ANTIMICROBIAL CHEMOTHERAPY

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Antibacterial Agents

Desired properties of antibiotics:

1. Selective toxicity.
2. Bactericidal > bacteriostatic.
3. Do not develop antibacterial resistance.
4. Broad spectrum.
5. Non-allergic.
8. Good tissue distribution (BBB-PBP).
Antimicrobial Agents

- **Def:**

- **In-vivo (Selective toxicity):**
  - Antibacterial (Antibiotics)
  - Antifungal
  - Antiviral

- **In-vitro:**
  - Antiseptics
  - Disinfectant
Antibacterial Agents

Mechanism of action:

- **Cell wall synthesis.**
  - Cycloserine
  - Vancomycin, Teichoplanin
  - Bacitracin
  - Penicillins
  - Cephalosporins
  - Monobactams
  - Carbapenems

- **Cell membrane function.**

- **Protein synthesis.**
  - Erythromycin (Macrolides)
  - Chloramphenicol
  - Clindamycin

- **DNA replication.**
  - Tetracycline
  - Spectinomycin
  - Streptomycin
  - Gentamicin, Tobramycin (aminoglycosides)
  - Amikacin

- **Other.**
Cell Wall Inhibitors

I. $\beta$ Lactam antibiotics

II. Glycopeptides

III. Polypeptides
Cell Wall Inhibitors

I. β Lactam antibiotics

1. Penicillin
2. Monobactam
3. Carbapenem
4. Cephalosporins
Cell Wall Inhibitors

I. β Lactam antibiotics - Penicillin

A) Classic penicillin: → Gram positive (Except S. aureus).
   - Penicillin G & V.
   - Procaine Penicillin.
   - Benzile penicillin.

B) Penicillinase resistant penicillin: → S. aureus.
   - Oxacillin.
   - Cloxacillin.
   - Flucloxacillin.
   - Amoxycillin/Clavulanic acid - Ampicillin/Sulbactam.

C) Broad spectrum penicillins: → Gram-negative (Except Pseudomonas).
   - Ampicillin.
   - Amoxycillin.
   - Carbenicillin.
   - Ticarcillin.

D) Ureidopenicillins: → Pseudomonas.
   - Piperacillin.
   - Mezlocillin.
   - Azlocillin.
Cell Wall Inhibitors

I. β-Lactam antibiotics - Monobactam

Aztreonam (Azactam)
- Resistant Gram-negative bacteria.
- Pseudomonas.

I. β-Lactam antibiotics - Carbapenem

Imipenem (Tinam)
- Resistant Gram-negative & Gram-positive bacteria.
- Pseudomonas.
# Cell Wall Inhibitors

## I. β Lactam antibiotics - Cephalosporin

<table>
<thead>
<tr>
<th>1&lt;sup&gt;st&lt;/sup&gt; G</th>
<th>2&lt;sup&gt;nd&lt;/sup&gt; G</th>
<th>3&lt;sup&gt;rd&lt;/sup&gt; G</th>
<th>4&lt;sup&gt;th&lt;/sup&gt; G</th>
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</thead>
<tbody>
<tr>
<td>+ve &gt; -ve</td>
<td>+ve = -ve</td>
<td>-ve &gt; +ve</td>
<td>+ve = -ve</td>
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<table>
<thead>
<tr>
<th>Pseudomonas X</th>
<th>Pseudomonas ✓</th>
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<table>
<thead>
<tr>
<th>Cephaloridin</th>
<th>Cefoxitin</th>
<th>Cefotaxime</th>
<th>Cefipime</th>
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<tbody>
<tr>
<td>Cephalothin</td>
<td>Cefamandole</td>
<td>Ceftriazone</td>
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<td>Cephalexin</td>
<td>Cefuroxime</td>
<td>Ceftazidime</td>
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<td>Cefaclor</td>
<td>Cefoperazone</td>
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<td>Cefonicid</td>
<td>Cefizoxime</td>
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<td>Cephradin</td>
<td>Ceforamide</td>
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<td>Cefotetan</td>
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Cell Wall Inhibitors

II. Glycopeptides

Vancomycin
- Resistant Gram-positive bacteria.
- MRSA.

III. Polypeptides

A. Cycloserine
Cycloserine
- TB

B. Bacitracin
Bacitracin
- Diagnostic
- Topical
Cell Wall Inhibitors

Penicillins and cephalosporins

Bacitracin, Vancomycin and cycloserine
# Protein Synthesis Inhibitors

<table>
<thead>
<tr>
<th>30 S</th>
<th>50 S</th>
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<tbody>
<tr>
<td>Aminoglycoside</td>
<td>Macrolide</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>Chloramphenicol</td>
</tr>
<tr>
<td>B-cidal</td>
<td>B-cidal</td>
</tr>
<tr>
<td>B.static</td>
<td>Both</td>
</tr>
<tr>
<td>Gm –ve &amp; Pseu</td>
<td>Gm +ve&gt; -ve</td>
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<tr>
<td>Spir-Rick-Chla</td>
<td>Enteric fever</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>Oxytetracycline</td>
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<td>Amikacin</td>
<td>Erythromycin</td>
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<td>Clindamycin</td>
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<td>Neomycin</td>
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<tr>
<td>Kanamycin</td>
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<tr>
<td>Streptomycin</td>
<td></td>
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</tbody>
</table>

- Chloramphenicol
- Macrolide
- Aminoglycoside
- Tetracycline
- B-cidal
- B.static
DNA Replication Inhibitors

I. Sulphonamides

- Bactiristatic
- UTI-Chemoprophylaxis - e.g. Trimethoprim.

II. Quinolones

- Bactricidal
- Broad spectrum
- Ofloxacin
- Gatifloxacin
- Ciprofloxacin
- Gatifloxacin
- Levofloxacin
- Nitrofurantoin (UTI)

III. Rifampicin

- Bactricidal
- TB

Inhibition of precursor

Inhibition of DNA polymerase

Inhibition of RNA polymerase
Cytoplasmic membrane Inhibitors

Polyenes

Bactiristatic

- *Polymyxin B* → topical
- *Amphotercin B* → antifungal
- *Mitronidazole* → anaerobes
Antibiotic Combination

- **Def:**

- **Synergism:**
  - 1 + 1 = > 2
  - Cidal + Cidal

- **Antagonism:**
  - 1 + 1 = 0
  - Cidal + Static

- **Addition:**
  - 1 + 1 = 2
  - Static + Static

1- Sequential block of a metabolic pathway
2- One drug may enhance the uptake of the other.
3- One drug may facilitate the entry of the second drug.
4- Suicidal ring.
Antibiotic Combination

- **Indications:**
  - Serious microbial infections.
  - Resistant pathogens.
  - Mixed infection.

- **Disadvantages:**
  - Side effects.
  - Antagonism (drug reaction).
  - Economic impacts.
Antimicrobial chemoprophylaxis

I) prophylaxis in persons of normal susceptibility exposed to specific pathogen.
- Prophylaxis from Rheumatic fever by long acting Penicillin.
- Prophylaxis from meningitis by Rifampicin.

II) Prophylaxis in persons of increased susceptibility:
- Heart diseases.
- Respiratory diseases (Chronic).
- Recurrent urinary tract infections.
- Immunosuppressed host.

III) Surgical prophylaxis
Bacterial Resistance to Antimicrobial Drugs

Mechanism:

- Decreased permeability.
- Inactivation.
- Alteration of target site.
- Alteration of metabolic pathway.
- Alteration of metabolic enzymes.
Bacterial Resistance to Antimicrobial Drugs

Origin of Drug Resistance

Genetic
  Chromosomal
  Extra-chromosomal
    Plasmids
    Transposonos

Non-genetic
Chromosomal Resistance
(Drug Resistant Mutants)

Mechanism:
- Spontaneous mutation $\rightarrow$ Altered target.
- Rare.
- Need the presence of antibiotic $\rightarrow$ selective pressure factor.
- Low frequency of transmission.

Example:
- P12 of 30 S ribosomal subunit $\rightarrow$ R (Streptomycin)
Plasmid Resistance
(R Factor)

Mechanism:

- Presence of R factor
- Enzymatic:
  - β-lactamases
  - Acetyl transferase
- No need for selective pressure factor.
- High frequency of transmission by

- Plasmid carry genes of resistance.
- If transmissible → epidimic resistance
Transposons Resistance
(jumping genes)

Mechanism:

- Presence of transposons ???
- Enzymatic:
  - B lactamases
- No need for selective pressure factor.
- High frequency of transmission by ???
Transposons & Plasmids
(Extra chromosomal resistance)
= Resistance exchange
Non-Genetic Resistance
(Biochemical Resistance)

- **Mechanism:**
  - Decreased permeability.
  - Alteration of target site.
  - Metabolic pathway.
  - Metabolic enzymes.

- **Characters:**
  - Non transmissible.
Antibacterial Agents

Choice of antibiotics:

1. Selective toxicity.
2. Bactericidal > bacteriostatic.
3. Do not develop antibacterial resistance.
4. Broad spectrum.
5. Non-allergic.
8. Good tissue distribution (BBB-PBP).
Good Luck

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