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Five Basic Mechanisms of Antibiotic Action against Bacterial Cells

Inhibition of Cell Wall Synthesis (most common mechanism)

Inhibition of Protein Synthesis (Translation) (second largest class)

Alteration of Cell Membranes

Inhibition of Nucleic Acid Synthesis

Antimetabolite Activity

 **Inhibition of Cell Wall Synthesis**

Beta-Lactams ---> Inhibition of peptidoglycan synthesis (bactericidal)

Resistance --->

(1) fails to cross membrane (gram negatives)

(2) fails to bind to altered PBP

(3) hydrolysis by beta-lactamases

Vancomycin ---> Disrupts peptidoglycan cross-linkage

Resistance --->

(1) fails to cross gram negative outer membrane (too large)

(2) some intrinsically resistant (pentapeptide terminus)

Bacitracin ---> Disrupts movement of peptidoglycan precursors (topical use)

Resistance ---> fails to penetrate into cell

Antimycobacterial agents ---> Disrupt mycolic acid or arabino glycan synthesis (bactericidal)

Resistance --->

(1) reduced uptake

(2) alteration of target sites

 **Inhibition of Protein Synthesis** (Translation)

30S Ribosome site

Aminoglycosides ---> Irreversibly bind 30S ribosomal proteins (bactericidal)

Resistance --->

(1) mutation of ribosomal binding site

(2) decreased uptake

(3) enzymatic modification of antibiotic

Tetracyclines ---> Block tRNA binding to 30S ribosome-mRNA complex (b-static)

Resistance --->

(1) decreased penetration

(2) active efflux of antibiotic out of cell

(3) protection of 30S ribosome

50S Ribosome site

Chloramphenicol ---> Binds peptidyl transferase component of 50S ribosome, blocking peptide elongation (bacteriostatic)

Resistance --->

(1) plasmid-encoded chloramphenicol transferase

(2) altered outer membrane (chromosomal mutations)

Macrolides ---> Reversibly bind 50S ribosome, block peptide elongation (b-static)

Resistance --->

(1) methylation of 23S ribosomal RNA subunit

(2) enzymatic cleavage (erythromycin esterase)

(3) active efflux

Clindamycin > Binds 50S ribosome, blocks peptide elongation; Inhibits peptidyl transferase by interfering with binding of amino acid-acyl-tRNA complex

Resistance > methylation of 23S ribosomal RNA subunit

**Alteration of Cell Membranes**

Polymyxins (topical) > Cationic detergent-like activity (topical use)

Resistance > inability to penetrate outer membrane

Bacitracin (topical) > Disrupt cytoplasmic membranes

Resistance > inability to penetrate outer membrane

**Inhibition of Nucleic Acid Synthesis**

DNA Effects

Quinolones > Inhibit DNA gyrases or topoisomerases required for supercoiling of DNA; bind to alpha subunit

Resistance >

(1) alteration of alpha subunit of DNA gyrase (chromosomal)

(2) decreased uptake by alteration of porins (chromosomal)

Metronidazole > Metabolic cytotoxic byproducts disrupt DNA

Resistance >

(1) decreased uptake

(2) elimination of toxic compounds before they interact

 RNA Effects (Transcription)

Rifampin > Binds to DNA-dependent RNA polymerase inhibiting initiation & Rifabutin of RNA synthesis

Resistance >

(1) altered of beta subunit of RNA polymerase (chromosomal)

(2) intrinsic resistance in gram negatives (decreased uptake)

Bacitracin (topical) > Inhibits RNA transcription

Resistance > inability to penetrate outer membrane

**Antimetabolite Activity**

Sulfonamides & Dapsone ---> Compete with p-aminobenzoic acid (PABA) preventing synthesis of folic acid

Resistance > permeability barriers (e.g., Pseudomonas)

Trimethoprim > Inhibit dihydrofolate reductase preventing synthesis of folic acid

Resistance >

(1) decreased affinity of dihydrofolate reductase

(2) intrinsic resistance if use exogenous thymidine