the use of financial incentives or disincentives. In theory, a "change" in physician behavior should reduce the marginal costs and thus the cost-benefit ratio by delivering high-quality healthcare.

In 1990, the Institute of Medicine (IOM) published *Medicare: A Strategy of Quality Assurance*, and defined quality of care as the "degree to which health care services for individuals and populations increase the likelihood of desired outcomes and are consistent with current knowledge." This definition is widely accepted and has proven to be a practical reference to quality assessment and improvement [29].

In the 2011 Report to Congress, the *National Strategy for Quality Improvement in Health Care (NQS)* was included in the ACA of 2010. The NQS pursued three broad aims:

1. Better Care: Improve the overall quality of care by making healthcare more patient-centered, reliable, accessible, and safe.
2. Healthy People/Healthy Communities: Improve the health of the US population by supporting proven interventions to address behavioral, social, and environmental determinants of health in addition to delivering higher quality care.
3. Affordable Care: Reduce the cost of quality healthcare for individuals, families, employers, and government.

The NQS has set six priorities to advance these quality goals. These priorities are based on the latest research, input from multiple stakeholders, and examples from around the country. NQS feels that these priorities have great potential to rapidly improve health outcomes and increase the effectiveness of care for all populations [29].

Table 66-12 describes the basis of what is happening right now with quality measures. Understand that these measures in one form or another are being instituted throughout American healthcare system.

TABLE 66-12. National quality strategy priorities and goals

Priority	Goal	Opportunities	Measures
Safer care	Eliminate preventable health care-acquired conditions	1. Eliminate hospital-acquired infections 2. Reduce the number of serious adverse medication events	Standardized infection ratio for central line-associated blood stream infection as reported by CDC's National Healthcare Safety Network
Effective care coordination	Create a delivery system that is less fragmented and more coordinated, where handoffs are clear, and patients and clinicians have the information they need to optimize the patient–client stewardship	1. Reduce hospital admission and readmissions 2. Prevent and manage chronic illness and disability 3. Ensure secure information exchange to facilitate efficient care delivery	All-cause readmissions within 30 days of discharge Percentage of providers who provide a summary record of care for transitions and referrals
Person and family-centered care	Build a system that has the capacity to capture and act on patient-reported information including preferences, desired outcomes, and experiences with health care	1. Integrate patient feedback on preferences, functional outcomes, and experiences of care into all care settings and care delivery 2. Increase use of EHRs that capture the voice of the patient by integrating patient-generated data in EHRs 3. Routinely measure patient engagement and self-management, shared decision-making, and patient-reported outcomes	Percentage of patients asked for feedback
Prevention and treatment of leading causes of mortality	Prevent and reduce the harm caused by cardiovascular disease	1. Increase blood pressure control in adults 2. Reduce high cholesterol levels in adults 3. Increase the use of aspirin to prevent cardiovascular disease 4. Decrease smoking among adults and adolescents	Percentage of patients 18 years or older with ischemic vascular disease whose most recent blood pressure during the measurement year is <140/90 mmHg Percentage of patients with ischemic vascular disease whose most recent low-density cholesterol is <100 Percentage of patients with ischemic vascular diseases who have documentation of use of aspirin or other antithrombotic during the 12-month measurement period Percentage of patients who receive evidence-based smoking cessation services (e.g., medications)
Supporting better heath in communities	Support every US community as it pursues its local health priorities	1. Increase the provision of clinical preventive services for children and adults 2. Increase the adoption of evidence-based interventions to improve health	Percentage of children and adults screened for depression and receiving a documented follow-up plan Percentage of adults screened for risky alcohol use and if positive, received brief counseling Percentage of children and adults who use the oral health care system each year Proportion of the US population served by community water systems with optimally fluoridated water
Making care more affordable	Identify and apply measures that can serve as effective indicators of progress in reducing cost	1. Build cost and resource use measurement into payment reforms 2. Establish common measures to assess the cost impacts of new programs and payment systems 3. Reduce the amoutn of health care spending that goes to undue administrative burden 4. Make costs and quality more transparent to consumers	To be determined

Clinical Integration and the Employed Physician: What About Contracting?

Physician Payment Reform Models are not "mutually" exclusive and can often be applied in combination with one another. Currently there is no certain understanding regarding which model works best, under what circumstances, and with what methods of implementation. One important point that I want to impress upon the reader is that the RBRVS system is and will be a part of the reimbursement to physicians in these alternative payment models.

I will discuss the different types of reimbursement models for surgeons that are being utilized in the market today. It will take into account economic definitions and models of payment. When surgeons decide on employment with a clinically integrated network, they are usually moving from a private practice environment. They will be negotiating an employment agreement and possibly sale of their practice. This section will discuss only the employment contract, and will include different models of reimbursement and other important aspects of these contracts.

If you are a trainee who has just finished residency or fellowship, you will be negotiating an employment contract that is not too dissimilar. So in most contracts there are a number of important categories that are usually included in the body of it, and one must consult an experienced attorney to assist in the legal interpretation and implications of these complex contracts (Table 66-13).

This section will concentrate on terms of agreement, signing bonus, compensation methods, incentive bonus, quality measures, and salary caps. A point for established surgeons moving into an employed position during negotiations: please realize that there is value to your seniority, "standing" in the community, board certification, and region of practice.

There are a number of compensation models utilized today to reach a total annual cash compensation package for a specified period of time including a fixed salary, base salary plus incentive bonus, treatment for an episode of care or specific services (FFS), capitation per member per month (patients or population), and performance-based pay with increases based on quality of care metrics. In this scenario, methods of payment can be defined as linear when a payment is made for each additional unit of service provided or non-linear when the payment is conditional on reaching a threshold/target or a series of thresholds/targets, or the amount of payment changes with each additional service provided.

The timing of the payments may also vary. One way is payment in advance, which includes a fixed overall budget, while the other is retrospective payment—after the service has taken place, with or without a cap on the total payments. The method of payment may also be reduced or withheld if "behavior" does not comply with what is required (e.g., financial penalty). These are basic principles of compensation models and are not mutually exclusive; therefore, before contract negotiations you should have an understanding of these models and just what your personal goal is. Usually, salary proposals are one of the few areas of these contracts that the surgeon may be able to modify during negotiations, so it is best to have a firm understanding of these concepts.

Many hospitals and healthcare networks utilize organizations like the Medical Group Management Association (MGMA) or American Medical Group Association (AMGA) that have been consulting with physicians, physician networks, hospitals, and integrated health care systems and have a vast data bank for recommendations that can give up-to-date national or regional physician salaries. Realize that most of employed physician salaries are based on a percentile of these national salaries represented by these organizations. The information that is available from these organizations is an invaluable resource for the surgeons during deliberations of salary. As was pointed out in this chapter the RBRVS, this becomes even more important when considering the wRVU is the basic component for valuing the compensation package. The Medicare conversion factor (currently at $35.082) is what the network will be utilizing as the bases for the value of the wRVU. Surgeons should make sure that the network conversion factor is a percentage greater than the Medicare conversion factor. The following models utilize many of the tenants of what has been discussed.

TABLE 66-13. Critical points to consider during contract negotiations

Employment agreements (non-academic)
Term of agreement
Duties and services
Performance standards
Location of services
Managed care contracts
Total annual cash compensation
Medical malpractice insurance/tail coverage
Salary caps
Compensation per wRVU (the conversion factor for Medicare is $35.082/RVU)
Signing bonus
Guaranteed base + Bonus
Pure production
Covenant noncompete clauses
Share of quality/utilization bonuses
Moving expense reimbursement

Fee-For-Service Model: Based on the Work-RVU

The physician reimbursement models that are being utilized today such as the guaranteed salary or the work-RVU based salary are very common and can be lucrative. However, the long-term outlook is not good, primarily because as the healthcare dollar reimbursement shifts to value-based purchasing and value-based modifiers, more and more employers will have to "adjust" physician reimbursement

according to these modifiers (Appendices 1–3). These models may be good for some surgeons who are looking for "short-time" employment, such as those planning on retirement soon or others working in an interim capacity.

In addition, all of these examples tend to have time limits for the "initial" contract. In some cases, it may be yearly, although 3–5 years should be the absolute minimum time frame. There will be changes in the compensation package after the initial contract comes to an end, and some contracts will utilize similar methods as the original contract and some may move to a "production only" method based on the wRVU and a conversion factor.

However, there are several models of reimbursement that have been shown to be successful that combine a base salary with an incentive bonus that is based on quality metrics that constructs a total annual compensation package that is competitive and fluid enough to modify as the economics continue to change. The two models that appear to have sustainable physician compensation models are the Geisinger Physician Compensation Model and the Massachusetts General Physicians Organization's Quality Incentive Program.

Geisinger Health System Physician Compensation Model

Geisinger Health System (GHS) of Pennsylvania believes that compensation systems can drive improvement in the value of care, and linking professional pride with improved performance. GHS ties employed physician salaries to the care they deliver and to patient outcomes. Most of the reimbursement is under a fee-for-service model. However 20 % of the total physician compensation (TPC) is based on performance incentives that are defined annually for each type of clinician. This is a "Fluid Model" allowing for modification from year-to-year, if necessary. The GHS compensation plan appears to be fair and reasonable because the organization is increasing the number of employed physicians with a low turnover rate (Table 66-14). A fundamental goal of the Geisinger Compensation Plan (GCP) is to maintain a total compensation package with an 80 % base salary paid monthly and 20 % variable (incentive) compensation that is directly dependent on both the annual performance of the individual and the group. The variable payment is given twice each year, once in March (reflecting July through December performance) and another in September (reflecting January through June performance) [30].

Base Salary

GCP defines the base component (80 % delivered in monthly paychecks) of each physician's compensation according to factors that describe his/her expected work effort (Table 66-15). Physicians within their specialty area are placed in quadrants based in relation to the 60th percentile (above or below) for both parameters (FFS production and compensation). Geisinger senior management, Geisinger's board management, and a compensation committee review all outliers with discordant performance and compensation data. As an example, physicians whose work production is high, but compensation is low according to national benchmark (or vice versa) will be reviewed under this policy [31].

Performance Incentives for Specialist Physicians

Geisinger's strategic vision of improving quality and efficiency through innovation and integration of care uses the variable portion of compensation (20 % of total) to incorporate that strategy into the work of every clinician. Each physician in a GHP service line has incentive goals that are developed by the service line members. These incentive goals are consistent with the system wide strategic aims of the GHP (Table 66-16).

The quality metrics are 40 % of the total incentive pool and 8 % of the total compensation. The financial metric is 25 % of the incentive pool, based on recent productivity of wRVUs at the 60th percentile of specialty-specific benchmarks, and thereby constitutes 5 % of the total compensation. In this formula this means extremely high levels of productivity do not necessarily translate directly into higher income.

Rather, innovation, legacy, and growth account for 35 % of the incentive compensation and ~7 % of total compensation (Table 66-17).

Overall it appears that Geisinger's compensation plan is successful, at least according to metrics that are also beneficial to the management of a delivery system. This is consistent with Geisinger Health System's national reputation as an integrated system that delivers high-quality, cost-effective

TABLE 66-14. Geisinger Health System of Pennsylvania composition

- Nonprofit integrated delivery system
- Tertiary/Community hospitals
- Outpatient facilities
- Sixty community practices
- Geisinger health plan (Insurance Company): 290,000 members/37,000 providers
- Employed physicians: 220 primary care/654 specialty physicians

TABLE 66-15. Geisinger compensation plan: base salary

- Work effort: includes teaching, research, and administrative activities measured in wRVUs[a]
- Increase or decrease depending on the physicians working above or below the expected ranges
- Depends on the physicians experience/specialty market rates
- GHS goal is for physician to exceed the 60 percentile for their specialty area in both FFS work unit production and compensation.

[a]Work-RVU metric is based on the relative value based upon time, skill, training, and intensity of the service delivered

Table 66-16. Geisinger compensation plan: performance incentives for specialists

Variable portion of compensation of 20 % of incentive payment:
Five general areas
Quality (40 %): Defined for each specialty through discussion with specialty leaders and senior management (average 4–5 measures)
Innovation (10 %): Development (example Wound Care Center)
Legacy (10 %): Under Geisinger's educational and research mission
Growth (15 %): Increase in Geisinger's patient population
Financial (25 %): Directly reflects wRVU recognized under FFS

Table 66-17. Geisinger compensation plan

Compensation plan	Basis/metric	Incentive pool (%)	Total compensation (%)
Base salary	FFS wRVUs		80
Performance incentives specialists			
	Quality	40	8
	Financial (wRVUs)	25	5
	Innovation	10	
	Legacy	10	
	Growth	15	
	Innovation/Legacy/ Growth	25	7

health care that has not based its productivity in FFS medicine. It also shows that integrated systems can be successful when the majority of reimbursement is provided by the FFS—at least for now.

When a compensation plan is based on work-RVUs, there is still a competitive tension that exists between individual incentives and unit-based incentives. This is especially true when measured under targets that depend on teamwork and collaboration among colleagues. This is a model that can and is utilized under bundled payments, and has the ability to be modified as health payment reform continues [30].

Massachusetts General Physicians Organization's Incentive Program

The Massachusetts General Physicians Organization (MGPO) incentive program was started in 2008 and was at the time an alternative method for the advancement of patient safety [31]. The MGPO is designed as an internal quality incentive program (QIP) based on several important features that keep physician acceptance and support (Table 66-18).

The MGPO employs almost 98 % of the physicians of the medical staff of the Massachusetts General Hospital, while simultaneously being a part of Partners Community Healthcare Inc. (PCHI). Over the years the PCHI network has evolved from the 1990s capitated payment model to a Pay-For-Performance (PFP) model of compensation in 2001. With the PFP model there was originally an income "withhold" based on a portion of payments due for services paid to hospitals and physicians. It was eventually paid to providers depending on meeting performance measures related to quality of care and efficiency that were prospectively negotiated.

Table 66-18. Massachusetts General Physicians Organization incentive program

Quality metrics are developed by the institutional management team and by quality leaders of each specialty
Competency in managing performance date and developing measures
Clear communication accompanied by consistent and accessible reporting
A fair process for adjudication appeals to performance decisions
Leaderships' commitment to setting priorities

Table 66-19. MGPO quality incentive program metrics

Tier	Physicians (%)	Work-RVU	Time lag measures[a]	Incentive payment $ (annual basis)
One	73	750 or >	Every 6 months	5000.00
Two	19	250–749	Every 6 months	2500.00
Three	8	50–249	Every 6 months	1000.00

[a]Three quality measures are identified: two measures are chosen by program leaders and apply to all physicians. One measure is specialty specific chosen by each clinical department or division

These original approaches evolved into the current model, because the targets were initially set at an aggregate level, and differed by major commercial payers within the region. In addition, the model was focused only on primary care (Table 66-18).

Another problem was with the data that was being captured to determine compensation. It was not current, and needed extensive review and adjustment in order measure incentives. This resulted in a long lag in subsequent incentive payments with the PFP model of up to 24 months. This delay in receiving payments reduced physicians' engagement and overall reduced the impact of the PFP model [32]. This does show the need for these networks to evolve from one model to another as the economics change or with changes in physician satisfaction.

Today the network has over 1700 clinically active physicians who have qualified for the program (Table 66-19). This program costs $3.0–3.5 million for each 6-month period. It requires four full-time equivalent employees (staff members) whose positions add ~7 % to the program overall cost per 6 months. The funding is from an already existing administrative fee that is a percentage of the practice expenses, and it covers all central MGPO management functions [32].

The MGPO incentive program measures 130 quality measures: though only 15 apply to all physicians, so the majority of these measures are specialty specific. The initial results of the MGPOs were reviewed and the percentage of program performance quality measures met in the 6-month time lag was 62 % over the first 13 terms, with over 90 % of the incentive dollars paid out.

Overall, the MGPO-QIP was felt to be successful in many ways, especially when looking at the program's affect on the organization's capacity to measure quality and improve the

collection and maintenance of data over time. The QIP led departments to develop protocols for the maintenance and review of performance data and allowed for changes in improvement priorities. Other benefits of the MGPO-QIP program included allowing physicians to become more accustomed to performance measures. By aligning the MGPO physician compliance with the federal governments meaningful-use-criteria for health information technology, this brought $15.5 million in incentive payments to the organization in 2013 [32].

These compensation packages are early models that are showing different levels of success. Yet, it is important to realize that these models are evolving and maturing along with the alternative payment models.

Summary

Health Care Reform has been moving at an incredible speed over the past several years and the main target of reform is the Fee-for-Service method of physician reimbursement. Over the last 3 decades there have been multiple attempts to modify or control the Medicare PFS, although all have been unsuccessful in containing the cost of healthcare in America. The Patient Protection and Affordable Care Act of 2010 has mandated and funded the application of Alternative Payment Models into the current Health Care Delivery System. The current models of physician reimbursement that are currently in the marketplace will evolve into the primary methods of reimbursement for the delivery of healthcare in the near future. These payment models require clinical integration in order to be successful in delivering care at a low cost, high-quality, efficient manner. The end result is that the majority of surgeons will have to integrate into these clinical networks in order to continue to deliver care and to financially survive.

Appendix 1: Physician Compensation: Model 1 Guaranteed Salary

One-year contract	$20,000 signing bonus
Base salary	$280.000/26 payments/40-hour workweek
Additional on call per diem	$500–750/day

Appendix 2: Physician Compensation Model 2

Work-RVU Based Compensation

Utilizing a dollar conversion factor: that is defined as the numeric factor which physicians multiply wRVUs to calculate physician compensation

Year 1: $40.00/wRVU
Year 2–5: $47/wRVU
Bi-weekly draws—approximately: $7000.00 (Year 1)
Reconciliations of draw: quarterly, semiannually "True Up Date"

These updates can mean an augmentation for increased production or a "reduction" at the next update for not covering overhead.

Appendix 3: Physician Compensation Model 3

Work-RVU Compensation with a Base Salary (Guaranteed)

Five-year contract	$20,000 signing bonus (returned if terminate employment before 24 months)
Base salary years 1–2	$300,000 which is approximately 6500 wRVUs at $45/wRVU
Base salary years 3–5	$300,000 but is subject to adjustment (calculated for a set time period) in advance of the first day of the next employment year and is based on a wRVU, over a period of time the preceding years.

Incentive bonus years 1–3

Work-RVU	Incentive compensation/wRVU
6501–7500	$51
7501–9000	$53
9001–10,500	$55
10,501 or >	$57

Incentive bonus years 4–5	is based on wRVUs generated by physician in excess of tier one baseline, which is multiplied by a "conversion factor" per wRVU which will be adjusted/based on an independent variable
Salary cap	approximately $600,000

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Ethical Issues in Colorectal Surgery

Jason D. Keune

Key Concepts

- Ethics is a formal way of examining what one should do.
- The four principles approach emerged from a common morality of health care.
- A moral dilemma occurs when the moral intuitions of individuals disagree.
- Informed consent is a process that is rooted in respect for patient autonomy.
- Surrogate decision-making is necessary should a patient become incompetent.
- Futility is a concept that is in evolution and should be based on a local definition.
- Disparities in outcomes from colorectal operations vary based on race.
- Financial conflicts of interest are a contemporary problem that has been addressed at the level of the federal government.

Introduction

Ethics, at its most fundamental level, is a way to answer the question, "what should we do?" Since surgeons are, first and foremost, doers in the world, it seems apropos that ethics should be a part of our study. Surgeons have a unique relationship with humankind, and ethics is a way of exploring this relationship deeply.

In this chapter, I will discuss what ethical problems in surgery are, and what a good, reasoned way to approach them might be. I will then discuss several twenty-first century issues in colorectal surgical ethics. This chapter should not be regarded as an exhaustive review, but rather a sampling of some of the most difficult problems faced by colorectal surgeons today.

The Ethical Dilemma

Surgical practice is similar to the practice of all medicine, in that it is conducted against a background of historical ethical problems that have achieved a relatively stable solution. We do not think twice now, for example, about obtaining informed consent prior to operating on a patient or enrolling him or her in a clinical trial. Part of our reasons for doing this may have to do with the legal framework that surrounds us, but should that legal framework be stripped away, informed consent intuitively seems a good thing that we ought to do. The individual *moral intuition* that we each have seems to march in lock step in this regard—rarely does anyone bring up an ethical dispute with getting good informed consent.

Occasionally, however, our moral intuitions disagree. What one surgeon views as "right," another views as "wrong." More commonly, the surgical team views one choice as right and the patient, or patient's family, views the choice as wrong. The story of Jahi McMath is a recent example of such a disagreement. McMath was a 12-year-old girl who suffered an irreversible anoxic brain injury while undergoing a tonsillectomy for obstructive sleep apnea at a hospital in northern California in 2013. While she was pronounced dead by brain-death criteria by her physicians, her family protested, claiming that she was not, in fact, dead. The family obtained a restraining order against the hospital and physicians and was successful in transferring her body out of the hospital. She remains on ventilator and nutritional support to this day [1].

New ethical dilemmas arise against the relatively stable background of an ethical surgical practice for several reasons. First, the contemporary practice of surgery is rooted in technological advancement. As new developments in technology arrive, there is a push to use them, especially in situations where a group of patients were in a position in which no good option was available until the new technology was

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invented. Second, we live in an increasingly plural society. The cultural, ethnic, and religious differences between a patient and physician can have a shrinking effect on the common moral ground between the two. Without some compensating effect, that contracted common ground can lead to the formation of an ethical dilemma.

Ethical dilemmas occur due to the time pressures inherent in surgical care as well. Leak, sepsis, and trauma may all invariably arise after hours. Not surprisingly (and not uncommonly), ethical dilemmas will accompany them, occurring in the middle of the night when ethics consultants are not available. In the case of an unstable patient, death may be imminent and there may not be enough time for an ethics consultant to arrive. Adding to this, communication can also be problematic when time is short. In many other situations, the meeting time is longer, but not by much: developing trust quickly is necessary, and there is little time to reflect on ethical common ground. Furthermore, dilemmas can be intensified, in part due to the fact that surgeons cannot easily "undo" their work. For these reasons, surgeons should have familiarity with the moral reasoning that is necessary to resolve ethical dilemmas.

Ethical Reasoning

Learning approaches to ethical reasoning can be daunting. The *four principles* approach puts forth what are known as "mid-level" principles: respect for autonomy, justice, beneficence, and nonmaleficence. These principles are valuable when trying to resolve ethical dilemmas, as they are general enough to be applicable to a wide range of situations, are commonly valued, and do not require much background or training in formal moral thought. The principles, which emerged from a common morality of healthcare, are defended by ethicists Tom Beauchamp and James Childress [2]. Moreover, they form the backbone of most clinical medical ethics discussions.

The principle of **respect for autonomy** states that clinicians ought to allow patients to make decisions about their medical care that is both free of coercion and fully informed. Obtaining informed consent, which I will discuss later in this chapter, is a good exemplar of the principle of the respect for autonomy. Of specific importance in granting autonomy to patients are the qualities of *liberty* and *agency.* Liberty emphasizes that patients should be given the opportunity to decide whether to undergo surgery and just what surgery that should be. Agency is the quality of granting the patient the knowledge necessary to make the decision and exercising that liberty.

"First do no harm" is an aphorism that describes the principle of **nonmaleficence** well. The obligation not to harm may arise in colorectal surgery practice in weighing the risks and benefits of a procedure, in end-of-life situations, and in drawing distinctions between killing and letting die. Harming should not be thought of only in the active sense, but passively as well, such as in cases of negligence or errors of omission.

Beneficence should be central to every colorectal surgeon's practice, since not harming is not enough. Beneficence implores physicians to do positive acts that benefit others. It exists on the same spectrum as nonmaleficence, but is distinct. Beneficence can come in conflict with respect for autonomy when a surgeon, intent on doing good, feels as though she should override a patient's wishes. When an act arises from beneficence, but violates respect for autonomy, it is called "paternalistic." Occasionally, a surgeon may ask, "how much beneficence?" If an act "goes beyond the call of duty," it is known as *supererogatory*, and is rarely morally required of a surgeon. The degree of beneficence required of a surgeon is therefore measured.

Justice is concerned with inequality. Colorectal surgeons should be cognizant of the fact that there are disparities in treatment outcomes, both in the baseline health and in the ability that patients have to access surgical care. Justice is prominent in the political debate about twenty-first century healthcare, especially considering the distribution of scarce resources, such as organs for transplantation, and determination about what rights individuals have to basic health care.

In the remainder of the chapter, I will review several prominent ethical problems that face colorectal surgeons. This should not be considered a comprehensive analysis, but rather a survey of some of the most common issues that may be encountered. My preference is to provide an in-depth analysis of several topics, rather than glossing over all of the ethical issues that a colorectal surgeon might face.

Informed Consent

Informed consent is a process, initiated by the surgeon, which enables the respect for patient's autonomy to be observed when a procedure is being planned, or another decision point is reached. Informed consent is also important in research. The general gestalt for the surgeon about informed consent is to describe the procedure in detail as well as the inherent risks, benefits, and alternatives. Tom Beauchamps and James Childress, in their classic text, *The Principles of Biomedical Ethics*, have done a more careful analysis of informed consent that can be useful for clinicians. Specifically, they have outlined seven elements in three categories for drafting an informed consent [2]:

Threshold Elements (Preconditions)

- Competence (to understand and decide)
- Voluntariness (in deciding)

Transformation Elements

- Disclosure (of material information)
- Recommendation (of a plan)
- Understanding (of 3 and 4)

Consent Elements

- Decision (in favor of a plan)
- Authorization (of the chosen plan)

The process of informed consent can be thought of as being comprised of elements that are categorized according to their role. The threshold elements, which are essentially preconditions to informed consent, include *competence* and *voluntariness*. The notion of competence rests on an evaluation about whether the patient has the cognitive abilities to both understand information about the procedure and to consider the consequences of the choice to undergo the procedure. Surgeons often encounter patients who are not competent—in this case a surrogate decision maker should be sought. The case of the marginally competent patient can be very complex. Surgeons may benefit from ethics consultation in cases such as these, as there are no straight-forward rules, and individual decisions regarding competency may widely vary. Voluntariness is the threshold element that is concerned with freedom from coercion. Patients should be able to make decisions about their care that is free from outside coercive influence.

The transformation elements include disclosure of material information, recommendation of a plan, and a confirmation of patient understanding. The disclosure of information can be considered central to attaining proper informed consent, and it is notable that a high-quality informed consent rests heavily on a high-quality disclosure. Beauchamps and Childress also address what composes a high-quality information disclosure [2]. I paraphrase this below:

- The facts that patients or subjects usually consider material in making decisions about whether to consent to the procedure
- Information the surgeon feels is material
- The recommendation of the surgeon
- The purpose of seeking consent
- The nature and limits of informed consent.

No informed consent process would be complete without the recommendation of a plan, as patients tend to see surgeons not only for their technical expertise, but also for a reasoned opinion about what the best treatment strategy should be. Patients should also be asked if they have questions, and the surgeon should ensure that the patient has a reasonable understanding of the proposed procedure.

The consent elements comprise the active portion of the process. A decision needs to be made in favor of or in opposition to a plan. Ensuring again that the decision is indeed free of coercion at this point is encouraged. For the informed consent procedure to be complete, however, the patient must signify, usually by signing a document, his or her authorization that the procedure may be carried out.

Surrogate Decision-Making

Many of the ethical dilemmas that arise for surgeons occur near the end of a patient's life. One such problem arises when a patient, previously competent about his or her own care, becomes incompetent. When such a situation arises, it is necessary to make decisions about care without the patient's direct input, but still maximize the ability to respect the patient's autonomy. Someone other than the patient must now be sought to make decisions for the patient. Two main questions should be asked:

1. Who should make decisions for the patient?
2. How should the surrogate decision maker best decide?

Advanced directives are instructions that are provided by patients that give direction to caretakers about how decisions should be made if the patient were to become incompetent. As this is not an infrequent situation, surgeons should have a thorough understanding of determining competence, as well as encourage their patients to have advanced directives and the process of surrogate decision-making when this is not available.

The two common ways that patients can provide direction to caretakers (should they become impaired) are (a) creation of living wills, and (b) the appointment of a durable power of attorney. A living will is a document prepared by a patient while competent that details the patient's preferences should they become incapacitated. It has been demonstrated that patients' preferences show stability over time [3]. Living wills can take a spectrum of forms, from being simple documents that specify only a few things that a patient would or would not want, to complex documents that specify what to do under a plethora of circumstances. Patients can also promote a set of wishes to die a natural death and not be kept alive by heroic measures or to promote the fact that the patient wants everything possible to be done to keep him or her alive.

Another way to have one's preferences recognized after one becomes incompetent is to appoint a durable power of attorney for healthcare. The durable power of attorney is a person who is appointed in advance by the patient to act as a surrogate decision maker. The power of attorney is "durable" because the power lasts beyond the point at which the patient becomes incompetent.

Unfortunately, not every patient has a living will, or a durable power of attorney. When this is the case, it is necessary to find a surrogate decision maker. Laws differ from state to state about how this plays out, but there is typically a hierarchical list: spouse, adult children, siblings, and down the line. If no family member can be found, most states allow for a court-appointed conservator. In situations where a conservator cannot be found, most states will then allow the healthcare institution to make decisions.

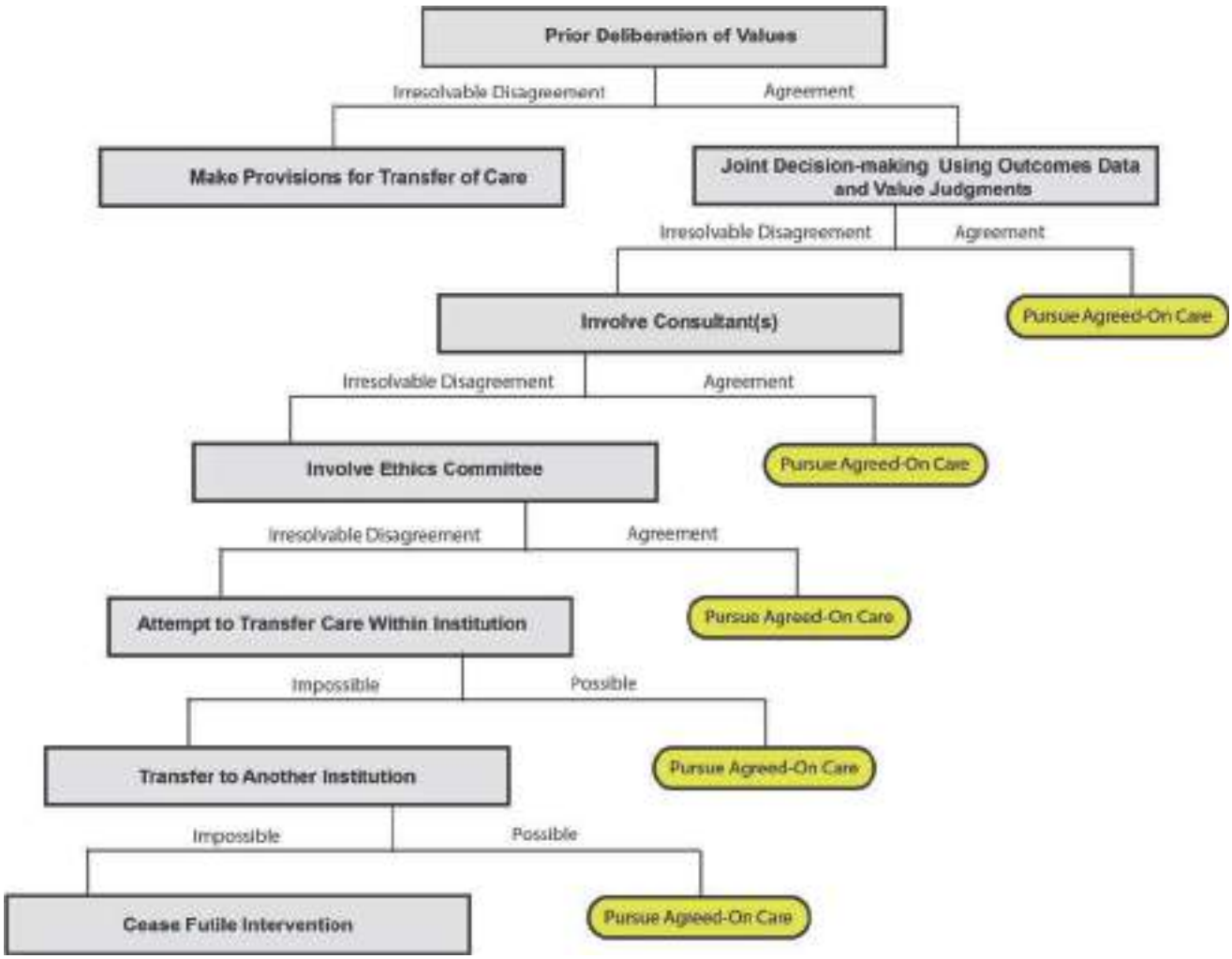

FIGURE 67-1. Fair process for considering futility cases. *Modified from Plows CW, et al. Medical futility in end-of-life care - report of the Council on Ethical and Judicial Affairs. JAMA. 1999;281:937–941* [5].

Simply designating a person is not enough, however, as the problem of how a decision maker ought to decide remains. The two most common standards involve: (1) the standard of substituted judgment, and (2) the best interest standard. In applying the standard of substituted judgment, the decision maker bases the decision on what he or she thinks the patient would want. This standard attempts to maintain respect for patient autonomy. In the best interest standard, which is rooted in beneficence, the decision maker makes choices based on what he or she thinks is best for the patient. This standard is best used when decision makers are not confident that they know what the patient would have wanted.

Futility

Colorectal surgeons are in the business of offering interventions to improve the health of patients. The problem of futility arises when the proposed treatment has such a small chance of being efficacious that the surgeon probably ought not perform it. The range of what is considered "futile" care tends to focus on lack of efficaciousness, lack of therapeutic "success," or care that is burdensome enough to outweigh any therapeutic benefit of the intervention. The concept of futility becomes especially important when one is discussing end-of-life care. Overall, there is a lack of a strict definition of futility that stems from a disagreement about what death is. Since some surgeons and families may have different views about death, the meaning of life-sustaining treatment may also differ.

Attempts to deal with the problem of futility have taken several forms over recent history. Initially, futility was defined in terms of specific *clinical* criteria, either by comparing one group to like patients in whom similar treatments have been useless or with the use of physiological goals. Yet, it was difficult to find consensus on such approaches because goal setting can be arbitrary and the definition of "useless" is by no means clear [4]. In response to the failure of such approaches, the American Medical Association Council on Ethical and Judicial Affairs recommended that a process-based approach to futility determinations should be taken [5] (Figure 67-1). This approach does not require a definition of

futility, but instead describes a process by which definitions might be agreed upon locally. The approach also does put a large amount of decisional power into the hands of ethics committees, which are often dominated by clinicians, and are of variable quality from organization to organization. Regrettably, the problem of futility is still relatively unsettled in the twenty-first century.

Refusal of Care

With sound mind and proper understanding, refusal of care is a patient's right. Yet, while the refusal may be "justified," this often leads to a dilemma when a treatment recommended by a surgeon is refused by a patient or their family. Especially if the treatment is considered standard of care, this can cause dissonance between surgeons and patients, as well as has the potential to alter outcomes. The refusal of blood products by Jehovah's Witnesses is one of the most common refusal scenarios encountered. On one hand, transfusion may be lifesaving in perioperative setting complicated by large volume blood loss. On the other hand, Jehovah's Witness patients that accept blood products are at risk of being shunned by his community. A policy put in place in 1945 by the Watchtower Society, the guiding organization of the church of Jehovah's Witnesses, required the "disfellowshipping" or expelling of members who willingly accept blood products. In 2000, though, the Watchtower Society changed the policy so that patients would not be "disfellowshipped" should they not comply with blood product refusal [6]. Though not official, the stigma on accepting blood products for this group seems to persist into the present era.

The respect for patient autonomy is prominent amongst the ethical principles in today's surgical practice. The strict observation of patient autonomy breaks down, though, when patients consent to a recommended procedure, but refuse to have certain elements of the care necessary to perform such procedures. Most surgeons standardize their practice in hopes of producing consistent surgical outcomes. Without being able to practice in the standardized way, however, surgeons are at risk of entering unfamiliar clinical territory. Most studies about death after low anterior resection, for example, assume that blood transfusion was available to the surgeons who performed the procedures. Calculating risks of doing such surgery without blood transfusion is therefore difficult.

It is necessary in such a situation to ensure that the patient who is refusing care or elements of care has full decisional capacity and is not being coerced. It should be pointed out that the ethics change as well when the patient is a minor and the patient's parents try to block certain aspects of care. Unless the decision is made in an emergency setting, parental consent is needed to perform a procedure on a child. The most common scenario for court intervention in such cases is when parents try to block the transfusion of blood products. The groundwork of a parent's right to make medical decisions can be found in a 1944 US Supreme Court case, in which the court ruled, "Parents may be free to become martyrs themselves. But it does not follow they are free, in identical circumstances to make martyrs of their children before they have reached the age of full and legal discretion when they can make that choice for themselves" [7].

Outcome Disparities in Colorectal Surgery

As John Rawls has put it, justice "is the first virtue of social institutions, as truth is of systems of thought." After reflection, one might recognize surgery to be as much of a social institution as it is a scientific one. One of the four "principles" of Beauchamps and Childress, justice can be thought of at its most fundamental roots as the ability "to be fair." Yet, when it comes to results following surgery, it follows that there is no moral justification for the outcome disparities that fall along racial lines. The statement by the American College of Surgeons that, "ethnic and racial health care disparities have no role in a humane and just society, and are ethically and morally antithetical to the practice of medicine and surgery," [8] highlights the problem, and makes it more mainstream. In addition, recent breakthroughs and public availability of large data management (e.g., SEER, NIS, NSQIP) have led to databases rich with racial and socioeconomic demographics, making comparisons between groups an obvious choice for study. Unfortunately, in many cases, no matter the question, distinct differences are detected along racial and socioeconomic lines.

In one example, Nestor Esnaola and colleagues identified 35,695 patients with non-metastatic rectal adenocarcinoma between 2003 and 2005 using the National Cancer Data Base [9]. They found that African American and Hispanic patients were more likely to present with advanced disease compared with white patients. They also found that only 85.1 % of tumors in African Americans were resected, compared with 90.7 % of whites, with a striking adjusted odds ratio of 0.62 (95 % confidence interval 0.54–0.71). The same group from the Medical University of South Carolina, when looking at the South Carolina Central Cancer Registry, noted the underuse of surgery for the black population [10].

Researchers at Mt. Sinai recently examined their own cohort of patients undergoing treatment for colon cancer, focusing specifically on racial and socioeconomic disparities as the complexity of the surgical options increases [11]. They found that patients undergoing the heated intraperitoneal chemotherapy for colorectal cancer (HIPEC) procedure were predominantly white, English speaking, privately insured, and had a higher mean income when compared to patients undergoing colectomy alone.

Another group from the Harvard Radiation Oncology Program analyzed over 1,000,000 patients in the SEER database who had diagnoses of lung, breast, prostate, or colorectal cancer. They found that the survival gap between black

and white patients (hazards ratio, 1.28; 95 % confidence interval 1.26–1.30 [$P<0.001$]) did not change over the period between 1988 and 2007. Interestingly, outcomes persisted independent of stage of disease and treatment, suggesting that efforts to improve screening and increase access to all parties may not solve the problem entirely [12].

Schootman and colleagues also recently examined colorectal cancer data from the SEER database from 1992 to 2005. They found that African Americans in high poverty neighborhoods had increased odds of an emergency diagnosis (AOR: 1.50, 95 % CI: 1.38–1.63). This may be a contributing factor to overall disparities that are seen in colorectal cancer outcomes by race [13].

Creatively designed research by Julie Freischlag and colleagues at the Johns Hopkins University tried to look for reasons behind these differences in outcomes that extended beyond the clinical realm. Their work revolved around the concept of the "unconscious biases" of medical students entering the Johns Hopkins School of Medicine. Using web-based clinical vignettes and the implicit association test to detect bias, they found that 69 % had implicit biases towards the white race and 89 % towards persons of the upper class [14]. These biases did not, however, impact the vignette-based clinical assessments, suggesting that the students did not allow this inherent bias to influence their clinical decision-making. A similar study was performed by the same group on 214 physicians at various stages in a surgical career. As with the previous report, bias was found, but clinical decision-making was not impacted [15].

The problem of disparities in surgical outcomes seems to be related to the problem of racial diversity in the surgical workforce. Diversity is a descriptive characteristic of a group of people that exhibit differences in their demographic makeup, cultural identities or ethnicity, training, and expertise [16]. Lee Bollinger, president of Columbia University, writing for a medical audience has remarked that developing an educational setting that is rich in diversity is the most important way to prepare students to work in a diverse society. Simply learning about ethnic and sociocultural diversity is not enough—students should be immersed in a learning environment that is rich with diversity itself [17]. There is a parallel here for surgeons: the more rich our diversity, the more prepared we will be to encounter a diverse patient population.

Unlike patient demographics, the demographics of surgeons working in the USA are poorly understood. The racial breakdown of the overall physician workforce is known, however, and it may be appropriately hypothesized that surgery parallels it. In 2008, Blacks, Hispanics, and Native American populations comprised 12.8 %, 15.4 %, and 1 % of the USA's population, respectively [18], but comprised only a mere 3.5 %, 4.8 %, and 0.1 % of the physician workforce [19]. Interestingly, while the American College of Surgeons does support a "Committee on Diversity Issues" [20], it does not collect racial demographics on its members. The American Board of Surgery likewise does not collect such demographics. How this data would ultimately affect future changes can only be speculated, yet could provide a baseline from which to launch future initiatives.

The vast amount of data that has been published to date regarding outcomes of surgery stratified by race and ethnography is due, in part, to the rich availability of demographic data that is available to researchers. It serves as a testament to the fact that surgeons care about this problem and want to focus on it. The situation will not change until researchers change their approach from observational studies to interventional ones, a change that will not happen until such studies are funded. One place to start would be the work of Lu Hong and Scott Page. They have shown in a modeling environment that a diverse group of intelligent agents will solve problems better than a group comprised of selected top performing intelligent agents [16]. It is time that such research is brought from "bench to bedside."

Physician Financial Conflicts of Interest

A conflict of interest exists in a state in which there is a dynamic interaction between two differing interests in the same person, such that one interest directly or indirectly impacts that person's ability to realize and possibly execute a pure motive in the other. As federal funding for research in colorectal surgery diminished through the 1990s, the need to fund research with funds from industry became much more prominent. Colorectal surgeons, too, have great decisional power with regard to resource use in their sphere, and therefore are often the targets of marking efforts by drug and device representatives. "Colorectal surgeon" was the most common profession amongst disclosures made from 2006 to 2009 given by presenters at the annual Clinical Congress of the American College of Surgeons [21].

The conflict of interest problem in the surgical profession comes about especially when one of the two interests is financial and the other is the well-being of the patient. The concern is that physicians will be unable to manage these potentially competing interests, leading to a diminished outcome for the patient. The high road of this dispute is to claim that surgeons ought not have any relationships that interfere with their interactions with patients, especially not ones of financial import. In reality, it would be hard to recognize an American healthcare system that was devoid of the for-profit pharmaceutical and device manufacturing companies that populate it. Though it is clear that surgeons should not let financial concerns impact decisions at the bedside, it is not clear that there should be a complete break in the relationship between surgeons and industry at the research and development level. In fact, this relationship can be beneficial. Safe and effective surgical innovation will not work without active surgeon input at every stage. This requires surgeons to interact with for-profit corporations, for the means of production of devices in the USA is in the private sector.

How to handle these potential conflicts is the major crux. At present, the management of financial conflicts of interest in the twenty-first century relies on the words of Justice Louis Brandies, who declared at the beginning of the twentieth century that "Sunlight is said to be the best of disinfectants" [22]. The Affordable Care Act, which became law in 2010, includes a section called the "Physician Payment Sunshine Provision," [23] which requires drug, biologics, and medical device companies to report all payments and transfers of value to physicians and teaching hospitals in excess of $10 per instance to the federal government. The payments are publically disclosed.

David Rothman hypothesizes that the result of such "Sunshine" will create a two-track career pathway for all physicians. One track is a "professional" one that is able to remain free from industry money to "simplify their clinical and organizational lives and allow their participation in various activities," while the other is an "entrepreneurial track for those who take pride in the size of their royalties" [24]. Such a black and white view may not be entirely appropriate for surgeons who want to participate in the evaluation and evolution of surgical devices. Working with industry also does not equate to an inability to make sound and non-bias judgments regarding patient care. Rothman's final statement of the commentary is spot on when he states, "It is too soon to chart the outcomes, but it would be surprising if physicians did not behave differently when watched." Only time will tell.

Conclusion

For those that have the power to make such significant change in the world, a study of what is right to do seems like a given. Ethics should be a part of every surgeon's training and ethical reasoning should be in every surgeon's toolkit, especially since surgeons are "doers." One never knows when an ethical dilemma will arise that will demand ethical reasoning. Who better than the surgeon to guide the resolution of the dilemma in a thoughtful reasoned manner.

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68
Welcome to Litigation

Dennis K. Ames

Key Concepts

- In litigation, preparation is the key to a successful outcome.
- Preparation should begin as soon as you become aware of an adverse outcome likely to lead to litigation.
- Don't conduct an independent investigation.
- Never appear at a deposition without consulting an attorney.
- Meet with your attorney early.
- Communicate with your attorney regularly.
- Know what you can expect of your attorney, and when.
- Know what is expected of you, and when.
- Do your homework; and make yourself available.

The unfortunate reality for today's physician is that he or she will almost certainly be sued for medical malpractice in his or her career. According to data published in the *New England Journal of Medicine* in 2011, general surgeons (the publication does not include a cohort for colon and rectal surgeons) face a 15.3 % annual probability of facing a medical malpractice claim. Along with other "high risk" specialties, 80 % of general surgeons are projected to face a claim by the age of 45 years, and, by age 65, fully 99 % of those physicians in "high-risk" specialties such as general surgery are projected to face a claim [1].

The pertinent question for today's surgeon is not "What should I do *if* I get sued?"; rather, it is now, "What should I do *when* I get sued?"

If there is comfort to be taken in this data, it is that while physicians, depending on specialty, face a 5–20% probability of facing a malpractice claim in a given year, the probability of any such claim leading to an indemnity payment is substantially lower.

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This chapter is designed to guide the physician-defendant toward achieving the ***best result*** the facts of the case allow. *Best result* is not measured only in the sense of winning or losing the case. As importantly, *best result* implies minimizing the human toll the process exacts on the physician-defendant, by reducing anxiety and frustration [2].

Anxiety is reduced by education and managing expectations. This chapter is organized to provide a general outline of each of the stages of the litigation process. It will describe each stage of the process, and define the role of the attorney and of the physician-defendant at each stage.

Frustration is reduced with preparation and being proactive in your defense. As a physician facing a malpractice claim, you have the right to expect your attorney to be well prepared at each stage of the litigation. As the physician-defendant you, too, have a significant role in the preparation of your own defense. To be prepared, you must know what to expect during the course of the litigation. You must understand the litigation process. You must understand what you have the right to expect from your attorney; and finally, you must understand what your attorney has the right to expect of you.

In an effort to minimize frustration, **TEACHING POINTS** are provided. These **TEACHING POINTS** include a list of things which the physician-defendant can do proactively at each stage of the litigation to assure himself or herself that everything which can be done in his or her defense is being done, and that his or her defense is not unwittingly being compromised.

Preparation: The Key to Success

The probability of a successful defense to any claim rests first on the underlying medical facts. Though relatively rare, true, "indefensible" surgical misadventures occur. Wrong-site surgery is one, for example. In such cases, the relevant medical facts may not be in dispute. If a claim arises from

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the occurrence of a true surgical misadventure, it may be prudent to posture the matter toward settlement from the outset. But even in these situations, understanding the entirety of the process, and advance preparation for it, remain critical.

Even if the case involves an admitted surgical error, it remains important for the physician and the lawyer to be cognizant that the litigation process for the physician likely will not end with settlement of the claim with the patient—there is still the matter of a possible future investigation of the case by the state medical board. In such a case, the physician might appropriately ask whether or not the *best result*, when consideration is given for potential medical board investigation, wouldn't be a settlement before a formal complaint is filed, or, if the complaint is already filed, before the surgeon or hospital staff is deposed. Preparation in this setting would include an early consultation with counsel to discuss the ramifications to you personally and professionally of an early settlement versus proceeding to protracted litigation.

In the great majority of cases, however, the facts are disputed. The dispute may or may not involve what happened in surgery. The disputed facts may include the indications for surgery; the consent discussion; pre-operative knowledge of the patient's relevant medical history, laboratory values, medications, or other contra-indications; the substance of discussions with other medical providers, referring physicians, nurses, or radiologists; the existence of alternative therapies or surgical approaches; or the patient's post-operative course.

The reality of litigation is that the "facts" of a case are what the jury says the facts are on its verdict form. Until that moment, there are no facts, there is only evidence of facts. In coming to its verdict, the jury determines the facts after balancing the evidence presented at trial, giving weight to the evidence on either side of an issue as the members of the jury, individually and in their cumulative wisdom, see fit. Experience establishes that evidence which either side believes to be clearly decisive on an issue, nevertheless, may be marginalized or discarded in whole or in part by the jurors.

Effective litigation requires effective accumulation of evidence and effective presentation of that evidence. Effective accumulation and presentation of evidence requires thorough and focused preparation. That process begins at the initial meeting between the lawyer and the physician-defendant, if not sooner, and continues through the conclusion of the litigation process.

There are certainly many aspects of the process over which the physician-defendant may have little or no control, but it remains incumbent for the physician to recognize those aspects of his or her defense that he or she can affect, and to do whatever is necessary to achieve the *best result*.

Stages of the Litigation Process

The litigation process can be divided into three stages:

1. Initiation of the litigation process
   (a) Notice of an occurrence likely to lead to litigation;
   (b) Notice of events which suggests that litigation is imminent: Handling requests for medical records;
   (c) Service of the summons and complaint: Initial meeting with counsel;
2. The discovery process
   (a) Written Discovery;
   (b) Your deposition;
3. Trial

Initiation of the Litigation Process

Notice of an Occurrence Likely to Lead to Litigation

The litigation process may commence in a number of ways. First among them is the unexpected occurrence of something adverse to your patient.

Something happens during surgery or in the post-operative period which you believe may lead to a lawsuit. For example, at surgery, an adjacent organ or vessel is punctured; there is profound blood loss or spillage of bowel contents resulting in significant compromise; or there is even an unexpected patient death. In the immediate post-operative period, or even after discharge, the patient becomes septic and decompensates. Imaging demonstrates a previously unappreciated rent in the bowel. The patient is taken back to surgery at which time the rent is identified and repaired, but the patient has a rocky course. Or, several months or even years after bowel resection surgery you notice, for the first time, that the pathology report had identified a potentially malignant lesion for which no additional investigation was conducted.

In these instances the litigation process may be said to be initiated by you, in anticipation of litigation. When these adverse events occur, the important thing for you to recognize is that there are pre-existing protocols and procedures in place for you to access which have been established for just such events. The purposes of those protocols and procedures are twofold: (1) to accumulate and preserve the necessary evidence about the event in a timely manner, and, (2) as appropriate, to protect the evidence from undue disclosure to the opposition by veiling it within the cloak of one or more legal privileges.

Know the reporting procedures for significant clinical events of your hospital, your medical staff, your risk management department, and your malpractice insurance company. These will typically include voluntary or mandatory incident

reporting which are in place for purposes of quality assurance or for reporting of events which will likely lead to litigation.

Although evidentiary rules vary among state and federal jurisdictions, as a general proposition, when a hospital, medical staff, or even an insurance company has in place a pre-existing procedure for reporting such events for quality assurance purposes, any statement or disclosure made in furtherance of that purpose of quality assurance is privileged from disclosure as a matter of public policy [3]. Likewise, statements made to a risk management department or to an insurance company representative in anticipation of litigation are typically protected from disclosure by the attorney work-product privilege (which is different from the attorney-client privilege).

Whether either of these "pre-litigation" privileges will apply to a physician's disclosure depends on *why* the disclosure is being made. For example, the quality assurance privilege belongs to the hospital or its medical staff. The hospital or medical staff is deemed the "holder" of the privilege. It is the hospital and medical staff's obligation to conduct periodic and incident reviews of its staff's conduct and to investigate significant or "sentinel" events. To fulfill those duties, the hospital and its medical staff have procedures in place for these events to be reported. The goal of these procedures and the attendant privileges is to promote candid disclosure and discussion, which may be adversely affected if the participants are fearful that any statement made can or will be used against them later in litigation—thus the privilege. Therefore, *if the reason* the physician discusses or reports an event is pursuant to pre-existing hospital protocol to ensure that an adequate investigation of the event occurs, the physician's disclosure is deemed to be in furtherance of the quality assurance process; and, generally, that disclosure will be protected from later discovery. Application of the privilege depends on the physician's mindset when the statement is made.

Teaching Points

1. By knowing the hospital's or medical staff's quality assurance and reporting procedures a physician can tailor his disclosures, and, later, his deposition testimony to be consistent with those procedures. At deposition,

   Q. "Did you discuss what happened in surgery with anyone?"
   A. "Yes."
   Q. "With whom?"
   A. "I told the operating room supervisor and the chairman of the department."
   Q. "Why them?"
   A. "Because I understood that the hospital quality assurance department requires that these kinds of events be reported and investigated."
   Q. "What did you tell them?"

   By defense attorney:
   "Objection, quality assurance or peer review privilege."

Unless the physician understands that such procedures exist, and knows the reporting requirements of those procedures, the physician may not be prepared to provide the necessary foundation to invoke the privilege. The foundational question to establish the privilege is: "Why did you make the disclosure?" The foundation for the quality assurance privilege is established if the disclosure was made in furtherance of an existing and known hospital or medical staff policy.

Similarly, in anticipation of litigation, malpractice insurance organizations and risk management departments have procedures in place for the physician to report adverse occurrences so that an investigation into the matter can occur while memories are fresh and potential witnesses and other evidence is available. The purpose of these pre-litigation procedures is to accumulate reliable evidence which, if litigation does ensue, can then be produced to the assigned counsel to promote the physician's defense. The rationale of these pre-litigation reporting procedures is that it is anticipated that the physician's attorney will need, and therefore will request from his physician client, a *summary of the occurrence*. This request for a summary of the occurrence will be better served if the summary is prepared soon after the event. Memories fade. Reports made to the insurance company early, without waiting for a formal claim to be made, may be more reliable. Thus, insurance companies have established early reporting procedures in anticipation of the attorney's needs. It is recognized at law that the insurance company collects these pre-litigation reports in furtherance of the physician's defense as an ostensible agent for, and on behalf of, the attorney—even though the attorney has not yet been retained.

Because the pre-litigation reports are presumably being collected on behalf of the attorney, the collection of these reports by the insurance company is deemed to be the "work product" of the attorney. Although there are exceptions, generally, these reports are protected from disclosure by the attorney work-product privilege, much like disclosures made by the physician directly to the attorney are protected by the attorney-client privilege.

Summaries prepared by the physician on his own, outside of the medical chart, may be protected if, but only if, the summaries are being made in anticipation of a request from the malpractice insurance company, or in anticipation of a request directly from the attorney, and are kept confidential.

Teaching Points

1. To avoid question as to why you are preparing a summary of the events outside the medical chart, and thus to bolster your position that the summary is protected by the attorney work-product and attorney-client privileges, begin the summary with, "The following summary is being prepared in anticipation of litigation, to be provided to

my attorney when litigation commences." Ask your malpractice insurance company if it has forms for you to use for such a purpose.

Caveat

1. Privileges can be waived. Summaries prepared in anticipation of later disclosure to the attorney can only be protected if they are kept confidential. Disclosure of the summary to others who are not in the line of communication with the insurance company or attorney likely will waive the privilege. For example, placing the summary in the patient's hospital or office chart, where it is open to review by hospital or office staff, defeats the presumption of confidentiality. The summaries must be kept separate and apart from the chart and may not be disclosed to others.

Teaching Points

1. By knowing the malpractice insurance company's procedures for collecting statements from its physician insureds, the physician can anticipate that request, and prepare a summary in a timely manner. By knowing that the statement must be kept confidential, the physician can take appropriate steps to assure that the statement is not disclosed to others or placed in the patient's chart. At deposition,

   Q. "Did you prepare a summary of the events?"
   A. "Yes."
   Q. "When?"
   A. "The day after the surgery."
   Q. "Where is the summary?"
   A. "I gave it to my insurance company."
   Q. "Did you keep a copy?"
   A. "Yes."
   Q. "Have you shown it to anyone else?"
   A. "Yes."
   Q. "To whom?"
   A. "To my attorney."
   Q. "Have you shown it to anyone else?"
   A. "No."
   Q. "Where is your copy?"
   A. "It is in a locked drawer in my desk."
   Q. "Why did you prepare the summary?"
   A. "I was told by my insurance company that when unexpected adverse results occur I should prepare a summary of the events and maintain it confidentially for later use by my attorney."
   Q. "Show me a copy of the summary."

   By defense attorney:
   "Objection, attorney work-product and attorney-client privilege."

   The work-product privilege may also apply to discussions among the physicians in a group practice, if the statements are made in furtherance of an established (and preferably written) pre-existing policy of the group which provides that such events are to be reported to the president or general partner of the group, so that they can then be reported to the malpractice insurance company or the group's attorney.

Notice of Events Which Suggest That Litigation Is Imminent: Handling Requests for Medical Records

You may be placed on notice of ensuing litigation for the first time by the patient or her attorney requesting a copy of her medical records from you (as opposed to asking that a copy of the records be provided to another physician for future care), or by the patient asking that a copy of her records be sent to an attorney. These requests must be handled carefully and consistently. The response to the request should include everything that is being requested. If requested, this must include the entire record. Once litigation ensues, you will be asked again to produce your records. The record produced then will no doubt be compared to the record produced to the patient when first requested. Any difference will need to be explained. Additions or deletions to the record which are found in the later production can be devastating to your case.

The law allows the patient to obtain a copy of his medical record from his physician. This may seem to be a simple task; yet, the prevalence of electronic medical records (EMR) has made this task anything but simple. To respond to a request to produce the office patient chart from an EMR, the medical record is "created" by someone sitting at a terminal and choosing which screens to print. That person decides what is, or is not, part of the record. The terminal operator will decide whether to include clinical notes, referral, demographic, or insurance information; and, data imported from outside sources (e.g., operative reports or consult notes from referring physicians or hospital consultants). The terminal operator will decide whether to include billing information or scheduling information.

The operator will also decide whether or not to include metadata. Metadata, or "data about data," exists in the EMR at several levels. The clinical record reflects the substance of the medical record entry—a history taken or examination findings. The metadata will include an entry log for that data, including when it was entered and by whom. At another level the metadata may include a "comments" section for the entry. Consistent production of records requires a consistent definition of what is part of the patient's "medical record," as opposed to what is merely part of the office "administration" record. The production request and/or the laws of your jurisdiction will define the scope of the request and, therefore, will define the scope of the physician's obligation to search for, create, and produce the "medical record."

In the context of litigation, a party or his custodian of records will be asked to verify under penalty of perjury that the records produced in response to the request are a true and complete copy of the entire record as requested. That verification serves the formal evidentiary purpose of certifying that this is the complete record and that it may be used as such by any party to the litigation from that point forward, up to and including at trial. You or your staff may be questioned about the production or about any perceived inconsistencies or inadequacies of the production in deposition or trial. To be an effective witness, you and your staff must be able to rely on the production. Effective preparation to be an effective witness on this issue requires that consistent procedures be in place and followed.

It is also important that there be a process in place by which the physician is notified that a patient has requested her own records, or has requested that a copy of the records be provided to an attorney. In that case the physician should acquaint himself or herself with the patient to determine, at least preliminarily, whether this patient suffered an unexpected complication that could reasonably lead to litigation. If there is concern about litigation, it is prudent for the physician to contact his insurance company or attorney and ask for direction.

Teaching Points

1. Have a formal, written procedure in place which defines the scope of your medical record for purposes of responding consistently to medical records requests on a day-to-day basis. Speak with your attorney to learn exactly what you are obliged to produce in response before you respond to a medical records request made in the context of active or anticipated litigation.
2. Systematically check to confirm that your policy is being followed consistently.
3. Be sure that whoever verifies the response knows the office practices for "creating" the medical record, and can appropriately verify that the procedures have been followed.

Service of the Summons and Complaint: Initial Meeting with Counsel

The formal civil litigation process starts when the patient files a complaint, has a summons issued, and personally serves the summons and complaint on the physician, giving the physician notice that he has been sued. The procedural requirements relating to how specific the allegations of the complaint must be vary widely depending on the state or federal jurisdiction in which it is filed. Local rules may require that the complaint be specific and detailed, and that it be verified (sworn to under penalty of perjury). More often the procedural rules only require that the complaint be specific enough that it identify who the plaintiff is; who the defendants are; the relationship among the plaintiff and defendants that creates the duty or obligations among them out of which the claim arises; the manner in which the duty was breached or the obligations unsatisfied by the defendant(s); a statement relating to the classification of injuries suffered; and a statement, or prayer, at the conclusion of the complaint outlining the categories of damages sought.

In a medical malpractice case, the plaintiffs named will include the patient and/or affected family members. The defendants will include any one or more of the healthcare providers who attended to the patient's care, and typically will include the facilities where the care was provided. The healthcare providers may include the individual physicians, the physicians' corporate or partnership entities or groups, and the physicians' attendant staff, such as nurse practitioners or physician's assistants. In appropriate cases, defendants may include medical instrument manufacturers or suppliers.

The required statement of the relationship among the parties which creates the duty or obligation may be general ("The defendants and each of them undertook to provide the patient's medical care…"), or it may be specific ("On or about January 1, 2015, Dr. A performed a colectomy with anastomosis…").

The statement outlining the breach of that duty may also be general or specific. The statement must, however, provide the defendant with notice of the classification of wrongdoing which the plaintiff is alleging. The classification of wrongdoing is called a *cause of action*. In most cases the cause of action stated is medical negligence, or medical malpractice.

Extraordinary causes of action may also be alleged, and there may be subtle differences among the causes of action which are important to recognize. For example, in most jurisdictions, failure by the physician to obtain the patient's "informed" consent prior to surgery is a type or subcategory of negligence. The complaint may set out a separate cause of action for failure to obtain informed consent, but in reality, this is a specification of the allegation of negligence. The elements of the cause of action and recoverable damages mirror those of a medical negligence cause of action.

A claim for failure to obtain "informed" consent must be distinguished from an alleged failure to obtain the patient's consent to perform the surgery which was performed; or a claim that the surgery that was performed was substantially different from the surgery to which the patient consented. Performance of a surgery without actual consent is battery, an unconsented to touching. The allowable damages in a battery cause of action can be substantially different from the damages allowed in a negligence claim. Damages in a battery cause of action may include punitive damages, awarded to punish the defendant rather than to compensate the plaintiff.

In most jurisdictions, battery is considered an intentional tort. The claim of battery in the complaint may create significant insurance coverage issues, as your medical

malpractice insurance contract may contain an exclusion for intentional tort claims. The laws of your jurisdiction may not allow an insurance company to indemnify you for damages awarded for battery, or for any other cause of action for intentional torts.

Similar concerns arise relating to claims couched in terms of fraud, concealment, or intentional infliction of emotional distress. For example, a patient might allege that the physician fraudulently concealed from her the injury to the adjacent organ which occurred during the surgery. Is the plaintiff alleging mere medical negligence, or is she claiming fraud?

Usually, the caption of the complaint will list the causes of action which are contained within the body of the complaint, but this isn't always true.

The allegations of injury, likewise, may be specific or general, depending on the jurisdictional procedural requirements and the plaintiff's lawyer's preference. The categories of injuries suffered generally include general damages or non-economic damages for physical or emotional injuries (e.g., pain and suffering); and special damages or economic damages for calculable injuries for past and future medical expenses, and/or for past and future loss of earnings, earnings capacity, or financial support. In the appropriate case, future medical expenses may include the cost of medical monitoring; for example, when the claim is based upon a delayed diagnosis of cancer for which monitoring for recurrence is advised. Each of these categories of damages are classified as compensatory damages–damages awarded to compensate the plaintiff for actual loss.

The classification of damages is important, especially as between general/non-economic damages, such as pain and suffering, and special/economic damages for specific, calculable economic losses (medical expenses and loss of earnings). In several jurisdictions, the classification of damages will determine whether the plaintiff's recovery is "capped" or limited to a specific maximum number as a matter of statutory law. The statutory maximums usually apply only to general, non-economic losses. Likewise, a defendant's liability for damages may be limited to his or her proportionate fault for general, non-economic damages, so-called *several liability*; whereas each defendant who is held liable at all or in any proportion (even 1 %) for *all* of the damages awarded to the plaintiff for special, economic damages, so-called *joint liability*.

When extraordinary causes of action are included in the complaint (e.g., to include claims of willful misconduct such as battery or fraud), the categories of damages requested may be expanded to include punitive damages. Like criminal penalties, punitive damages are awarded to punish the defendant financially, with the secondary effect of deterrence of similar conduct in the future. To punish or deter, the damages must "hurt." Thus, the damages awarded must be in some proportion related to the defendant's wealth. The defendant's income and total financial assets become relevant; and, therefore, at some point during the trial the court may require the defendant to disclose his personal financial information to be used by the jury to calculate just how much must be awarded in punitive damages against that defendant to serve the purposes of punishment and deterrence. Moreover, it is because punitive damages are imposed to punish and deter *the defendant* that public policy precludes an insurance company from indemnifying the defendant from such damages.

The presence of extraordinary causes of action within the complaint creates insurance coverage issues and potential personal financial exposure for the defendant physician. The physician needs to be counseled early on in the litigation about these possible ramifications, so that the issues can be managed effectively.

Once the complaint is filed, a summons is issued. The right of the court to "summon" citizens to answer charges brought against them is rooted in the procedures of English common law. A defendant is deemed "summoned" to respond after proper service of the summons and complaint. The methods of effective service and the time and manner in which the served defendant must respond are established by the state's local procedural laws. The time in which to respond begins to run once the summons and complaint have been served on the defendant.

The complaint will identify each of the defendants who are being sued, but it is the summons which identifies who, among the defendants, is being served, and, therefore, who is obliged to respond. For example, the complaint may name as defendants an individual doctor, the doctor's personal corporation, and the doctor's practice group. That's three different defendants. To effect service on each of the three defendants, the plaintiff will have issued and served three different summonses.

If you practice as an individual doctor, and have established a personal corporation (e.g., Dr. Smith, Inc.), and practice as part of a group practice, and you are sued in each capacity, you may be served three different times. You will receive three summonses, which may appear identical, except that on one line, which identifies "person served," the wording will be slightly different. A separate copy of the complaint will be attached to each summons. Your attorney will need to obtain copies of all three sets of documents, even though they may appear identical to you. Keep all documents with which you are served, and forward each set of documents to your insurance company or attorney as soon as you receive them.

The time allowed for the defendant to file responsive pleadings is short, usually 30 days or fewer from the date of service of the summons and complaint. Before responding to the complaint, the defense attorney must analyze the complaint, and the relevant facts and law to determine, among other things:

- Who has been sued?
- Have the defendants been properly identified?
- Was the complaint timely filed, or is it potentially barred by the statute of limitations?

- Has the complaint been timely and properly served, and upon whom?
- Are the causes of action adequately pleaded?
- Does the complaint raise extraordinary causes of action, which require special handling or counseling?

Based on this analysis, the defense attorney will determine whether a routine response, an answer to the complaint, is appropriate, or whether a more involved pleading is necessary to challenge the scope or validity of the claims being made. This analysis and the preparation of a formal response by the attorney take time. The time allowed by law is short, so the process must begin as soon as possible. This requires that the physician notify his attorney or insurance company of the service of the complaint as soon as possible.

Teaching Points

1. You and your office need established procedures to handle legal documents and filings.
2. When a summons and complaint is received, keep the envelope in which it was served.
3. Make a notation of when specifically (date and time) it was received, and how it was received (by mail or in person).
4. Look on the summons to determine who has been served (the doctor, the doctor's corporation or the practice).
5. Notify your insurance company or attorney immediately, and provide a copy of the summons and of the complaint to them.
6. Review the complaint to determine whether any extraordinary causes of action (anything besides medical negligence or wrongful death) are listed on the first page of the complaint.
7. Look at the last paragraph of the complaint, the prayer, to determine which categories of damages are being requested.

If you haven't heard from an attorney within 10 days of providing a copy of the complaint to your insurance company, contact the insurance company to identify who has been retained on your behalf. Request that the attorney contact you immediately to discuss any concerns you may have about the timeliness of the complaint and the proposed response.

1. Confirm with the attorney that an appropriate and timely response has been or will be made on your behalf.
2. Confirm that an appointment with the attorney is made, and ask what you need to have available at that first meeting.
3. Create a file separate and apart from your medical chart, and keep a copy of the complaint and any other legal correspondence in that separate file. This is also where you should keep any summaries you may have created in anticipation of litigation.
4. Do not speak with anyone (including your partners or office staff) or do any independent research relating to the case, until you have received direction from your attorney.
5. Do not alter or supplement your records in any way; ***I repeat, do not alter or supplement your records in any way***.

The attorney's first task is to acquire a very basic understanding of the nature of the claim and to respond to the complaint. The procedural rules of the jurisdiction will dictate how specific the response or answer to the complaint must be, just as the rules define how specific the allegations of the complaint must be. The rules may require a point-by-point response admitting or denying each allegation contained in the complaint or it may require that the defendant merely file a general denial—a summary statement denying each and every allegation of the complaint without specification. Some jurisdictions require that the defendant verify the pleading by signing the answer under penalty of perjury, confirming that the admissions or denials contained in the answer are true.

A point-by-point response may be a time intensive process for the attorney and the physician-defendant, as each allegation is considered in light of the then-known information. It may require more than one conference and sifting through medical records. On the other hand, if only a general denial is required, the physician may play no role whatsoever in preparation of the responsive pleadings. The pleading requirements of the jurisdiction should be part of the initial contact between the attorney and the physician, so that the physician will know what is expected of him in this process.

In general, the responsive pleadings will serve to notify the court and opposing counsel that the defendant denies any wrongdoing, that the defendant disputes that anything he has done or failed to do has caused any injury to the plaintiff, and that the nature and extent of any injury alleged to have been suffered is disputed as well. In other circumstances, the responsive pleadings may set forth a legal challenge to the form of the complaint or the adequacy of its allegations to support the cause of action alleged. It may challenge the timeliness of the claim, with a contention that the allegations within the complaint itself establish that it is barred by the statute of limitations. It may challenge the right of the plaintiff to seek extraordinary damages such as attorney's fees or punitive damages, if the complaint contains prayers for these categories of damages.

Successful initial legal challenges to the complaint are rare. The overwhelming public policy is that all factual disputes between the parties are to be decided by a jury, in a trial, after the parties have had an adequate opportunity to conduct discovery in preparation for trial. Judges don't determine what the facts are, juries do. Judges decide what the law is and apply the law to the facts as determined by the jury. Therefore, in deciding whether to sustain or overrule an initial challenge to the complaint, the judge may not adjudicate any factual dispute. The judge must accept as true what is alleged in the complaint. A defendant's legal challenge is

sustained only if, "accepting everything alleged in the complaint as true," the defendant's challenge is still valid.

This legal standard is particularly frustrating to defendants when the complaint includes allegations which are patently false. The plaintiff alleges that the physician undertook the subject surgery without his informed consent, without discussing the risks, benefits or alternatives, and alleges further that if she had been told that there was a risk of injury to an adjacent organ she never would have consented to the surgery. You recall specifically speaking to the patient about the massive adhesions you expected to encounter and the attendant risks of injury to adjacent organs. You recall discussing the relative advantages of laparoscopic versus an open laparotomy approach, specifically as regards potential injury to adjacent structures. Your office medical record for the preoperative encounter includes a detailed note in your own hand outlining your discussion of these very risks and alternatives. Your chart includes a two-page detailed consent form which you and your partners have developed over the last 15 years, outlining the specific risks and alternatives, initialed by the patient in three different places, signed and dated by the patient and an office staff member. There is a similar document signed by the patient in the hospital. Yet, your lawyer tells you, and correctly so, that you have no right to bring this evidence to court at the pleading stage to challenge the complaint. She tells you that despite all existing evidence to the contrary, because the complaint says that you didn't obtain informed consent, the judge (as opposed to the jury) must accept as true that the issue of informed consent is in dispute, and this issue cannot be decided by the judge at the pleading stage.

Your patience will be similarly tested repeatedly throughout the litigation process. You will repeatedly inquire, "What's going on?"; "Why is this taking so long?"; and "Why hasn't this ridiculous case been dismissed already?" You will be told, "These things take time"; or, "It doesn't work that way"; or "There's nothing else we can do for now."

You've read in the complaint that you are being sued for unspecified amounts, based on what you know, or at least perceive, to be unfounded allegations, and now your lawyer is telling you that there is nothing you can do about it "for now." Rather, you must wait until the case or any issue in it is ripe for adjudication, and this may not be until trial. You are overcome by an overwhelming since of frustration, and justifiably so.

The frustration quotient establishes:

$$\textbf{FRUSTRATION} = \frac{\textbf{RESPONSIBILITY}}{\textbf{AUTHORITY TO ACT}}$$

To avoid frustration in any situation it is imperative that someone who bears the responsibility for an outcome should also have the authority to act as to effect a *best result*. The king was rarely frustrated. He could simply deny responsibility for anything while maintaining complete authority over the kingdom and his subjects. Surgeons undertake great responsibility for surgical outcomes and patient well-being. Their frustration level is manageable because, generally, the surgeon has the authority to act to effect a positive surgical result. That is the circumstance to which the surgeon has become accustomed. The duty and authority to act to fix the problem is ingrained in the very being of a surgeon, and is the only way to avoid intolerable frustration.

On the other hand, surgery and the healing process can be terribly frustrating for the patient, who perceives herself to be helpless and totally dependent on you for her care. To help reduce that frustration it is incumbent on the surgeon to educate the patient to manage expectations and to maximize her chance for a favorable outcome. The patient must be told in advance for how long she will be bedridden or unable to return to her activities of daily living, and what she can do to accelerate her healing process.

In litigation, the physician-defendant's authority to act is muted by the procedural processes. Initially, the physician-defendant may feel helpless and totally dependent on his attorney. Frustration abounds.

What can you do? Just as you educate your patients so that they can manage their anxiety and frustration, you must seek to educate yourself about the litigation process and manage your expectations and efforts accordingly. This can only be accomplished with an open dialogue between attorney and client. While you may not be able to run to court and protest your innocence, you don't need to sit by idly either. Speak with your attorney. Know what your role is; learn what will be expected of you and when; ask what can you do to best prepare yourself to succeed in your role; and, as importantly, ask what you should avoid doing so as not to inadvertently undermine your case.

There *are* things for you to do to achieve your *best result*. You have the authority to prepare yourself as directed, and to manage your own expectations within the parameters of the process. This can and will reduce your anxieties and frustration level.

Teaching Points

1. At the initiation of litigation learn what you can do affirmatively to achieve *your best result*.
2. Speak with your attorney early. Ask whether he intends to challenge the legal adequacy of the complaint. Ask what you need to do "now." What information and records need to be assembled? This not only includes medical records, but also increasingly includes fax, e-mail, and office telephone or cell phone billing records to establish the existence, date, time, and substance of communications between you and the patient or hospital staff.
3. Learn how long the process is expected to take. The estimate you receive may be broad, but it will provide you with some reasonable expectation. Tell your attorney how you would prefer to be contacted: office or personal cell

phone. Tell your attorney what mailing address to use: office or home. Tell your attorney whether there is someone in the office other than yourself who can be contacted regarding the case, e.g., an office manager, or if all communication should be with you only.

4. Ask when it will be necessary for you to be personally involved? Are there court hearing dates or deposition dates pending at which you must appear? Is a trial date set? If not, find out how much notice will be given to you when your personal attendance is necessary. Tell your attorney about any plans you have to be out of the area for any significant period of time for vacations or conferences. Update your attorney when new plans are made or when plans change.
5. Be patient! This will take time.

The Discovery Process

Written Discovery

In most jurisdictions, claims for medical malpractice are resolved in a jury trial. From the time the complaint is served on the defendant until jury selection is commenced, the parties to the lawsuit and their attorneys participate in a formalized accumulation and exchange of information which ultimately will be used at trial to educate the jurors about the relevant facts of the case. This is the discovery process.

To conduct discovery, the attorneys invoke legally sanctioned discovery procedures and the authority of the court to enforce those procedures, including the court's subpoena power. Basically, the law allows a party to subpoena or formally request relevant documents, such as medical records or employment records. The law allows parties to serve written inquiries to opposing parties, usually in the form of written questions called interrogatories. Most importantly, the law allows parties to interview opposing parties or witnesses under oath by way of deposition.

The procedural law of each jurisdiction sets forth in detail the manner in which parties may conduct this discovery. What the physician-defendant needs to know is that the discovery process is to be taken seriously as it has serious consequences.

Any party to a lawsuit may request information from any other party in the form of written interrogatories. The process is controlled by local rules of procedure. Some jurisdictions have created form interrogatories approved by the judicial council of that state. The form interrogatories cover a wide range of topics, which may or may not be relevant to the specific case. The attorney who propounds the interrogatories (i.e., asks the questions) simply checks the boxes on the form relating to the questions to be answered. The rest of the questions on the form can be ignored.

Other jurisdictions do not have judicially approved interrogatories, so that the attorney propounding the interrogatories must formulate the specific questions. Jurisdictions which use judicially approved interrogatories allow the propounding attorney to supplement the judicially approved interrogatories with special interrogatories, specifically drafted by the attorney, but maintain limitations and rules of procedure to do so.

By using judicially approved form interrogatories, the propounding party avoids objections as to the form of the question (e.g., vague, ambiguous, overbroad), which streamlines the process substantially.

The scope of the inquiry allowed by interrogatories is extremely broad. It includes personal and biographical data, insurance information, factual data relating to the underlying occurrence and medical care, information relating to potential witnesses, and to legal issues such as contentions of negligence, causation or damages, or affirmative legal defenses such as the statute of limitations.

Interrogatories are directed from one party to another. Although the interrogatories are directed to a party, the interrogatories are deemed to be directed to the party's attorney as well. The responding party is obliged to include within his response non-privileged information which is known or reasonably obtainable by the party "by inquiry to other natural persons or organizations, except where the information is equally available to the propounding party" [4]. Therefore the response must include information which the responding party may obtain by a reasonable inquiry to his office staff and his attorney. The responding party and his attorney are required to make a good faith search through the medical chart, the physician's personal files, and the attorney's files.

The local rules of procedure dictate the form of the questions and the timing and form of the response. Typically, the responding party must serve the responses within 30 days of his attorney's receipt of the questions. A party may request an extension of time within which to respond. The extension can be obtained by mutual agreement of the parties, or, if necessary, by the responding party's going to court and requesting a court order granting additional time by which to respond.

Within the time allotted to respond, much must be accomplished. The good faith inquiry necessary to respond should begin immediately. As the physician-client, you can expect your attorney to have in place office procedures to notify his clients immediately when interrogatories are served. That notification should include a copy of the interrogatories and clear instructions regarding the division of labor: which of the interrogatories the attorney is going to answer, and for which of the interrogatories the attorney is requesting assistance from the physician-defendant.

The notification from the attorney should also include a timetable for the response. Generally, the attorney's notification will include a date by which the physician's preliminary responses are due to him. The attorney may also ask the names of key office personnel who may be the source of additional information. There should be an agreement between the attorney and physician-defendant specifying who will be in contact with these additional personnel.

In each case, confidentiality must be maintained. Any person contacted must be told not to discuss the conversation or inquiry with anyone outside of the office management staff, the physician, the attorney or the attorney's staff.

The attorney will organize the information from each of the sources and will draft formal responses to the interrogatories. These responses may include both objections to the interrogatories and answers to the questions. Once the responses are prepared, the responses will be presented to the physician-defendant for verification.

A verification is a signature by the responding party, made under oath or penalty of perjury, which, depending on local rules, may or may not need to be notarized. The signature attests to the accuracy and completeness of the information contained in the response, at least to the best of his or her knowledge.

Once verified, the responses become affirmative statements of the responding party. The other parties to the litigation may justifiably, and legally, rely on the responses as being complete and accurate. The parties may use the responses for any relevant purpose in the litigation, up to and including trial. In some cases, the response to an interrogatory may be used as an admission against that party, and can be presented to the jury as such at trial.

One important purpose of interrogatories is for the propounding party to inquire about additional potential sources of information. This could include the names of potential witnesses or other sources of documents and records. The propounding party is entitled to rely on the response to include a complete list of these additional sources, to direct further discovery efforts.

Local rules of procedure provide sanctions and other consequences for a party's failure to provide timely and complete answers. For example, objections contained in the response may be deemed waived as a matter of law if the response was not served timely. Likewise, if the interrogatory has asked for the identity of witnesses (which could include office or operating room staff or assistants), and the responding party has failed to identify a specific potential witness, either out of inadvertence or because of a failure to conduct a good faith inquiry into the records, the responding party may be barred from producing that witness at trial.

It is rarely acceptable to simply respond that the requested information is equally available to the propounding party through alternative means (e.g., looking through the hospital records himself).

As with all aspects of the litigation process the interrogatory process may be time-consuming, and burdensome. But it must be taken seriously. Inadequate or inaccurate responses will be detrimental to your defense.

Teaching Points

1. Expect that you will be asked to answer interrogatories.
2. Expect that your responses will need to include biographical and personal data from you.
3. Expect that you will be asked to include the names of witnesses to the occurrence including relevant office staff, hospital staff, assistant surgeons, anesthesiologists, and consultants.
4. You don't need to wait until you are served with interrogatories, and the time period for responses starts to run, before you begin compiling the necessary information. At your initial meeting, ask your attorney if your jurisdiction has judicially approved form interrogatories which are used by attorneys in that area; or if there are other interrogatories which you likely will be asked to answer. Obtain a copy of the anticipated questions, and begin immediately to compile proposed responses. If the opposition will want this information, your attorney should have it as well, and soon.
5. Obtain assurance from your attorney that you will be notified as soon as interrogatories are served, and that the notification will include the date by when your preliminary responses will be expected. You also have the right to expect that your attorney will anticipate the need to respond to interrogatories, and will have begun a search of the relevant data sources in advance of the interrogatories being served. You also have the right to expect that your attorney will provide you with the proposed formal responses with sufficient time in advance of the deadline to respond so that you can go through the questions and answers with your attorney before you sign the verification.

You can expect that at deposition or trial your responses to the interrogatories will be presented to you. You will be asked to confirm that the verification includes your signature. You will be asked about the scope of your inquiry before providing the responses, and whether you read and considered the responses before verifying their accuracy under penalty of perjury. Therefore, conduct a good faith and thorough search in providing responses; and read and understand your responses before signing the verification.

There are other kinds of written discovery as well, such as requests for admissions, requests for production of documents (e.g., insurance policies, office protocols, licenses, and certifications), or requests for authentication of documents. In each case, the procedures are similar to responding to interrogatories. Be sure that you understand the time parameters for response and the scope of inquiry which is necessary, and that you have reviewed the proposed response before signing the verification.

Your Deposition

Unquestionably, the most important aspect of pre-trial discovery for the physician-defendant is the deposition. Giving an effective deposition requires effective preparation, and you have the right to expect that your attorney will aid you in that preparation. It is likely that your attorney attends depositions weekly, if not more frequently. He may have represented physicians at deposition hundreds of times or more.

He may be completely comfortable with the process. But this is *your* deposition.

The situation is analogous to taking a patient to surgery. As an experienced surgeon, you have taken part in hundreds, if not thousands, of surgeries before. You have a well-founded expectation concerning what you are about to undertake. However, this may be your patient's first surgery. As a surgeon you have the responsibility of educating your patient concerning what the patient must do to prepare herself in advance to maximize the likelihood of success at surgery. You must educate the patient regarding what is likely going to occur during surgery, including the risks associated with the process; and, you must provide the patient with a spectrum of potential outcomes so that the patient's expectations will be reasonable. You are the surgeon, but this is *the patient's* surgery.

The first step in preparing for a deposition is to know what a deposition is. A deposition is a recorded question and answer session during which the attorneys for all parties to the litigation, including the opposing party and all co-defendants, have the right to ask you questions. The scope of questioning is extremely broad. As a general rule the witness may be asked questions concerning any topic which might be directly relevant to the case, and concerning any topic which might be reasonably calculated to lead to the discovery of relevant evidence. In short, this is the one time that the parties are entitled to conduct a "fishing expedition." Be patient. The deposition may take hours, or even days. Your performance in the last one-half hour is every bit as important as your testimony in the first 1 h.

Your deposition may be a videotaped deposition. The party who schedules the deposition will give notice of whether he intends to videotape it. Be sure you know whether it will be videotaped and dress and present yourself accordingly. In your practice, you wear your lab coat, with physician designation. This may or may not be appropriate when presenting yourself for deposition. One issue you will want to discuss with your attorney in advance is what to wear.

The use of videotaped depositions is becoming more prevalent in recent years. I've never thought it necessary for a physician to wear a lab coat in deposition; however, my opinion on this is changing. Jurors are patients. Patients have an expectation of what physicians look like. The videotaping of depositions has two purposes: to intimidate the witness, and to present a video record to the jury at trial. You are a doctor. You have the extensive education, experience, and license to justify your use of the title, "Doctor." Wearing your lab coat at deposition provides an ongoing reminder to the audience or jury that you have earned and maintained that status, and that your testimony should be considered and weighed, accordingly. Being a doctor doesn't necessarily make you more believable; but it should add weight to your learned observations and opinions.

It is unlikely that you will be asked to wear your lab coat at trial. The stark difference between your appearance in a lab coat at deposition and in a suit and tie at trial may make your appearance at deposition seem staged. The decision whether to wear your lab coat, or any other questions regarding your presentation and attire, should be discussed with your attorney. In all cases, you should present yourself in business attire.

A deposition is a "legal," "formal" interview. The legality of the process is established by local rules of procedure. Foremost among them is that prior to beginning testimony, the court reporter, who is a designated officer of the court for this purpose, administers the oath. The words may vary, but the upshot is that you are being asked to swear or affirm that the answers you are about to give in deposition "are the truth, the whole truth, and nothing but the truth…" (Notably, the attorneys who are asking the questions aren't under oath. However, as the deposition is in the realm of judicial proceedings, rules of professional conduct oblige attorneys not to make material misrepresentations of fact or law at deposition.)

At the conclusion of the deposition, a transcript of the deposition will be prepared by the court reporter. It will look like a script. The questioner will be identified, and a verbatim transcript of the question will appear. The question will be followed on the page with your answer. You will be provided with a copy of the transcript. Within the parameters of your jurisdiction's procedural rules, you will have the opportunity to review the transcript and to make any changes to your answers which you believe are necessary to accurately reflect your testimony. (You may not make changes to the questions, although you may note typographical or transcription errors.) Your changes may be to form or substance.

The court reporter may have misunderstood or mistranscribed a word, or may have left out a word which you believe was spoken and which you believe is necessary for the transcript to accurately reflect your testimony. You may make those kinds of corrections.

You may also make substantive changes to your testimony. For example, you may have been asked at deposition whether, before proceeding to perform surgery, you took the opportunity to review the labs or consult notes. Consistent with your customary practices, you may have answered "Yes," to that question at deposition. Upon further review of the chart or upon further reflection after the deposition, it may become apparent to you that one of the consult notes didn't appear on the chart until after you began your surgery, so that, at least as to that consult note, your appropriate response should have been "No, it wasn't on the chart yet."

You may make that kind of substantive change to the testimony, but you must be cautioned that any substantive changes you make to the transcript can be commented upon by the opposing counsel at trial, and you may be asked why you gave a different answer at deposition. These kinds of changes can adversely affect your credibility at trial, and may have an adverse affect on your case. For that reason it is important that you give your best answers at deposition to minimize the need for changes later.

Because substantive changes can adversely affect your case, it is important that you consult your attorney before marking or making changes on the original transcript. A good practice is to make any proposed changes on a copy of the transcript or a different piece of paper and then to preview the proposed changes with your attorney before they are finalized.

Once you have reviewed the transcript, and made any changes you deem appropriate, you are asked to sign the deposition under penalty of perjury. Your signed deposition transcript becomes your testimony, for the trial and for any other subsequent legal proceedings. (In some jurisdictions, there are provisions for use of an uncorrected or unsigned certified copy of the deposition as if it were a signed and corrected original. These provisions may apply if you or your attorney have not notified the court reporter or the parties of any proposed changes within the time limitations provided by law, or, if the signed original hasn't been returned to the court reporter within the time frame allotted by law.)

Because the deposition is a legal proceeding, you have the right to have counsel present. Whether you are being deposed in a case in which you are a defendant, or simply as a witness, it is important that you be represented at the deposition by an attorney. If you are subpoenaed for deposition as a witness in which you are not a party, contact your attorney, risk manager, or insurance company and ask for representation. Too often, a non-defendant witness is lulled into a false sense of security, appears at deposition without an attorney, and, without proper preparation or representation, provides potentially incriminating testimony which provokes the patient's attorney to name the witness as a new defendant in the case. Depositions are too important to be taken lightly. You need proper representation.

It is your attorney's job to prepare you for the deposition and to represent you at the deposition. Preparation is imperative, but it is important that you be guided by counsel in that preparation. As with many aspects of the case, preparation for the deposition begins with the initial meeting. It is very important that you understand what is expected of you in anticipation of your deposition. Know what your counsel wants you to review in preparation for deposition, and what he doesn't want you to review. For example, the case may involve technical aspects of the patient's medical care, such as pulmonary issues or endocrine issues, which you, as a surgeon, may not have studied since medical school. You are familiar with the issues and general management, but not with the current state of knowledge regarding ventilation settings or esoteric thyroid stimulation medications. Before beginning a literature search on these or any issues, be sure that the attorney wants you to do so.

Typically, the attorney will want you to be familiar with the documentation which was available to you at the time of your treatment of the patient, as it would be this information which formed the basis of your differential diagnoses, and your treatment alternatives.

As discussed more fully below, the primary liability issue in a medical malpractice trial is whether the physician's care was negligent, i.e., was it below the applicable standard of care? Though language differs by jurisdiction, basically, the standard of care requires the surgeon to act as other duly competent and careful surgeons would act *under the same or similar circumstances.*

Though seemingly tautological, it remains true that *you* acted as you did under the circumstances which then-existed. Presuming that you are a reasonable and competent surgeon, and accepting that you acted as you did and intended to act, then your conduct under the circumstances that then-existed is, by definition, within the standard of care: You, a competent and careful surgeon, acted as you did, under the circumstances as they actually existed at the time.

It is your job at deposition to fill in the facts necessary for your lawyer to make this argument. You must be prepared to testify to your qualifications and experience, as to establish that you are a reasonable, competent, and careful surgeon. You must also be prepared to testify regarding your knowledge of the facts that existed at the time of your treatment of the patient.

The single most effective way to cross-examine a physician-defendant (or an expert) is to establish that the facts which the physician-defendant believed to be true at the time of his surgery, and which formed the basis of his actions or opinions, were not the facts as they truly existed. In that case, the physician was acting under the facts and circumstances as he *thought* them to exist, not as they, in fact, existed. In that case, the physician loses the value of the tautological argument. Knowledge of new or different facts may not have changed the conduct, but it infuses doubt.

The relevant facts would include the patient's recent and distant medical and surgical history; the existence of any peculiar risk factors, co-morbidities, or contra-indications; recent lab values, imaging studies, or consults; or even something as simple as whether blood had been typed and cross-matched before surgery, and was therefore available immediately, if needed.

By the time the deposition takes place, it is probable that you will have forgotten these details. With your attorney's assistance, refresh yourself, so that when questioned at deposition you can recount your knowledge of the relevant facts as they existed at the time, consistently and accurately. Ask your attorney to provide you with copies of the relevant records prior to the deposition so that you have the time and opportunity to refresh your recollection. But don't access additional records unless and until you are instructed to do so by your attorney. There are specific, strategic reasons for this advice.

In most instances the deposition of the physician-defendant occurs relatively early in the litigation process. The physician-defendant is being deposed as a percipient witness to the occurrences which form the basis of the case. As a percipient witness, the scope of inquiry generally includes exploration of all percipient observations. In the

litigation process, perception goes beyond the primary senses. In addition to what the doctor saw, heard, felt, smelled, or tasted, the physician is in the unique position of knowing and, therefore, to testify to *what he was thinking at the time of the events*.

Typically, inquiry into the physician's contemporaneous thoughts is fair game for deposition. Thus, he cannot only be questioned regarding what he saw or read before surgery, he can also be questioned regarding his decision-making and thought processes. This would normally include any percipient opinions, opinions *which he came to at the time of his care of the patient* concerning what may have caused or contributed to the patient's adverse outcome.

Opinions which are developed based upon supplemented or retrospective analysis of the facts are expert opinions. They differ from contemporaneous or percipient opinions. While inquiry into *contemporaneously developed* thoughts or opinions is considered appropriate during the physician's deposition as a percipient witness, opinions reached since the litigation ensued, or made retrospectively in reconsideration of the circumstances in anticipation of litigation, or in furtherance of the defense, may be handled differently. Again, this is dependent upon procedural differences among the various jurisdictions, but as a general rule, where a physician-defendant processes information in anticipation of litigation, which may include information obtained from the physician's attorney, the conclusions and opinions which are the product of those processes remain the work-product of the attorney, unless and until the physician's status as a witness changes from percipient witness to expert witness. This change in status usually occurs in one of two ways: (1) at the deposition, the attorney for the witness declares his intention to proffer the witness as an expert witness at trial; or (2) during the exchange of expert designations among the parties, the attorney for the physician formally discloses his intention to call his client as an expert. In that case, the plaintiff may have the right to depose the physician-defendant a second time to explore his expert opinions and the bases for those opinions.

Assuming, however, that it is not your attorney's intention to elicit expert testimony from you (or at least he is not in a position to declare his intention to do so on the day of your deposition), then the scope of your deposition will be limited to opinions you came to at the time of your care. In preparing for your deposition, understand the difference between percipient and expert opinions, and whether either or both are subject to inquiry at your upcoming deposition.

At deposition, you will be asked questions concerning your recollection of facts and occurrences. The party asking the questions is entitled to your best current recollection of those facts, even if that recollection is cloudy, vague, or non-specific. In addition, generally, the questioner is entitled to know what documents, if any, you have accessed or reviewed to refresh your recollection. And, he is entitled to question you regarding those documents. For example, you may be asked what the estimated blood loss was during the procedure. You may recall that there was nothing significant about the blood loss, but otherwise you can't provide a reasonable answer. Or, you may have recently reviewed the operative report in preparation for the deposition, and noted that the stated blood loss was actually substantial, and estimated to be 500 ml. Reading and being reminded by this note sparks a memory, and you now actually recall that there was an estimated blood loss of 500 ml.

Arguably, your present testimony of the facts is dependent upon what the operative note says. You may, therefore, also be asked, "If the note had referenced an estimated blood loss of 800 ml, would that have been your testimony?" In other words, did the entry in the chart actually spark a memory from which you are now testifying; or, are you merely accepting as true and accurate what is written in the chart? Are you testifying, or is the chart testifying?

If you are testifying from refreshed memory, you may be asked a series of questions about what it is about this entry that has sparked the memory. If you testify that you are merely accepting what is written in the chart, the follow-up questions may relate to how and when the document was prepared and stored, in an attempt to call into question the accuracy of the document, as opposed to the accuracy of your memory.

For these reasons, the questioner will almost certainly ask you to list all documents reviewed in preparation for the deposition, or documents reviewed to help refresh your recollection of the events. Your attorney is going to want to know in advance of the deposition what you are intending to review or have reviewed; he is going to want to control the universe of information to which you have had access in preparing for the deposition. By doing so, he will have some control over the scope of allowable inquiry.

For example, you may want to brush up on your infectious disease medicine before the deposition, out of fear that you will be asked something in that area of medicine. If you do so, you may be questioned about what you reviewed, and why. The implication may be that if you *now* believe that this information is important for you to know, why didn't you do your homework before the surgery? Don't conduct independent research before the deposition unless you are directed to do so by your attorney; or without first consulting your attorney.

Similarly, it may be that your attorney has provided you with a summary of the records or of the deposition testimony of other witnesses. As a general rule, that information from your attorney is privileged. It was provided to you in furtherance of your defense, not to prepare you for deposition. Know in advance whether you are to review your attorney's correspondence before the deposition; and tell your attorney that you have done so, so that he can be prepared with appropriate legal authorities to support and to invoke the attorney-client privilege in a timely manner.

At deposition, the questioner is entitled to your best estimate of anything that can be quantified. How many surgeries do you do in a year? How long does it typically take you to get to the hospital from your home? How many lap sponges

did you use in this case? How long did it take to perform this aspect of the case, or that aspect of the case?

The questioner is not entitled to your speculation, or to ask you to guess. Often the line between an estimate and a guess is difficult to define. Ultimately, at trial the judge is the arbiter of what information does or does not go to the jury. The first step toward admissibility is for the judge to determine whether the information is reliable. Speculation and guesses typically do not go to the jury because they aren't reliable. Therefore, fundamentally, the difference between an estimate and a guess is whether you have a reasonably reliable basis or evidentiary foundation for your answer. The foundation may include your observations and memory of the case; or, it can be based on your customary practices.

To demonstrate the distinction, a lawyer may ask you to estimate the length of the table in front of you. You don't have a tape measure, but based on your ability to observe the table, and your presumed fundamental knowledge of units of length, you can give an estimate. Your ability to see the table is the foundation necessary to provide your estimate. If you are then asked to estimate the length of the table in the attorney's private office, where you have never been, you lack the fundamental foundation to provide such an estimate. You may have knowledge about how long office tables usually are, but that is not the question. The question is, "How long is the table in this attorney's office?" You don't even know if there is a table in his office. Any answer you might give to that kind of question is pure speculation, and should not be offered. In that case, your answer should be a direct, "I don't know."

This same principle would apply to any question posed to you relating to events or conversations you did not witness. Likewise, you would rarely have a reliable answer to any question relating to the thought processes of other individuals. You may have knowledge of how nurses usually go about taking a history from a patient in the pre-op holding area. However, if asked whether a specific nurse asked a specific patient a specific question in this case, and you weren't there, the answer to that question is, "I don't know, I wasn't there." It is not, "Usually the nurse does ask that question." Let the nurse testify regarding what happened.

Similarly, you may have an understanding as to why a prior surgeon may have decided to do a direct repair of the colon rather than performing a diverting colostomy. Don't guess or presume what he was thinking; let him testify to his rationale. This will minimize the chance of inadvertent conflicts in testimony that could call into question the credibility of both witnesses.

The questions asked at deposition must be fair. To be fair, they must be relatively intelligible and unambiguous. You have the right to understand the question, and to ask the questioner to rephrase a question if you don't understand it. Exercise that right. If you don't understand a question, ask for it to be rephrased until you do understand it. If you answer a question, the presumption at deposition and at trial will be that you understood it before answering.

Ambiguous questions are troublesome. The trouble is that certain words are inherently ambiguous, such that they may have different meanings in ordinary speech as opposed to how they are used in medicine. One such word is "emergency." In ordinary parlance, "emergency" is used to describe a potentially dangerous situation for the patient which may require immediate (another word fraught with ambiguity) action. In surgical scheduling parlance, however, an emergency surgery is any surgery not otherwise scheduled as an elective surgery.

You may be asked whether the surgery you performed was an "emergency" surgery. In fact, the surgery was performed in the early evening after all scheduled surgeries were performed that day. It was performed after all appropriate preoperative testing was performed as to confirm the diagnosis and indications for surgery. It was performed by the operating room staff who were regularly on duty at that time. No one was called in. All typical time and care was taken in preparation of the patient for surgery. In anticipation of the potential need for the surgery the patient was kept NPO since the prior evening. From the standpoint of the surgeon, this was not an emergent situation and it was not an emergency surgery.

Yet, there on the intra-operative nursing records and on the anesthesia record the surgery is identified as "emergency surgery." Their designations are based not on patient acuity, but because it was not a scheduled surgery. However, if you answer the question, "Was this an emergency surgery?" with an emphatic "No," the plaintiff's attorney will no doubt challenge you at trial with the records prepared by the other practitioners who said it *was* an emergency surgery. This could lead to uncomfortable explanations, contradictions, and perceived back-pedaling.

There are two ways to avoid this kind of situation. In my experience one is much preferred. The first way to avoid this ambiguity is for the deponent (the person being deposed) to ask the questioner, "What do you mean by 'emergency?'" This kind of response may escalate the situation. The questioner responds, "Doctor, do you know what an emergency is?" To which the physician answers, "I know what an emergency is, but I'm not sure that you do…" This kind of dialogue is rarely productive, and may be affirmatively destructive if the jury believes the physician is being obstreperous or evasive.

The second way to handle the situation, and in my opinion the far better way, is for the deponent to answer the question as asked, but to include in that answer his or her definition of the potentially ambiguous word or phrase to clarify his or her answer. This avoids the ambiguity, the dialogue, and any suggestion that the physician is trying to avoid answering the question:

Q. "Doctor, was this an emergency surgery?"
A. "If, by emergency, you mean a surgery which needed to be performed that hour, or before thorough preparation could be made, no."

Or

Q. "Doctor, was this an emergency surgery?"

A. "If, by emergency, you mean a surgery which was not a surgery on the operating room's regular schedule, yes."

If the questioner wishes to reconstruct the question to define the word differently, he can do so, and you can answer the new question accordingly.

Adjectives and adverbs used by the questioner must always be considered for their potentially ambiguous usage. The usage may be innocent, but the usage of such words must be tempered with a thoughtful response.

The potential significance of the deposition process cannot be overstated. Once the deposition is completed and signed, it is your testimony. It can be used affirmatively by the opposition at trial to establish facts stated. It can be used by the opposition to contradict the testimony given at trial.

In most jurisdictions, the trial court will actually instruct the jury concerning the effect and significance of deposition testimony. The jury will be instructed in substance, as follows:

> A deposition is the testimony of a person taken before trial. At a deposition the person is sworn to tell the truth and is questioned by the attorneys. You must consider the deposition testimony that was presented to you in the same way as you consider testimony given in court. [5]

The opposing party may, therefore, literally begin his case against the physician-defendant by showing a videotape of portions of the deposition. The jury must consider that deposition presentation as if the same testimony was given by you live in court. The most common use of the deposition at trial is to emphasize possible contradictions or inconsistencies in your testimony as impeachment.

In addition, your deposition testimony can be used against you in virtually any future proceedings whether those proceedings relate to the same case, or if you are giving potentially conflicting testimony in some future case. For example, if there is an investigation of the occurrence by the state licensing board, they will typically request copies of any depositions taken in the case. Or, in the future, you may be retained as an expert in other cases. It is not uncommon for parties to a case to seek and obtain copies of past depositions given by the experts. Therefore, you could well be cross-examined concerning the testimony you are giving as an expert based upon the deposition testimony you gave in a case 5 years ago.

The deposition process is a "formal" interview. The process proceeds with question, answer, question, answer. The court reporter is obliged to report and transcribe the statements made at a deposition verbatim, in the exact order in which the statements are made. Thus, for example, if, in answering a question, you anticipate the end of the question and begin answering it before the questioner has completed the question, that is exactly how the transcript will read. This leads to broken, and potentially ineffective, testimony.

In addition, your attorney has a job to do at the deposition. That job is to assure that the questions asked are appropriate as to form (relatively clear, unambiguous, and not argumentative). The attorney must also assure that the question does not call for the disclosure of privileged information which would be subject to objection. The attorney cannot do his job if you do not allow some interval after the question is asked before you begin your response.

Wait until the questioner has completed his question. Think before answering. Respond to the question directly, and succinctly.

Answer the question which is asked. This would seem to be a simple instruction, easy to follow. In my experience, however, it is the instruction which my clients find most difficult to follow. The deposition process is in the form of an interrogation. It is not a conversation. In conversation, people often answer the question which they assume is being asked rather than literally answering the question which is asked. That is not the process of a deposition.

In conversation you are asked, "Do you know what time it is?" In response, you look at your watch, or your cell phone, note the time, and respond, "About 2:30." A perfectly appropriate course in conversation; but, a perfectly inappropriate course in deposition. The question was, "*Do you know* what time it is?" The answer to that question is "Yes," or "No." By answering the question in a conversational manner, you have not only not answered the question which was asked, you have potentially provided the questioner with invaluable information to which he was not entitled by asking the question he asked.

You have demonstrated that you use a watch as your timepiece; or, that you have a smart phone. Demonstrating that you have a smart phone could lead to a series of conversations concerning to what additional sources of information the smart phone is tied. Do you receive texts on the smart phone? Do you receive e-mails otherwise addressed to your office on the smart phone? Do you use the smart phone for your pages? This then could lead to additional discovery concerning your smart phone records, especially if the timing or duration of telephone calls ultimately becomes an issue.

This is not to say that the same information might not otherwise be gleaned if and when the appropriate questions are asked. It is to say that the opposition is not entitled to open that door by simply asking, "Do you know what time it is?" Don't invite him in.

Invariably, when cases go to trial, the physician-defendant reviews his deposition critically. As invariably, when reviewing the deposition the physician will note several potentially harmful answers which could have been avoided if he or she had simply answered the question asked.

The doctor is asked, "Did you examine the patient's abdomen?" The physician responds "I don't recall, but I usually do, and note my findings in the chart." A quick review of the chart by opposing counsel reflects no reference to an examination. Rightfully, or wrongfully, the implication based on

your expanded answer is that since no examination was recorded, no examination of the abdomen was made. All because the physician failed to restrict his answer to the question asked.

This is not to say that every answer should be "Yes," or "No." In fact, from time to time it may well be appropriate to provide a more comprehensive response to the question. For example, the question is: "Did you examine the patient's abdomen?" The physician responds, "I don't recall." The next question is: "When you examine the abdomen, do you chart your findings in the records?" The response is: "Sometimes I do; sometimes I don't." The physician would like to expand the answer to indicate that whether or not he charts his examination may be dependent upon his findings. He would chart any abnormal findings but would not necessarily chart the absence of significant findings. The proper way for a witness to expand his answer is not to simply continue to talk. A better way to expand the answer is to remark, "May I explain?" If the questioner responds, "Yes," the physician has the opportunity to expand his answer with notice of his intention to do so to his attorney. If the questioner says "No," thus restricting the doctor's opportunity to explain his answer, that can certainly be noted at trial by your attorney.

Finally, thanks to hours of television police shows we all know the basic Miranda warning, "You have the right to remain silent, anything you say can and will be used *against* you in a court of law." These Miranda rights relate to criminal proceedings. In a civil proceeding, such as a claim for medical malpractice, you don't have a right to remain silent, so you must appear and respond to questions at deposition. It remains appropriate, however, to know that everything you say at deposition, can be used *against* you at trial. The deposition is a tool for your opposition; rarely can it be used by your attorney. Every word spoken is potentially an arrow going straight from your mouth to the opponent's quiver, to be loaded in his bow and shot back at you if and when he sees fit to do so.

The foregoing is in no way intended to suggest that you should unduly limit or manipulate your answers. It is important that you answer the question which is asked, and not expand your answers unnecessarily. Yet, in all respects, you must feel free to answer all questions truthfully and, as necessary, to include within your response all information which you believe is required to give a thoughtful, complete, and meaningful response.

Teaching Points

1. Always consult with counsel before a deposition, and be represented by an attorney at a deposition, whether you are or you are not a party to the litigation.
2. Consult with your attorney sufficiently in advance of your deposition so that if additional record review or preparation is necessary you have the opportunity to do it.
3. Know what your attorney wants you to review prior to the deposition, and what she doesn't want you to review or access.
4. In every case you should be familiar with the details of your own care, including the substance of all records, consults, or notes which you had available to you at the time of your management of the patient, so that you can reiterate at deposition the basis of your management decisions.
5. Understand the difference between giving testimony based upon your memory being refreshed by review of documents, and giving testimony based strictly on your acceptance of what the document states. Are you testifying, or is the document testifying?
6. Understand in advance whether your attorney intends on your giving expert testimony based on a retrospective analysis, or whether you are giving testimony only as a percipient witness, in which case you will testify only regarding thoughts, conclusions, and opinions you actually came to while treating the patient.
7. Understand the difference between an estimate and a guess.
8. Don't give answers relating to conduct of others which you did not witness or the rationale for the conduct of another, unless that person told you why he did what he did. Knowing why someone might do something is not the same as knowing why this person did what they did on this occasion.
9. Have available at your deposition a list of the documents you reviewed in preparation for the deposition or to refresh your memory, and provide that list to your attorney in advance of the deposition.
10. Understand the question before you answer it. If a word used in the question is inherently ambiguous, define the word in your answer to clarify your response.
11. Wait until the questioner has completed his question. Think before answering. Respond to the question directly and succinctly.
12. Know if your deposition is going to be videotaped, and discuss your attire, accordingly.
13. Be prepared to give your best and most complete answers at the deposition so as to avoid the need to make substantive corrections when reviewing the transcript.
14. List proposed changes to your deposition on a separate piece of paper and discuss the proposed changes with your attorney before correcting the original transcript.

The Trial

As the process moves toward trial, your role in many respects changes. Up to the time of your deposition, you have acted primarily as a relatively silent party to the process. After the deposition, and as you move toward trial, however, you can become the most valuable and effective asset your team has. It is unlikely that any expert that your attorney retains will

have as much knowledge of the situation which you encountered as you do. Often, you will be as well educated and experienced as your expert. Frankly, there will be no one who is more invested in investigating and sorting out the pertinent records and testimony than you are. No one will have more at stake.

While the practices of attorneys vary, I believe that, after the deposition and as we proceed toward trial, it is important to provide my physician clients with everything which has been compiled during discovery. This includes the depositions of all of the parties, and all of the experts. It includes all of the records and literature.

At trial, the defense has one distinct advantage. Present at counsel table throughout the trial, defense counsel has a built in expert, knowledgeable of the facts and of the medicine, and fully invested in the defense of the case: You. It is my opinion that the defense lawyer should leverage the situation to his best advantage, by providing you with all relevant information.

In doing so, the attorney has the right to assume that you will read and analyze the information provided to you. This will be time-consuming. Often, the information fills two or three banker's boxes.

To facilitate this exercise, it is best for the information to be provided to the physician-client as it is accumulated, rather than delivering all the boxes to the doctor's doorstep the night before trial. Communicate with your lawyer. Know what he intends your role to be at trial. Know what he intends to provide to you, and ask that it be sent to you sooner rather than later.

You must make yourself available to meet with your attorney to prepare for trial. This may take as much as a day or two, or longer. It will mean time away from your practice and your family. But the work must be done.

It is very important that you be present at trial preferably throughout the trial, but certainly as often as you possibly can be.

The plaintiff will be there. The jury will quickly understand that the plaintiff believes in her case and that she considers the proceedings important enough to her that she has placed all other aspects of her life aside to be present in the courtroom.

The jury is ordered to be in the courtroom. They are told they must arrive on time, they must be present everyday, and they must be attentive throughout the day.

They will expect no less from you. If you are not present, your absence will be noticed. Even if it is assumed that you are literally in surgery saving lives, the jury will nevertheless resent the fact that their lives and the important things that they do have been ordered to be put on hold, while you apparently are free to conduct your personal and professional life. That is not the image the defense wishes to portray. It is far preferred to portray to the jury from the outset that these proceedings, the jury's time and attention, and the outcome of this case is as important to you as it is to the plaintiff.

During the course of the trial day, the jurors will be watching everything which occurs in the courtroom. Do not be disruptive or inattentive. Keep your cell phone turned off, or at least on vibrate. Do not answer texts in the courtroom. If it is absolutely necessary, alert your attorney to the situation, excuse yourself from the courtroom (assuming this is permitted by the court), conduct the necessary business, and return to the courtroom.

The trial itself will proceed pursuant to the local rules of the jurisdiction, including any particular courtroom rules of your particular judge. Trial schedules vary significantly. Rarely will a trial judge devote his entire courtroom day or week to a pending trial. There is other business to which the court must attend. Rarely will trials proceed all day, Monday through Friday.

More often, the trial court will not be in session for trial on one or more days during the week. The court's trial schedule will be made known at the outset. Most courts provide attorneys with advance notice of their trial schedules. Ask your attorney on what days the trial will be in session, when you are expected to be present, and on what days there will be no trial (days on which the court is "dark"). This will help you plan your schedule as well.

Alert your attorney as soon as possible to any vacations or schedule conflicts that might impede your ability to be present during the trial. The attorney may be able to have the trial schedule altered to accommodate your schedule, but the likelihood of her being able to do so will be greatly diminished without advance notice.

Although practices vary, trials are typically scheduled to begin on Mondays. Your attorney will appear at trial at the appointed date and time. Often, the court will have scheduled more than one trial to begin on the same day. Most cases don't go to trial; they settle or are otherwise disposed of. Still, the court may have two or more cases ready to begin on the same day, or his courtroom may be occupied with an ongoing trial. Ask your attorney what the likelihood is of your case actually starting on the date assigned, so that you can attempt to accommodate your professional schedule.

Once your case is assigned to a specific courtroom, the attorneys and judge typically proceed with pre-trial procedural matters. This may take a small portion of the day, or it may take the entire day. Your attorney should be able to provide you with some preview of whether your personal attendance will be necessary in the morning of the first day of trial, in the afternoon of the first day of trial, or not until the following day.

Once the preliminary matters are completed, the judge will typically call up a panel of jurors who will then be interviewed by the judge and the attorneys to determine their suitability for your trial.

The jury selection process, called *voir dire*, is often time-consuming. Nevertheless, your attendance during jury selection is extremely important.

First, it is within the jury selection process that the prospective jurors make their first impression of the case. You don't want the jury's first impression to be that you are absent from the courtroom.

Likewise, jury selection is the first opportunity you will have to form your first impressions concerning each of the jurors. Observe the jurors. Observe their mannerisms and their willingness to make eye contact. Listen to their comments. Listen to their concerns about their own experiences with the medical profession. Your "gut feeling" about the jurors is important.

In most jurisdictions, your attorney will have the opportunity to excuse jurors without specifying a reason. These peremptory challenges are exercised based as much on *gestalt* as on any science. Your ability to evaluate the perspective jurors' response to the parties, the attorneys, the court, and the process is likely just as valuable as your attorney's. At the appropriate time, share your observations and thoughts. They might be important to the attorney.

Once the jury is selected, and this could take an entire day or longer, the attorneys for each party are invited to make an opening statement. The opening statement is not an argument. Rather, it is merely a summation of what the attorney believes the evidence will establish. Some attorneys use a broad approach. Other attorneys provide a detailed analysis of what they believe the evidence will show.

Listen to the opening statements. The plaintiff's attorney may well expose his intentions, which may provide you with additional information concerning what aspects of your testimony need to be better prepared. Do not comment or gesture or react to the statements. To do so is inappropriate and disruptive, and you likely will be admonished by the court.

Your attorney's opening statement will include what she expects the evidence to prove. Implicitly, she is telling the jury what she expects you to tell them when you testify. Listen to what she says. If there have been mistakes made by your attorney about the facts or the medicine, point it out *after* she completes her opening statement so that the errors won't be perpetuated.

The parties then begin presentation of the evidence. The plaintiff has the burden of proof and therefore goes first. The plaintiff's attorney may or may not call you in his case in chief (i.e., the legal term for the initial portion of the trial in which the plaintiff puts on his case).

If you are called to testify by the opposing attorney, he will be questioning you as an adverse witness. This will entitle him to ask you leading questions. Be respectful of the process. Answer the question which is asked. Do not insist on attempting to expand or explain your answers, except, as in deposition, by asking, "May I explain?" Direct your comments to the questioner, not to the judge. By asking the questioner if you can explain, you have once again placed him on the horns of a dilemma. If he answers, "Yes," he's inviting a narrative which will no doubt be adverse to his case. If he answers "No," the jury will infer that the lawyer is trying to hide the true facts from them.

The most common derogatory comment made by jurors about any witness is that the witness was evasive, argumentative, and non-responsive. Don't be.

If your attorney believes that additional testimony from you is necessary on any topic, she will be prepared to ask you those questions herself. Trust her to do so.

During the course of the questioning, the opposing counsel may read from your deposition. Do not try to object to this; it is his right to do so. Do not comment about the passage read by saying that it was taken out of context, etc. Rather, patiently and confidently await your opportunity to explain the answers when asked to do so by your attorney.

During the course of the testimony always direct your answers to the questioner, unless asked to do otherwise. Unduly directing your comments to the jury may appear patronizing and unduly solicitous. Looking to your own counsel during your answer may appear to be a sign of weakness, as if you are looking for help.

There are other specifics concerning how to present yourself as the best possible witness, which you should discuss with your attorney.

While other witnesses are testifying, be respectful of them as well. Do not gesture as if in disbelief. Do not be dramatic. Present yourself always as the respectful professional that you are. Ultimately, most cases are greatly influenced by the testimony of the physician-defendant. Direct, confident, and responsive answers are always appreciated.

The roles of the judge and jury in a trial are different. It is the jury's duty to determine the facts of the case. The judge determines the law of the case. The jury hears the relevant evidence, deliberates amongst themselves, and then responds collectively to the questions on the verdict form. Although the questions on the verdict form may have several variations or subparts, there are really three inquiries:

(1) Was the defendant negligent in the medical diagnosis or treatment of the plaintiff?; if so,
(2) Was the negligence of the physician a legal cause of injury to the plaintiff?; and, if so,
(3) What dollar amount of damages do you award to compensate the plaintiff for the injuries, which you have determined were caused by the defendant's negligence?

Most often, the case turns on question No. 1:

Was the doctor negligent in the diagnosis or treatment of the patient?

The plaintiff has the burden of proof with respect to each of these questions. Generally, this means that in order to prevail, the plaintiff must persuade the jury, by the evidence presented in court, that what he or she is required to prove is "more likely to be true than not true." The jury will also be instructed that "if, after weighing all of the evidence,… you cannot decide that something is more likely to be true than not true, you *must* conclude that the party did not prove it." (Emphasis added.) If the plaintiff has not proven that you were negligent (if, for example, the jury determines

that the evidence on this issue is evenly balanced), the jury must decide the issue of negligence in the favor of the defendant [6].

How then can jurors, who are not doctors, decide whether a doctor was or was not negligent?

The jury will be given jury instructions by the judge, which outlines their task and how they are to go about satisfying that task.

The court will instruct the jury on the doctor's duty to conduct himself or herself in accordance with the standard of care, and on what evidence the jury should consider in coming to this conclusion.

The basic standard may be expressed as follows:

> A surgeon is negligent if he or she fails to use the level of skill, knowledge, and care in diagnosis and treatment that other reasonably careful surgeons would use in similar circumstances. This … is sometimes referred to as "the standard of care." [7]

In directing the jury as to what evidence the jurors may consider when deciding whether the doctor did or did not act as other reasonably careful doctors would act under similar circumstances, a basic instruction is as follows:

> You must determine the level of skill, knowledge, and care that other reasonably careful surgeons would use in the same or similar circumstances, based *only* on the testimony of the expert witnesses [including the defendant] who have testified in this case. (Emphasis added.) [7]

In most circumstances, the standard of care is defined as a standard of conduct, not a standard of result. The fact that a patient has suffered an unexpected or unintended adverse consequence is not, in and of itself, evidence of negligence. Again, while the verbiage of any instruction on this issue to the jury may vary depending on the jurisdiction, a basic statement of the applicable standards is as follows:

> A surgeon is not necessarily negligent just because his efforts are unsuccessful or he makes an error that was reasonable under the circumstances. A surgeon is negligent only if he was not as skillful, knowledgeable, or careful as other reasonable surgeons would have been in similar circumstances. [8]

The jury typically also will be instructed that simply because the experts on either side differ on what their personal preference is concerning proper management of the situation or that reasonable alternative methods for diagnosis or treatment were available, does not necessarily mean that the physician's choice of one approved method over another, even if the defendant's choice, in retrospect, proved to be the wrong choice, was negligent. This tenet of the law can be expressed as follows:

> A surgeon is not necessarily negligent just because he chooses one medically accepted method of treatment or diagnosis and it turns out that another medically accepted method would have been a better choice. [9]

"A difference of medical opinion concerning the desirability of one particular medical procedure over another does not… establish that the determination to use one of the procedures was negligent" [10]. Likewise, "[m]edicine is not a field of absolutes. There is not ordinarily one correct route to be followed at any given time. There is always the need for professional judgment as to what course of conduct would be most appropriate with regard to the patient's condition" [11].

It is important for the physician-defendant to understand these various legal propositions and the significance of each of them.

In deciding whether or not the physician-defendant was negligent, the jury is to consider only the testimony of the experts. Ultimately, the jury's decision will come down to which party's experts were more persuasive. The court may also instruct the jury concerning how they might go about weighing the conflicting testimony of the experts. One such instruction is as follows:

> … [I]t is up to you to decide whether you believe the experts' testimony and choose to use it as a basis for your decision. You may believe all, part, or none of an expert's testimony. In deciding whether to believe an expert's testimony, you should consider:
> (1) the expert's training and experience;
> (2) the facts the expert relied on; and
> (3) the reasons for the expert's opinion. [12]

Additionally,

> If the expert witnesses disagreed with one another, you should weigh each opinion against the others. You should examine the reasons given for each opinion and the facts or other matters that each witness relied on. You may also compare the experts' qualifications. [13]

In short, the weight to be given an expert's opinion is to be determined not only by the qualification of the experts, but more specifically, by considering the reasons given for each opinion and the facts or other matters relied on.

The fundamental question is whether the physician-defendant acted reasonably under the established circumstances. The fundamental method used to invalidate an expert's opinion is to establish that the facts stated as the basis for the opinion are inaccurate, or incomplete. An opinion is of no greater value than the facts upon which it is based. An opinion without proper factual foundation must, necessarily, collapse.

In preparation for trial, therefore, as your own advocate in the case, you should be well acquainted with the identities and opinions of the experts on either side. You must likewise be acquainted with the factual basis for each of those opinions. And, you should be prepared to guide your attorney to the records which you believe discredits the factual basis of the opinions of your opposing expert and to the records which confirm and support the factual basis of the opinions of your own experts.

In addition, you should be prepared to tailor your own testimony, mindful of the value of testimony you give which contradicts the factual basis of the opposing expert and supports the basis of your own expert. Knowing the bases of the

opinions of the experts on both sides, and tailoring your efforts and testimony to contradict the plaintiff's expert and to support your own expert, is the best way that you can contribute toward a successful defense of your case.

In the proper situation, as noted above, it is not fatal to your case to recognize that alternative methods and diagnosis also existed. In fact, it may be beneficial for you to explain that you were aware of these alternative methods, and considered them, but ultimately selected your method for reasons on which you are prepared to elaborate. By being prepared to discuss (both in deposition and trial) your knowledge of alternative treatments and the rationale for choosing the course you chose after discussing the options with your patient, you are potentially providing your defense with the factual foundation necessary to promote the "alternative methods of treatment" defense.

Familiarize yourselves with the applicable legal standards and instructions used in your local jurisdiction. Doing so immediately before trial, and at trial, is valuable. Doing so at the commencement of the case, as early as your first meeting with your counsel, is far more valuable.

At the conclusion of the evidence, the attorneys will proceed with their summation of the case or final argument. Because the plaintiff bears the burden of proof, traditionally the plaintiff goes first, the defense attorney then makes his argument, and the plaintiff's attorney makes the rebuttal and final comments to the jury. It is within the court's discretion to instruct the jury either before or after final argument.

Once the evidence has been completed, and the jury has received the final arguments of counsel and instructions from the court, the jurors will then proceed into the jury deliberation room. The documentary evidence will be delivered to them for their consideration.

During the course of deliberation, the jury may ask questions which will be considered by the court and counsel and responded to. The jury may also request that the testimony of one or more witnesses be read back to them. In that case, depending on the jurisdiction, either the jury will be brought into the courtroom, at which time the court reporter will recite the testimony; or, the court reporter will proceed into the jury deliberation room and read the requested passages to them.

Some jurisdictions require that the jury decide the cases unanimously. Other jurisdictions require a so-called super majority, typically 3/4 of the jurors must agree to decide any single question. Once the requisite number of jurors have come to a conclusion, the jury is then returned into the courtroom and their verdict is announced.

Based on the factual findings, or verdict, by the jury, the judge then will enter judgment in favor of one side or the other. The jury decides the fact of whether or not the physician-defendant was negligent and records that decision on the verdict. With that factual question answered, the judge then decides the legal effect of that answer (decides who wins), and incorporates that decision into his decision in the form of a judgment.

After the jury returns its verdict, either party to the case may ask that the jury be "polled." In that case, each individual juror will be asked his or her response to each of the questions. In this way, it will be confirmed that the requisite number of jurors have responded and agreed on the answer to each question so that it is a competent verdict.

Even if the case is won at trial, it will undoubtedly exact a huge toll on you personally and professionally. Jury trials are extremely expensive in terms of time, effort, and money. The jury system is not perfect, but in my experience, far more often than not, the jury gets it right.

Teaching Points

1. At trial, you are your attorney's best technical asset.
2. In preparation for trial, obtain copies of all relevant records and depositions, especially your deposition and all expert depositions.
3. Analyze the data with a focus on knowing the circumstances as they existed when you treated the patient; point out where the plaintiff's expert is wrong in his assumption of the facts, and be prepared to support the factual basis of your expert's opinion.
4. Know the basic legal standards that will be applied to define "medical negligence," so that you can tailor your testimony to meet that standard.
5. Understand the significance of "alternative methods" of treatment.
6. Alert your attorney to any schedule conflicts as soon as possible.
7. Consult your attorney regarding when exactly the trial is set to begin and when your personal presence is necessary.
8. Be present at trial, including jury selection.
9. Be cognizant of the opening statements of both sides; it will provide you with valuable insights relating to the proposed testimony.
10. Do not react to testimony with gestures or speech. Don't be disruptive of the proceedings or of your attorney's efforts.
11. When testifying, direct your responses to the questioner, not to the jury, the judge or your own counsel.
12. Do not expand your answers beyond the question asked, unless you have asked to do so, e.g., "May I explain?"
13. Recognize that preparation at each stage requires knowledge of the process and the respective roles of attorney and client; and that preparation is the key to achieving your personal *best result*.

Concluding Remarks

It has been the goal of this work to provide a primer for those not acquainted with the litigation process. It is intended as a guide to facilitate timely and effective communication

between physician-defendants and their attorneys. It is further hoped that by affording the physician-defendants a better understanding of the process, they can come to a better understanding of what is expected of them as clients, of what they can expect from their attorneys, and of how the attorney and client can work together toward managing expectations, minimizing anxiety and frustration, and formulating a strategy to achieve the *best result* available under the circumstances.

Communication is the key. Meet early. Discuss the case regularly. Know what is expected of you, and when. Know when your personal presence is likely to be necessary. Do your homework; and make yourself available.

If you prepare to succeed, the likelihood of achieving your *best result* will improve exponentially.

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2. This is not a law review article. It is intended to be of general application to clinicians. Citations to relevant laws are kept to a minimum, as the letter of the law varies from jurisdiction to jurisdiction. I practice in California. The citations included are to California legal authorities, and may not be specifically applicable in your jurisdiction. Consult your attorney for a more detailed discussion of the law as it applies to your case.
3. See, e.g., Cal. Evid. Code section 1157, et seq.
4. See, e.g., Cal. Code of Civ. Proc. section 2030.220 (c).
5. Judicial Council of California, *Civil Jury Instructions*, Instruction 208.
6. Judicial Council of California, *Civil Jury Instructions*, Instruction 200.
7. Judicial Council of California, *Civil Jury Instructions*, Instruction 501.
8. Judicial Council of California, *Civil Jury Instructions*, Instruction 505.
9. Judicial Council of California, *Civil Jury Instructions*, Instruction 506.
10. *Clemens v. Regents of Univ. of Cal.* (1970) 8 Cal.App.3d 1, 13.
11. *Barton v. Owen* (1977) 71 Cal.App.3d 484, 501–502.
12. Judicial Council of California, Civil Jury Instructions, Instruction 219.
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Surgical Education

Bradley J. Champagne and Helen M. MacRae

Key Concepts

- The dramatic changes in healthcare and surgical training have forced educators to adopt a new approach with an emphasis on outcomes and competence.
- A major impediment to surgical education is the lack of hospital or administrative support. The fiscal solvency of most academic institutions is more dependent on a high volume, cost-effective, and efficient department of surgery than ever before.
- Work hour restrictions are another major impediment to training. Residents must now make the most of all learning opportunities, as learners no longer have the "luxury" of unlimited clinical immersion.
- Simulation and surgical skills laboratories will, over time, have an increasing role in training for general technical skills, such as knot tying and procedure-specific skills. The successful application for procedure-specific training with virtual reality systems has recently been demonstrated in several trials.
- Competency-based medical education (CBME) is "an approach to preparing physicians for practice that is fundamentally oriented to graduated outcome abilities and organized around competencies derived from an analysis of societal and patient needs."
- To meet ACGME requirements, multiple assessments will be required to ensure milestone progression along all of the competencies. Assessments that are commonly used include the In-Training Evaluation Report (ITER), 360-Degree evaluations (including patient surveys), chart stimulated recall, oral examinations, multiple choice examinations, portfolios, and simulations and models.
- Post-graduate medical education now demands an increase in support at a time of waning resource allocation and protected time. In this climate, education often takes a backseat.

Introduction

Major changes in the way we train surgeons are occurring in several areas. One of the developments in medical education over the past decade which will have the largest impact on graduate education has been a shift in the focus from the processes of education to the outcomes of education, or development of competencies and attainment of milestones [1, 2]. This focus on outcome assessment and milestone achievement will require that training programs make better use of other advances in surgical education, such as simulation. Simulation-based training has also been used to help accelerate learners' growth in knowledge, skills, and attitudes, prior to entering the clinical arena, and the literature evaluating the use of simulation-based learning will be examined. As well, a competency-based framework requires that multiple formative and summative assessments be used to ensure that the required outcomes are achieved. To help in assessing the outcomes of training, practical methods that are available to assess learners in the six broad competencies of the Accreditation Council for Graduate Medical Education (ACGME) outcome project will be discussed. Finally, we will use examples from the Colorectal Surgery Milestones from the American Board of Colorectal Surgery and ACGME milestones project to demonstrate how one can integrate simulation and evaluation into a colorectal residency to help ensure all residents achieve milestones in a timely fashion.

Challenges to Surgical Education

Surgical education has seen many challenges over the past 2 decades. Surgical care is in an era of increased emphasis on accountability and outcomes [3]. Physicians need to be better trained to weigh the cost and value of diagnostic and therapeutic interventions, as there is more focus on cost

S.R. Steele et al. (eds.), *The ASCRS Textbook of Colon and Rectal Surgery*, DOI 10.1007/978-3-319-25970-3_69

containment [4]. At the same time, there is a stress on patient safety and error mitigation [5]. Work hour restrictions require that residents must make the most of all learning opportunities, as learners no longer have the "luxury" of unlimited clinical immersion [6]. With fewer duty hours, some learning has moved away from the clinical environment to simulated environments to ensure learning objectives are met, and so that residents can make the most of learning opportunities presented to them in the limited hours available [7]. All of these factors impact on the ability to rely on the traditional Halstedian model of graduate medical education, whereby learners would iteratively learn to deal with most surgical problems through stepwise progression in training, enhanced by a large volume of exposure. Although this model served surgical education quite well for the past century, many would argue that it led to deficits in knowledge for practitioners, with "lacunae" of knowledge, or skills deficits. Because passing through the system was based on meeting an overall minimum standard, surgeons could graduate without adequate exposure or expertise in some clinical areas. Furthermore, insufficient attention to areas such as quality improvement, the use of new technologies, and ability to respond to shifting patient expectations, patient demographics, and health care delivery systems led to practitioners potentially unable to adequately serve the needs of the population [3].

These challenges have created a monumental task for trainees and educators that must be supported from the top down. Contemporary post-graduate medical education demands an increase in support at a time of waning resource allocation and protected time. As we move away from a Halstedian model, and try to make more of each teaching hour available, the teaching demands on faculty increase. Administration must recognize this when allocating resources, or resident teaching will suffer. At each academic institution, the vision of education imparted from the department chair and or administration must be articulated and clearly outlined. Unfortunately, allocating additional time for surgeons to teach residents, both inside and outside the operating room, has not been a major priority for administration, but rather, almost a foreign concept. This is, and will continue to be, a major impediment to training the surgeons of the future. More recently, several institutions have also exchanged their salary-based system for faculty with an incentive-driven compensation plan for increased volumes. This alteration may further impact on resident training. In essence, academic surgeons are being asked to do more with less clinically, while maintaining their research interests and training responsibilities. These changes have the potential to foster a pessimistic and apathetic attitude amongst academic surgeons in regards to training, however, we must recognize the critical role that our residents play in patient care. Without residents, patient volumes would diminish, our academic aspirations would wane as we would have even less protected time, and our lifestyles would dramatically change. Academic surgeons should ideally have their clinical volumes evaluated as a 90 % FTE (Full Time Employee) with 10 % allotted for teaching. This argument can be strengthened by numerous publications demonstrating that cases with trainees take significantly longer [8]. Without this fundamental change, many may argue that they are not being paid to teach. This may be true in principle, but faculty who feel they derive no benefit from residents should take their own patient calls on the floor, do consults in the emergency room, enter orders on patients, and take over all of the other duties residents perform. Irrespective of the frustrations that exist with administration, the relationship of the trainer and trainee is give and take. Trainees are also often frustrated with the system, and in general, are trying to become the best surgeons possible. Remembering that the deficiencies in reimbursement, time commitment, and resources allocation lie more with the system than with the residents can help faculty to deal with some of the frustrations inherent in teaching.

Competency-Based Medical Education

A fundamental change in residency may be required to deal with many of the changes that have evolved. A major focus of new models in post-graduate medical education is a focus on demonstration of attainment of competency, with a shift away from time and objective-based training to a competency-based framework. Examples of this change in culture can be appreciated in different Health Care Systems. The Outcome Project of the ACGME in the USA [1] and CanMEDS Competency by Design in Canada [2] focus on outcomes and abilities of the learner, with explicit competencies as the organizing principle of curricular design. With the Next Accreditation System (NAS) of the ACGME, and Competency by Design within the Royal College, the focus of accreditation will move away from assessing the objectives and processes of education, and towards assessing the outcomes of education. Programs will have to demonstrate that their trainees have acquired the knowledge, skills, and attitudes of the competencies required for safe and effective practice. Three concepts that have been forwarded in this move towards competency-based education are competencies, milestones, and entrustable professional activities (EPAs). These build upon each other.

Competency-based medical education (CBME) is "an approach to preparing physicians for practice that is fundamentally oriented to graduate outcome abilities and organized around competencies derived from an analysis of societal and patient needs. It de-emphasizes time-based training and promises greater accountability, flexibility and learner-centeredness" [9].

Competencies integrate knowledge, skills, and attitudes. They are observable and can be measured. Ideally, learners will demonstrate progressive attainment of competencies as they move from novice to expert, assembling competencies like building blocks as they develop knowledge, skills, and attitudes. These building blocks are the stepping stones to

milestone attainment. By explicitly identifying milestones that learners should achieve, competency-based education helps move learners along the pathway to excellence. A milestone is a defined, observable marker of an individual's ability along a developmental continuum [1]. Milestones are useful for planning and teaching, as frequent assessment of the milestone attainment of residents allows the program to assess where the learner is, where deficits might be, and plan learning opportunities accordingly. Although a competency-based curriculum is generally planned in terms of milestones, the eventual goal of a post-graduate training program is to ensure that graduates can carry out the essential tasks of the specialty. An Entrustable Professional Activity (EPA) is an essential task of a "discipline" that an individual can be trusted to perform independently in a given context [10]. Based on the demonstration of sufficient competence, the supervisor feels the resident is able to do the task independently. EPAs can be used for overall assessment and decisions as to when residents are ready for independent practice. Typically an EPA integrates multiple milestones. EPAs are the tasks or activities that must be accomplished (for example, manage a patient with rectal cancer), whereas milestones are the abilities of the individual on a continuum (for example, able to "assess imaging information and justify a TNM-based treatment strategy").

A central tenet of CBME is that learners must assume greater responsibility for their own learning and the assessment of their learning than in traditional approaches. Learners become responsible for developing a learning portfolio, and collecting formative and summative assessments to demonstrate they have achieved the desired outcomes. Thus, the competency-based framework places more onus for ownership of learning on the trainee, who must ensure they are actively seeking experiences to enable them to achieve milestones. They must also demonstrate, through assessment tools, their achievement. By putting more onus on the learner to take charge of their own development during post-graduate medical education, and focusing on the need to seek out learning opportunities and ensure milestones are reached, the hope is that competency-based education will better ensure that learners have the skills needed for lifelong self-directed learning and continuing professional development as they move along the medical education continuum into independent practice.

Strategies Outside of the Operating Room

In addition to increased accountability, the current paradigm of surgical education also advocates non-clinical, or ex-vivo, methods of training to improve clinical performance by providing practice opportunity in a safe environment. Surgical educators uniformly agree that technical skills exercises and training in the surgical skills center, designed specifically to allow the resident to optimize their operative learning and experience, will play a critical role. The American Board of Surgeons Resident Review Committee has made it mandatory that all surgical training programs have a means of training outside the operating room [11]. Therefore, simulation and surgical skills laboratories will, over time, have an increasing role in training for general technical skills, such as knot tying and procedure-specific skills (Figure 69-1). In its broadest terms, simulation is defined as the act of imitating the behavior of some situation or some process by means of something suitably analogous. Therefore, the majority of non-clinical technical skill exercises, regardless of the model, qualify as "simulation." Current platforms vary considerably in level of fidelity, from box trainers to technologically advanced Virtual Reality (VR) programs.

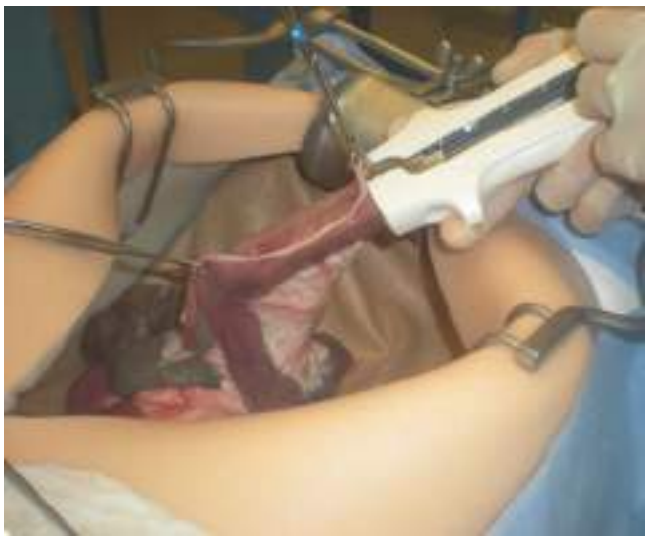

FIGURE 69-1. Pelvic Pouch Skills Lab Station at the Institute for Surgery and Innovation at Case Medical Center, Cleveland, OH.

Simple box trainers for laparoscopic skills such as the validated MISTELS (McGill Inanimate System for Training and Evaluation of Laparoscopic Skills) are effective at the junior trainee level and should be readily incorporated into any laboratory curricula. VR platforms have also been shown to improve performance in the operating room. More specifically, dedicated practice with VR simulators have correlated with improved operative times, and efficiency of movement for clinical laparoscopic cholecystectomy. Seymour et al. evaluated 16 residents of varying levels and compared clinical laparoscopic cholecystectomy outcomes between residents who received training on a VR system versus those who did not. They found no difference in baseline assessments between the two groups, but found that residents who trained on the simulator were faster, made fewer errors, and were less likely to injure the gallbladder in the operating room [12]. Grantcharov et al. also evaluated 16 residents and compared training on a VR simulator to a control group. They found improved economy of movements and fewer errors in residents who were trained on a VR simulator [13].

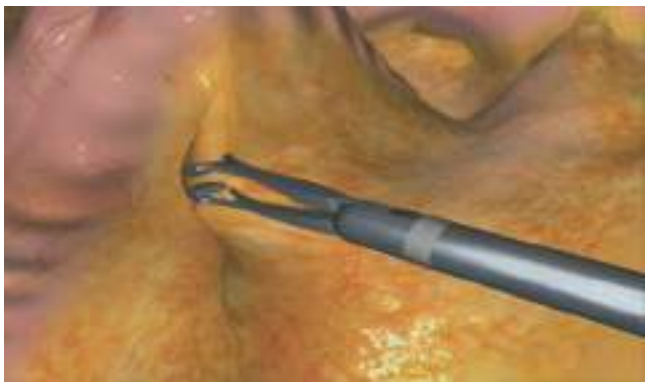

FIGURE 69-2. Virtual reality laparoscopic sigmoid module (Simbionix, Cleveland, OH).

Beyer and colleagues evaluated transfer of skills from simulators to the operating room using the Global Operative Assessment of Laparoscopic Skills (GOALS), a validated laparoscopic skills assessment model [14]. Their prospective trial involving 19 residents found improved GOAL scores in residents who were trained on a simulator when compared to those who were not.

Simbionix (Cleveland, OH) offers a VR (LAP Mentor) model for laparoscopic sigmoid colectomy that more accurately portrays resection in the operating room than previous hybrid systems [15] (Figure 69-2). Evidence of face, content, and construct validity have been established for general procedures with the LAP Mentor VR system [16]. More recently, evidence of construct validity was established for certain metrics, specifically with the laparoscopic sigmoid model [17]. In this study, the metrics assessing the instrument path length, the accuracy of the medial peritoneal mobilization, and the quality of the IMA dissection demonstrated the strongest ability to discriminate between general surgeons and expert colorectal surgeons. However, construct validity was not established for technical errors, as the model could not differentiate between experts and novice surgeons using this metric.

The successful application for procedure-specific training with VR systems has recently been demonstrated in several trials. Calatayud et al. tested "warm up" with a VR system prior to laparoscopic cholecystectomy and found that Objective Structured Assessment of Technical Skill (OSATS) global rating scales were better after practice [18]. Palter and Grantcharov developed a comprehensive ex-vivo preoperative training curriculum that improved performance for LC [19]. This study involved preparation with simulation, cognitive training, and participation in a cadaver lab. In this study, residents were PGY-2 through 4, having previously completed FLS and possessing some advanced laparoscopic experience. Using an entire curriculum that addressed multiple aspects of performance, which included procedure-specific simulation, overall laparoscopic colectomy skills were enhanced. While this impressive approach was successful, having all trainees perform this labor intense program prior to operative procedures may not be practical. The cost and time requirements of this model are likely not likely sustainable in most training programs outside of a trial. However, this well-designed trial most importantly demonstrates that preparation can improve performance for laparoscopic colon resection. More recently, Singh et al. [20] utilized a validated virtual reality laparoscopic cholecystectomy curriculum to study the role of video-based coaching in teaching laparoscopic skills. The authors found that video-based coaching enhanced the quality of laparoscopic performance on both virtual reality and porcine models. Simulation curriculums for endoscopic procedures have also been studied and found to be effective. Williams et al. compared general surgery residents to gastroenterologists in their ability to perform colonoscopy after the trainees completed an endoscopic simulation-training curriculum. They discovered that the trainees were capable of achieving quality measures equivalent to faculty gastroenterologists [21]. Furthermore, Iordache et al. recently validated a cadaver model with simulated training to place endoscopic colonic stents. They found that the model had reliability and evidence for construct validity [22].

Each academic institution may choose to incorporate one of these preparation models or a variation on this theme. The VR studies for basic laparoscopic skills training have routinely incorporated a proficiency-based model, whereby trainees have proficiency targets to meet, rather than time on task as a training goal [23].

Understanding Competency-Based Medical Education

Traditionally, residency has been primarily time-based, with time spent on rotations used as a surrogate for competence. In a pure CBME model, demonstration of defined competence in a time-free model would be used. This time-free approach is usually not practical, as rotations need to be somewhat structured, and learners gain competencies at very different rates. Thus, a hybrid model, in which learners move through rotations and other structured learning approaches (such as simulation-based learning), but only graduate once milestones are met, is advocated. Summative assessments are used to ensure competencies are attained, and residents are progressing satisfactorily with milestone achievement. Teachers ensure learners have the necessary learning opportunities, and use real time direct observation to evaluate achievement.

Carraccio [24] has compared traditional time-dependent models of curriculum development to pure competency-based curricula, which are time free (Table 69-1). In a time-dependent model, the main organizing structure would be time spent on rotations, as opposed to progression of competence. Rotations, with academic half days and formal teaching

TABLE 69-1. Comparison of competency-based education and traditional curricular models

Variable	Traditional model	Competency based
Goal of educational encounter	Acquisition of knowledge	Application of knowledge
Responsible for driving process	Teacher	Learner
Assessment	Emphasis on summative	Emphasis on formative with ongoing feedback
Assessment tools	Indirect, proxy assessment	Direct assessment, observation of real tasks of profession
Evaluation standards	Norm referenced (in relation to peers)	Criterion referenced (in relation to objective measures)
Rotations and program completion	Fixed time	Variable time based on demonstration of competence

Adapted from Carraccio C, Wolfsthal SD, Englander R, Ferentz K, Martin C. Shifting paradigms: from Flexner to competencies. *Acad Med*. 2002;77:361–7 [24]

are the main structures of this type of curriculum, with the learning goals being predefined objectives of training. In-training assessments are used to ensure that rotations are passed, but are usually completed at the end of a pre-defined time. Teacher's roles are primarily supervision and teaching, and learners provide service, attend academic sessions, and study for exams. In a time-free model, progression of competence, rather than rotations is the main organizing structure, with rotations seen as one of many resources to aid learning. Milestones are the learning goals, and the role of timed rotations is irrelevant. Assessment is focused on documentation of milestone achievement, with summative assessment used to ensure attainment of competencies. Teachers supervise, teach and also directly observe in clinical settings to ensure competencies are achieved. Learners must take ownership of their learning, plotting a course for progression of competence through a variety of learning activities. Once the competencies have been demonstrated to have been met, learners move on. Realistically, most programs will use a hybrid of these extremes, as development of a pure competency-based model is difficult to structure and monitor.

Some of the major challenges when thinking of implementing CBME are similar across specialties. In Internal Medicine, three of the major challenges identified were: incorporating practice-based learning and improvement and systems-based practice into the curriculum; evaluating residents across the competencies; and ensuring advancement based on competence, rather than time [25]. All of these will be major challenges for colorectal programs, which are short compared to most residencies, especially as the incoming residents may already require some degree of remediation [26]. However, practice-based learning and improvement can be incorporated into the everyday clinical context. For example, residents can be involved in quality initiatives, identifying and pursuing improvement processes, structured morbidity and mortality conferences, and provided with opportunities to identify gaps or improve measures. Furthermore, systems-based practice can be best addressed during transitions in patient care, from inpatient to outpatient and other settings.

Evaluating residents across all of the competencies is also challenging. A discussion of assessment modalities follows, but in general, direct observation in the clinical setting will likely be the most feasible method of assessment for a small program, as more structured assessment tools, such as standardized patient encounters, and performance-based assessments can be expensive and difficult to administer for only a few residents. The challenge for programs is to ensure they are documenting enough evaluative feedback to ensure milestone assessment is reliable and valid.

Assessment of Performance

Assessment of performance during post-graduate training can be either formative (meant to give feedback, or direction to learners) or summative (high stakes, end-of-training, such as certification decisions). Within a CBME framework, assessment of learning becomes vital to the entire process, and the assessment framework must be robust enough to ensure that developmental milestones are accurately assessed. Formative assessment is done frequently, to enhance reliability and validity, and is based around real clinical work. This allows for performance to be assessed across all of the competencies.

In a CBME model, the assessment process must become "more learner driven, learner focused and formative" [26]. Multiple types of assessment tools are available to help the Clinical Competency Committee (CCC) [27] make valid judgments about the milestone progress of their learners. To meet ACGME requirements, multiple assessments will be required to ensure milestone progression along all of the competencies. Programs will have to use a variety of assessments to provide their CCC with robust data.

Assessments that are commonly used include the In-Training Evaluation Report (ITER), 360-Degree evaluations (including patient surveys), chart stimulated recall, oral examinations, multiple choice examinations, portfolios, and simulations and models. Table 69-2 outlines these commonly used tools, and what competencies are best evaluated through their use. Evaluations used specifically for technical skill assessment in colorectal surgery include Performance Based Assessments (PBAs), operation-specific rating scales (e.g., those used for laparoscopic colectomy), outcome measures (e.g., cecal intubation rates), and final summative assessments [e.g., the Colorectal Objective Structured Assessment of Technical Skills (COSATS)]. Each of these evaluation tools will be briefly discussed.

TABLE 69-2. Evaluating outcomes in the core competencies

Core competency	Competency based
Patient care	Direct observation forms, oral examination, chart-stimulated recall, ITERs, 360-degree evaluation, procedure/case logs with reflection, PBAs, OSATS global ratings, portfolios (OSCEs)
Medical knowledge	MCQs, oral examinations, written examinations, chart stimulated recall, direct observations, portfolios
Practice-based learning and improvement	Portfolios, QI project, 360-degree ratings, MCQs, oral examinations, direct observations
Interpersonal and communication skills	360-degree, patient surveys, direct observations, ITERs
Professionalism	360-degree rating, patient surveys, oral examination, direct observation, ITERs
Systems-based practice	360-degree evaluation, direct observations at care transitions, patient surveys, portfolios

ITER in-training evaluation report, *OSCE* objective standardized certification examination, *MCQ* multiple choice questions, *PBA* performance based assessments

In-Training Evaluation Report

Assessment during post-graduate training has traditionally relied on the ITER. The ITER has the positive attributes of theoretically being comprehensive, being able to assess across all of the competencies, and being relatively easy to use, even in small programs, such as colorectal surgery. However, although in theory ITERs have the potential to give feedback on real world performance, the way in which they are operationalized in many programs make them suboptimal. Often, they are completed long after the training period, when recall may not be ideal. Assessors often use the "above average" portion of the form almost exclusively, and are reluctant to fail residents. Because of the failure to use the range of marks, the reliability of ITERs has been poor. As well, as a formative tool, the ITER often does not provide trainees with meaningful data on their own strengths and weaknesses. However, in terms of utility as an assessment tool, ITERs have many positive characteristics. They can be reliable, especially if multiple assessors are used to complete the ITER [28]. Qualitative and narrative components on an ITER, if based on specific traits with formative feedback, rather than generalities, can be very useful, and have been shown to be a predictor of overall and long-term competence [28]. Unfortunately, the educational impact on the learner is poor, especially if ITERs are completed long after the fact, without the opportunity for learners to discuss and reflect on areas needing improvement, however, if done on a more frequent basis, with formative feedback, while residents can still act on the results, ITERs have the potential to have a positive educational impact. They are cost effective, and have good acceptability to learners and assessors, as they theoretically are based on actual clinical performance. The challenge, then, is how to improve the ITER as an assessment tool to ensure all of the theoretical positive attributes are achieved.

ITER report quality can be improved with structured feedback to faculty on their ITER completion. Faculty overall feel that ITERs are worthwhile, however, in a study on faculty perspectives on the ITER, Watling et al.[29] found that evaluators felt their ability to produce a meaningful approach to ITERs was compromised by time constraints, lack of continuity between educational assignments, and the challenge of giving negative feedback. These areas need to be addressed in order to improve ratings. Engagement of faculty and residents in the ITER process is a critical factor in ensuring the ratings are improved. Thus, overall ITERs have many of the attributes required for a useful assessment tool, but programs must ensure faculty and residents are engaged in the process in order to get the most useful ratings. They likely will remain an important component of the evaluation system, but perhaps will become a committee-driven evaluation, and may better employ milestones and their assessment in the future.

Mini-CEX

The mini-CEX was developed by the American Board of Internal Medicine as a workplace-based assessment tool that would be feasible to implement in the real clinical setting, be useful for feedback, and give reliable data [30]. In the mini-CEX, the trainee is responsible for selecting a clinical encounter, where they will ask an assessor to observe them in the real patient setting. Thus, a snapshot of the doctor–patient interaction is observed. The assessor collects information on the encounter on a structured evaluation form, with immediate feedback to the resident on their performance. Trainees are responsible for selecting from a range of problem groups and assessors, so over time, they have a collection of assessments in their learning portfolio, leading to more stable (reliable) ratings. History and physical examination skills, communication, professionalism, organization, and efficiency, as well as overall clinical care are covered on the mini-CEX.

An instrument for assessment of surgical skills, with many aspects similar to the mini-CEX, was developed by a group in Ottawa [31]. This tool can be used by surgical programs to help evaluate many of the items important for surgical management.

360-Degree Evaluation

The 360-Degree evaluation is a measurement tool completed by multiple people, with different perspectives, who each interact with the resident. Patients, nurses, allied health personnel, peers, subordinates, and other related specialists might all complete surveys. Generally, these are best used for evaluation of competencies such as interpersonal and

communication skills, as well as professionalism. Practical considerations involve the logistics of distributing and collecting the forms (though online programs exist), and ensuring the evaluators are providing reliable data and not simply using this as a "gripe" session. It is important to assess how many of the evaluations being used are needed for the data to be reliable in order to keep the administrative burden acceptable. Usually, 10–20 completed forms are needed for reliable data. Studies in different domains suggest that 360-Degree forms correlate reasonably well with preceptor as well as self-reports of performance [32].

Oral Examinations

The oral examination has traditionally been used to assess clinical judgment. A structured oral examination is likely best to ensure reasonable reliability for formative or summative assessment. Medical knowledge, patient care, interpersonal and communication skills, and to an extent, professionalism can be assessed on an oral examination if it is well structured. As the structured oral remains an important component of board examinations, it is useful to provide residents the experience of participating in this type of assessment. In terms of utility, a structured oral has reasonable reliability and validity, is educational and acceptable to learners and other stakeholders, and is cost effective. Many of these properties will likely ensure it continues to be used for high stakes evaluation for the foreseeable future, thus, it should remain a part of the assessment toolbox for residency programs.

Portfolios

A learning portfolio is an important assessment tool in a competency or outcome-based learning framework [33]. The learner is responsible for developing the portfolio, and providing evidence of learning and achievement related to the competencies that have been mastered. A learning portfolio might include items such as self-evaluations, articles related to specific outcomes, presentations they have made around a topic, and results of both formative and summative assessments such as the mini-CEX, CARSITE examination, or oral examinations, all helping to support promotion decisions. Ideally, this learning portfolio would follow the individual into independent practice, and become part of maintenance of certification.

Technical Skills Assessment

Logbooks and Case Numbers

Logbook numbers can be seen as a surrogate for technical skill assessment. Although increased numbers of cases are associated with improved outcomes, the learning curve varies greatly between trainees, as does the number of cases required for proficiency [34]. Case numbers, other than identifying deficiencies, do not give meaningful feedback to residents on where they need to improve. However, they are useful for training programs to assess the operative experience provided to their residents, and to identify potential deficits.

Procedure-Based Assessment

Procedure-based assessments (PBAs) are completed via direct observations of entire operations [35]. The assessment covers consent, the preoperative planning, preoperative preparation, exposure/closure, intraoperative technique, and postoperative management. The United Kingdom has the most experience with using PBAs, where they are required for many technical specialties. For colorectal surgery, the Operative Competency Committee of the ASCRS has developed PBAs for several technical areas, which are available on the program director's website.

Because the PBA captures performance in a "real-life" environment, it is an ideal form of evaluation to demonstrate milestone achievement. However, the feasibility of its use as a high stakes assessment is questionable, as residents cannot be left to "fail" the examination. Within a competence-based curriculum, however, PBAs used formatively could help provide evidence of milestone achievement.

Simulation/Virtual Reality in Technical Skill Assessment

Simulation-based assessment can be used to assess many areas of competence, including professionalism [36], team-based skills [37], patient communication and interpersonal skills [38], and technical skills [39], Realistically, the use of these types of simulations will likely be in primary residency programs, where the larger number of residents justify the infrastructure and development costs required.

Simulation of technical procedures can include non-live animal models, synthetic tissue, computer-based models, cadaveric tissue, live animal, and hybrid platforms. An example of a simple model for basic technical skill assessment is the MISTELS system used in the Fundamentals of Laparoscopic Surgery program [40]. Virtual reality simulators have also been used for more complex skills, notably, simulators for colonoscopy and for laparoscopic colectomy. A recent Cochrane review [41] found that VR simulation led to improvements in operative time and "performance," but the impact on patient outcome was unclear.

GAS and LCAT of the National Training Programme in England

The National Training Programme (NTP) for Laparoscopic Colorectal Surgery in England used the global assessment scale (GAS) for feedback [42] as part of the training program.

Once a trainee within the program was deemed proficient, DVD recordings of two independently performed cases were submitted and reviewed by two blinded accredited assessors, using the laparoscopic competency assessment tool (L-CAT) [43]. The L-CAT is comprised of a 16-item marking sheet (4 task components for each of the 4 domains), incorporating 22 items identified. The tool was shown to perform well, with excellent reliability and evidence of validity. However, the examinees were surgeons in practice who performed their cases independently, thus the tool might not be suitable for a residency training program where intervention must occur for poor performance.

Colorectal Objective Structured Assessment of Technical Skills

The COSATS [44] exam is an assessment tool developed for summative assessment of colorectal technical skills. It is a derivation of the OSATS examination [39], which has been used in many specialties. In the COSATS, the candidate performs tasks specific to colorectal surgery, using a combination of virtual reality and bench models to simulate the selected skills.

Performance is assessed at each station using a task-specific checklist and a global rating scale, and pass–fail decisions are made based on the performance across eight stations. To date, reliability and evidence of validity are very good to excellent for a high stakes assessment. However, the COSATS is best seen as a summative assessment, as the feasibility of individual programs developing and setting up this examination for a few residents at a time is questionable.

Global Rating Forms

The global rating scale of the OSATS, and modifications of it, such as the GOALS [45] and the GAGES [46] to assess endoscopic skills, have been used to assess residents' technical skill in the operating room and in endoscopy, and to assess surgeons in practice [47], all with good evidence of reliability and validity. The global rating form is a relatively straightforward tool to use to collect a series of assessments on the operative skills of residents.

In summary, programs will need a variety of assessments to gather the evidence required by a clinical competence committee to make decisions on milestone attainment by their residents. Resident portfolios will likely become an important component of resident assessment, and shift some of the onus for collecting and collating evidence of competence attainment on the learner. These portfolios could then be carried into practice to aid in the maintenance of certification.

How Can CBME Be Applied to Colorectal Residency Training?

Colorectal milestones have been developed by the American Board of Colorectal Surgery and the ACGME. Residents are coming into programs with varying degrees of experience and competence, thus it is likely important to assess their starting point (along the milestones early in their residency) to ensure there is time to address areas of deficiency within a short training period. Deficits in technical or other skill sets need to be diagnosed as soon as possible within the training program to ensure adequate progression along the milestones occur.

An example of a Colon and Rectal Surgery Milestone is the Patient Care for Rectal Cancer. Multiple competencies related to rectal cancer care are included in the milestones, including imaging, choice of operating, surgery, and postoperative management and surveillance. For one of the components of competence, an entry level resident would be expected to list some imaging options for TNM staging. This competency would be relatively easy to assess with a quick written or oral examination. As residents progress, they are expected to be able to formulate strategies for imaging the rectal cancer patient and interpret the results. This likely would be taught in the program in several ways, including seminars or readings on imaging of rectal cancer, coupled with multidisciplinary rectal cancer rounds, where imaging is reviewed with radiologists, and other strategies for imaging might be discussed. In contrast, Level 4 (graduating resident) would expect that the resident is able to assess imaging information and justify a TNM-based treatment strategy. Again, this is currently done to an extent in multidisciplinary rectal cancer rounds; however, for a competency-based curriculum, the resident would have to gather data to show that they had been assessed on this competence. A direct observation of the resident's performance in cancer rounds, an oral examination, or a case write-up in which imaging is used to justify a TNM-based treatment strategy could all be used to assess the resident, and demonstrate competence in this area. The technical components of competence could be assessed with the COSATS global rating scale, or with a PBA for low anterior resection. Multiple components of the patient care competencies would be taught on the oncology rotation, or in the clinical setting, in rounds and during direct patient care. Overall, a move to a competency-based curriculum requires assessment to demonstrate that the resident is mastering the component pieces of rectal cancer patient care, and ensuring they move along the milestone progression expected of them. Assessment in a patient care setting would be expected for many of the components.

As the milestone committee meets, the evidence of competence assessment would be reviewed, and the milestone achievement marked for the resident. If there are competencies that are following below expected, targeted learning interventions towards these areas would be implemented.

For example, if a resident is noted to be deficient in some of the operative components, they could spend time in the simulation center practicing enabling skills for the procedures. The program would then try to ensure they have increased exposure to rectal cancer cases, preferably with known strong clinical teachers, allowing them to use their clinical time for refinement and milestone progression. Medical knowledge deficits identified early might lead to a structured reading program, or use of resources such as CARSEP or CREST.

Residents should develop a learning portfolio, which would include, among other things, direct observation assessments, self and other identified areas for improvement, quality improvement initiatives, and their case log information. Reflection on cases, especially in areas of difficulty, might also be helpful. The learning portfolio allows for the clinical competence committee to have multiple sources of information on the resident, enabling more accurate milestone assessments. For the resident, it allows them to see areas for improvement, enhancing self-reflection, and movement towards excellence.

Conclusions

CBME has arrived and will be an integral part of surgical training. As surgeon educators, we must strive to implement these measures in the most effective way possible and resist the urge to "check the boxes." Furthermore, we must take responsibility to make trainees understand the importance of both maximizing their learning experience for each case and becoming immersed in the learning environment outside of the operating room. Lastly, we must resist some of our own selfish interests and decide where the education of trainees falls on our priority list. In his essay on leadership [48]. John Maxwell recites, "The Law of the Big Picture" as "People do What People See." Therefore, it is unlikely for residents to prepare for cases well if they are not receiving instruction during the case or feedback after from disinterested faculty. Trainees must know and perceive that their trainers have a sincere interest in their education, or they will question the sincerity of the feedback and evaluative comments they receive. Although a move to a focus on the outcomes of education in many ways seems daunting, it is educationally sound, and, by moving some of the onus for improvement onto the learner, will hopefully improve lifelong learning in the profession.

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Maintenance of Certification: Current Status and Future Considerations

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Key Concepts

- Approximately 6–12 % of physicians "fail to meet professional standards of practice" as defined by deficits in knowledge, disruptive behavior, systems problems impeding physicians' care of patients, increasing physician age, problems unrelated to medical care (i.e., licensure issues or allegations of insurance fraud), physical illness, psychiatric illness, and substance abuse.
- The American Board of Colon and Rectal Surgery (ABCRS) ended time-unlimited certificates in 1989, and began issuing certificates that required diplomates in Colon and Rectal Surgery to pass a secure "recertification" examination every 10 years intended to demonstrate continued mastery of content sufficient for specialty practice.
- Parts I (maintenance of unrestricted license and good professional standing), II (lifelong learning and self-assessment), and IV (practice performance assessment and improvement) of the Maintenance of Certification (MOC) were designed to run concurrently in repeating 3 to 5 year cycles, with successful performance on the Part III secure specialty examination required at or about every 10 years to maintain specialty certification.
- Part II and Part IV of MOC continue to evolve, with Part II requiring a defined number of CME credits that incorporate a self-assessment activity, which physicians have to pass with a 75 % correct grade.
- ABCRS' Part II of MOC self-assessment requirement may be satisfied with, among other activities, completion of the Colon and Rectal Self-Assessment Program (CARSEP) every 3 years, or completion of the Surgical Education and Self-Assessment Program (SESAP), a product of the American Board of Surgery (ABS).
- Part III of MOC consists of the secure high stakes examination designed to assess broad knowledge of the specialty (previously the "recertification" exam).
- ABMS and member Boards continue to receive criticism regarding the financial and time burden of MOC requirements, redundancy with other professional and regulatory requirements, and most especially lack of relevance to physicians' practices and an absence of proof that MOC produces improved patient outcomes.

> Rules are not necessarily sacred; principles are.
>
> — Franklin Delano Roosevelt

Introduction: How We Came To Be Here

Evaluation of the literature dealing with medical error shows three major potential sources: healthcare delivery systems, insurer practices, and individual practitioners at various levels—physicians, nurses, pharmacists, and other healthcare workers [1]. The physician remains the single most identifiable individual in the healthcare system—the individual who directs and coordinates the activities of nurses, pharmacists, and other healthcare workers according to the plan of care. However, exponential growth of innovation in technology, pharmacology, and new scientific knowledge has produced a medical care system that is far more complex than ever before, and many discrete parts of the whole must interact smoothly to deliver healthcare that is safe, timely, and cost-effective. Within the complexity of the modern healthcare system, physicians have recognized a gradual but progressive diffusion of autonomy affecting decisions regarding patient care. At the same time, physicians are increasingly required to accept responsibility for an ever-expanding volume of practices and regulations that take time away from patient care activities, are often frustratingly redundant, and produce little or no demonstrated improvement in healthcare delivery or patient outcomes.

In general, physicians are highly educated individuals who are well used to self-directed learning as well as assessment of their knowledge and performance, having successfully

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progressed through college, medical school, residency, and often fellowship training—mastering the high stakes examinations at each level. The vast majority go on to perform successfully on the rigorous secure cognitive Board certification examination in their chosen specialty. Some boards have additional requirements for certification, such as oral examinations, medical record audits or case log reviews, or observation of the candidate's performance with standardized or real patients [2]. As physicians progress through their professional careers, each has pursued ongoing educational activities guided by personal assessment of his or her own relative deficits or needs related to individual practice patterns. Over time, documentation of continuing medical education (CME) credit accrual has been increasingly required by the hospital or health system at which each physician practices.

Board certification initially had no expiration date. In the 1980s, the American Board of Medical Specialties (ABMS), the umbrella organization for the 24 member specialty boards that certify physicians trained in ACGME-approved training programs, signaled that lifelong certification without demonstration of ongoing mastery was no longer sufficient to assure the public that physicians were maintaining clinical competence and continuing to provide high quality care throughout their career. Specialty boards responded in part by no longer issuing certificates without expiration dates. The American Board of Colon and Rectal Surgery (ABCRS) ended the process of issuing time-unlimited certificates in 1989, and began issuing certificates that required diplomates in Colon and Rectal Surgery to pass a secure "recertification" examination every 10 years intended to demonstrate continued mastery of content sufficient for specialty practice. Ongoing self-directed learning continued as before, with individual physicians selecting learning activities based on their assessment of their own needs.

In 2000, ABMS adopted Maintenance of Certification (MOC) as a policy with general standards for its member Boards (Table 70-1). Parts I, II, and IV were designed to run concurrently in repeating 3-year cycles, with successful performance on the Part III secure specialty examination required at or about every 10 years to maintain specialty certification. Institution of MOC was based on empiric data interpreted to determine that such a program was necessary for physicians to prove to the public that they maintained mastery of specialty content [3]. Between 2000 and 2009, ABMS and its member Boards had many discussions regarding the shape that Part II, Lifelong Learning and Self-Assessment, and Part IV, Practice Performance Assessment and Improvement, might take. Some stakeholders encouraged immediate increased rigor with regard to MOC standards and proof of physician engagement in MOC. However, few additional requirements were presented to individual diplomates for maintaining board certification at that time.

In 2009, the pace of MOC accelerated, with the process intended to be more continuous than episodic, with participation required on a more regular basis. The American Board of Emergency Medicine (ABEM), American Board of Internal Medicine (ABIM), and the American Board of Pediatrics (ABP) moved toward requiring active MOC participation every 2 years [4]. It was made clear that ABMS expected Part II of MOC to include a defined number of CME credits that incorporated a self-assessment activity, which the physician had to pass with a 75 % correct grade. Importantly, while the concepts contained in the four parts of the MOC program were not new to physicians, the specificity set forth by ABMS raised a new set of challenges for practicing physicians and member Boards.

Table 70-1. ABMS MOC program

The ABMS program for maintenance of certification has four separate parts
• Part 1: Licensure and professional standing. Diplomates are required to hold a valid unrestricted medical license in at least one state or jurisdiction in the USA, its territories, or Canada
• Part 2: Lifelong learning and self-assessment. Physicians participate in educational programs that meet specialty-specific standards set by their certifying board and that include a self-assessment component
• Part 3: Cognitive expertise. Physicians must pass a high stakes exam to show they possess fundamental practice related knowledge to provide quality care in their specialty
• Part 4: Practice performance assessment and improvement. Physicians compare their outcomes with peers and national benchmarks

ABMS American Board of Medical Specialties

The Reasoning and Evidence for Institution of the ABMS MOC Program

Hawkins et al. authored a monograph explaining the theory and evidence that supported the concept and framework for the ABMS MOC program [3], stating that development of the evidence base in support of MOC is "conceptually similar to validation of an assessment method and involves two related, sequential processes". First, empiric data should determine that such a program is necessary; second, developers of the program should collect evidence to see if the program is performing as it should, and use this evidence to guide continued improvement. The next several sections discuss the MOC program in its current iteration and the data considered to support its institution. However, evidence regarding whether the program is exerting the desired effect remains controversial.

Central to the data cited in support of the need for the MOC program are estimates that 6–12 % of physicians "fail to meet professional standards of practice" [5]. These include deficits in knowledge [6], disruptive behavior (though this data suffers from a low survey response rate) [5], systems problems impeding physicians' care of patients [7], increasing physician age [6], problems unrelated to medical care (such as licensure issues or allegations of insurance fraud) [8], physical illness, psychiatric illness [9], and substance abuse [10]. A 2009 study which used surveys, focus groups,

and in-depth interviews with physicians in practice and licensing authorities, along with analysis of Federation of State Medical Boards Action Data Bank records, to find areas of concern in physician performance, identified five themes including communication, economics, ethics/behavior, knowledge and skills, and competency and assessment. Underlying causes common to these themes included increasing complexity of health care systems, decreasing insurance reimbursement, inadequate staffing, physicians practicing in isolation, problems with documentation and record-keeping skills, failure of teaching team approaches to medical care, and the general punitive approach to physician performance problems [11]. Another concern is the finding that physicians seem not to be very good at assessing their own areas of relative strengths and weaknesses [12, 13], supporting the concept of activities with scored assessment that can then be used to guide further learning activities. Taken together, these studies suggest that at any given time, a minority of practicing physicians experience challenges regarding professional standards of practice. Also acknowledged is the fact that many of the underlying causes for concerns in physician performance have roots in dysfunctional systems issues. Regardless, this data was seen to indicate a need for a more narrowly defined national program applicable to physicians in all specialties, overseeing aspects of physician professional standing, lifelong learning, and practice patterns and outcomes. This became the current MOC program of ABMS, designed "to assure the public that individual physicians maintain good professional standing as well as mastery of specialty content," though evidence suggested that the vast majority of board-certified physicians were already doing so. There has been no comparable national attempt to address the dysfunctional systems issues identified in many of these studies discussed above.

Hospitals, health care systems, and third party payers clearly value board certification, as evidenced by the increasing requirement of certification to gain privileges, to the point where non-board-certified physicians have lower earnings and have found it difficult to practice in many markets within the USA [14]. However, methodology used to assess how consumers value certification-accreditation processes has provided an unclear answer, perhaps in part because patients do not understand the processes [15]. Patients of a family medicine clinic were surveyed in 1998, and agreed that board certification was the most valued attribute for their physician [16]. Parents of pediatric patients who responded to a web-based survey in 2010 noted that recommendation from friends or family was equally as important as board certification in choosing their child's physician; 77 % also agreed they would be likely to change physicians if the physician did not maintain certification [17]. In an unpublished Gallup poll commissioned by ABIM in 2003 and subsequently reported by Brennan et al., general public respondents agreed that they valued certification and MOC, and agreed that physicians should be evaluated more frequently than required at the time [18]. Respondents also agreed they would change their physician if s/he failed to maintain certification, and agreed that they would choose a board-certified physician over a non-certified physician recommended by a family member or friend [18]. It is important to recognize the design limitations of these studies; participants are constrained in their responses by the necessity of choosing among statements to "agree" or "disagree" with.

Is the MOC Program Performing as It Should?

Part I, maintenance of unrestricted license and good professional standing, is familiar to every physician as a routine part of maintaining standing at the hospitals and/or healthcare systems one works within. On a regular basis, each physician must submit proof of valid unrestricted licensure and details of medical and specialty training, including board certification in most cases, to secure privileges to practice within most hospitals, healthcare systems, and third party payer systems. The MOC program, however, was not constructed with the thought of capturing this information from any existing database. As a result, each diplomate is required to supply for the MOC program the same information already submitted to various other bodies for licensure and hospital/surgery center privileges. Member Boards have been tasked with collecting and storing this information for ABMS; this and other burdens imposed on Boards are discussed at more length below. Though ABMS has been urged to accept the responsibility of collecting and storing this data to reduce the additional burden imposed on individual diplomates and member Boards, it has not moved to do so.

The general punitive approach to physician performance problems has often been identified as a barrier to physicians seeking help when it is needed [11]. Rules regarding how this sensitive matter is handled vary widely from state to state. Some states have well-developed confidential Physician Health Programs for problems including mental health, substance abuse, and professionalism issues, in which as long as the physician under treatment complies with all requirements of the program, the license is not reported as restricted [19]. Other states take a "legal" rather than a "treatment" approach [20]. In such jurisdictions, physicians may be forced to leave practice, at least temporarily, during treatment, and reinstatement can be an onerous and sometimes problematically public process. The ABMS MOC program does not contain any provision for how such licensure and professional standing instances might be managed within the program.

Part II contains a newly mandated requirement that within each 3-year cycle a specified number of CME credits must include a self-assessment (test) component, with a score 75 % or higher required to claim the CME credits. This represents a new hurdle for individual physicians as well as member Boards. Diplomates now have to seek out CME activities that

Table 70-2. The six core competencies defined by ACGME

1. Medical knowledge
2. Patient care
3. Professionalism
4. Interpersonal communication
5. Practice-based learning and improvement
6. System-based practice

ACGME accreditation council for graduate medical education

are both suitable for their specialty and self-identified needs that also include a self-assessment piece. Most of the self-assessment CME activities currently available are proprietary products, thereby adding an additional cost burden for diplomates, many of whom had often previously obtained CME credits at regional and national meetings at no additional cost.

The recognition that many issues with respect to professional standards can be related to one or several of the six competencies (Table 70-2) led ABMS first to encourage, then to require, that Part II activities have a clear definition of the competency or competencies each activity is meant to assess. At this time there is not a more specific requirement regarding whether or how each of the six competencies must be included in Part II activities.

Diplomates must report their Part II activities to their Board, noting the number with an associated self-assessment activity; the Boards are newly tasked to monitor and store this mass of data. Some larger Boards with more resources have undertaken to identify, or even produce, activities that the Board deems appropriate for their diplomates; other Boards have not done so for a number of reasons, including workforce and financial resource limitations. The member Boards have requested the ABMS develop or provide resources for a "clearinghouse" for Part II self-assessment activities that Boards might use to share or identify Part II activities suitable for their diplomates, with the hope of decreasing the burden for diplomates by identifying acceptable Part II activities. A joint project between ABMS and the American Association of Medical Colleges (AAMC) was recently announced that will develop the ABMS MOC Directory. MOC activities suitable for Parts II and IV may be submitted by members of the continuing professional development (CPD) and CME communities. ABMS will then work with member Boards to review and approve submitted activities that would be suitable for diplomates. Preliminary information suggests that member Boards will have the ability to approve activities, and ABMS will serve primarily as a facilitator. Potential cost to member Boards or diplomates for this service and/or the rights to a learning activity have not been defined to date.

With the specification of 90 credits every 3-year cycle for Part II, two-thirds or so of which must include self-assessment, member Boards have been tasked to police the efforts of their diplomates in a more exacting way. Still, member Boards currently retain the ability to determine what self-assessment activities are acceptable for Part II credit. Many boards have chosen to accept a wide variety of Category 1 American Medical Association (AMA) CME activities that include a self-assessment piece; although some boards have specified that the activity subject matter be closely related to the specialty or the diplomate's practice. ABCRS' self-assessment requirement may be satisfied with, among other activities, completion of the Colon and Rectal Self-Assessment Program (CARSEP) every 3 years. ABCRS also accepts completion of the Surgical Education and Self-Assessment Program (SESAP), a product of the American Board of Surgery (ABS) for Part II self-assessment requirement.

Data is mixed on whether participation in MOC can be shown to improve patient care or outcomes. Several studies have shown no difference in outcomes for patients cared for by internists with ABIM time-limited vs time-unlimited certificates across a panel of ten primary care performance measures [21], and no difference in ambulatory care-sensitive hospitalizations when comparing internists with ABIM time-unlimited and time-limited certificates [22], though there was a small reduction in the growth differences of costs for a cohort of Medicare beneficiaries [22]. Diplomates of American Board of Family Medicine (ABFM) who completed Performance in Practice modules related to hypertension showed improvement in most quality measures evaluated; however, though most had chosen lipid control as their quality improvement focus, no improvement was seen for that particular measure [23]. A similarly designed study evaluating ABFM diplomates' performance in diabetes care showed that while all physician and patient quality measures improved, no consistent association was seen between improvement and processes of care when comparing physicians with time-limited vs time-unlimited certificates [24]. The difficulty in defining what variable or set of variables might lead to improvement is again reflected in a study comparing a cohort of ABFM diplomates who participated in linked Part II and Part IV activities related to type 2 diabetes. Those who participated in the linked activities showed greater improvements in 11 of 24 process and outcomes measures when compared to diplomates who had not participated, though all groups demonstrated improvement [25].

Part III, the secure high stakes examination designed to assess broad knowledge of the specialty (previously the "recertification" exam), has remained largely unchanged. An examination is easily understood by the public as a measure of competence, and is acceptable in theory to most diplomates, as examinations are an essential part of the medical education process. As more diplomates progressed through their first 10-year cycle, however, nearly every Board received feedback from examinees that the secure MOC exam lacked relevance to their practices. Critics note that the examination tests material not relevant to everyday practice. As a result, the exams are perceived to have lower face and content validity. There is also little evidence that MOC examination scores can predict clinical competence in daily practice, as the requisite knowledge to pass a multiple-choice

examination may not correlate with real life clinical problems that require more nuanced solutions. Nevertheless, pass rates for MOC exams are high, as would be expected when testing a group of experts. Noting the high pass rates, some in ABMS adopted the stance that an examination that the majority of test-takers passed was a poor measure of continued content mastery, despite the fact that all examinees were by definition a highly educated and trained group of experts well versed in the majority of the content to be tested. Most member Boards did not share this view, expressing confidence in their MOC examinations' content and security. Interestingly, the first-time failure rate on the American Board of Internal Medicine's (ABIM) MOC exam has increased from 10 to 22 % over the past 5 years [26], with ABIM diplomates voicing a belief that the examination was being made intentionally harder to pass. While most candidates successfully passed the exam on retaking it, there was a great deal of consternation, increased costs, and more time away from active practice among diplomates who had not passed initially.

Evidence linking successful completion of the MOC exam with improved practice or patient outcomes is largely lacking. One study of ABIM diplomates showed that physicians who scored in the top quartile of the ABIM MOC exam were more likely to perform processes of care for diabetes and mammography screening than physicians who scored in the lowest quartile; however, no difference was seen for lipid testing in cardiovascular disease [27]. A study evaluating data from ABIM and ABS showed similar findings for surgeons and internists: those most likely to pass the MOC exam were younger, had higher scores on the initial certification exam, were in group (not solo) practice, and were US graduates. However, aside from performance on initial certification exam, the observed effects were small [28]. On the other hand, a study of ABFM diplomates showed that family physicians who maintained certification performed better on the MOC exam than recent graduates, with scores reaching their highest point 28–31 years after a diplomate's initial certification. Multiple comparison analyses confirmed the trend was significant; however, sub-analysis showed that while the trend remained significant for US medical graduates, it did not for international medical graduates. Family physicians who did not maintain certification performed significantly worse on the MOC exam than recent graduates [29]. In summary, although the individual and system variables that influence scoring on the MOC examination have been identified, there is limited evidence that higher scores on the examination are associated with higher quality patient care.

Part IV, Practice Performance Assessment and Improvement, has been the most difficult part of MOC to address in a way both meaningful to diplomates and also not overly burdensome. As with Part II activities, individual Boards were at first allowed considerable latitude in the activities each Board would accept for Part IV. For this reason, fulfillment of Part IV was initially attainable without undue burden for most ABCRS diplomates, since participation in NSQIP, SCIP, and a number of other regional and national databases and registries widely available in medical centers was considered acceptable (Table 70-3). An initial requirement for each diplomate to include patient satisfaction surveys in Part IV activities was placed on hold after ABMS received feedback from member Boards communicating concern over undue burden for diplomates in executing these as prescribed, as well as implications regarding data interpretation. However, advocates of a more stringent definition for Part IV activities have recently gained ground at ABMS, culminating in a new plan for Part IV activities that pursue reportable improvement of individual physician outcomes data. These activities would require diplomate participation in quality improvement activities endorsed by an ABMS-approved body, along with accurate documentation of substantial participation in aspects of project design as well as execution. This degree of specificity departs sharply from improvement activities already in wide use (such as Morbidity and Mortality Conference, and multidisciplinary disease management or service line conferences) with respect to acceptable activity structure, type and form of reported outcomes, and degree of individual participation in activity development and direction. There is considerable concern among member Boards that such requirements would pose a significant burden for a large fraction of diplomates. Quality outcomes are dependent on a number of discrete factors, many of which are outside the control of an individual physician. Few diplomates in active medical practice have had formal training in the methods of designing and executing a quality improvement and assessment project. Many well-designed quality improvement projects enfold a number of stakeholders that must interact to produce the desired outcome, and may require years for maturation of data. From the diplomates' point of view, the time and

Table 70-3. Registry participation accepted by ABCRS for Part IV MOC credit

- ACS surgeon specific case log system (with tracking of 30-day complications) https://www.facs.org/quality-programs/ssr
- Cancer quality improvement program (CQIP)
- Florida surgical care initiative
- Hospital consumer assessment of healthcare providers and systems (HCAHPS)
- Mayo clinic
- Michigan surgical quality collaborative (MSQC)
- National cancer database (NCDB)
- National surgical quality improvement program ACS (NSCIP)
- Ongoing professional practice evaluation (OPPE)
- Piedmont society program
- Press Ganey
- Surgical care and outcomes assessment program (SCOAP) (Washington State)
- Surgical care improvement project (SCIP)
- University health system consortium (UHC)
- VHA surgical quality improvement program (VASQIP)

ABCRS American Board of Colon and Rectal Surgeons, *MOC* maintenance of certification

effort that would be expended in design and participation in these studies represents an additional unfunded mandate, in addition to less time available for patient care activities that could impact compensation for many. ABMS has recently begun consideration of "group" or "team" MOC initiatives, chiefly as Part IV activities, in a nod to the recognition that many of the challenges posed to practitioners are systems or team based. Design of such activities has barely begun; consideration of how to execute and monitor these activities remains to be seen.

ABMS has set up a Multi-Specialty Portfolio Approval Program, dealing with quality projects that may be eligible for Part IV credit. The Portfolio Project began in 2009 as the "Primary Care Board QI Approval Pilot" with Mayo Clinic as the first "Pilot Portfolio Sponsor." The Portfolio Program subsequently became part of ABMS in 2014. The Portfolio Program does not produce quality improvement (QI) projects, but reviews proposals from outside sources, and grants approval (or not) for ABMS MOC Part IV credit for participating diplomates. Potential benefits for Portfolio Sponsors (i.e., medical schools, hospitals, medical groups, healthcare consortiums, and the like) include having diplomates in their organization receive MOC Part IV credit for current QI initiatives that originate in the home institution (after a favorable review by the Portfolio Project), and reduced time and effort for approval of QI projects applicable to diplomates in several specialties compared to applying to several Member Boards for project approval. The potential benefits for Member Boards would principally be a route for awarding ABMS MOC Part IV credit to diplomates for QI projects that receive a favorable review by the Portfolio Project, and potentially using the Portfolio Project as a more granular way to track the QI efforts of diplomates. The Portfolio Project has publicized that upwards of 6500 physicians, less than 2 % of American physicians currently meeting MOC requirements, have received MOC Part IV credit through projects vetted by the Portfolio Project. The cost for application and initial 2-year participation in the project has recently been raised to $7500. The Portfolio Program is only one pathway for physicians to obtain MOC Part IV credit; individual Boards offer a variety of other pathways for physicians to receive MOC Part IV credit.

Challenges Presented to Diplomates

Physicians remain committed to lifelong learning and improvement in practice. However, MOC has received at best a lukewarm response from individual diplomates; there are many reasons. ABMS and member Boards continue to receive criticism regarding the financial and time burden of MOC requirements, redundancy with other professional and regulatory requirements, and most especially lack of relevance to physicians' practices and an absence of proof that MOC produces improved patient outcomes. Approximately 375,000 board-certified physicians (about half the number that the 24 ABMS member boards certified initially) currently meet MOC requirements, according to ABMS [30]. However, as of 2012, 74 % of ABIM diplomates waited until the 9th year of their 10-year cycle before taking action to recertify [4]. Results of a survey of Oregon physicians showed that 91 % of respondents were board-certified; 95 % of those with time-limited certificates planned to recertify. However, they reported that their practice groups provided few to no resources for participation in the MOC process [31]. A study utilizing data from ABIM diplomates initially certified between 1990 and 1999 showed that physicians who participated in MOC tended to have higher initial certification scores, were younger, were US graduates, practiced as subspecialists and in the Midwest, worked in nonsolo practices, or were employed in counties with less than 20 % of persons in poverty [32]. A mail survey of 1693 pediatric diplomates with time-unlimited certificates had a response rate of 77 %, and found that while only one-quarter of generalists and 13 % of subspecialists agreed they would be willing to participate in general pediatrics MOC, fully half of the subspecialists would be willing to participate in subspecialty MOC, highlighting the importance of MOC relevance to one's practice. Three-fourths of both generalists and subspecialists did not agree that MOC was necessary for keeping up to date in clinical pediatrics [15]. The perception of MOC's lack of relevance to current practice is most often raised by subspecialty practitioners [15; personal communications.]

Physicians with fewer resources to devote to the MOC process (lack of practice support for MOC; solo practice; or practice in areas of poverty) appear to be those most at risk for non-participation, and therefore, for loss of board-certified status [32]. Physicians in solo practice, international graduates, and physicians with a higher percentage of poor patients all do worse on MOC exams [32]. A study of surgeons taking the MOC examination in 2008 showed that increased levels of peer interaction were associated with a higher score and a higher likelihood of passing the exam. Physicians in solo practice had fewer peer interactions, received lower scores, and were less likely to pass the exam. However, solo practitioners with high levels of peer interaction performed as well as those in group practice [33]. A study of ABIM diplomates showed that more frequent use of electronic resources was associated with modestly enhanced MOC exam performance. The authors also noted that physicians involved in residency education clinics and hospital inpatient practices had higher MOC exam scores than physicians working in private practice settings [34]; perhaps, this is related to more frequent peer interactions. A survey of American Board of Anesthesia (ABA) diplomates found that the majority perceived board certification to be of value in demonstrating competence. However, the elements of Part I, Professional Standing, and Part II, Lifelong Learning and Self-Assessment, were perceived as significantly more relevant to practice than Part III, the Cognitive Exam, or Part IV, Practice Performance Assessment and Improvement activi-

ties. ABA diplomates expressed concerns about the cost and complexity of MOC, a lack of evidence that MOC improves practice, and a belief that the Cognitive Exam covered topics not relevant to their current practice [30, 35]. Other frequent critiques of the MOC program as currently designed include a lack of assessment of appropriateness of care, and insufficient system-based evaluation [36].

Challenges for Member Boards

The MOC standards are intended to apply equally to all member Boards regardless of Board size, available resources, or specialty. This presents several difficulties, the most obvious being that of an unfunded mandate. Compliance with the standards requires significantly more work by each Board's support staff. Some of the subspecialty Boards have staffs as small as four full-time employees, and strategies to meet the need for the increased administrative workload are still being determined. Many Boards also recognized a need for website expansion to provide newly mandated diplomate services, as well as to house the growing body of data requiring storage as well. Website and server expansion is dependent on funds sufficient to support the desired capacity. The function and mission of Boards is the certification of specialty diplomates and related activities; fees for certification-related activities and the occasional bequest have historically been the financial foundation of most Boards, with Board resources therefore having a direct relationship to the size of the diplomate pool. However, Boards by definition have a finite and closed membership comprised of their diplomates; no drives can be held to gain new members. As a direct result of the increased administrative and website workload which are expected to be ongoing requirements, most of the ABMS member Boards felt there was no option other than to levy MOC fees to support this unfunded mandate. In the lay press, charges have been leveled at ABMS and its member boards that MOC exists largely as a revenue-raising tool. Costs for the 10-year MOC cycle range from $1250 (ABS) to $4280 (American Board of Plastic Surgery, or ABPS). Of ABIM's total revenue of $49 million in fiscal year ending June 2012, 62 % was derived from certification fees and 36 % from MOC fees [30].

In early February 2015, ABIM responded to a stream of continued strong criticism from its diplomates regarding the MOC program and suspended the Practice Assessment, Patient Voice and Patient Safety requirements (Part IV) for at least 2 years, changed the language used to publicly report a diplomate's MOC status on its website from "meeting MOC requirements" to "participating in MOC," and made plans to update the Internal Medicine MOC exam to better reflect what ABIM general internists are doing in practice with plans to do so in subspecialties as well. The ABIM also rolled MOC fees back to 2014 levels with a commitment to keep them at that level until at least 2017, and affirmed a plan to recognize most forms of Accreditation Council for Continuing Medical Education (ACCME)-approved CME for demonstration of self-assessment of medical knowledge. Many ABMS member Boards have also chosen this time to enact a moratorium on new MOC requirements, and are opening dialogues with diplomates to better assess their needs, with more user-friendly, meaningful, and value-added MOC programs as a goal.

Decreasing the Burden of MOC

Cook et al. proposed an integrative practice-based model for MOC, allowing Part II and IV topics to emerge from and remain embedded within the local clinical practice; directly improving patient care, ensuring that needed skills are developed and maintained, and providing context to stimulate knowledge retention [37]. The authors also postulated a smoother interaction for the parts of MOC: Part II learning would prepare diplomates for Part III, and might provide skills required for Part IV; Part IV could be used to define learning agendas for Part II; and feedback on Part III would also inform Part II learning agendas. ABMS recently incorporated this last suggestion into the MOC program with an expectation that diplomates receive feedback regarding performance on the MOC exam to help guide their individual learning and self-assessment activities in the next cycle.

It is clear that some form of individual evaluation will remain a part of the MOC process. The ABMS held a symposium for its member boards in June 2014 to discuss the future of Part III. Some boards have instituted novel approaches to Part III that seem to better serve the needs of their diplomates. In Plastic Surgery, for example, diplomates complete a core section for Part III and then choose their remaining test material from three of four defined subspecialty areas. As of 2014, the American Board of Anesthesiology began a pilot project to revamp Part III called the "MOCA minute". The program consisted of a continuous dynamic web-based assessment with focused content to assess knowledge and guide the diplomat to appropriate resources. Questions were sent out on a weekly basis and answered on line by the diplomate, who received immediate feedback in the form of the correct answer, a full critique, key points, and references. The pilot was very successful and was integrated into MOCA Part III as of January 2015. Progress will be monitored by the program; each individual will receive immediate reports on their own performance broken down by topic area to allow them to tailor their own MOC program accordingly.

There have been initiatives external to ABMS that may work to reduce the burden of MOC for individual diplomates and improve compliance. The AMA House of Delegates passed a resolution in June 2013 to determine if periodic secure recertification examination is needed, and to explore alternatives [38]. Evidence supporting alternatives to secure closed-book exams as proof of specialty knowledge content exists as far back as 1996, when Norcini et al. showed that an

open book web-based recertification exam was as reliable as a secure high stakes exam [39]. The ABIM recently conducted a structured review of the evidence for open versus closed-book exams, concluding that closed-book exams drive learning while open book exams decrease anxiety. Movement to an open book examination would improve face validity by reflecting real-time practice, provided there was access to multiple information sources such as Google Scholar, Uptodate, WebMD, ACP pier, Isabel/Watson, texts, journals, and crib sheets. This process is under review by the ABIM. A related option adopted by other Boards is for remote exam proctoring, in which a candidate logs in to a secure website and takes the examination on their own time and space.

Physicians who participated in both MOC and PQRS (Medicare's Physician Quality Reporting System) were eligible to receive a 1.5 % bonus in 2011 and a 1 % annual bonus between 2012 and 2014, in addition to regular Medicare fees. However, physicians who chose not to report these quality measures to the PQRS program by 2015 would have their Medicare fees reduced by 1.5 % in 2015 and by 2 % in 2016. Additionally, the Federation of State Medical Boards (FSMB) recommended in 2010 that physicians actively participating in MOC "could substantially meet" the more stringent requirements of Maintenance of Licensure. However, at this time only Massachusetts has announced a start date (2015) for such a reciprocity program.

ABCRS: Current Requirements; Initiatives Under Consideration

The ABCRS instituted its MOC program in 2011. The current requirements for the ABCRS MOC Program are listed in Table 70-4. When a diplomate initially certifies with ABCRS, or recertifies with successful completion of the Part III exam, s/he qualifies to have 50 self-assessment credits applied toward the Part II requirement in the 3-year MOC cycle immediately following. ABCRS is also considering awarding credit applicable to Part II self-assessment requirements for diplomates who author questions for the ABCRS examination process.

The ABCRS is keenly aware that a majority of its diplomates also maintain certification by the ABS, with the requirements that dual Board certification entails. ABCRS and ABS have agreed that Part II credits can be applied to both the ABCRS and the ABS MOC programs. In addition, each Board will accept completion of CARSEP or SESAP toward Part II credit. However, a diplomate must still successfully pass the MOC Part III exam for ABCRS and ABS separately to maintain certification by each Board.

The MOC Committee of the ABCRS is considering changes to the MOC program based in part on the practices of other Boards who have piloted innovative models for their MOC programs as well as feedback from ABCRS diplomates. There is a good deal of interest in a modular-type Part III examination, in which each diplomate completes a central module common to all examinees, but then may choose two to three modules from a range of three to five of specialty content. Another novel way to manage Part III would be to have each diplomate complete a set number of secure multiple-choice questions annually with more timely feedback rather than 200 every 10 years. The questions would be accessible on line for a set time period and feedback would include the answer, keypoints, a critique, references, and a link to provide feedback on the questions. The diplomat would also be asked to evaluate the confidence of their answer which could be used summatively by the candidate to identify gaps in their knowledge. This should allow for more intensive longitudinal assessment and targeted self-directed Part II learning activities, and could lead to Part IV involvement with direct applicability to one's practice. Ongoing involvement in learning, practice improvement, and quality activities requiring less dedicated time per episode, along with clear application to one's practice, may provide diplomates with more accessible and meaningful ways to manage their MOC needs.

Table 70-4. ABCRS MOC required components 2015

Part I. professional standing (every 3 years)
• Documentation of full-licensure in the state in which you practice
• Documentation of privileges for colon and rectal surgery at your hospital
• Letter of recommendation from the chief of staff at your hospital
Part II. Lifelong learning and self-assessment (every 3 years)
• Ninety hours of category 1 CME credits, 50 with a self-assessment activity (which can include CARSEP or SESAP)
Part III. Cognitive expertise (every 10 years)
• MOC cognitive exam
Part IV. Evaluation of performance in practice (every 3 years); suggested activities include:
• Communications and interpersonal skills activities
• Clinical practice data—Ongoing participation in a national, regional or local outcomes database or quality assessment program (see Table 70-3)

MOC maintenance of certification, *CME* continuing medical education, *CARSEP* colon and rectal self-assessment program, *SESAP* surgical education and self-assessment program

How Other Nations Manage MOC

In Canada and the United Kingdom, the processes that parallel our MOC program are mandatory for physicians to practice. Some interesting lessons may be learned from examination of these processes and their history. The Canadian process involved Fellows (the equivalent of Diplomates) early during the program's design, and continues to do so. All Fellows are automatically registered in the MOC program of the Royal College and are required to meet all of the requirements to maintain the designation Fellow of the Royal College of Physicians of Canada (FRCPC) or Fellow of the Royal College of Surgeons of Canada (FRCSC). All provincial licensing boards

require active participation in MOC to maintain licensure. Fellows must complete a minimum number of credits in each 5-year cycle, which are entered into an online database maintained by the College. Credits are self-reported in one of six areas and classified by the competency that is addressed. This must be supported by documentation, of which a portion must be sent in annually to the College. Each year a random sample of Fellows are audited for complete documentation. The recommendation of the Royal College Council to not include a secure exam as part of the process has been repeatedly supported by fellows, national specialty societies, and medical educators since the early 1970s [40]. At the present time Canadian Fellows involved in MOC through the Royal College can submit their MOC reports from the Royal College to the ABCRS for MOC credit. However, they are also required to take the ABCRS MOC examination to complete ABCRS recertification.

The process in the United Kingdom is not a system developed by doctors for doctors, but rather a "centralized system using employer (National Health Service) to employee (physician) relations to ensure accountability" [41]. The UK system is compulsory for all doctors who wish to practice in the UK, including doctors in training, in public or private practice, and those visiting the UK and practicing medicine. The system consists of the Good Medical Practice guidelines, which supply the core ethical guidance for UK medical practitioners, and Fitness to Practice, which incorporates general medical knowledge and skills along with elements of professionalism which "may include matters not directly related to professional practice." The main areas of scrutiny are professional standing and professionalism, in part due to several high-profile medical scandals in the past decade. There is no required specialty knowledge test that parallels the MOC examination.

Conclusions

At the present time, board certification and MOC is voluntary in the USA. Realistically, however, many hospitals require board certification for granting hospital privileges. In many fields of practice, a lack of certification leads to lower earning power [14]. In the future, participation in MOC may become a mandatory component for continued licensure and privileging. As a professional group we need to set the standards of our own educational assessment and evaluation. We must maintain the social contract with the public where there is a collective social trust with the expectation of self-management. The administration of MOC must remain under the control of physicians at the specialty Board level to avoid takeover by an external body who may develop a process that is more onerous, with a foreign agenda and little relevance to the practicing physician. The Boards themselves must evolve from simply developers and administrators of tests to organizations engaged in quality assessment and quality improvement.

Evidence considered to support the concept of MOC enfolds physician-specific factors, patient-specific factors, and systems issues [3]. At the present time diplomates are concerned regarding the cost and time involved in completing the process without solid evidence that it improves patient care. While physicians accept the concept of lifelong learning and personal development, the optimal approach has yet to be determined and awaits the results of ongoing research and innovation.

Some developments that may make the present process less onerous include structuring MOC so that it fulfills the requirements for all the different entities that assess physician performance; devising ways to have Parts II, III, and IV be more relevant to each diplomate's practice; addressing the real burden of both time required and financial costs for individual diplomates as well as member boards; and finding methods to assess the "systems issues" portions of practice that do not result in penalization of the diplomate for situations beyond his/her control. New considerations from ABMS for "team quality activities" may be a recognition that much of modern medical practice is related to factors separate from and not under the control of the individual physician; however, it is far from clear what place such activities would have, whether in the MOC setting or the local practice setting under the aegis of a hospital or healthcare system's quality improvement program. Context and relevance to practice of the individual diplomate also needs more attention within the MOC program. The specific care delivered by physicians working in different health care areas may vary greatly, dependent largely on systems issues [36]. However, the question of added burden for individual diplomates and boards has yet to be truly addressed.

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71
Quality and Safety in Colon and Rectal Surgery

Elizabeth C. Wick and Jonathan Efron

Key Concepts

- Measurement of quality can be separated into structural, process, and outcome-based.
- Quality measures in colorectal surgery are both process and outcome-based.
- Transforming healthcare to a high reliability organization will provide the infrastructure for continuous quality improvement.
- Creating a culture of safety is essential for delivering high quality care.
- Patient and family engagement has emerged as a new and equally important domain of quality.

Background

In 2000, the Institute of Medicine (IOM) published the report *To Err Is Human*: *Building a Safer Health System*, a landmark document which raised awareness of the magnitude of the problem of medical mistakes, and remains the most frequently cited document in the medical literature in recent years [2]. The IOM report shocked both the healthcare community and the public by concluding that 44,000–98,000 deaths and over 1 million injuries occurred each year in American hospitals due to medical error. In fact, preventable medical errors represent one of the eight leading causes of death in hospitalized patients. As this report was disseminated, general awareness about medical errors increased, and physicians and other health providers began speaking openly about mistakes and the difficulties they face when dealing with them. The IOM report brought much-needed attention to the field of quality and safety. In addition, it standardized the language used to describe errors in medicine, defining important terms for future research and quality improvement. Following its publication, interest in the field increased exponentially and health services researchers began to collaborate with scientists from other disciplines such as engineering, psychology, and informatics to develop innovative solutions to longstanding lapses in quality and safety.

A follow-up report in 2001, *Crossing the Quality Chasm*: *A New Health System for the 21st Century*, provided a framework for how to re-work healthcare delivery in the USA [3]. The report called for federal and state policymakers, public and private purchasers of care, regulators, organization managers, governing boards, and consumers all to commit to reducing the burden of illness and to improve the health of the American population by focusing on making healthcare safe, effective, patient-centered, timely, efficient, and equitable (Figure 71-1). To meet these goals, the report outlined ten rules for redesign:

1. Care is based on continuous healing relationships.
2. Care is customized according to patient needs and values.
3. The patient is the source of control.
4. Knowledge must be shared and information flows freely.
5. Decision-making should be evidence-based.
6. Safety is a system property.
7. Transparency is necessary.
8. Needs need to be anticipated.
9. Waste should be continuously decreased.
10. Cooperation among clinicians is a priority.

The next milestone for the safety and quality movement was the *Patient Protection and Affordable Care Act* (i.e., "Affordable Care Act" or "Obama Care"), which was signed into law on March 23, 2010. While the primary goal was to increase the availability, quality, and affordability of insurance coverage, the Affordable Care Act was also designed to be a catalyst for the reinvention of the healthcare system with a particular emphasis on ensuring that the ten rules outlined in the IOM report were integrated into the delivery system. Specifically, the Affordable Care Act implemented policies and procedures that will over time shift the paradigm of care in the USA from being volume to value-driven. Policy makers further proposed that for healthcare, value equals the cost of care divided by a measure of quality

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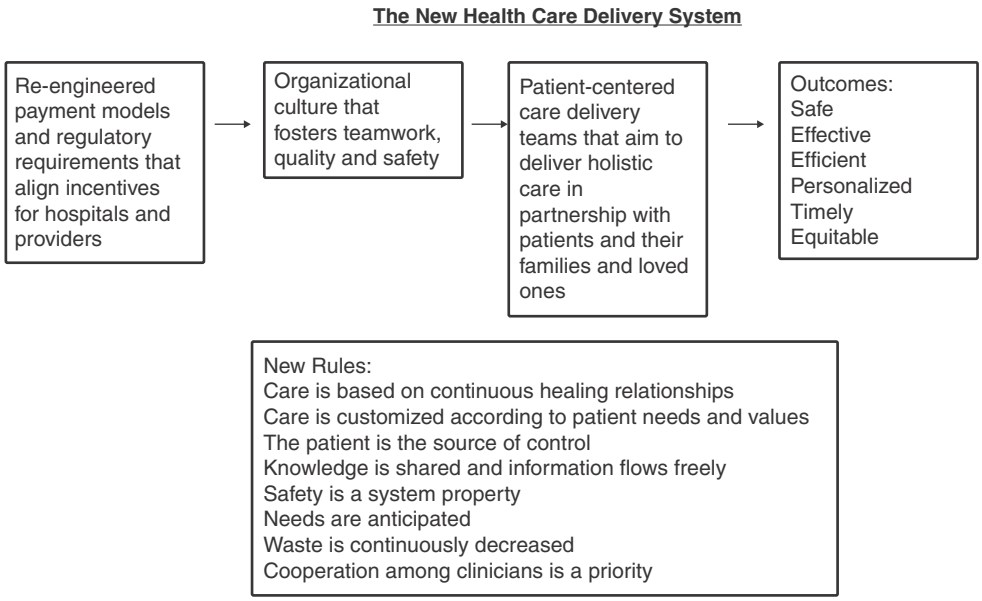

FIGURE 71-1. The new health care delivery system.

TABLE 71-1. Strategic priorities of 30 Medicare ACOs

	Degree of near-term priority											
	Very low		Low		Medium		High		Very high		Don't know or missing	
Strategy	No.	%	No.	%	No	%	No.	%	No.	%	No.	%
Avoid wasted resources due to lack of care coordination	0	0	0	0	3	10	7	23	19	63	1	3
Reduce unnecessary surgery	4	13	12	40	10	33	2	7	1	3	1	3
Manage high-cost or high-risk patients	0	0	0	0	1	3	6	20	21	70	2	7
Reduce overuse of specialists	3	10	8	27	10	33	4	13	4	13	1	3
Reduce unnecessary imaging	0	0	7	23	13	43	3	10	5	17	2	7
Reduce duplicative testing	0	0	5	17	9	30	6	20	9	30	1	3
Reduce avoidable hospital readmissions	0	0	0	0	0	0	5	17	24	80	1	3
Reduce avoidable ED visits	0	0	0	0	1	3	11	37	17	57	1	3

Source: Authors' analysis

Notes: Survey respondents were asked to "Please indicate the priority you are placing on each of the following strategies in the first performance year of your ACO."

ED emergency department

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(value = cost/quality). One of the best examples of shifting the value equation is the enhanced recovery program following all types of surgery, including colorectal. Initially popularized in Europe, they have now gained significant traction in the USA—no doubt, in part because of the shifting healthcare climate. For example, recent implementation in colorectal surgery at an academic medical center resulted in a 2 day reduction in the length of stay, lower morbidity (50 % reduction in SSI), increase in patient satisfaction, and ~$2000 reduction in hospital costs (unpublished data, Elizabeth Wick).

A key tool for driving this transition to value instead of volume is the redesign of payment models, with a shift away from fee-for-service reimbursement in favor of global budgets, population health models, and accountable care organizations (ACO). While the cost-savings with the early experiments in these care delivery models have been mixed, there is no doubt that more regions of the country will see iterations of these models implemented [4]. Much of the early focus has been on primary care and avoiding preventable utilization of acute services like emergency rooms and hospitals, eliminating variations in care, and enhancing care coordination in cohorts of medical patients like those with diabetes mellitus, chronic kidney disease, congestive heart failure, or chronic obstructive pulmonary disease. In the years to come, ACOs will likely focus more on surgical care—highlighted by a survey of ACO leadership groups which listed eliminating unnecessary surgery as a prime area of interest (Table 71-1). In the interim, as we are in a state of flux, both Medicare and private payors have instituted value-based payment contracts with the goal of incentivizing hospitals and providers to focus on reducing preventable harms like falls, hospital acquired infections, and venous thromboembolisms [5]. For more on the evolution and changes in healthcare economics, see Dr. Orangio's extensive review in Chap. 66.

The Conceptual Model of Quality Measurement: Donabedian Model

Moving to this new paradigm of care is predicated on establishing standard measures of "quality." Presently, for surgery, there is little consensus on what the key reliable, attainable, generalizable, and meaningful measures will be. One of the most common conceptual models used to describe quality measurement is the Donabedian model. Avedis Donabedian was an early health services researcher whose seminal work was "Evaluating the Quality of Medical Care," presented in 1966 [6]. The Donabedian model of measuring quality identifies three main types of improvements: changes to structure, process, and outcome (Figure 71-2). *Structure* refers to the context in which care is delivered—this includes the facility and services, workforce, and payment structure. Structural measures ask, "Are the appropriate services, equipment, incentives, and people available?" *Process* is the application of these tools, equipment, and policies/procedures to patients (i.e., good practices and evidence-based medicine). Process measures ask, "Are the right tools, policies, and equipment being used for all patients?" *Outcome* is the result on patients. Outcome measures ask, "How often are patients harmed?" In this model, structure (how care is organized) plus process (what we do) influence patient outcomes (the results achieved) [7].

Structural Measures

Much of the early focus on quality in surgery revolved around structural measures, as they tend to be the most straightforward to assess. For example, researchers correlated outcomes in colorectal surgery to hospital factors (procedural volume and specialty service availability) as well as surgeon training (colorectal board certification) and availability of ancillary services (trained pathologists for rectal cancer) [8–10]. For colorectal cancer surgery, hospital and surgeon volume, as well as board specialization, are associated with a reduction in operative morbidity and 5-year mortality [11]. Additional relationships have been identified between high-volume providers and sphincter-preserving procedures in rectal cancer—i.e., surgeons who operate on rectal cancer patients regularly are less likely to do an abdominal-perineal resection for patients in whom a sphincter-preserving operation can be considered [12].

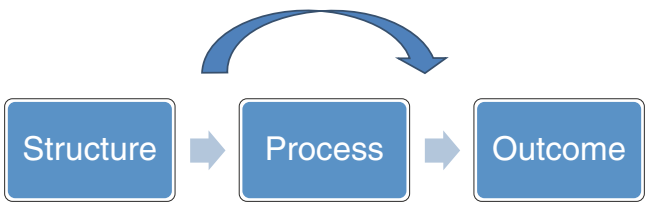


FIGURE 71-2. The Donabedian model of quality of care.

Although not as widely studied, similar relationships have been identified in complex inflammatory bowel disease surgery as well [13]. While relatively easy to quantify, the downside of volume as a measure is that it is a proxy measure and not easily "actionable" for quality improvement. There is no doubt that we all can identify some outstanding "low-volume" colorectal surgeons and as well as some "high-volume" colorectal surgeons who do not meet basic standards.

Accreditation programs are formalized processes for controlling structural measures. The most mature example of the accreditation process is in bariatric surgery. A joint venture of the American College of Surgeons (ACS) and the American Society for Metabolic and Bariatric Surgery, the Metabolic and Bariatric Surgery Accreditation and Quality Improvement Program (MBSAQIP) sets hospital standards for key physical, and human resources, as well as practice standards for bariatric surgery, and compliance is monitored with site visits. All centers are required to monitor and report their surgical outcomes to the MBSAQIP database [14–16]. CMS endorsed the program and mandated that all Medicare patients undergoing bariatric surgery must be treated in an accredited center. Although procedures done in centers of excellence were associated with superior quality by many measures, this was not reflected in a Medicare analysis and CMS endorsement of the program was discontinued in 2013 [17]. The American Society of Colorectal Rectal Surgeons and the Consortium for Optimizing the Treatment of Rectal Cancer (OSTRiCh) are a proponent of implementation of a standardized care pathways and a Centers of Excellence program for patients with rectal cancer, and has recently received an endorsement from the ACS [10, 18]. Founded in 2011, OSTRiCh currently has 144 institutions all aimed at a unified effort to improve safety and outcomes for patients with rectal cancer. The partnership is collaborating with the ACS Commission on Cancer and creating the "CoC Rectal Cancer Accreditation Program" based on their five core principles of evidence-based rectal cancer care:

- Total mesorectal excision (TME)
- Measurement of quality of surgery by specific techniques of pathology assessment
- Specialist imaging techniques identifying those patients at high risk of local recurrence
- The use of newer more effective neo-adjuvant and adjuvant therapies include radiotherapy and chemotherapy
- Multidisciplinary team (MDT) approach that identifies, co-ordinates, delivers, and monitors the ideal treatment on an individual patient-by-patient basis

Process Measures

Process measures focus on the details of care that likely lead to good clinical outcomes. Advantage of measuring quality through process measures is that most measures are evidence-based (frequently supported by high quality randomized

Table 71-2. Commission on cancer colorectal cancer measures

Colon			
ACT	Accountability	Standard 4.4 90 %	(NQF #0223) Adjuvant chemotherapy is considered or administered within 4 months (120 days) of diagnosis for patients under the age of 80 with AJCC Stage III (lymph node positive) colon cancer.
12RLN	Quality improvement	Standard 4.5 85 %	(NQF #0225) At least 12 regional lymph nodes are removed and pathologically examined for resected colon cancer.
Rectum			
RECRCT	Quality improvement	Not applicable	Preoperative chemo and radiation are administered for clinical AJCC T3N0, T4N0, or Stage III; or Postoperative chemo and radiation are administered within 180 days of diagnosis for clinical AJCC T1-2N0 with pathologic AJCC T3N0, T4N0, or Stage III; or treatment is considered for patients under the age of 80 receiving resection for rectal cancer.

AJCC American Joint Commission for Cancer

controlled trials), relatively easy to monitor for compliance, and have imminently actionable results. The major downside is that for the most part excellent compliance with surgical process measures has failed to translate into improved outcomes. The best example of this in colorectal surgery is the Surgical Care Improvement Project (SCIP) [19, 20]. The measures, originally part of a pilot termed Surgical Infection Prevention (SIP), were intended to help hospitals adopt evidence-based practices for SSI prevention. SIP was transitioned to SCIP in 2006 and endorsed by multiple organizations, including the Joint Commission and CMS, with mandatory participation. Ultimately, measure compliance was publically reported via the hospital compare website and tied to value-based purchasing contracts. SCIP measures important for the practicing colorectal surgeon were those related to timing, selection, and discontinuation of antibiotics for surgical prophylaxis (i.e., surgical site infection [SSI]) prevention, maintenance of normothermia in the operating room (SSI prevention), use of venous thromboembolic event (VTE) chemoprophylaxis, and removal of the Foley catheter by postoperative day 2 (catheter-associated urinary tract infection [CAUTI] prevention). For the past decade, hospitals devoted significant resources to implementing the SCIP measures, and for many, success was associated with a "system fix" as opposed to "work arounds," which are unfortunately rampant in healthcare—frequently harnessing the electronic health record. On the positive side, there is no doubt that surgical care is in a better place today as compared to 2003, when less than 60 % of patients were receiving antibiotics pre-operatively and many patients were recovering on inpatient units with urinary catheters in place long after they were needed. However, despite these great strides in improving care processes, it was rare for hospitals to observe associated improvements in outcomes [21, 22]. The SCIP measures were officially retired in December 2014 with a commitment by CMS to move to more outcome-based measures over the next couple of years.

Another example of process measures relevant to the practicing colorectal surgeon are the colorectal cancer measures included in the Commission on Cancer site reports and endorsed by the National Quality Forum (NQF) (Table 71-2) [23]. The NQF is a non-profit organization with representation from over 400 different stakeholder organizations and has representation from consumers, payors, medical professionals, government agencies, drug companies among others. These measures, covering factors such as pathological examination of rectal cancer specimens and (neo)adjuvant chemoradiation, highlight the multidisciplinary approach to colorectal cancer. However, the ultimate impact on those institutions that do (or do not) follow these measures remains to be determined.

Outcomes

Ultimately, the quality movement aims to make meaningful improvements in **patient outcomes**. There is no doubt that outcome measures resonate the strongest with clinicians. The challenge is that collecting, validating, and risk-adjusting outcome measures are not trivial. The two major types of outcome measures available today are from administrative data and/or clinical registries [24]. Administrative data is derived from hospital billing information and relies on the accuracy of the clinical documentation and medical coders, and is heavily focused on the inpatient stay. Examples of sources of administrative outcome data include the University Health Consortium (UHC), Premier Advisor, and Medicare. Although some measures like readmissions and length of hospital stay may be reliably obtained from this type of data, more complex clinical outcomes like SSI, pneumonia, and CAUTI are not [24]. In contrast, surgical registry data, usually nurse abstracted, audited, and risk-adjusted, is outstanding for these complex clinical variables. In colorectal surgery, the American College of Surgeons' National Surgical Quality

Improvement Program (NSQIP) is considered the "best in class" registry. The leadership has prioritized data validity, and all data is collected by a trained abstractor and the data integrity is periodically audited. The program was originally developed in the Veterans Affairs Health System (National Veterans Administration Risk Study) in the 1990s as a means to benchmark 30-day outcomes for VA hospitals to the rest of the nation. Risk adjustment was a key focus of the program, as the Veterans Affairs Hospital population was notably different than other health systems with a preponderance of older, male patients with multiple co-morbidities [25]. The program, in addition to being successful for comparing hospitals, also turned out to be a catalyst for process improvement. In 2001, with support from the Agency for Healthcare Research and Quality (AHRQ), this was expanded to the private sector in collaboration with the ACS as ACS-NSQIP [26–28]. Colorectal surgery has been a key area of focus for the program with special colectomy and proctectomy disease specific variables developed within the program (see Appendix 1). Of note, in 2015, the program was awarded the Eisenberg Award for its contributions to patient safety and quality [29].

In colorectal surgery, SSIs have emerged as one of the first outcome measures embraced as a national metric. Beginning in 2013, hospitals were mandated to monitor SSIs after colon surgery using the National Healthcare Safety Network (NHSN) program of the Centers for Disease Control and Prevention, a public registry-type database that is available free of charge to hospitals. Given, the open access nature of the program, there is little quality control, and many elements are left for interpretation by individual sites. There are three types of SSI defined by NHSN: superficial, deep, and organ space; however, the public reporting metric only includes risk-adjusted *organ* space rates. NHSN uses the standardized infection ratio to risk-adjust hospital rates for patient co-morbidities. Yet, even with this limited scope, there is great variability in the "accuracy" of the NHSN SSI rates for colectomy. As evidence, when NHSN rates are compared to those abstracted via ACS-NSQIP at the hospital level, there is little correlation—further emphasizing the complexity of developing accurate surgical outcomes measures of quality [30].

A separate domain of outcome measurement is the patient experience. Today, the CMS requires the patient experience be measured using the Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) survey. Hospitals send the survey to a sampling of patients discharged after an acute care stay. The goal is to assess hospital performance in domains that are meaningful to the consumer. Starting in 2012, hospital HCAHPS performance was included in value-based purchasing programs as legislated by the Affordable Care Act. To facilitate consumer assessment and data transparency, results are also compiled and published on the hospital compare website. As of 2015, hospitals are now rated based on survey performance using a star system [1–5].

While the Donabedian model provides a good framework for understanding elements of quality measurement, some contend that this oversimplifies the equation. An alternative is to consider composite measures which are a more global assessment of quality and include weighted structure, process, and outcome measures. An example of a composite measure is the Leapfrog Patient Safety Score for the US hospital. This measure is designed to be a standardized score for patients, providers, and healthcare purchasers to compare patient safety across hospitals, and includes 26 structural, process, and outcome measures. It is anticipated that more composite measures will be developed specific to disease management or procedures.

It is important to note that the structure, process, and outcome components of quality measurement all occur within the context of an organization's overall *culture*. The local culture impacts all aspects of the delivery of care because it affects how frontline personnel understand and deliver safe patient care. In fact, culture (i.e., the collective attitudes and beliefs of caregivers) is increasingly being recognized to be the fourth measurable component to the *structure–process–outcome* model. This recognition is based on growing evidence that local culture is linked to a variety of important clinical outcomes [7]. For any new patient safety initiative to be deemed successful, any change in structure or process must lead to a corresponding positive change in patient outcomes [31].

Safety

Patient safety is a discipline that applies safety science methodology toward creating a reliable healthcare delivery system that continuously strives to eliminate adverse events. Examples of events that stem from breaches in patient safety include wrong-site/wrong-procedure surgeries, retained foreign objects (sponges and instruments), mislabeled endoscopy or operating room specimens, unchecked blood transfusions, and overlooked allergies—all are potentially catastrophic events that can be prevented by implementing safer hospital systems. A key realization in patient safety is that adverse events occur because of a **breakdown in the system in which we operate** and are **not caused by a single person's actions**. A cornerstone of the patient safety movement is limiting blame—in the past, medical errors were thought to reflect incompetence and frequently clinicians tried to keep them undercover, essentially preventing organizations from learning from these events. There has been a dramatic change in this culture in the past decade, with all hospitals now being required to have non-punitive avenues for event reporting as well as forums for discussion and accountability for developing fixes to prevent recurrent events. Another important advance for the field was broad acceptance of "systems" thinking in healthcare—the idea that redesigning systems using a combination of clinician

input, human factors principles, systems engineering, and health information technology (among others) could result in mistakes being dramatically reduced. This approach to addressing defects and preventing adverse events can be applied at both the "micro" (e.g., developing surgical staplers that prevent accidental misfiring) and "macro" (e.g., hospital organizational structures where leaders are accountable for decisions) level.

Regrettably, healthcare is considered a high-risk system with a high error rate, but these two characteristics are not and do not have to be always correlated. In fact, other high-risk industries have managed to maintain an impeccably low error rate such as the nuclear power industry, commercial airlines, and amusement parks [32]. In the nuclear power industry, much of the credit for their safety record is due to the culture, with its insistence on individual ownership, responsibility, attention to detail, professionalism, moral integrity, and mutual respect. These characteristics have created the cultural context necessary for high quality communications under high-risk, high-stress conditions. Each reactor operator is aware of what is going on at all times and is responsible for understanding the implications and possible consequences of any action. Communication flows freely between operators and executives, and information about any mistakes that occur are dispersed rapidly through the entire system so that other workers can learn how to prevent similar mistakes in the future. Many of the principles and tools, including crew resource management and high reliability, used in these other industries are now being adapted for healthcare as tools to promote patient safety.

High Reliability Organizations

Focusing on the principle of high reliability has been proposed as a strategy to transition healthcare from a high-risk, high error rate to a high-risk, low error rate industry. Mark Chassin, the director of The Joint Commission, has been a key proponent of this approach. Writing in the April 2011 issue of *Health Affairs*, Dr. Chassin states, "What has eluded us thus far…is maintaining consistently high levels of safety and quality over time and across all healthcare services and settings. The pockets of excellence coexist…with enormously variable performance across the delivery system. Along with some progress, we are experiencing an epidemic of serious and preventable adverse events" [33]. However, high reliability organization theory suggests that proper oversight of people, processes, and technology can handle complex and hazardous activities and keep error rates acceptably low [34]. Studies of multiple high reliability organizations have demonstrated that the following principles are embraced [35]:

1. HROs are sensitive to operations (continually strive to improve the system).
2. HROs are reluctant to accept "simple" explanations for problems (do not finger point or accept simple reasons for adverse events).
3. HROs have a preoccupation with failure (always vigilant and looking for ways to prevent adverse events).
4. HROs defer to expertise (not committed to hierarchy and training, respect frontline wisdom).
5. HROs are resilient.

Developing these characteristics is an important step toward achieving a low error rate in any organization. Recognizing that the transition in healthcare will be slow and labor intensive, the Joint Commission has outlined a framework with 14 components to facilitate the transformation [33]. The components fall into three domains: leadership, safety culture, and robust process improvement. Many hospitals and health systems are mandating HRO training for all employees. Connecticut has even gone so far as to legislate this approach for all hospitals in the state with HRO training now mandatory.

Creating a Culture of Safety

Culture is to an organization what personality is to an individual—a hidden, yet unifying theme that provides meaning, direction, and mobilization [34]. One way to think about it is that one person's opinion is an attitude, while everyone's opinion is a reflection of the culture. Organizations with effective safety cultures share a constant commitment to safety as a top-level priority that permeates the entire organization. These organizations frequently share the following characteristics [36]:

1. An acknowledgment of the high-risk, error-prone nature of an organization's activities.
2. A non-punitive environment where individuals are able to report errors or close calls without fear of punishment or retaliation.
3. An expectation of collaboration across ranks to seek solutions to vulnerabilities.
4. A willingness on the part of the organization to direct resources to address safety concerns.

Traditional surgical culture stands almost in direct opposition to the values upheld by organizations with effective safety cultures for several reasons. Surgeons have been hesitant to discuss errors; rather mistakes have been equated to incompetence. Surgeons also tend to minimize the effects of stress on their ability to make decisions [37]. The surgical culture, especially in the operating room (OR), is extremely hierarchical with the surgeon at the leader. Ultimately, while there needs to be clear role clarity, hierarchy can prevent nurses and other OR staff from pointing out potential errors or mistakes made by the team, resulting in potentially preventable adverse events. Moreover, this culture is not limited to the OR. Medicine strongly values professional autonomy, which frequently promotes individualism over cooperation, but often to the detriment of patient care [38]. Finally, patient safety, although often viewed as important, is seldom promoted as an organizational priority or an organizational value.

Finally, organizations often do not feel the need to devote resources to overhauling their patient safety systems as long as they perceive their existing processes to be adequate.

Measuring Safety Culture

Efforts to foster cultural change within an organization with regard to patient safety have been limited in the past by the inability to measure the impact of any given intervention. However, studies have shown that employee attitudes about culture are associated with error-reduction behaviors ranging from the aviation industry to medicine with central line-associated blood stream infections. The Safety Attitudes Questionnaire (SAQ) and the HSOPS (Hospital Survey on Patient Safety Culture) are validated survey instruments that can be used to measure culture in a healthcare setting [39]. The Joint Commission encourages all hospitals to measure safety culture every 18 months to 2 years. The surveys consist of a series of questions measuring six domains: teamwork climate, safety climate, job satisfaction, perception of management, stress recognition, and working conditions.

As an example, in the SAQ survey, the safety climate scale portion of the questionnaire consists of the following seven items:

1. I am encouraged by my colleagues to report any patient safety concerns I may have.
2. The culture in this clinical area makes it easy to learn from the mistakes of others.
3. Medical errors are handled appropriately in this clinical area.
4. I know the proper channels to direct questions regarding patient safety in this clinical area.
5. I receive appropriate feedback about my performance.
6. I would feel safe being treated here as a patient.
7. In this clinical area, it is difficult to discuss mistakes.

Although perceptions of teamwork climate can differ as a function of one's role in the OR, perceptions of safety climate are relatively consistent across OR providers in a given hospital. Using a survey, hospitals can compare culture between different types of healthcare workers within a department as well as culture between departments throughout the institution. Scores can be compared to those of other participating institutions to compare safety climates. This allows hospitals to collaborate with one another to implement programs to improve safety culture. In addition, scores can be used to evaluate the effectiveness of safety interventions by comparing the survey safety climate scores post-implementation to baseline scores.

Strong teamwork is at the core of any effective organization and is a key element to ensuring patient safety in the OR. Teamwork is dependent on the underlying culture and patterns of communication. The ability for all team members to "speak up" about patient safety concerns is one of the most important elements of creating a culture of patient safety.

Teamwork and Communication

According to the Joint Commission, communication breakdown is one of the top three root causes of sentinel events such as wrong-site surgery. Poor communication contributed to over 60 % of sentinel events reported to the Joint Commission on Accreditation of Healthcare Organizations in 2011 [40]. Good communication is an essential component of teamwork and is especially important in the OR, one of the most complex work environments in healthcare.

Within the realm of patient care, there are enormous amounts of information being exchanged between healthcare providers on a daily basis. Much of this information, if prioritized correctly, has the potential to prevent unintended medical errors and serious harm to patients. The importance of good communication in preventing medical error is undeniable; however, it is surprisingly difficult to achieve. The traditional surgical hierarchy can prevent OR personnel from sharing important patient data and expressing safety concerns. One perioperative field study showed a 30 % rate of communication failure in the OR, with 36 % of these breakdowns having a substantial impact on patient safety [41].

In addition to overcoming the cultural barrier to better teamwork and communication, Christian and associates' prospective study of patient safety in the OR demonstrated that the standard workflow of the OR itself presents many opportunities for the loss or degradation of critical information [42]. Handoffs of patient care from the OR to other locations or providers are particularly prone to information loss, which has been demonstrated in other clinical settings. Handoffs and auxiliary tasks, such as the surgical count, frequently take place during critical portions of the case and place competing demands on provider attention from primary patient-centered activities. Communication between the surgeon and pathologist also is vulnerable, as the communication often occurs through secondary messengers such as nurses or technicians. This information loss can lead to delays, overuse of staff and resources, uncertainty in clinical decision-making and planning, and oversights in patient preparation.

Measuring Teamwork

Research in commercial aviation has demonstrated a strong correlation between better teamwork and improved safety performance. Cockpit crew members' reluctance to question a captain's judgment has been identified as a root cause of aviation accidents. Good attitudes about teamwork are associated with error-reduction behaviors in aviation, and have also translated to medicine with improved patient outcomes in ICUs and decreased nurse turnover in the OR. It is also associated with higher job satisfaction ratings and less sick time taken from work.

Safety culture surveys can be used to measure teamwork and provide benchmarks for departments or hospitals seeking to measure and improve their teamwork climate [43].

The teamwork scores are responsive to interventions that aim to improve teamwork among operating teams, such as the implementation of crew resource management or team training, executive walk rounds, and preoperative briefing team discussions. The communication and collaboration sections of the surveys reflect OR caregiver views on teamwork and can be used to distinguish meaningful interventions from impractical and ineffective programs.

In a survey of operating room personnel across 60 hospitals, the SAQ identified substantial differences in the perception of teamwork in the OR depending on one's role. Physicians frequently rated the teamwork of others as good, while nurses at the same institutions perceived teamwork as poor. These discrepancies can be attributed to differences in the communication skills that are valued by surgeons and nurses. For example, nurses describe good collaboration as having their input respected, while physicians describe good collaboration as having nurses who can anticipate their needs and follow instructions. Efforts to improve the communication that takes place between physicians and nurses can directly improve the perception of teamwork and collaboration by the OR team. Empowering well-respected surgeons to promote principles of teamwork and communication can go a long way toward transforming attitude and behavioral changes in fellow physicians, as well as other members of the surgical team. Surgeons are increasingly encouraging the respectful and timely voicing of concerns of OR personnel, and that will likely pay dividends.

Tools for Improving Safety Culture, Teamwork, and Communication

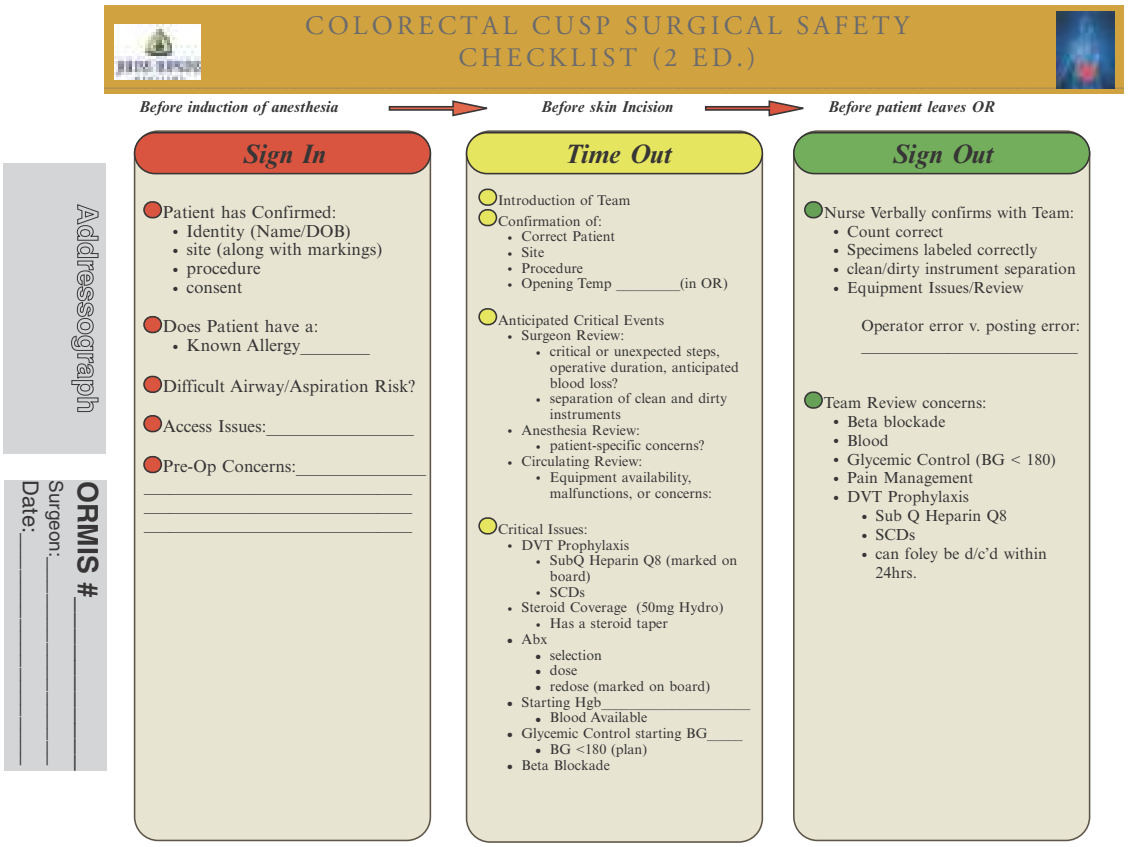
A hallmark of high reliability organizations is the frequent use of tools such as prompts, checks, standard operating protocols, and communication interventions such as team briefings and debriefings. These tools identify and mitigate hazards and allow an organization to complete tasks more efficiently. They also foster a culture of open communication and speaking up if a team member senses a safety concern. Safety checks and standardized team discussions serve as prompts to help "engineer out" human error, providing quality assurance and improving information flow. They also can prevent errors related to omissions, which are more likely to occur when there is information overload, multiple steps in a process, repetitions in steps, planned departures from routine processes, and when there are other interruptions and distractions present while the process is being executed. These same interventions have been shown to improve patient safety in ORs and ICUs [44, 45].

Preoperative briefings and checklists, when used appropriately, can help to facilitate transfer of information between team members. A briefing, or checklist, is any pre-procedure discussion of requirements, needs, and special issues of the procedure. Briefings are best when locally adapted to the specific needs of the specialty. They have been associated with an improved safety culture, including increased awareness of wrong-site/wrong-procedure errors, early reporting of equipment problems, reduced operational costs, and fewer unexpected delays. In one study, 30.9 % of OR personnel reported a delay before the institution of OR briefings, and only 23.3 % reported delays after briefings were instituted [46, 47]. OR briefings are increasingly being used to ensure evidence-based measures, such as the appropriate administration of preoperative antibiotics and deep vein thrombosis (DVT) prophylaxis, are used. Briefings also allow personnel to discuss potential problems *before* they become a "near miss" or cause actual harm.

The World Health Organization (WHO) has developed a comprehensive perioperative checklist as a primary intervention of the "Safe Surgery Saves Lives" program—an effort to reduce surgical deaths across the globe [48]. The WHO checklist includes prompts to ensure that infection prevention measures are followed, potential airway complications are precluded (e.g., anesthesia has necessary equipment and assistance for a patient with a difficult airway), and the groundwork for effective surgical teamwork is established (e.g., proper introductions of all OR personnel). Aspects of the Joint Commission's pre-procedure "Universal Protocol" (or "time-out") also are included in the checklist (e.g., checks to ensure operation performed on correct patient and correct site). The initial WHO checklist study was associated with significant reduction in mortality worldwide, but follow-up studies evaluating the efficacy of the checklist in governmental programs have failed to reproduce the same impact on morbidity and mortality. It is now understood that the efficacy of checklists is largely dependent on the safety culture in which they are implemented [47]. Simply mandating use is unlikely to change the quality of care delivered, but a system of comprehensive interventions to improve safety culture and implement checklists ***will*** likely result in meaningful improvement. Similar to briefings, it is important to adapt checklists to the local environment (Figure 71-3).

Tools such as checklists, sign outs, briefings, and debriefings improve communication between healthcare providers and create a safer patient environment. Although their use in healthcare is still highly variable, several specialties that have incorporated them, such as intensive care and anesthesia, have made impressive strides in patient safety. Currently, communication breakdowns, information loss, hand off, multiple competing tasks, and high workload are considered "annoying but accepted features" of the perioperative environment [17]. As physician attitudes toward errors, stress, and teamwork in medicine become more favorable toward the common goals of reducing error and improving teamwork and communication, medicine will likely achieve many of the milestones in safety that high reliability industries such as aviation have already accomplished.

As a major example, the comprehensive unit-based safety program (CUSP) was initially designed for the intensive care



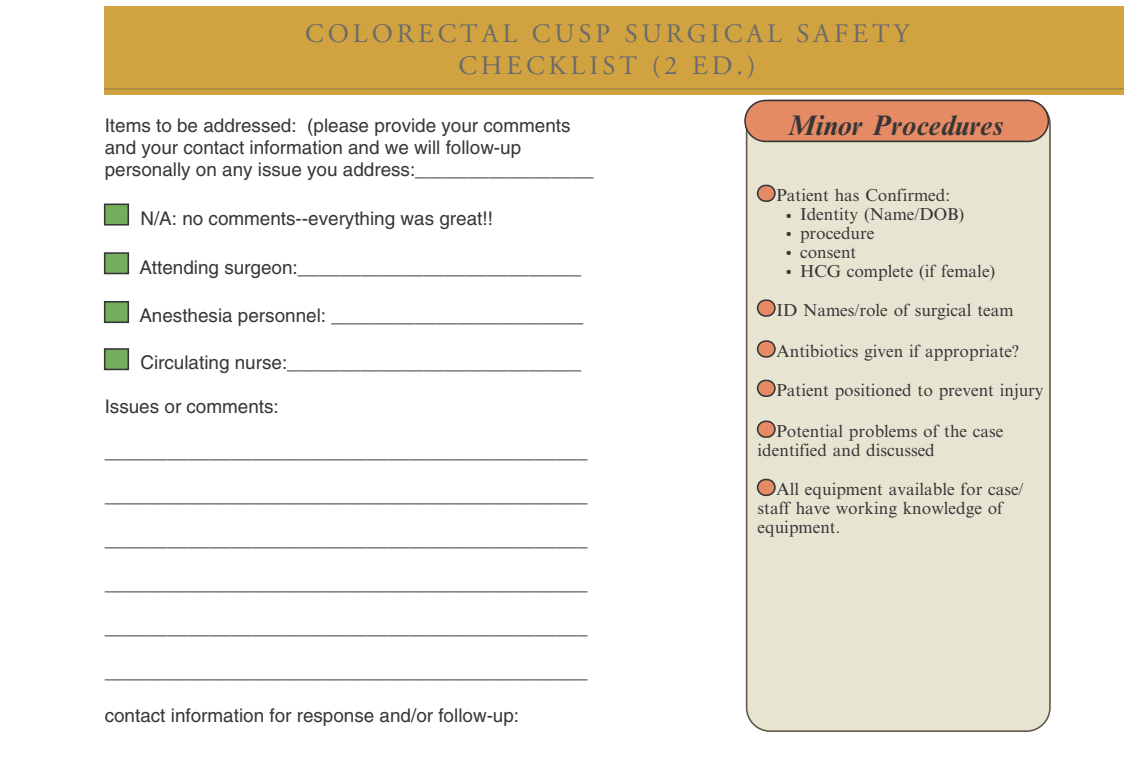


FIGURE 71-3. Local adaptation of briefing checklist to colorectal surgery. *With Permission from Hicks CW Improving Safety and Quality of Care With Enhanced Teamwork Through Operating Room Briefings JAMA Surg. 2014;149(8):863–868. doi:*10.1001/jamasurg.2014.172. *© American Medical Association 2014.*

unit, but has been translated to different clinical areas [49]. CUSP is an effective tool for improving both safety culture and clinical outcomes. Every clinical area that implements CUSP assembles a multidisciplinary team and follows five iterative steps: training on the science of safety, identify patient safety hazards, partner with senior executive, learn from defects, and implement tools to improve teamwork and communication. All teams include providers from relevant disciplines such as nurses, physicians, hospital infection control practitioners, technicians, advanced practice providers, resident physicians, and clerks. This approach has been successfully used to reduce colorectal SSIs from 27 to 18 % in a university based setting [50]. It has also been adapted to other perioperative settings across the country through a national implementation project in collaboration with the ACS [51].

"Never Events" in Surgery

Never events are errors in medical care that are clearly identifiable, preventable, and serious in their consequences for patients, and that indicate a real problem in the safety and credibility of a healthcare facility [52]. The term was popularized by Dr. Ken Kizer after the IOM report.

Criteria for inclusion as a "never event" are listed below. The event must be:

- Unambiguous (i.e., the event must be clearly identifiable and measurable, and thus feasible to include in a reporting system);
- Usually preventable, with the recognition that some events are not always avoidable, given the complexity of healthcare;
- Serious, resulting in death or loss of a body part, disability, or more than transient loss of a body function;

And any one of the following:

- Adverse and/or,
- Indicative of a problem in a healthcare facility's safety systems and/or,
- Important for public credibility or public accountability.

These events are not a reasonable medical risk of undergoing surgery that the patient must accept, but medical errors that ***should never happen***. The occurrence of any of these events signals that an organization's patient safety culture or processes have defects that need to be evaluated and corrected (Table 71-3).

Table 71-3. "Never Events"

1.	**Surgical or invasive procedure events**
1A.	**Surgery or other invasive procedure performed on the wrong site (updated)** Applicable in: hospitals, outpatient/office-based surgery centers, ambulatory practice settings/office-based practices, long-term care/skilled nursing facilities
1B.	**Surgery or other invasive procedure performed on the wrong patient (updated)** Applicable in: hospitals, outpatient/office-based surgery centers, ambulatory practice settings/office-based practices, long-term care/skilled nursing facilities
1C.	**Wrong surgical or other invasive procedure performed on a patient (updated)** Applicable in: hospitals, outpatient/office-based surgery centers, ambulatory practice settings/office-based practices, long-term care/skilled nursing facilities
1D.	**Unintended retention of a foreign object in a patient after surgery or other invasive procedure (updated)** Applicable in: hospitals, outpatient/office-based surgery centers, ambulatory practice settings/office-based practices, long-term care/skilled nursing facilities
1E.	**Intraoperative or immediately postoperative/postprocedure death in an ASA Class 1 patient (updated)** Applicable in: hospitals, outpatient/office-based surgery centers, ambulatory practice settings/office-based practices
2.	**Product or device events**
2A.	**Patient death or serious injury associated with the use of contaminated drugs, devices, or biologics provided by the healthcare setting (updated)** Applicable in: hospitals, outpatient/office-based surgery centers, ambulatory practice settings/office-based practices, long-term care/skilled nursing facilities
2B.	**Patient death or serious injury associated with the use or function of a device in patient care, in which the device is used or functions other than as intended (updated)** Applicable in: hospitals, outpatient/office-based surgery centers, ambulatory practice settings/office-based practices, long-term care/skilled nursing facilities
2C.	**Patient death or serious injury associated with intravascular air embolism that occurs while being cared for in a healthcare setting (updated)** Applicable in: hospitals, outpatient/office-based surgery centers, long-term care/skilled nursing facilities
3.	**Patient protection events**
3A.	**Discharge or release of a patient/resident of any age, who is unable to make decisions, to other than an authorized person (updated)** Applicable in: hospitals, outpatient/office-based surgery centers, ambulatory practice settings/office-based practices, long-term care/skilled nursing facilities
3B.	**Patient death or serious injury associated with patient elopement (disappearance) (updated)** Applicable in: hospitals, outpatient/office-based surgery centers, ambulatory practice settings/office-based practices, long-term care/skilled nursing facilities
3C.	**Patient suicide, attempted suicide, or self-harm that results in serious injury, while being cared for in a healthcare setting (updated)** Applicable in: hospitals, outpatient/office-based surgery centers, ambulatory practice settings/office-based practices, long-term care/skilled nursing facilities

(continued)

TABLE 71-3. (continued)

4. Care management events

4A. Patient death or serious injury associated with a medication error (e.g., errors involving the wrong drug, wrong dose, wrong patient, wrong time, wrong rate, wrong preparation, or wrong route of administration) (updated)
Applicable in: hospitals, outpatient/office-based surgery centers, ambulatory practice settings/office-based practices, long-term care/skilled nursing facilities

4B. Patient death or serious injury associated with unsafe administration of blood products (updated)
Applicable in: hospitals, outpatient/office-based surgery centers, ambulatory practice settings/office-based practices, long-term care/skilled nursing facilities

4C. Maternal death or serious injury associated with labor or delivery in a low-risk pregnancy while being cared for in a healthcare setting (updated)
Applicable in: hospitals, outpatient/office-based surgery centers

4D. Death or serious injury of a neonate associated with labor or delivery in a low-risk pregnancy (new)
Applicable in: hospitals, outpatient/office-based surgery centers

4E. Patient death or serious injury associated with a fall while being cared for in a healthcare setting (updated)
Applicable in: hospitals, outpatient/office-based surgery centers, ambulatory practice settings/office-based practices, long-term care/skilled nursing facilities

4F. Any Stage 3, Stage 4, and unstageable pressure ulcers acquired after admission/presentation to a healthcare setting (updated)
Applicable in: hospitals, outpatient/office-based surgery centers, long-term care/skilled nursing facilities

4G. Artificial insemination with the wrong donor sperm or wrong egg (updated)
Applicable in: hospitals, outpatient/office-based surgery centers, ambulatory practice settings/office-based practices

4H. Patient death or serious injury resulting from the irretrievable loss of an irreplaceable biological specimen (new)
Applicable in: hospitals, outpatient/office-based surgery centers, ambulatory practice settings/office-based practices, long-term care/skilled nursing facilities

4I. Patient death or serious injury resulting from failure to follow-up or communicate laboratory, pathology, or radiology test results (new)
Applicable in: hospitals, outpatient/office-based surgery centers, ambulatory practice settings/office-based practices, long-term care/skilled nursing facilities

5. Environmental events

5A. Patient or staff death or serious injury associated with an electric shock in the course of a patient care process in a healthcare setting (updated)
Applicable in: hospitals, outpatient/office-based surgery centers, ambulatory practice settings/office-based practices, long-term care/skilled nursing facilities

5B. Any incident in which systems designated for oxygen or other gas to be delivered to a patient contain no gas, the wrong gas, or are contaminated by toxic substances (updated)
Applicable in: hospitals, outpatient/office-based surgery centers, ambulatory practice settings/office-based practices, long-term care/skilled nursing facilities

5C. Patient or staff death or serious injury associated with a burn incurred from any source in the course of a patient care process in a healthcare setting (updated)
Applicable in: hospitals, outpatient/office-based surgery centers, ambulatory practice settings/office-based practices, long-term care/skilled nursing facilities

5D. Patient death or serious injury associated with the use of physical restraints or bedrails while being cared for in a healthcare setting (updated)
Applicable in: hospitals, outpatient/office-based surgery centers, ambulatory practice settings/office-based practices, long-term care/skilled nursing facilities

6. Radiologic events

6A. Death or serious injury of a patient or staff associated with the introduction of a metallic object into the MRI area (new)
Applicable in: hospitals, outpatient/office-based surgery centers, ambulatory practice settings/office-based practices

7. Potential criminal events

7A. Any instance of care ordered by or provided by someone impersonating a physician, nurse, pharmacist, or other licensed healthcare provider (updated)
Applicable in: hospitals, outpatient/office-based surgery centers, ambulatory practice settings/office-based practices, long-term care/skilled nursing facilities

7B. Abduction of a patient/resident of any age (updated)
Applicable in: hospitals, outpatient/office-based surgery centers, ambulatory practice settings/office-based practices, long-term care/skilled nursing facilities

7C. Sexual abuse/assault on a patient or staff member within or on the grounds of a healthcare setting (updated)
Applicable in: hospitals, outpatient/office-based surgery centers, ambulatory practice settings/office-based practices, long-term care/skilled nursing facilities

7D. Death or serious injury of a patient or staff member resulting from a physical assault (i.e., battery) that occurs within or on the grounds of a healthcare setting (updated)
Applicable in: hospitals, outpatient/office-based surgery centers, ambulatory practice settings/office-based practices, long-term care/skilled nursing facilities

Although there is widespread agreement that surgical never events are preventable and despite several national and local programs being launched to decrease them, never events are still a significant problem. A study from Mehtsun et al. showed that from 10/1990 to 10/2010, there were 9744 paid malpractice claims for never events in the USA alone. Of these, mortality was reported in 6.6 %, permanent injury in 33 %, and temporary injury in 59 %. The cost of the never events totaled 1.3 billion dollars. Also, of physicians who were named in a surgical never event claim, 12.4 % were named in another future never events claim [53].

An unintended retained surgical item refers to any surgical item found to be inside a patient after he or she has left the OR, thus requiring a second operation to remove the item [39]. Estimates of retained foreign bodies in surgical procedures range from one case per 8000–18,000 operations, corresponding to one case or more each year for a typical large hospital or approximately 1500 cases per year in the USA [54]. This estimate is based on an analysis of malpractice claims, but is likely to *underestimate* the true incidence. Retained surgical items in colorectal surgery are usually laparotomy pads, needles, or instruments. The risk of having a retained surgical item increases during emergency surgery, when there are unplanned changes in procedure (due to new diagnoses encountered in the OR), long procedures with multiple surgeons, nurses, and scrub technicians, and in patients with higher body-mass index [54]. Retained foreign objects are most commonly identified on postoperative imaging, either incidentally or as part of an evaluation for pain or obstructive symptoms. In virtually all cases where there is a delay in identifying the retrained foreign object, review of the original operating room record will reveal a correct surgical count—a "falsely correct count." This occurs in 21–100 % of cases with retained foreign object [55]. Given this, it is recommended that an X-ray is obtained at the completion of an operation if there is any concern for a foreign body based on confusion regarding the counts by even a single member of the OR team, or in the presence of a risk factor. There is also growing interest in using sponges with radiofrequency identified laparotomy pads to eliminate human error from the equation. While these systems virtually eliminate retained laparotomy pads, other items can still be retained. Interestingly, retained foreign objects do still occur even when the final count is "incorrect"—though this usually occurs when there is poor communication among the operating room team. Institutional policies for standard operating protocols in the case of an incorrect count (such as requiring a mandatory radiograph while the patient is still in the OR) can avoid conflict among caregivers and mitigate the likelihood of a retained surgical item occurring as a result of a known incorrect count. Additionally, fostering a culture of safety in the operating room where everyone feels comfortable speaking up in the case of an adverse event will also go a long way to preventing this unfortunate scenario.

Patient and Families as Partners

Historically, risk management professionals and legal counsels have recommended against open lines of communication between providers and patients about patient safety events and medical errors; however, one of the hallmarks of the patient safety movement is a new commitment to disclosure of the risks associated with procedures, occurrence of patient safety events, and the recognition of the patient as an essential partner in the delivery of safe, cost-effective care. In the chronic disease literature like diabetes, hypertension, and congestive heart failure management, it is clear that patients who are active participants in their care achieve better outcomes. It is less clear what this looks like in the acute care setting. A study by Waterman et al. revealed that most hospitalized patients very much want to participate in their care (91 %) to prevent medical errors, but it was highly variable as to the tasks they would embrace—with 85 % being agreeable to asking about medication indications versus only 46 % willing to question providers about hand hygiene. Many believe that shared decision-making is the pinnacle of patient-centered care. At present, though, what encompasses shared decision-making in surgery is evolving. It is generally defined as the patient and physician sharing responsibility in the clinical decision-making process (two way dialogue), and incorporating the patients' values and beliefs in that process. Technology and decision support aids are emerging as an important tool in implementing this approach in surgery. While medicine has yet to fully incorporate and achieve buy-in for this concept, it represents another component of allowing all members of the healthcare team, patient, and providers to actively participate in achieving the best outcomes possible.

Conclusions

The fields of quality and safety have seen exponential growth in the past 15 years. Much of the terminology is now commonplace. Ultimately, to realize meaningful improvement in surgical care, we need valid, meaningful, and transparent measures available for all hospitals. Policy makers must support development of a culture where hospital leaders can declare a goal of zero preventable harm and work to establish an enabling infrastructure, and a system of accountability [56]. As colorectal surgeons, we must be dedicated to acquiring the competencies and serving as leaders in improvement efforts.

Appendix 1

American College of Surgeons National Quality Improvement Program Targeted Colectomy and Proctectomy Procedure Measures. With permission from © American College of Surgeons.

AMERICAN COLLEGE OF SURGEONS
NATIONAL SURGICAL QUALITY IMPROVEMENT PROGRAM
PROCTECTOMY
PROCEDURE TARGETED WORKSHEET

*IDN _____ Cycle Number _____
LMRN _____ Case Number _____

DEMOGRAPHICS

Last Name: _____ First: _____ MI: _____
Street Address: _____
City/Town: _____ State/Province: _____ Zip: _____ Country: _____
Home Phone (____) _____ Work Phone (____) _____ Cell Phone (____) _____
*DOB: ____/____/____ *(mm/dd/yyyy)* Gender: ☐ *Male* ☐ *Female*
Race: ☐ White ☐ American Indian / Alaska Native ☐ Asian
☐ Black / African American ☐ Native Hawaiian / Other Pacific Islander ☐ Unknown
Ethnicity: Hispanic - ☐ *YES* ☐ *NO* ☐ Unknown Preferred Language: ☐ ENGLISH ☐ SPANISH

SURGICAL PROFILE

Principal Procedure _____ CPT® Code _____

Patient Status: ☐ *Inpatient* ☐*Outpatient* Elective Surgery: ☐ *YES* ☐ *NO* ☐ *Unknown*

Origin Status:
☐ Not transferred, admitted directly from home
☐ Transfer from other (i.e. Spinal Cord Injury Unit or other facility not listed)
☐ Acute Care Hospital (inpatient status only)
☐ Transfer from outside Emergency Department
☐ Nursing Home/Chronic Care Facility/Intermediate Care Unit
☐ Unknown (if transferred from unknown location or Facility)

Hospital Admission Date: ____/____/____ *Operation Date: ____/____/____

Anesthesia Technique:
☐ General ☐Spinal ☐ Epidural ☐ Regional ☐ Local ☐ MAC/IV Sedation ☐None ☐Other ☐Unknown

Additional Anesthesia Technique(s)
☐ General ☐Spinal ☐ Epidural ☐ Regional ☐ Local ☐ MAC/IV Sedation ☐None ☐Other ☐Unknown

*Surgical Specialty: *(select one)*

1. General Surgery 3. Thoracic 5. Orthopedics 7. Urology 9. Plastics
2. Vascular 4. Cardiac 6. Neurosurgery 8. Otolaryngology (ENT) 10. Gynecology
11. Interventional Radiologist

Surgeon NPI: _____

Attending Surgeon's Name: _____ Attending Surgeon's IDN: _____

LCN: _____ Encounter Number: _____

Preoperative Risk Assessment

GENERAL				RENAL		
Height	_____	*Inches*	*CM*	Acute Renal Failure w/in 24 hrs	*YES*	*NO*
Weight	_____	*Pounds*	*KG*	Currently requiring or on Dialysis w/in 2 wks	*YES*	*NO*
Diabetes Mellitus	*Non-Insulin*	*Insulin*	*NO*	NUTRITIONAL/IMMUNE/OTHER		
Current Smoker w/in 1 year		*YES*	*NO*	Disseminated Cancer	*YES*	*NO*
Dyspnea	*Mod. Exertion*	*At Rest*	*NONE*	Open Wound (w/ or w/out infection)	*YES*	*NO*
Functional Health Status	*I*___ *PD*___	*TD*___	*Unk*___	Steroid/Immunosuppressant use for chronic condition	*YES*	*NO*
PULMONARY				>10% loss of body wt. last 6 months	*YES*	*NO*
Vent. Dependent w/in 48 hrs		*YES*	*NO*	Bleeding disorders	*YES*	*NO*
COPD (severe)		*YES*	*NO*	Preop Transfusions (RBC units w/in 72 hrs)	*YES*	*NO*
HEPATOBILIARY				Sepsis w/in 48 hours	*SIRS*	*NO*
Ascites w/in 30 days		*YES*	*NO*		*Sepsis*	
CARDIAC					Sep Shock	
CHF w/in 30 days		*YES*	*NO*			
Hypertension req. meds.		*YES*	*NO*			

Tumor Location in the Rectum
☐ N/A ☐ Lower Third ☐ Middle Third ☐ Upper Third ☐ Unknown

Chemotherapy within 90 Days
☐ Yes ☐ No ☐ Unknown

Radiation Therapy within 90 Days
☐ Yes ☐ No ☐ Unknown

Pretreatment Clinical Staging- Primary Tumor "T"
☐ N/A ☐ Tx ☐ T0 ☐ Tis ☐ T1 ☐ T2
☐ T3 ☐ T4 ☐ T4a ☐ T4b ☐ Unknown

Pretreatment Clinical Staging- Regional Lymph Nodes "N"
☐ N/A ☐ Nx ☐ N0 ☐ N1 ☐ N1a ☐ N1b
☐ N1c ☐ N2 ☐ N2a ☐ N2b ☐ Unknown

Pretreatment Clinical Staging- Distant Metastasis "M"
☐ N/A ☐ M0/Mx ☐ M1 ☐ M1a ☐ M1b ☐ Unknown

Complete Evaluation of the Colon Preoperatively
☐ Yes
☐ No-no study identified
☐ No-study was incomplete, obstructing lesion in the colon
☐ No-study was incomplete, entire colon could not be visualized
☐ No-study was incomplete, prep was inadequate
☐ Unknown

Patient Marked for Stoma Preoperatively
☐ Yes
☐ No

Laboratory Data

LABORATORY DATA: *(report preop lab values closest to the Procedure/Surgery start date & time)*
Preop values should be within 90 days prior to surgery

PREOPERATIVE LAB DATA	Value 90 days	unknown	Date
Serum Sodium (Na)		☐	___/___/___
Blood Urea Nitrogen (BUN)		☐	___/___/___
Creatinine (Cr)		☐	___/___/___
Albumin (ALB)		☐	___/___/___
Total Bilirubin (TB)		☐	___/___/___

Serum Glutamic-Oxaloacetic Transaminase (SGOT)/(AST)		☐	___/___/___
Alkaline Phosphatase (Alk Phos)		☐	___/___/___
White Blood Count (WBC)		☐	___/___/___
Hematocrit (Hct)		☐	___/___/___
Platelets (Plt)		☐	___/___/___
Internat'l Normalized Ratio (INR)		☐	___/___/___
Partial Thromboplastin Time (PTT)		☐	___/___/___

OPERATIVE INFORMATION

Emergency Case: ☐ YES ☐ NO

Wound Classification: ☐ *Clean* ☐ *Clean/Contaminated* ☐ *Contaminated* ☐ *Dirty/Infected*

Surgical wound(s) closure:
☐ All layers of incision (deep and superficial) are fully closed by some means
☐ Only deep layers of incision are closed; superficial layers are left open
☐ No layers of the incision are surgically closed

ASA Class *(circle one)*: *1 2 3 4 5 6 None Assigned (for local ones. only)*

OPERATIVE TIMES: Procedure / Surgery Start: _____:_____ Procedure/Surgery Finish: _____:_____

Pathologic Staging- Primary Tumor "T":
☐ N/A ☐ Tx ☐ T0 ☐ Tis ☐ T1 ☐ T2
☐ T3 ☐ T4 ☐ T4a ☐ T4b ☐ Unknown

Pathologic Staging- Regional Lymph Nodes "N"
☐ N/A ☐ Nx ☐ N0 ☐ N1 ☐ N1a ☐ N1b
☐ N1c ☐ N2 ☐ N2a ☐ N2b ☐ Unknown

Number of Nodes Evaluated
☐ _____ ☐ Unknown ☐ N/A

Pathologic Staging- Distant Metastasis "M"
☐ N/A ☐ M0/Mx ☐ M1 ☐ M1a ☐ M1b ☐ Unknown

Margins-Radial
☐ N/A ☐ Yes, margin was clear ☐ No clear mass: margin was positive ☐ Unknown

Clear Radial Margin cm
☐ CM_____ ☐Unknown

Margins-Distal
☐ N/A ☐ Yes, margin was clear ☐ No clear mass: margin was positive ☐ Unknown

Clear Distal Margin cm
☐ CM_____ ☐Unknown

Operative Approach:
☐ Open (planned)
☐ Laparoscopic
☐ Laparoscopic with open assist
☐ Laparoscopic with unplanned conversion to open
☐ Robotic
☐ Robotic with open assist
☐ Robotic with unplanned conversion to open
☐ Endoscopic
☐ Endoscopic with open assist
☐ Endoscopic with unplanned conversion to open
☐ NOTES
☐ NOTES with open assist
☐ NOTES with unplanned conversion to open
☐ SILS
☐ SILS with open assist
☐ SILS with unplanned conversion to open
☐ Other MIS Approach
☐ Other MIS Approach with open assist
☐ Other MIS approach with unplanned conversion to open
☐ Combination of approaches not otherwise specified
☐ Combination of Approaches not otherwise specified with open assist

☐ Combination of approaches otherwise specified with unplanned conversion to open
☐ Other
☐ Unknown

Additional Operative Procedures

Other Procedure	CPT
1.	
2.	
3.	
4.	
5.	
6.	
7.	

Concurrent Procedure	CPT
1.	
2.	
3.	
4.	
5.	
6.	
7.	

Occurrences

POSTOPERATIVE OCCURRENCES: ☐ YES ☐ NO
(Although not required for this program, you may wish to document 'treatment' and 'outcome to date' of the occurrence for internal quality monitoring)

			Date	Treatments / Outcomes / Comments
Wound Occurrences				
Superficial Incisional SSI	☐ YES	☐ NO	____/____/____	_____
Present at Time of Surgery?	☐ YES	☐ NO		
Deep Incisional SSI	☐ YES	☐ NO	____/____/____	_____
Present at Time of Surgery?	☐ YES	☐ NO		
Organ/Space SSI	☐ YES	☐ NO	____/____/____	_____
Present at Time of Surgery?	☐ YES	☐ NO		
Wound Disruption	☐ YES	☐ NO	____/____/____	_____
Respiratory Occurrences				
Pneumonia (PNA)	☐ YES	☐ NO	____/____/____	_____
Present at Time of Surgery?	☐ YES	☐ NO		
Intraop OR Postop Unplanned Intubation	☐ YES	☐ NO	____/____/____	_____
Pulmonary Embolism	☐ YES	☐ NO	____/____/____	_____
On ventilator > 48 hours	☐ YES	☐ NO	____/____/____	_____
Present at Time of Surgery?	☐ YES	☐ NO		
Urinary Tract Occurrences				
Urinary Tract Infection (UTI)	☐ YES	☐ NO	____/____/____	_____
Present at Time of Surgery?	☐ YES	☐ NO		
Report the most significant level				
Progressive Renal Insufficiency	☐ YES	☐ NO	____/____/____	_____
Acute Renal Failure	☐ YES	☐ NO	____/____/____	_____
CNS Occurrences				
Stroke / CVA	☐ YES	☐ NO	____/____/____	_____
Cardiac Occurrences				
Intraop OR Postop Cardiac Arrest req. CPR	☐ YES	☐ NO	____/____/____	_____
Intraop OR Postop Myocardial Infarction	☐ YES	☐ NO	____/____/____	_____
Other Occurrences				
Transfusion Intraop/Postop (72h of surgery start time)				
(transfusion of 1-200 units)	☐ YES	☐ NO	____/____/____	# of units transfused: _____
Vein Thrombosis req. Therapy	☐ YES	☐ NO	____/____/____	_____
Sepsis: Sepsis	☐ YES	☐ NO	____/____/____	_____
Present at time of surgery?	☐ YES	☐ NO		
Septic Shock	☐ YES	☐ NO	____/____/____	_____
Present at time of surgery?	☐ YES	☐ NO		
Other Postoperative Occurrences (ICD-9 code):			____/____/____	(ICD-9 code) _____

Anastomotic Leak:
☐ No
☐ Yes-Leak, no treatment intervention of any kind documented
☐ Yes-Leak, treated with NPO, antibiotics, TPN or other non-interventional, non-operative means
☐ Yes-Leak, treated with percutaneous/radiological/endoscopic interventional means
☐ Yes-Leak, reoperation
☐ Unknown

Prolonged Postoperative NPO or NGT Use: ☐ Yes ☐ No ☐ Unknown

Hospital Discharge Information / Readmissions / Mortality / Reoperations

Acute Hospital Discharge Date: _____/_____/_____ *(mm/dd/yyyy)*

Discharge Destination:
☐ *Skilled Care Facility, not Home* ☐ *Home* ☐ *Expired*
☐ *Unskilled Facility, not Home* ☐ *Separate Acute care (transferred to another acute care facility)* ☐ *Unknown*
☐ *Facility which was Home* ☐ *Rehab*

Post-op ICD.9 Code _____ **Diagnosis:** _____

Still in hospital > 30 days: ☐ *YES* ☐ *NO*

Death:
Death during operation OR Postop Death w/in 30 days: ☐ YES ☐ NO
Date of death: _____/_____/_____ ☐ Unknown

Postop Death > 30 days: *(if remained in acute care)* ☐ YES ☐ NO
Date of death: _____/_____/_____ ☐ Unknown

Readmission: (Multiple Readmissions Can Be Entered)

Was there a readmission for any reason within 30 days of the principal operative procedure?
☐ YES ☐ NO ☐ Unknown
If yes, date: _____/_____/_____
Information Source (select one) ☐ Medical Record ☐ Patient/Family Report ☐ Other

Was this readmission unplanned at the time of the principal operative procedure? ☐ YES ☐ NO

Was this readmission likely related to the principal operative procedure? ☐ YES ☐ NO

•If likely related, choose the primary suspected reason (postoperative occurrence)

Superficial SSI	Pulmonary Embolism	Intraop or Postop Cardiac Arrest req CPR	Other: ICD-9 code_____ Free Text:_____
Deep SSI	On ventilator > 48 hours	Intraop or Postop Myocardial Infarction	
Organ / Space SSI	Progressive Renal Insufficiency	Transfusion Intraop/Postop (72h of surgery start time)	
Wound Disruption	Acute Renal Failure	Vein Thrombosis Requiring Therapy	
Pneumonia	Urinary Tract Infection (UTI)	Sepsis	
Intraop or Postop Unplanned Intubation	Stroke / CVA	Septic Shock	

•If the readmission is unrelated, choose the primary suspected reason (postoperative occurrence)

Superficial SSI	Pulmonary Embolism	Intraop or Postop Cardiac Arrest req CPR	Other: ICD-9 code_____ Free Text:_____
Deep SSI	On ventilator > 48 hours	Intraop or Postop Myocardial Infarction	
Organ / Space SSI	Progressive Renal Insufficiency	Transfusion Intraop/Postop (72h of surgery start time)	
Wound Disruption	Acute Renal Failure	Vein Thrombosis Requiring Therapy	
Pneumonia	Urinary Tract Infection (UTI)	Sepsis	
Intraop or Postop Unplanned Intubation	Stroke / CVA	Septic Shock	

Unplanned Reoperation:

Did the patient have an unplanned return to the operating room for a surgical procedure w/in the 30 day postoperative period? ☐ *YES* ☐ *NO*

If yes, Surgery Date or Unknown: ____/____/_____

Source *(select one)* ☐ Medical Record ☐ Patient/Family Report ☐ Other

CPT code _____

If yes, was the return to the OR for a postop occurrence likely related to the principal operative procedure?
☐ YES ☐ NO

If yes, record the ICD code _____ or diagnosis description_____

Did the patient have a SECOND unplanned return to the operating room for a surgical procedure, w/in the 30 day postoperative period?
☐ YES ☐ NO

If yes, Surgery Date or Unknown: ____/____/_____

Source *(select one)* ☐ Medical Record ☐ Patient/Family Report ☐ Other

CPT code _____

If yes, was the return to the OR for a postop occurrence likely related to the principal operative procedure?
☐ YES ☐ NO

If yes, record the ICD code _____ or diagnosis description_____

Were there more than two unplanned re-operations for a post op occurrence likely related to the principal operative procedure within 30 days? ☐ *YES* ☐ *NO*

FOLLOW-UP

Follow Up Within 30 Days

Were you able to follow the case for the full 30 days? ☐ *YES* ☐ *NO*
(NOTE: Answer yes for death w/in 30 days)

If you were unable to obtain the 30-day follow up information:

A) How many days (0-29) were you able to follow this case? _____

B) Which attempt methods were used for follow-up? Select all that apply.
(A minimum of three attempts should be made to contact the patient)

Method	# of attempts	Method
☐ Phone	_____	☐ Documentation
☐ Letter	_____	☐ Other

Patient Contact Management:

Contact date: ____/____/_____ Contact Action: ☐ Phone ☐ Letter ☐ Document ☐ Fax ☐ E-mail ☐ Other

Contact Results:

☐ No Answer	☐ Letter Received	☐ Incorrect Number
☐ Left Message	☐ Talked to Patient	☐ Patient Refused
☐ Letter Sent	☐ Talk to Family	

Contact Notes:

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72
Practice Management

Eric M. Haas

Key Concepts

- Lack of awareness about practice management could lead to poor career decisions, financial distress, and surgeon burnout.
- If joining a hospital model, a surgeon may have benefits of a work RVU-based compensation, as well as the support and resources of the institution. However, the surgeon may need to align their personal goals to the goals of the institution and accept lack of autonomy for purchasing and decision-making.
- In the private practice model, the physician is essentially self-employed, their goals and practice mission are basically aligned, and decisions are made real-time to meet the immediate needs of the practice. However, the financial state of the practice figures into decision-making and can limit the physician's ability to realize their goals.
- Revenue in the private practice model is based on professional fee collections and ancillary investments, while the hospital model generates revenue through professional fees, facility fees, downstream revenue, market share, and outcome incentive programs.
- Effective marketing and networking are necessary to develop and maintain relationships with patients and referring physicians.

Introduction

While solid medical knowledge and sound surgical skills are paramount for colorectal surgeons, practice management is an essential—and often overlooked—consideration for a successful career. Practice management is a broad term that covers all daily operations of a surgical practice, including the practice model, office operations, financial planning, patient interaction, personnel, technology, medical records, marketing and business development, coding, billing, reimbursement, practice set up, and compensation. Most commonly, the principles of practice management are not considered at the start of one's career, and many of the key concepts are not addressed in residency or fellowship. The subject of the "business of medicine" is often thought of as distasteful, and therefore not discussed among young surgeons. As a result, new surgeons may not be aware of many considerations and the implications of their decisions when accepting a job and joining a specific practice model.

Patients are consumers, and consumers demand high quality care at a low cost to be satisfied. To meet these needs, physicians and practice administrators must think outside of the box when designing their practice model. They need to look to a model that is reliable, efficient, and effective at producing a high quality outcome and a happy customer. That ideal business may be a fast-food chain restaurant. Fast-food restaurants are a demanding, high-volume, customer-focused industry. Proper management in these chains has a system of consistent, reproducible products and customer satisfaction in place before the restaurant opens, and management continues to oversee the daily operations to ensure the systems meet pre-determined goals at every level. Regardless of the time of day, geographic location, or franchise specifics, they are a model of efficiency, reproducibility, standardization, and excellent customer service to meet expectations. A customer can walk into a McDonald's in Houston, Texas at 6 am or a McDonald's in Cleveland, Ohio at 6 pm, place the same order, and receive the same product at the same price with the same overall experience. This cannot occur without a system of process control, standards, check and balances, and quality improvement. The same concepts apply to medical practice management.

In reality, the paradigm that discussing the business of medicine is uncouth should be replaced with the model that unawareness of practice management could lead to poor career decisions, financial distress, and surgeon burnout. Awareness of the many business-related aspects of practice management can help meet the current challenges with

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patient satisfaction, physician satisfaction, and financial solvency. In today's practice environment, the business of medicine may dictate one's ultimate aspirations, achievements, and job satisfaction. Burnout is a critical issue, impacting an estimated 25 % of surgeons [1]. Studies have demonstrated burnout is directly associated with a diminished quality of life, quality of practice, and quality of care provided, by increasing the likelihood of medical errors [1–3]. Without addressing the root causes, more serious complications can result, including depression, suicidal ideation, and alcohol abuse [1–3]. Practicing in an unfit environment is a main factor leading to burnout, as physicians cannot achieve their optimal work-life balance needed for personal and professional career satisfaction [4]. Colorectal surgery has been reported as the surgical specialty with the highest job satisfaction in young surgeons within their first 10 years after board certification [5]. Thus, understanding practice management and guiding colorectal surgeons to the best fitting practice model to continue reports of high job satisfaction and high performance is a challenge for the American Society of Colon and Rectal Surgeons.

While surgeons can control outcomes in the operating room, understanding practice management is essential to actually practicing medicine and running a successful operation in line with one's expectations and goals. This chapter cannot replace the detailed books and course offerings essential when setting up a practice; however, it's a good introduction to the fundamental key concepts of practice management. This chapter also uniquely focuses on the physician and physician satisfaction. The concentration is on finding the best environment for the surgeon to start and maintain a successful practice, with the assumption that a surgeon must be content, comfortable in their environment, and working in line with their own expectations in order to provide quality surgical care and produce excellent patient outcomes and satisfaction. In this chapter, we aim to describe the key principles of practice management for colorectal surgeons. Unlike other chapters in this text, "Practice Management" is not written based on the history, evidence, and published literature on the topic. The chapter is written based on personal experiences, anecdotal learning, best practices, and pearls from colleagues in private practice, hospital, and academic settings on opening, developing, and practicing in an ideal colorectal surgery practice model.

Practice Models

For the purposes of this chapter, there are two main practice models in which a colorectal surgeon can practice: institution-based and private practice. The institution-based model encompasses hospital, university, and academic institutions. Under this broad umbrella are the environments of hospital employee and university employee. Integrated Health Care Models, such as Kaiser Permanente, which offer not-for-profit health plans and insurance, a tax-exempt shelter for the for-profit medical groups, and physician-owned for-profit partnerships, are also considered in the institution-based category [6]. Private practice models include solo and group practices, including single specialty and multispecialty group practices. Each model has unique merits and limitations and regardless of which model you work in, there are common considerations. To simplify, we will refer to the models as "hospital" and "private practice" throughout this text.

Practice Philosophies in Hospital and Private Practice Models

There are several philosophic differences between the hospital and private practice models that are important to understand and consider before deciding which pathway to follow. Entering into an agreement without fully understanding and addressing the philosophical and practical components of the work environment is what often leads to physician discontent, underperformance, and burnout. When choosing a practice model, multiple factors must be taken into consideration including the overall mission and goals of the workplace, the practice environment, compensation and benefits packages, future opportunities and job advancement, performance and production expectations, and levels of autonomy. With the various models and considerations in mind, one can choose the best fitting model for their individual needs, professional expectations, and career success. A summary of the distinctions between the hospital and private practice models is seen in Table 72-1.

The Hospital Model

The primary mission of the hospital or institution-based model centers around serving the needs of the community to improve overall patient care and offering value over competitors in the marketplace. These lofty goals are not necessarily aligned with the individual needs and goals of the employed surgeon. The hospital administrators' goals are for the hospital system to be profitable, serve the community, achieve local, regional, and national recognition, and advance research and teaching. In theory, this will lead to increased patient market share, physician resources, institutional name recognition, and professional growth for both the institution and the physician. Many of the components for success in the hospital model may not result in the individual surgeon's personal job satisfaction. Once part of the larger hospital model, the surgeon may need to conform their personal goals and agenda to the goals of the division, department, and institution. When joining a hospital model, the physician is an employee and, as such, loses the ability to make independent decisions regarding staffing, purchasing, recruiting, growth and expansion, and office administration and processes. Even when afforded certain levels of decision-making, there are generally layers of bureaucracy in place,

Table 72-1. Distinctions between the hospital and private practice models

Overall gestalt	Carry out the global goals of the hospital's strategic mission	Concentrate on patient care and the needs of the doctors
Role of the hospital	Employed	Self-employed; voluntary medical staff member to facilitate patient care
Practice philosophy	Physicians exist to help meet the mission of the hospital and assure the hospital is profitable	Hospital exists to help me care for my patients
Management	CEO, CFO, Board of Directors, Vice Presidents, and many clinical/administrative department, division, and group heads	Managing partner, practice administrator, office manager
Decision-making process	Formal processes of committees, administration, and the Board of Directors; decisions take a longer time to make and are met with resistance, and often require negotiation for action	Made by individual or group of physicians; decisions often be made to address immediate needs
Time frame of action	Weeks to months for action; layers of bureaucracy to navigate through and consideration of the hospital's strategic plan and budget cycles	Real-time implementation to address current needs
Communication	Bureaucratic, numerous meetings, and politics	Autonomist, consensus decision-making
Resources	More resources available, but acquisition more difficult	Limited resources based on financial state of the practice
Culture	Group, formal organization	Individual, informal organization
Staffing	Run by the institution's Human Resources department. Formal processes for hiring and firing, which may interfere with physician's staffing preferences	Physician has direct control over staffing decisions
Compensation	Salary, Relative Value Unit (RVU) based	Collections based
Outcome metrics	Data acquisition and reporting supported by the hospital system and data widely available; source of revenue for the hospital	Data acquisition not feasible: expensive and labor intensive

which delay adaptation of changes. In the typical employed environment, the surgeon is accountable to a direct boss, and multiple levels of supervisors—many of which are not physicians—and may not always see patient care and professional needs through the eyes of the surgeon.

Physician advancement in the hospital model is generally based on a combination of performance evaluations and financial productivity. Institutions may also provide incentives for high patient satisfaction, clinical outcomes, academic achievements, and participation in graduate medical education. Financial productivity is assessed on meeting the budgetary calculations of the employed surgeon's proforma, their individual total "cost" with salary, benefits, and overhead. The proforma is composed of the surgeon's calculated cost center, which factors in overhead, salary, and benefits. The concept of a cost center is important to understand and is germane to most institution's budget calculations. A surgeon's cost center is the total costs based on calculated direct and indirect costs attributed or assigned to each individual employed physician. The components of one's cost center may vary from hospital to hospital, but is imperative to understand what overhead is assigned into one's budget. Achievement of cost neutrality based on one's individualized budget will be assessed at a quarterly and yearly basis and, if not achieved, may result in salary reductions and other negative consequences. Clinical outcome metrics are typically measured using federal programs, such as the National Surgical Quality Improvement Program (NSQIP) and the Centers for Medicare and Medicaid Physician Quality Reporting System and Readmission Reduction Program [7–10]. Some institutions offer bonuses or incentives for the surgeon to achieve at or above expected outcomes benchmarks. Additionally, patient satisfaction is often measured using the Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) survey of patients' perspectives of hospital care [11, 12]. HCAHPS are important for hospitals to realize national incentives.

There are numerous benefits specific to joining a hospital model. First, in the current unstable healthcare environment, being employed by a hospital or institution lends stability and security. Contracts range from 3 to 5 years, and many surgeons find the appeal of "guaranteed" income outweighs the potential for higher income in private practice. The hospital model provides layers of support, experience, and expertise, allowing for multidisciplinary care of complex surgical patients that would be difficult to achieve in the private practice model. With that support comes layers of administrative help to mitigate the non-medical responsibilities of the physician, and experts in the legal, compliance, and coding fields to attenuate exposure to scrutiny and liability. There is also the prestige of association with an established, recognized hospital system. In addition, there are greater opportunities for mentoring, research, and career development in the hospital model than a private practice due to the sheer size, funding, and infrastructure of the institution. The hospital model has greater market share and holds significantly more leverage over payers, resulting in much higher contracted fee schedules for reimbursement than private practice. This can further translate into a stable environment in regards to salary expectations. There are additional benefits, such as the built-in referral base from the large number of referring doctors employed by the hospital. Lastly, hospital models usually offer robust benefit packages and a resource-based relative value scale compensation model that will be addressed in the next section.

The Private Practice Model

In private practice, the mission of the practice and physician are basically aligned at every level. However, the financial state of the practice can limit the physician's ability to realize many of their goals and aspirations. The primary goal of a private practice model is to provide a working environment that fosters best practices in patient care and satisfaction among patients, staff, and physicians—all while proving to be a viable and profitable arrangement. The private practice administrator's goals are to provide a sound workflow, a profitable system for the doctors, and high rates of job satisfaction. This will ultimately lead to high patient satisfaction, which will bring in more patients and lead to continued growth to successfully compete in the community and service area. The philosophy of a private practice is to meet the immediate needs of the doctors and the patients with the surgeon as autonomous. Surgeons in private practice are self-employed and serve as a voluntary medical staff member at the hospital to facilitate patient care. Decisions are made in the best interest of the practice, and made real-time to meet the immediate needs of the practice. The practice may make expenditures without a formal review or budget approval regarding the financial consequences. In contrast, institutions will usually need to justify the cost, benefit, budget, and cost centers at multiple levels before making any decisions or purchases, leading to frustrating delays. The private practice physician usually needs to seek a consensus from their associates or partners, but there is little bureaucracy governing needs, rationing requests, or granting permissions.

In private practice, physician advancement is typically based on the individual's productivity measured in patient collections and the time they have been a part of the practice. Although national recognition and academic pursuits into graduate medical education and scientific research may be an important part of a private practice, these components are secondary to the financial success of the practice. The support systems that are offered by the hospital model cannot be duplicated in the setting of private practice. Private practice models lack the infrastructure, economic resources, and incentives to perform intensive data collection and reporting efforts for formal benchmarking programs. Private practices generally do not measure clinical outcomes, patient satisfaction, or productivity against national standards. Clinical outcomes are followed anecdotally and measured through conference participation, such as multidisciplinary tumor boards and morbidity and mortality to gauge individual outcomes. Patient satisfaction is measured from individual relationships with patients, colleagues, referral sources, and Internet-based patient reviews rather than federal HCAHPS programs. Productivity metrics and financial viability of the practice is also generally addressed with the practice accounting firm in a less formal process compared to the hospital setting. Monthly accounting-based metrics are personalized to the practice needs and rarely involve a formal budgetary process.

There are specific benefits to the private practice model. There is the freedom of being your own boss, making your own decisions, and implementing changes to meet the immediate needs of the patients and the practice. The physician can maintain personal goals, preferences, and identity without the need to negotiate with third part administrators. There is also no restriction on the ability to invest in ancillary health care services, such as outpatient surgery or endoscopy centers, which have become a significant source of additional income for many practicing surgeons. In contrast, hospital model doctors rarely have the ability to participate in physician-owned businesses or maintain entrepreneurial interests in future developments. Lastly, one can maintain the intellectual property and patents on any research or devices in the private practice model. These rights are usually owned by the hospital when employed.

The Basics of Payment, Compensation, Profits, and Billing

To first understand compensation, it is important to understand the financial platforms from the perspective of the private practice and hospital models. In private practice, the financial relationship with the hired surgeon is based primarily on collections from professional fees generated by the surgeon. Professional fees are relatively universal and based primarily on Medicare and federal allowable rates, as well as negotiated rates from third party commercial payors. In the private practice model, salary and compensation plans are closely linked to the profitability of the surgeon, which is reflected in the amount of collections they bring into the practice, less the overhead attributed to that surgeon. Maximizing workflow, efficiency, and productivity financially rewards the surgeon. Although professional fee collections are the main source of practice income, many private practice surgeons seek outside healthcare-driven investments as secondary income sources. These secondary sources of revenue are generally physician-owned or physician-partnered surgery, endoscopy, or ancillary service organizations. There are many financial, legal, and ethical considerations that factor into a decision to partner with an investment entity. Although there are many successful and profitable agreements, there is a certain level of risk and exposure with any agreement, and professional accounting and legal investigation of the investment is paramount regardless of how tempting the investment may appear. In general, outside investment opportunities are not offered until the practice surgeon has established a sound patient base and reputation.

While the private practice model bases revenue streams on professional fee collections and, to a lesser extent, ancillary investments, the hospital model has several major avenues to generate revenue including professional fees, facility fees, downstream revenue, market share, and outcome incentive

programs that are not available in the private practice setting. Professional fee reimbursement is usually a percentage higher than private practice since the hospital or institution usually has market share, which allows them to negotiate a higher allowable fee schedule. Facility fee reimbursement is the allowable amount of fee that a hospital collects for having the procedure or encounter performed at their institution. Facility fees are multiples of the professional fees, making a tremendous profit for the hospital facility with each procedure and visit. In addition, downstream revenue adds further to the profitability. Downstream revenue is the revenue generated through the patient's utilization of hospital services during their encounter, including radiology, pathology, radiation oncology, medical oncology, cardiac catheter labs, and other services. The professional fees generated from consulting doctors are also a source of downstream revenue if those doctors are hospital-employed physicians. Hospitals also generate profit by gaining market share of a service area. Once a hospital accrues a critical mass of physicians, it has a sizable market share and can represent physicians collectively to negotiate with third party commercial carriers for reimbursements above Medicare rates and even above private practice negotiated rates. Finally, the fifth source of revenue stream is realized through federal incentives and reimbursement programs by accumulating and reporting data points of outcomes and satisfaction metrics. The greater the volume of patient encounters, the greater the ability to receive incentives based on the volume of data points. Employed physicians should understand the multiple ways hospitals gain profitability through their employment relationship to gain negotiating leverage.

The downside of employing a surgeon from the hospital perspective is the high associated costs and inefficiencies of management and administration of a doctor's practice. Hospitals are notorious for abundant and excessive layers of administration and human resources with resulting higher indirect costs that far exceed those of a private practice model. The overhead of the employed surgeon usually outweighs the revenue generated from the professional fee collections. Although there are many variations by institution, for each employed colorectal surgeon, the hospital may assume an estimated loss of up to $200,000 per year. The goal of the hospital administrator is to achieve cost neutrality, where the overhead of the surgeon is equal to the revenue generated from professional fees alone. In this scenario, the hospital achieves pure profit from the other revenue streams generated from every patient encounter that the surgeon brings to the hospital through facility fees, downstream revenue, market share, and incentives programs. The pros and cons of the two main models are seen in Table 72-2.

There are other models that exist where the hospital system functions as an academic center, with well established direct and tertiary referrals independent of the surgeon employee. In this setting the surgeon is usually offered a salary and incentives that may be independent of financial productivity.

Compensation

There are several different compensation models used in practice. Depending on the practice model, various models may be offered. In this section, we will address the most common types for each practice model, with emphasis on the relative value scale system, which plays a role in all models.

Relative Value Scale System

Hospital models usually follow a Resource-based relative value scale (RVU). The RVU system was developed by the Centers for Medicare and Medicaid Services in 1992, based on the Medicare Physician Fee Schedule, to assign numeric value to encounters and procedures based on the difficulty of the service provided, the risk involved, and the overall care requirements of the patient [13]. In the USA, Medicare uses RVUs and nearly all health maintenance organizations (HMOs) to determine how much money providers should be paid for physician services, including office visits and surgical procedures [14]. Every procedure and Current Procedural Terminology (CPT) procedure code has an RVU assigned to it for reimbursement rates. Each RVU has three components associated with calculation for payment: physician work (54 %), practice expense (41 %), and malpractice overhead (5 %). The work component reflects the physician's relative time and intensity associated with furnishing a service and is known as work RVU (wRVU). The practice expense component reflects the costs of maintaining a practice, including costs for office space, supplies and equipment, and staff. The malpractice overhead piece represents the costs of malpractice insurance. Each of the three RVU components is adjusted by geographic region (GPCI) to create a compensation level for that service.

Table 72-2. Pros and cons of the hospital versus private practice model

Model	Hospital	Private practice
Pros	– Stable environment	– Maintain freedom, autonomy, and personal goals and aspirations
	– Prestige of institution	– Better total compensation
	– Mentoring and research opportunities	– Opportunities to supplement income with outside investments
	– Favorable benefits, RVU compensation	– Maintain intellectual property over research and devices
	– Federal incentives for participation in data collection and outcomes metrics	
Cons	– Cannot invest in ancillary care centers	– No formal benchmarks for outcomes or satisfaction
	– Own the individual's intellectual property, research, and patents	

RVU-Based Compensation

While the RVU system was initially developed as a payment method for the Medicare fee schedule, the role of RVUs has expanded and been adapted for physician compensation and productivity. Many institutions use the work component of the RVU system as the basis of their compensation package. In this model, a base salary is calculated based on an expected amount of production measured as wRVU. Annual compensation reports and benchmarked trends are available annually from the Medical Group Management Association (MGMA) and the American Group Medical Association (AGMA) [15, 16]. Recent surveys estimate the 50th percentile salary for colorectal surgeons in the first 5 years of practice between $262,000 and $360,000, [17, 18], and the median wRVUs at approximately 6500 [19]. Based on these estimates, hospitals will generally set the wRVU expectations or threshold at 50 % MGMA, then use the MGMA salary data to offer a salary commiserate with the 50 % level for colorectal surgeons. RVUs are weighted to reflect patient complexity and standardized nationally, so they can also serve as a valid metric for clinician productivity [13]. The hospital will reassess these benchmarks at the end of each year, and may adjust the wRVU threshold, which will affect the base salary. Some contracts allow a 2- or 3-year ramp up period in which to achieve the threshold wRVU without incurring reductions in salary.

When negotiated appropriately, the wRVU-based compensation model serves the employed physician well, and can be a major advantage of joining a hospital practice. Benefits of the wRVU-based system are that physicians can concentrate more on patient care and less on uninsured rates or insurance type. Since the hospital model usually assigned the coding and billing to a separate center out of the immediate control of the employed surgeon, there is comfort in that actual collections does not directly effect the surgeon's compensation. It is important for new physicians to realize they will likely not attain their wRVU threshold in their first year after entering practice. A common mistake in the wRVU-based model is to set one's wRVU threshold low for fear of not meeting goals. The disadvantage here is that income will also be reduced, as the wRVUs are linked to a specific salary. We recommend setting the wRVU level at least at the 50th percentile, and having a contract stipulating no penalties for not meeting threshold during the initial 2 years.

Production-Based Compensation

The second model is "production-based compensation." In this model, compensation is closely linked to surgeon's actual collections rather than wRVU. A surgeon joining the practice will usually be offered a starting salary based on established MGMA values for the first year or two and then is offered partnership or a compensation plan where the salary is proportionate to collections less overhead. There are rarely any wRVU calculations figured into this model, as it is the actual collections that translate into profitability. Table 72-3 demonstrates Medicare allowables for common colorectal procedures. Bonus plans are based on excess cash flow once collections attributed to the surgeon are offset by the surgeon's salary and attributed expenses. In this model, the surgeon needs to be very involved in billing and collections because unlike the hospital model, where wRVU-based compensation is received regardless of billing, in the production-based compensation model actual collections received by the practice are the most important factor.

TABLE 72-3. Example of wRVU payment formula for common colorectal procedures

Common colorectal procedures	wRVU value per unit	Medicare allowable
CPT 99203—New patient visit, moderate severity	1.42	$110.09
CPT 46221—Rubber band ligation	2.36	$278.46
CPT 45378—Screening colonoscopy	3.69	$223.34
CPT 46260—Surgical hemorrhoidectomy	6.73	$493.84
CPT 44204—Laparoscopic-segmental colectomy	26.42	$1604.27
CPT 44145—Open low anterior resection	28.58	$1728.83

The conversion factor is 35.7547 for Houston, TX

Non-Production Based Compensation

Non-production based compensation is typically a salary-based plan seen in the university academic setting. The incentive plan is based on various determinants—patient care production in the form of wRVU, education, research, and academic endeavors. Academic centers set the average compensation on MGMA or AGMA benchmarks, then adjust the overall salary based on the percentage of time attributed to each of the parameters. For instance, a surgeon scientist may have 30 % of their salary dedicated to research and education requiring a lower wRVU threshold by 30 %. Other centers offer a baseline salary that is set according to the level of scholarship, and offer bonus incentives based on academic achievements.

Bonus Structure

Bonus payments may also differ between hospital and private practice models. Hospital-based bonuses are usually wRVU-based. Once one reaches the threshold wRVU established in their contract, a bonus is calculated by multiplying each wRVU above the threshold level by a conversion factor. For example, with an individual's threshold of 6500 wRVU, each wRVU above that level will be multiplied by a conversion factor ranging from 20 to 75 dollars per wRVU, resulting in the bonus. The conversion factor differs significantly among institutions. Some institutions build in a security gap—an arbitrary, set number of wRVUs above your threshold where no bonus is paid out until exceeded. For instance, in the individual with a threshold of 6500 wRVU, if a gap of 500 wRVU is set, they will not realize their bonus until 7000 wRVU has been achieved. From the hospital's vantage point,

this gap helps guard against losses from wRVUs that may not be reimbursed, such as indigent care.

The second form of hospital-based bonuses is a collection-based model. In a collection-based structure, the surgeon recoups a percentage of collections minus expenses once the threshold wRVU number is attained. This model places risk on the surgeon, who has little control over collections in the hospital setting and should be avoided when possible.

Private practice bonus models usually begin 1 or 2 years after employment and correspond with the surgeon's ability to bring in revenue above expenses. Some practices have a formal partnership offer after 1–3 years. The downside is that most of these partnerships come with a "buy-in" provision. The concept of partnership varies significantly among practices and the surgeon candidate should fully understand the partnership arrangements before signing the initial employment contract.

In summary, for a hospital-based model, the most favorable contract is production based using a wRVU model with threshold that is at the 50th percentile of national benchmarks for base salary. We recommend a wRVU-based bonus structure because it guarantees a bonus after reaching threshold regardless of the uncertainty of reimbursement, allowing the colorectal surgeon to maintain a level of control. In the private practice model, beginning salary should be at MGMA levels and once the surgeon is able to attain collections above expenses, they should be eligible for bonus structure.

Budgets, Billing, and Collections

In a hospital model, a budget is created by the hospital, including expected income and expenses, with quarterly reviews. As a hospital employee, you have limited control over multiple parts of the budget, especially indirect costs, and you will be held accountable for staying in the black. In the hospital model, the surgeon also surrenders control over billing and collections. There are dedicated departments to code and bill. This can be advantageous in that these responsibilities can be cumbersome and at times overwhelming as long as collections do not directly affect your pay scale as it does in private practice. It is still highly recommended to be knowledge of billing and coding fundamentals and to be able to review what the hospital is processing. Even if not directly linked to your salary, under-coding and under-billing for your work will reflect poorly on your budget in one way or another.

In private practice, there is no budget per se. There is a dynamic balance sheet that tracks the current state of the practice's finances without holding any individual accountable for the financial state. Billing is the engine of the ship for private practice models. Whether to have an in-house billing department or outsource billing is a very important decision to consider. Establishing an in-house billing department should be the final step of independent practice management. Initially, outsourcing billing is recommended as it gives the surgeon proper time to dedicate to developing a practice, establishing patient flow, and all having all aspects of the business process in place before taking on the responsibilities of billing, coding, and compliance. Outsourcing also provides a valuable learning resource in the billing company to help the physician understand the billing, coding, and revenue cycles. The ultimate goal is to transition the billing tasks in-house, as no third party billing company has the personal stake in collections for your practice that you do. Ensure you understand the basics and have your practice system running smoothly before making this change to ensure efficient and effective billing practices.

When moving the billing system in-house, ensure a billing manager is appointed to oversee the financial side of the practice. A financial "Checks and Balance" system should also be in place. We recommend three levels where numbers and revenue cycles are evaluated to minimize risk of exposure and theft from the practice. Options to assess the numbers are a professional accountant, the billing manager, the surgeon, and the practice manager. We caution against having any one person evaluate the numbers alone. Finally, the role of the front office should be stressed in billing. The front office staff is responsible for verifying insurance coverage and creating a "superbill" for each office visit, so education on billing and collections should include this part of the practice.

Billing and Coding

Billing and coding are an essential part of today's medical practice, and a basic comprehension of these principles is essential fund of knowledge for a colorectal surgeon in any practice model. There are many facets to billing and coding for time and procedures, and the systems are continually undergoing modifications, so the colorectal surgeon needs to understand the basics and stay on top of new developments.

While coding may be auto-generated through electronic Practice Management Systems, the surgeon should be as familiar with the coding points, levels, and compliance as they are with staging of colon cancer. If encounters are over- or under-coded, you could expose yourself, your practice, and your institution to scrutiny. Regardless of the model in which you practice, it is recommended that you code for patient encounters and procedures yourself. In the hospital model, compliance officers and coding personnel will review the operative reports and patient encounters to generate the codes to submit to payors. It is important that the employed surgeon assumes an active role in this process and reviews the codes, as well as provides feedback to the coding officers. This is the ideal collaborative model, as the surgeon enlightens the coders of the technical aspects of the encounters and procedures, while the certified coding personnel understands tips and tricks to optimize reimbursement. While this will initially be time consuming, it's an important part of practice management to do this regularly. Furthermore,

the process will become streamlined quickly, as the coding team becomes familiar with your practice and common procedures, and the surgeon learns the key elements to include in the documentation process. In the private practice model, the billing departments may outsource to a third party billing company; in this scenario, the coding process is similar to that of the hospital. In private practice models where billing is performed in-house, it is important to consider having a certified coder as part of the billing department to perform self-audits and review coding practices. There are educational resources on billing and coding for the surgeon, including the American College of Surgeons CPT Coding Workshops [20]. Often more than one course is needed to learn the full breadth of technical billing details. At a minimum, the physician should aim to learn from these courses (1) how to bill for office visits and be compliant with regulations, and (2) how to bill for surgery.

There are two main types of billing and coding for reimbursement that applies to surgeons—one reflects patient encounters in the office or hospital setting, called Evaluation and Management, and the other represents surgical procedures, called CPT codes. Evaluation and Management (E/M) codes are the billing codes used to document the patient–doctor encounter such as a history and physical exam. They were introduced in the 1992 update of Physicians' CPT, with published documentation guidelines updated in 1997 by the Centers for Medicare and Medicaid Services. Full documentation for the 1992 and 1997 guidelines is available online in the Evaluation and Management Services Guide provided by the Centers for Medicare and Medicaid Services [21]. The E/M codes have very specific reporting, documentation, and compliance guidelines. The codes for each encounter are detailed on a "superbill," an itemized record of services generated by the office for an outpatient visit and the main data source for creation of healthcare claim. It is strongly recommended to become very familiar with the guidelines to ensure proper coding and compliance.

For surgical procedures, CPT procedure codes are used. CPT was developed by the American Medical Association, and new editions are updated annually. Each procedure is assigned a CPT code with descriptors. CPT codes for surgery of the digestive system include 40490–49999. Regardless of whether an E/M or CPT code is used, all codes require a diagnosis code. For diagnosis, International Statistical Classification of Diseases and Related Health Problems, ninth edition (ICD-9) codes are currently used, but will be evolving to ICD-10 codes. ICD-9 codes are similar to E/M and CPT codes, except that they identify the diagnosis on the claim, not the procedure performed. These codes link the diagnosis to the patient encounter, and it is imperative to document the appropriate codes to avoid denials from the insurance plans. Common ICD-9 codes for colorectal surgery are seen in Table 72-4. The importance of proper coding cannot be emphasized enough. If the CPT or E/M codes and the ICD-9 diagnosis codes are not properly chosen, the claims may be deemed medically unnecessary and not covered by payors.

TABLE 72-4. Common ICD-9 diagnosis codes for colorectal surgery

(078.11) Condyloma acuminatum
(211.3) Benign neoplasms/polyps of the colon
(211.4) Benign polyps of the rectum or anal canal
(153) Malignant neoplasm of colon
(154) Malignant neoplasm of rectum and anus
(455.2) Internal hemorrhoids with other complication
(455.4) External thrombosed hemorrhoids
(455.9) Residual hemorrhoidal skin tags
(555) Regional enteritis
(555.0) Crohn's, small intestine
(555.1) Crohn's, large intestine
(556.9) Ulcerative colitis, unspecified
(562.1) Diverticulosis of colon
(562.11) Diverticulitis of colon, NOS
(564.01) Slow transit constipation
(564.02) Outlet dysfunction constipation
(564.1) Irritable bowel syndrome
(565) Anal fissure and fistula
(565.0) Anal fissure nontraumatic
(566.0) Abscess perianal
(569.1) Rectal prolapse
(569.3) Bleeding rectal
(787.6) Incontinence of feces
(787.99) Change in bowel habits

The approval or denial of services will be relayed to patients in an Explanation of Benefits (EOB). An EOB is how the insurance company processes a claim. After an encounter or surgical procure, an EOB statement will be generated and sent by the health insurance company to the covered patient and provider explaining the treatments and services covered by the payor. It is good practice for physicians to review EOBs frequently to better understand how the system actually works and appreciate the patient's point of view when undergoing a medical encounter. The EOB will show the surgeon's codes and allowable reimbursements, as well as the adjusted rates and any reasons for denials of the claim. By reviewing EOBs often, the surgeon will gain a better appreciation of the work entailed with insurance processes and enrich their understanding of how to code and bill appropriately and effectively.

In summary, it is essential for the physician to be familiar with E/M, CPT, and ICD-9 coding, as well as billing documentation, such as the superbill and the EOB to ensure proper practice management. We also recommend the physician participates in billing and coding to stay actively involved in reimbursement and proper compliance for their procedures and services.

Setting Up Your Office

Starting a practice and setting up your office in any model requires many considerations in order to be successful. When you sign a contract and join a practice or hospital, patients and referrals are not usually lined up at your door. There is a fine art to recruiting and retaining patients, fostering relationships with referral sources, colleagues, and staff. This

section discusses the basics of contracts, how to attract patients and referral sources, as well as joining and leaving a practice.

Attracting Patients

Healthcare is a business, and patients are the customers; without them, the practice will fail. The classic three A's of medicine continue to be true and pertinent—a physician must be available, affable, and able. In reality, attracting and retaining patients goes far beyond the classic A's, and is an essential part of practice management. There are four main methods to attract patients: physician referrals, insurance referrals, word of mouth, and marketing. The paramount referral source is from fellow physicians, however, there are many obstacles in this path. Most established physicians have already developed strong bonds and referral relationships with other surgeons that will be difficult to tap into. Younger, less established doctors may be more open to developing relationships with new surgeons; however, they usually do not have large patient base. In addition, there are now outside pressures on many referring physicians to direct referrals to certain locations and surgeons depending on the economic environment they practice in. For instance, referring physicians may participate in a hospital or outpatient partnerships and will tend to refer patients to other participant surgeons in that entity. Hospital employees may also be directed to refer to other fellow employees. Despite this reality, physician referrals are by far the most valuable referral source. Primary care physicians and gastroenterologists are the major focuses for a colorectal surgeon. A busy gastroenterologist will refer out an estimated 2–4 patients per month in need of a colorectal resection. Try to identify these gastroenterologists in your community and align yourself with them. Most will refer to a set list of surgeons. The established gastroenterologist will usually initiate basic anorectal and straightforward referrals to a new surgeon in the community to develop a comfort level with their patient care before referring patients for colon resections. If one positions themselves as the eager recipient of all referrals, you will quickly establish a very positive reputation with referral sources.

Another avenue to develop relationships with referring physicians is to find physicians who may not have an established, "go-to" colorectal surgeon. Gynecologists and urologists are potential sources of many referrals, which may be open to establish a relationship with you. These specialties are highly concentrated on preventive care and screening, which could be a rich referral source for colonoscopy. Another approach is to seek doctors outside of your immediate medical service area who do not have a colorectal surgeon in their community. These outside physicians need a tertiary-level referral, have typically never met the referring physician, and will instantly develop a special personal relationship with you for giving them the respect of traveling out for a face-to-face visit.

Networking is another essential way to meet and retain referring doctors when starting in practice. There are two main ways to network: office visits or working the doctor's lounge. An office visit can be frustrating, as the surgeon may need to wait, reschedule their own activities to take time out during the day, and meet opposition from the targeted physician's staff for disrupting the office flow. Despite these obstacles, it is very important to try to meet the doctors in their office. If you make an office visit, be sure to make an impression and try to make a personal connection to have that impression last. Be especially cognizant in your interactions with the office staff, as the front office personnel may be in control of your cards and referrals. Ask specifically if there is a referral coordinator or referral nurse. It would be valuable to explain your line of service and make a connection with them. If you just leave cards or leave the office with the feeling that the physician will not send you patients, the premonition is likely correct. Additionally, realize that the doctor's staff may just as important as the doctor to obtain future patients. The other valuable way to network is in the doctor's lounge of the hospital. New partners in our practice are encouraged to put on the "Freshman 15" by making the doctor's lounge their home outside of the operating room, being present for every meal there at every hospital they work at. Networking and meeting the other doctors in the hospital can bring a plethora of referrals. There are other methods of networking to be aware of: insurance plans are a minor referral source, as you will be listed as a provider for all plans you accept, but a source nonetheless. Word of mouth is a more powerful source of referrals. However, a physician typically needs to be established in practice and have earned a solid reputation from clinical outcomes and patient experiences before word of mouth occurs.

Finally, marketing has great potential to bring in patients. The effort you put into marketing will be directly related to your outcomes. Consider hiring a consultant familiar with the region of your practice to assist with networking and business development in the community. It is essential to provide a presence on the internet and have a landing page linking your practice site to the hospitals website, where potential patients can understand who you are, what you do, and what might set you apart from other surgeons. The importance of Internet presence cannot be over emphasized. Harness the power of social media on sites like Facebook, Twitter, LinkedIn, Google+, Doximity, Sermo, and doc2doc, which allow direct connections and education to an unlimited number of potential patients and referral sources. After seeing satisfied patients, professionally direct them to online ratings to share their experience and expand your name as a quality colorectal surgeon in the community. Encourage satisfied patients to write reviews, on physician and other popular review sites such as Vitals, Healthgrades, RateMDs, and Ucompare. Review sites have become a key source to pick-

ing a doctor, and are used by as many as 25 % of patients to help choose physicians. A negative review is inevitable, and best countered by having a plethora of positive reviews. Finally, market yourself directly by giving grand rounds in the hospitals, sponsoring community events, and working with local chapter of relevant colorectal agencies, such as the Colon Cancer Alliance and the Crohn's & Colitis Foundation of America.

Playing Nicely with Others

It is essential to learn how to practice effectively without estranging referrals, as alienating other physicians can hurt your reputation and bottom line. A prime example is colonoscopy by the colorectal surgeon. Since gastroenterologists' per capita can be the largest referral source, a new colorectal surgeon entering a practice area should be cautious when performing colonoscopies. With this regimen, you could alienate yourself from the established gastroenterologists, who may feel you are attempting to cut into their practice. Consider the consequences of promoting yourself as performing routine, screening colonoscopies. If you choose to perform a substantial volume of screening colonoscopies, a prudent option may be to perform the procedures in a center where you are not directly competing with established gastroenterology colleagues. Also, be very cautious of performing future surveillance colonoscopy on a patient who was referred to you for a colon resection by a gastroenterologist. Often the colorectal surgeon is placed in a precarious position as the patient will entrust the surgeon for future care and insist they not return to the original referring gastroenterologist. In this situation, it is very important to remain loyal to your referring doctor, and not assume the future colonoscopies, or you could lose future referrals. Another word of advice is to avoid performing upper endoscopy procedures. While you are trained and may be proficient in these procedures, performing upper endoscopy as a colorectal surgeon is likely to be seen as a threat to your referring doctors. For patients that require both upper and lower scopes, consider referring them to a gastroenterology colleague. This will strengthen your relationship with your possible referral source, show respect for their line of work, expertise, and established practice patterns, and the single referral will come back to you in spades. It may also be beneficial to refer patients who will require medical management to gastroenterology initially, such as Crohn's disease patients, to scope, diagnose, initiate treatment, and medically optimize. These situations are an opportunity to spare your patients from repetitive procedures and build your relationship with your referring doctor.

Another important consideration is your relationship with the general surgeons. Colorectal surgeons are fully trained and competent to perform most general surgery procedures following fellowship. It may be tempting to market yourself as a "full service" colorectal surgeon, who is happy to perform common general surgery procedures, such as a laparoscopic cholecystectomies and inguinal hernia repairs. One may even choose to be in the general surgery call rotation, as a means to keep busy, earn extra income, and establish relationships with consultants and referring doctors. However, there are major consequences of including general surgery duties in your practice, and this decision should be carefully considered. First, marketing yourself as a general and colorectal surgeon may alienate the established general surgeons. While your goal may be to increase your overall case volumes, network, and establish referrals, you may instead cost yourself referrals, damage your reputation, and jeopardize acceptance by established peers in your new practice environment. A better strategy is to align yourself with the general surgeons. Show your colleagues you are not a threat, can work side-by-side with them, and even assist them with undesirable cases, like the inevitable perianal abscess consult in the middle of the night. With this strategy, before long, the general surgeons will refer you the complex anorectal and colorectal procedures as well. A second concern before incorporating general surgery into your practice is that once you develop the reputation as performing general surgery, it will be difficult to transition to a colorectal-based practice. Your general surgery referral sources that helped you get busy initially will not take well to the fact when you inevitably want to remove yourself from the general surgery arena. In addition, as you move away from general surgery cases to concentrate on colorectal cases, it will be very difficult for you to pick and choose which referrals you will accept without offending your referring physicians. If you cherry pick your patients in this manner, you run the risk that your referral base could run dry for both general and colorectal cases.

Staff and Colleagues

In private practice, hiring and terminating staff and associates to ensure all patient needs are being met falls under the role of practice management. Adding new staff to your practice is one of the most costly aspects of practice management and can entail extensive research, interviewing, and training to ensure that staff member is appropriate for the practice and their position. When interviewing staff members, take note of how often the candidate has moved from prior jobs, their reasons for leaving, and their attitude towards prior employers. A staff member with a history of a job changes every few months is likely to continue that trend. Almost as important as interviewing the candidate is communicating with the candidate's most recent employer and references provided for a more in-depth view of the applicant and their work habits. Be weary of the candidate who does not permit you to contact their supervisor, under the pretense that their employer does not know they are looking for a job and might fire them for going out to interview. It is essential to com-

municate with a candidate's current or prior employer so you can make an informed decision about hiring them.

Successful practice management requires effective communication from the staff with patients. The first impression a patient obtains of you is often through your staff and often the patients misidentify your staff's words as coming directly from you. When your staff talks to a patient, the patient often feels the information relayed is directly from the physician, which is most often not the case. While it may seem superficial, appearances matter and reflect the professionalism of the surgeon. Assure the potential staff member's appearance will be perceived as friendly, approachable, and appropriate. Take the time to train staff on effective patient communication techniques, as all medical office personnel come into contact with patients in some capacity. Also, take the time to appropriately educate the staff on aspects of colorectal surgery and your specific practice preferences. Good patient communication at the office level will improve customer satisfaction, reflect positively on the professionalism of the doctor, and often lead to positive feedback back to your referring doctors. Conversely, poor or inappropriate communication will often portray the surgeon as incompetent, uncaring, and unprofessional, even though the surgeon may have no idea that such conversations are occurring. You might be surprised to hear your staff turn down potential patient because they do not understand all of the services you provide or give (un)solicited medical advise that goes well beyond their duties and responsibilities. As a new surgeon, take the time to educate your staff, listen to how they communicate with your patients, and give continuous feedback until you are confident that your practice is being represented appropriately.

Contracts

When joining any practice, an employment contract is part of process. Having a contract attorney review the terms and conditions before entering into any arrangement is a strong recommendation. While considering a contract, there are two main questions to answer: (1) What am I getting into, and (2) What are the options if things do not go as planned. The items to deliberate to answer the first question include compensation, bonus structure, benefits, causes for termination, coverage duties and call responsibilities, cure period to address and "cure" issues before termination, tail coverage and insurance, practice restrictions (confidentiality, proprietorship), and the contract term (automatic renewal versus set time frame). At the start of a surgeon's career, it is common to have a 2–3 year contract, and then different terms offered thereafter. If a short-term contract is presented, you should try to negotiate the terms of the second contract at the time of the original contract, as your negotiating power is significantly diminished after signing the original contract.

How to exit a practice is an important but often overlooked part of a contract. Regardless of how promising the opportunity appears you should always understand all option and consequences of early termination. Often these terms are not discussed, reviewed, or understood until the physician is ready to make a change. It is better to negotiate the possibility of leaving at the start of an exciting position than when trying to exit, as the physician may be desperate and lack negotiating power.

Finally, before entering into any contractual employment agreement, it is essential to seek professional legal representation. There are specialized lawyers for the healthcare industry who can explain the nuances of the language, terms, conditions, and penalties detailed in the contract to assure you fully understand what you are entering into before signing. All too often, young surgeons choose to bypass legal consultation, either for the cost, time involved or belief that it is just not necessary. This is an unnecessary risk that can be very detrimental, especially at the start of ones career. Avoid the risk and assure you obtain legal representation before committing to an employment agreement. The essential components of an employment contract and terms of termination are seen in Table 72-5. These variables are broken down into two overall themes—terms of employment and terms of termination of employment. These variables are not meant to incorporate every aspect of a contract, but to direct you to the key features that need to be addressed.

Considerations When Moving Between Practice Models

An increasing number of physicians are selling their practices to hospitals and becoming hospital employees. Key trends driving the increase are cuts in reimbursement, a rise in the uninsured population, reform challenges, practice expenses, and work-life balance [22]. Hospitals welcome the trend, as physician employees enhance their competitive position in local and regional markets, generate revenue and patient volumes to maintain the financial strength of the hospital, advance improvements in clinical and translational research, achieve synergies among academic and clinical program development activities, and leverage new models for healthcare delivery and health services management [21]. There are many factors to consider when transitioning from private practice to a hospital system. First, there is the change in practice model philosophies. The private practice surgeon will give up various degrees of autonomy. They will now have a boss and levels of non-physician employees to report to. The goals and success of the hospital are often not aligned and independent of the physician's goals and happiness. Further, they may feel that the goals of their superiors interfere with their practice. This will require understanding, compromise, and preparation. The compensation model

Table 72-5. Essential components of an employment contract

	Hospital model	Private practice model	Notes
a. Terms of Employment:			
Reporting structure	X		Responsible party or parties that you directly report to and the chain of command
Partnership tract		X	The criteria to become a practice partner; usually defined by time invested in the practice
Salary and compensation	X	X	Collections based versus RVU based
Bonus structure			Various models exist and can be individualized based on your practice environment
Benefits	X	X	Health and dental insurance, paid time off, retirement, medical malpractice, life, and disability insurance
Continuing medical education (CME)	X	X	Allowance for continuing medical education, including conferences, travel, and housing accommodations
Intellectual property	X	X	Rights to research, patents, inventions, and other creations developed during terms of employment
Clinical duties and responsibilities	X	X	Service area of admitting hospitals and practice locations, call coverage
Academic responsibilities	X		Expectations of productivity, presentations, teaching, mentorship, and publications
Secondary income from healthcare related interests	X		Ownership interests in surgical centers, hospitals, pathology labs, radiology centers, and other healthcare entities
Consulting income	X		Consulting, honoraria, educational courses and lectures, and expert witness legal fees
b. Terms of termination:			
Causes for termination	X	X	Defined causes for termination including loss of license, misconduct, fraud, failure to perform duties defined in the contract
Tail coverage	X	X	Malpractice coverage extending after employment to cover any claims made while employed in prior coverage
Cure period	X	X	A specified period of time to adequately and appropriately correct a material breach in duties before termination
Accounts receivable		X	The outstanding payments due to the doctor from patents and insurance companies for charges submitted
Non-compete (restrictive covenant)	X	X	The physician agrees not to practice in competition with their current employer for a defined time and geographic scope
Non-solicitation of staff	X	X	Agreement not to solicit employees to leave for the benefit of a competitor if employment is terminated
Confidentiality agreement	X	X	Agreement forbidding disclosure of any confidential or proprietary information to a third party in competition with the practice or hospital

usually shifts from a collection-based to RVU-based revenue stream. At the end of the fiscal year, if one does not meet the budget, compensation and bonus structure could be adjusted accordingly. Staffing and administrative support are controlled by the institution. Once your staff is brought to the hospital, you lose the ability to make significant changes, so choose wisely. The hospital model will almost always have an electronic medical records (EMR) system in place. The physician will need to transition to the new system, which will decrease efficiency and productivity, increase work hours, and consume tremendous amounts of staff and resources during the transition phases. Negotiating a scribe to assist with documentation while the physician becomes proficient with the new EMR might be beneficial to all parties. To transition the physical goods from private practice to the hospital system, a Bill of Sales or Purchase Agreement is required to negotiate the hard assets of the practice, including furniture, exam tables, computers, manometric equipment, and scopes. The hospital evaluates the equipment, taking depreciation (approximately 20 % per year) into account. The physician generally overvalues hard assets, so they should be prepared for the purchase agreement to be significantly less than expected. The physician should also be aware that ancillary income sources could be restricted. Ownership stakes in outpatient surgical centers and outside medical ventures that supplement private practice compensation are commonly restricted or banned as a hospital employee.

Conclusions

Practice management is a vital component of a successful surgical practice. While there is little emphasis on the principles of practice management during surgical training, knowledge of these tenets is essential for every colorectal surgeon to make informed decisions about their career. Abasic understanding of practice management will help a surgeon decide the best practice model to meet their personal and professional goals, reimbursement and billing patterns in each model, how to be professionally successful in their chosen model, and, if needed, how to leave for other pursuits.

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Correction to: The ASCRS Textbook of Colon and Rectal Surgery

Scott R. Steele, Tracy L. Hull, Thomas E. Read, Theodore J. Saclarides, Anthony J. Senagore, and Charles B. Whitlow

Correction to:
S. R. Steele et al. (eds.), *The ASCRS Textbook of Colon and Rectal Surgery*, https://doi.org/10.1007/978-3-319-25970-3

This book was inadvertently published with the incorrect copyright holder name. This has now been amended in the book and the correct one is ASCRS (American Society of Colon and Rectal Surgeons). An erratum for this book can be found at https://doi.org/10.1007/978-3-319-25970-3_73.

The updated online version of this book can be found at https://doi.org/10.1007/978-3-319-25970-3

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