CHAPTER 3
CHEMOTHERAPY

Year III Pharm.D
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OBJECTIVES:

General principles of chemotherapy for other drugs govern antimicrobial chemotherapy also. However, there are principles that are more pertinent to the use of antimicrobial agents as a group. Particular attentions should be directed to the following:

1. Mechanisms of actions of different groups of antibiotics.
2. Mechanisms by which pathogens acquire and express resistance to antibiotics.
3. Combination therapy (use of two or more drugs concomitantly).
4. Host determinants that influence the selection and efficacy of antibiotics.
INTRODUCTION TO ANTIMICROBIAL CHEMOTHERAPY
(GENERAL PRINCIPLES)

PROTOTYPES

Penicillin G          Rifampin
Polymyxin             Ciprofloxacin
Choramphenicol        Sulfamethoxazole
Streptomycin
CONJUGATION

1. A sexual process that requires cell-to-cell contact through pili.

2. The transferable materials consist of two different DNA sequences:
   (1) R Determinant Plasmid for resistance mechanism
   (2) Resistant Transfer Factor (RTF) that is needed for conjugation.

3. Combination of the two plasmid is called R-Factor

4. Many Gram (-) organisms acquire resistance to multiple antibiotics by conjugation mechanism. Multiple drugs resistant Enterobacteriaceae became a serious world-wide problem.
EFFECTIVENESS OF COMBINATION THERAPY

1. Synergistic Effect: When two bactericidal antibiotics are used in combination. One of the two drugs must show at least 4-fold increase in antibacterial activities (or a decrease in MIC to ¼) for a synergism is said to exist between the two drugs. (e.g. penicillin + streptomycin).

2. Additive Effect: When two bacteriostatic agents with the same mechanisms of action are used.

3. Antagonism: Usually bacteriostatic antibiotics are antagonistic to bactericidal agents. (e.g. Chloramphenicol has been shown to antagonize the bactericidal activities of penicillin in the treatment of Pneumococcal meningitis.)
IMPORTANT HOST DETERMINANTS

a) Hepatic function: Erythromycin, clindamycin, rifampin, Chloramphenicol, etc depend on liver metabolisms for the inactivation of antimicrobial mechanisms. Patients with impaired liver function may accumulate in the body active form of the drugs to a toxic level if the dosage adjustment is not made.

b) Kidney function: Normal kidney function is essential for disposal of β-lactams, aminoglycosides, vancomycin, etc. Active form of these drugs may accumulate in the patient with renal diseases.

c) Host defense mechanism: A chemotherapeutic regimen that is perfectly adequate for immuno-competent patient may be totally ineffective for immuno-incompetent patient. Immuno-incompetence may be due to deficiencies in (1) immunoglobulin, (2) phagocytic cells and (3) cellular immune system.
UNTOWARD EFFECTS OF ANTIBIOTICS

1. Reactions due to toxic properties of antibiotics.
2. Hypersensitivity reactions
3. Superinfection (or also called Suprainfection)
B) SULFONAMIDES

**Mechanism of action:**
- Competitive inhibitor to dihydropteroate synthase enzyme.
- Inhibit bacterial growth by blocking folic acid synthesis.
Figure 46–2. Actions of sulfonamides and trimethoprim.
ANTIBACTERIAL ACTIVITY

- Gram-positive and gram negative.
- Nocardia, chlamydia trachomatis, some protozoa.
PHARMACOKINETICS

1) Oral absorbable:
   - Short acting e.g. sulfisoxazole
   - Intermediate e.g. sulfadiazine & sulfamethxazole
   - Long acting e.g. sulfadoxine
   - They are absorbed from stomach & intestine
   - Distributed widely including C.N.S. & placenta.
Metabolized in liver to inactive metabolites. Excreted through kidney.

Rate of excretion increases in alkaline urine.

2) Oral non-absorbable e.g. sulfasalazine

3) Topical: sulfacetamide, mafenidic acid, silver sulfadiazine.
THERAPEUTIC USES

- Urinary tract infections
- Upper respiratory tract infections
- Nocardiosi
- Sulfasalazine in IBD.
- Sulfacetamide in bacterial conjunctivitis & trachoma
- Silver sulfadiazine for prevention of infection of burn wounds.
ADVERSE EFFECTS

- Hypersensitivity reactions
- N.V.D.
- Crystalluria, hematuria, renal obstruction.
- Allergic nephritis
- Haemolytic anaemia, aplastic anaemia, thrombocytopenia.
- Kernicterus in new born
Trimethoprim-Sulfamethoxazole Combination (Co-trimoxazole)

Mechanism of action:
- Sequential blocking of purine synthesis (synergism).
- Trimethoprim inhibits dihydrofolate reductase enzyme so inhibits tetrahydrofolic acid synthesis.
- The combination is bactericidal.
Figure 46–2. Actions of sulfonamides and trimethoprim.
CLINICAL USES

- Acute or Complicated or recurrent urinary tract infections especially in females
- Upper respiratory tract infections
- Pneumocystis jiroveci pneumonia
- Toxoplasmosis
- Shigellosis
- Nocardiosis
Typhoid fever
Salmonella infections
Prostatitis
Community –acquired bacterial pneumonia
ADVERSE EFFECTS

- Megaloblastic anemia, leukopenia & granulocytopenia (can be prevented by administration of folic acid)
- All side effects associated with sulfonamides
C) THE BETA-LACTAM ANTIBIOTICS

- Cell wall active agents
  - Prevent the final step in the synthesis of the bacterial cell wall

- Range from very narrow spectrum to very broad spectrum
β-LACTAMS

β-lactam ring

Cephalosporin

Penicillin
**Mechanism of Action:**

1. The β-lactam binds to Penicillin Binding Protein (PBP)
2. PBP is unable to crosslink peptidoglycan chains (UDP-N-acetyl muramic acid pentapeptide and UDP-N-acetyl glucosamine)
3. The bacteria is unable to synthesize a stable cell wall
4. The bacteria is lysed
PK/PD

- The β-lactams are “time-dependent” killers
  - The effect is directly proportional to the amount of TIME the concentration of the antibiotic at the site of infection is ABOVE the MIC of the organism.

- The β-lactams are BACTERIOCIDAL (at therapeutically attainable levels)
CLASSIFICATION OF PENICILLINS

- Natural penicillins
  - PenG, Benzathine Pen, Procaine Pen
- Acid-resistant alternative to PenG
  - PenV (Phenoxyethyl Pen)
  - Ampicillin, Amoxicillin
- Penicillinase-resistant Pen (Anti-Staphylococcal)
  - Methicillin, Cloxacillin, Oxacillin, Dicloxacillin
- Extended Spectrum Pen
  - [Amino] Ampicillin, Bacampicillin, Amoxicillin (E.coli, H.influenzae)
  - [Carboxy] Carbenicillin, Ticarcillin (Pseudomonas)
  - [Ureido] Piperacillin (Klebsiella)
CLASSIFICATION OF CEPHALOSPORINS

- **1\(^{st}\) Generation**
  - Cefazolin, Cephalexin, Cephradine
- **2\(^{nd}\) Generation**
  - Cefoxitin, Cefuroxime, Cefaclor
- **3\(^{rd}\) Generation**
  - Cefotaxime, Ceftriaxone, Cefixime, Cefibuten
- **4\(^{th}\) Generation**
  - Cefepime, Cefpirome
**Penicillin G**

- **Drug of Choice (DoC)**
  - T. pallidum, N. meningitidis, Group A Strep, and Corynebacterium diphtheriae, Clostridia

- **Resistance**
  - Penicillinase (Majority of Staph)
  - Penicillin tolerance by decreasing affinity for the enzymes
  - G-ve porin channel alteration influencing permeability

- **Adverse Reactions – other than skin rash**
  - Local irritancy and direct toxicity
  - Superinfections
  - Penicillin “serum sickness”/drug fever
  - Jarisch-Herxheimer reaction (1° and 2° syphilis)
  - Hemolytic anemia, pancytopenia, neutropenia
Uses for PenG
- Streptococcal, Pneumococcal, Meningococcal infections
- Gonorrhea, Syphilis, Diphtheria, Tetanus
- Gas Gangrene

Uses of others
- Ampicillin-UTI, Gonorrhea, RTI, Meningitis, Cholecystis
- Carbenicillin- Pseudomonas, Proteus, UTI, septicaemia
- Piperacillin-Klebsiella, burns, serious G-ve infections
**β-LACTAMASE INHIBITORS**

1. Use a non-β-lactam agent
2. Steric Inhibition
   - Penicillins with large side chains
   - Cephalosporins
3. β-lactam + β-lactamase inhibitors
   - Not all β-lactamases are inhibitable
Clavulanic Acid

- From Streptomyces clavuligerus
- Progressive suicide inhibitor
- Spectrum: Staph.A and H. flu, E.coli, Proteus, Salmonella, Klebsiella
- Clav is responsible for most of the GI side-effects seen with Amox/Clav
SULBACTAM

- Semisynthetic inhibitor related to Clav. acid
- Combined with ampicillin as progressive inhibitor
- DoC: N. gonorrhoeae, mixed aerobic and anaerobic infections, intra-abdominal, gynaecological
- Sulbactam alone is very active against Acinetobacter spp.

Tazobactam
# The Cephalosporins (Generalized)

<table>
<thead>
<tr>
<th>Generation</th>
<th>Activity</th>
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<tbody>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; Generation</td>
<td>Gram (+)</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; Generation</td>
<td>Decreasing Gram (+) and Increasing Gram (-) and anaerobes except <em>P. aeruginosa</em></td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt; Generation</td>
<td>Gram (-), but also some on <em>Pseudomonas</em> but less active on G (+) and anaerobes</td>
</tr>
<tr>
<td>4&lt;sup&gt;th&lt;/sup&gt; Generation</td>
<td>Gram (+) and Gram (-)</td>
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**CEPHALEXIN/CEFAZOLIN**

- Susceptible against Staph B-lactamase
- Spectrum: Streptococci, clostridia, gonococci and meningococci, most E. coli, and some Klebs
- DoC: surgical prophylaxis, bacterial peritonitis
- ADRs
  - Positive Coombs’ test (though, hemolytic anemia is rare)
CEFUROXIME

- Resistant to G(-) B-lactamases
- Extensive use in pediatrics
- Spectrum: PPNG, ampicillin-resistant H. flu, N. meningitidis
- DoC: uncomplicated CAP (esp. H. flu), UTI
CEFOTAXIME

- Resistant to G(-) B-lactamases
- Spectrum: Strep pneumo, Neisseria spp., most Gram (-) enterics, M. catarrhalis and H. flu (including β-lactamase +)
- DoC: bact meningitis (esp. in peds + amp if < 4 weeks), CAP, complicated UTI/pyelonephritis, Bacterial Peritonitis
CEFTRIAXONE

- Once daily dosing (95% protein bound = long half-life)
- Spectrum: Strep. pneumoniae, most Enterbacteriaceae
- Excretion: 50% urine, 50% bile = no need to adjust for renal insufficiency
- CSF penetration: 5-15% in meningitis, 1.5% with out inflammation
- DoC: bacterial meningitis, CAP, Strep. viridans endocarditis (+ gent)

ADR
- Hypoprothombinaemia
- Bleeding
- Haemolysis
- Cholestasis
- Elevated bilirubin (displacement)
- Diarrhea
CEFTAZIDIME

- Spectrum: Enteric GNR (including *Pseudomonas*; some *Acinetobacter*)
- No anaerobic activity (same for cefotaxime and ceftriaxone)
- DoC: *Pseudomonas* infx
CEFEPIME

- Spectrum: similar to 3rd generation plus P.aeruginosa and Staph.aureus
- Stable vs. de-repressed chromosomal β-lactamases, but not ESBL
- Less β-lactamase induction than 3rd Cephs
- DoC: HAP, febrile neutropenia, bacteraemia, septicaemia
CARBAPENEMS

- Imipenem, Meropenem, Ertapenem
- Broad-spectrum coverage:
  - Gram positive: PSSP, MSSA, VSE
  - Gram negative: most gram-negative organisms (Acinetobacter sp., Pseudomonas sp.)
- Lack of coverage:
  - Ertapenem: Pseudomonas sp., Acinetobacter sp.
  - All: Stenotrophomonas, Legionella sp., MRSA, VRE
CARBAPENEMS

- Distribution: similar to penicillins
- Excretion: renal clearance
- Adverse reactions:
  - Hypersensitivity: rash, urticaria, cross-reactivity
  - Imipenem: seizures (rare)
    - High doses
    - Renal dysfunction
  - Most likely can occur with all carbapenems at high doses
**Carbapenems**

- **Resistance:**
  - Gram negative: usually combination of mechanisms (Carbapenemase production + decreased entry)
  - Imipenem
    - Decreased production of OprD (outer membrane protein for carbapenems)
    - Imipenem utilizes OprD > meropenem, ertapenem
    - Pseudomonas, Enterobacter
    - Susceptible to efflux system in Enterobacter
  - Meropenem: substrate for multi-drug efflux systems
    - May have increased MIC for meropenem but not imipenem
  - All: low affinity PBPs
**MONOBACTAMS**

- Monobactams: Aztreonam
- Spectrum: ONLY \(\rightarrow\) Gram negative aerobic bacteria
- Lack of Coverage:
  - Some resistant P. aeruginosa, E. cloacae, and C. freundii
  - Acinetobacter sp., Stenotrophomonas sp.
- Pharmacokinetics:
  - Well distributed into tissues, esp. inflamed tissues
  - Excretion: renal clearance
- Adverse reactions:
  - Skin rash
  - No cross-reactivity with Beta-Lactam class
D) CHLORAMPHENICOL

**Mechanism of action**
Inhibits protein synthesis (50 s subunit)
- prevent transfer of elongating peptide chain to newly aminoacyl t-RNA at P site

**Antibacterial activity**
- H. Influenzae
- N. Meningitidis
- S. Pneumoniae
- Rickettsiae
- clostridium &
- S. typhi
- E. coli
- V. cholera
- Anaerobes-
- B. fragilis
CHLORAMPHENICOL ( CONT. )

Pharmacokinetics
Rapidly & completely absorbed from GIT
50-60 % protein bound
Metabolized by liver – glucuronidation (Dose adjustment in cirrhotics and neonates)
Well distributed, including CNS and CSF
Excreted in urine
CHLORAMPHENICOL CONT.

Clinical uses
Limited because of potential toxicities
(aplastic anaemia & circulatory collapse in neonates)
1. Typhoid fever - S. typhi (quinolones are preffered)
2. Meningitis – H.influenzae, N.meningitidis, S.pneumoniae (Ceftriaxone is preffered)
3. Anaerobic infections - B. fragilis (Metronidazole is the drug of choice)
4. Rickettsial infections – Doxycycline is preffered
5. Bacterial conjunctivitis (topical)
CHLORAMPHENICOL ( CONT. )

Side effects
1. Hypersensitivity - low incidence
   May ppt hemolysis in G6PD deficient pts
2. Aplastic anaemia, agranulocytosis, thrombocytopenia, pancytopenia (fatal)
3. Grey baby syndrome
4. Suprainfections
5. Interaction with other drugs:
   Inhibits liver microsomal enzymes
   Phenytoin
   Tolbutamide
   Chlorpropamide
   Anticoagulants
Macrolide Antibiotics

- Macrolides are a group of macrocyclic antibiotics containing:
  - A large non-planar strain less lactone ring (12-16 atoms)
  - An amino sugar linked glycosidically to the lactone ring,
  - A neutral sugar linked to the ring or the basic sugar
  - And contains a ketone group.

- Hydrolysis of the glycosidic bonds takes place in acid solutions, saponification of the lactone ring; in basic-media.

- The macrolides are principally active against Gram positive bacteria and show useful activity against penicillin-resistant strains. Also exhibit effectiveness against gram-negative cocci.
MODE OF ACTION

- Bacteriostatic, bind to 50 S ribosomal subunit to prevent the translocation step
- of bacterial protein synthesis
**ERYTHROMYCIN (ERYTHROCIN)**

- Erythromycin on hydrolysis provides
- a neutral sugar cladinose
- Desosamine (a basic sugar)
- and the aglycone, erythronolide.

- Clarithromycin semisynthetic
- erythromycin
- OH at C6 converted to methyl ether
OLEANDOMYCIN

- Oleandolide is a 14-atom ring that contains an exocyclic methylene epoxide on carbon 8

  Semisynthetic oleandomycin; triacetyl derivative. (TAO); troleandomycin

A combination of oleandomycin with tetracyclines, on the basis that it provides a synergistic effect and provides protection against resistant microorganisms (sigmamycin).
SPIRAMYCIN (ROVAMYCIN):

- Spiramycin is a macrolide antibiotic produced by the growth of certain strains of streptomyces ambofaciens which has been used similarly to erythromycin. It has also been used to treat protozoal infections and toxoplasmosis.
AZITHROMYCIN

- Semi synthetic erythromycin with ring enlargement by introduction of N-CH3 between C9 and C10.

- It has the following advantages:
  - More stable to acid degradation
  - Longer half life once a day dosage
  - More potent against gm -ve
V. LINCOMYCIN

They are known as Sulphur containing Antibiotics, act via 50S ribosomal subunit binding & protein synthesis inhibition.

They are used in extra CNS anaerobic infections, Penicillin sensitive patients except in respiratory tract infections.
VI Polypeptide Antibiotics

- The most powerful antibiotic agents but limited for renal toxicity.
  - Used mainly locally in burns.
  - Inhibit mucopeptide cell wall synthesis and interfere with semipermeability of cell membrane.
VII. POLYENE ANTIBIOTICS
- Macro cyclic lacton 38 atoms
- Conjugated polyenes
- Amphoteric

AMPHOTERICIN (B)