Bacterial Structure and Mechanisms of Antimicrobial Action

Mazen Kherallah, MD, FCCP
Mkherallah@msn.com
www.mecriticalcare.net
MECHANISMS OF ACTION OF ANTIBACTERIAL DRUGS

• Inhibition of cell wall synthesis
• Inhibition of protein synthesis
• Inhibition of nucleic acid synthesis
• Inhibition of metabolic pathways
• Interference with cell membrane integrity
Prokaryotic Organization

- No nucleus
- DNA held in *nucleoid*
- Cytoplasm dense:
  - Ribosomes
  - Storage granules
  - Limited membranes
- Plasma membrane
- Corkscrew flagellum
- Cell wall is complex
  - Outer membrane
  - Peptidoglycan layer
  - Capsule
  - Pili extend from cytoplasm
INHIBITION OF CELL WALL SYNTHESIS
Gram –ve

LPS

Peptidoglycan

Cell membrane

Gram +ve
(a) Gram-positive cell wall

N-Acetylmuramic acid (NAM)

N-Acetylglucosamine (NAG)

l-Ala
d-Glu
l-Lys
n-Ala

Pentaglycine cross-link
Inhibition of cell wall synthesis

Vancomycin
Binds to the amino acid side chain of NAM molecules, interfering with peptidoglycan synthesis

β-lactam drugs
Interferes with the formation of the peptide side chains between adjacent strands of peptidoglycan by inhibiting penicillin-binding proteins

Peptidoglycan (cell wall)

Cytoplasmic membrane

Bacitracin
Interferes with the transport of peptidoglycan precursors across the cytoplasmic membrane
Weak cell wall results in osmotic lysis.
Competitively inhibits function of penicillin-binding proteins

Inhibits peptide bridge formation between
The weakness in the cell wall causes the cell to lyze.
As the autolysins continue to break the peptide cross-links and new cross-links fail to form, the bacterium bursts from osmotic lysis.
N-acetylglucosamine
N-acetylmuramic acid
d-ala
L-glu
Lys
d-ala
d-ala

Cell wall

Cell membrane

Transpeptidases (PBP’s)
Mechanism of action of Vancomycin

Vancomycin blocks cell wall synthesis
By binding to the d-alanyl-d-alanine site on the growing peptidoglycan chain

N-acetylglucosamine
N-acetylmuramic acid
d-ala
L-glu
Lys
d-ala
d-ala
INHIBITION OF PROTEIN SYNTHESIS
There is no corresponding tRNA for a stop codon - UGA in this case. The completed protein is released from the last tRNA and the ribosomal subunits separate.
Inhibition of Protein Synthesis

**Aminoglycosides**
Block the initiation of translation and causes the misreading of mRNA

**Tetracyclines**
Block the attachment of tRNA to the ribosome

**Macrolides**
Prevent the continuation of protein synthesis

**Chloramphenicol**
Prevents peptide bonds from being formed

**Lincosamides**
Prevent the continuation of protein synthesis

**Streptogramins**
Each interferes with a distinct step of protein synthesis

**Oxazolidinones**
Interfere with the initiation of protein synthesis
In this example, the codon GGA codes for the amino acid glycine. As a result of misreading, a near-match tRNA with the anticodon CAU pairs with the GGA codon. This tRNA, however, carries the amino acid histidine not glycine.
The aminoglycosides bind irreversibly to the 30S subunit of bacterial ribosomes. In addition to interfering with the proofreading process as described in mechanism 1, there is evidence that aminoglycosides also prevent the transfer of the peptidyl tRNA from the A-site to the P-site, thus preventing the elongation of the polypeptide chain.
The tetracyclines block bacterial translation by binding reversibly to the 30S ribosomal subunit. This prevents the binding of the aminoacyl tRNAs (charged tRNAs) to the A-site of the ribosome.
Macrolides bind reversibly to the 50S subunit of bacterial ribosomes. Macrolides are thought to inhibit elongation of the protein by preventing the enzyme peptidyltransferase from forming peptide bonds between the amino acids.
The macrolides bind reversibly to the 50S subunit of bacterial ribosomes. In addition to interfering with peptide bond formation as described in mechanism 1, there is evidence that macrolides also prevent the transfer of the peptidyl tRNA from the A-site to the P-site, thus preventing the elongation of the polypeptide chain.
The oxazolidinones bind to the 50S ribosomal subunit and interfere with formation of the complex that associates the mRNA, the f-met-tRNA, and the 50S ribosomal subunit.
Inhibition of Nucleic Acid Synthesis
**Fluoroquinolones:**
Inhibit action of topoisomerase DNA gyrase

**Rifamycins:**
Block prokaryotic RNA polymerase
Block initiation of transcription
Inhibition of Metabolic Pathways
Para-aminobenzoic acid (PABA)

\[
\text{H}_2\text{N} - \text{Ph} - \text{COOH}
\]

Sulfanilamide

\[
\text{H}_2\text{N} - \text{Ph} - \text{SO}_2\text{NH}_2
\]

(a)

Precursor #1

\[
\text{PABA} \xrightarrow{\text{Enzyme } \#1} \text{Enzyme } \#1
\]

Precursor #2

\[
\text{Glutamate} \xrightarrow{\text{Enzyme } \#2} \text{Enzyme } \#2
\]

Dihydrofolate

\[
\text{Enzyme } \#3
\]

Tetrahydrofolate

\[
\text{Multiple enzymes and reactions}
\]

Thymine, guanine, and adenine nucleotides

(b)

Sulfa drugs

Trimethoprim
Interference with Cell Membrane Integrity
Interference with cell membrane integrity

- Polymixin B most common
- Binds membrane of Gram - cells
  - Alters permeability
    - Leads to leakage of cell and cell death
  - Also bind eukaryotic cells but to lesser extent
Daptomycin’s Mechanism of Action

- Irreversibly binds to cell membrane of Gram-positive bacteria
  - Calcium-dependent membrane insertion of molecule
- Rapidly depolarizes the cell membrane
  - Efflux of potassium
  - Destroys ion-concentration gradient
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Thank You