Unit 3
Chemotherapy

Disclaimer

All the content material provided here is only for teaching purpose.

Chemotherapy (Antimicrobial drugs)

Drugs in this class differ from all others in that they are designed to inhibit/kill the infecting organism and to have no/minimal effect on the recipient. This type of therapy is generally called chemotherapy which has come to mean ‘treatment of systemic infections with specific drugs that selectively suppress the infecting microorganism without significantly affecting the host.

Antibiotics: These are substances produced by microorganisms, which selectively suppress the growth of or kill other microorganisms at very low concentrations.

Classification:

A. Chemical structure

1. **Sulfonamides and related drugs:** Sulfadiazine and others, Sulfones—Dapsone (DDS), Paraaminosalicylic acid (PAS).
2. **Diaminopyrimidines:** Trimethoprim, Pyrimethamine.
3. **Quinolones:** Nalidixic acid, Norfloxacin, Ciprofloxacin, Prulifloxacin, etc.
4. **β-Lactam antibiotics:** Penicillins, Cephalosporins, Monobactams, Carbapenems.
5. **Tetracyclines:** Oxytetracycline, Doxycycline, etc.
7. **Aminoglycosides:** Streptomycin, Gentamicin, Amikacin, Neomycin, etc.
8. **Macrolide antibiotics**: Erythromycin, Clarithromycin, Azithromycin, etc.

B. Mechanism of action

1. *Inhibit cell wall synthesis: Penicillins*, Cephalosporins, Cycloserine, Vancomycin, Bacitracin.

2. 2. *Cause leakage from cell membranes:* Polypeptides—Polymyxins, Colistin, Bacitracin. Polyenes—Amphotericin B, Nystatin, Hamycin.

3. *Inhibit protein synthesis: Tetracyclines*, Chloramphenicol, Erythromycin, Clindamycin, Linezolid.

4. *Cause misreading of m-RNA code and affect permeability: Aminoglycosides*— Streptomycin, Gentamicin, etc.

5. Inhibit DNA gyrase: Fluoroquinolones— Ciprofloxacin and others.

6. Interfere with DNA function: Rifampin.

7. Interfere with DNA synthesis: Acyclovir, Zidovudine.

8. Interfere with intermediary metabolism: Sulfonamides, Sulfones, PAS, Trimethoprim, Pyrimethamine, Metronidazole

Beta lactam antibiotics

Penicillin

All penicillins are derivatives of 6-aminopenicillanic acid (thiazolidine ring is attached to a β–lactam ring that carries a secondary amino group (RNH–)) and contain a beta–lactam ring structure that is essential for antibacterial activity.

Beta–lactam antibiotics are narrow spectrum and bactericidal drugs. Peinicilins are obtained from P. cryssogenum.

Penicillins degrade by the acidic pH and amide linkage destruction through β–lactamase enzyme which is producedby gram negative bacteria. β–lactams acts only multiplying cells.

Mechanism of action

β–lactams bind with specific receptors (penicillin-binding proteins; PBPs) and inhibit the transpeptidase and carboxypeptidase enzymes that act to cross-link linear peptidoglycan chains which form part of the cell wall → cross linking does not take place → cell becomes incapable of withstanding the osmotic gradient → cell death.

Pharmacokinetic: Penicillins degrade by the acidic pH and amide linkage destruction through β–lactamase enzyme which is produced by gram negative bacteria. β–lactams acts only multiplying cells.

- **Adverse effect**
- *Thrombophlebitis: Pain and inflammation at the site of* injection.
- Hypersensitivity reaction: Due to degrade ptoduct of penicillin (penicilloic acid). Anaphylactic shock (IgE) and
- *Diarrhea: Due to disruption of normal balance of intestinal* micro flora.
- *Jarisch–Herxheimer reaction in syphilitic patient.*

β–lactamase Inhibitors

Clavulanic acid Obtained from Streptomyces clavuligerus and inhibits to β–reclaimant or penicillinase → prevents the degradation of β–lactam antibiotics. It is a suicidal inhibitor.

Coamoxiclav = Amoxicillin + Clavulanic acid

- Sulbactam semisythetic β–lactamase inhibitor related with clavulanic acid.

  Sultamicillin tosylate = Ampicillin + Sulbactam

  Tazobactam β–lactamase inhibitor like sulbactam.

- Piperacillin in combination with tazobactam is used in antibacterial therapy.

Cephalosporins

Cephalosporins comprise a large group of semisynthetic drugs, most of which are derived from cephalosporin C, a substance obtained from a species of Cephalosporium. Chephalosporins have β–lactam ring and a dihydrothiazine ring (7–aminocephalosporanic acid).

Cephalosporins have greater acid and β–lactamase resistance property and wide range of antibacterial activity.

Most cephalosporins excreted primarily by renal tubular secretions → probencid inhibits tubular secretion like penicillins.

Cephalsporin Drugs

Oral Compounds	Parentral Compounds
First generation: Cefalexin, Cefradine, Cefadroxil	First generation: Cefalotin, Cefazolin
Second generation: Cefaclor, Cefuroxime axetil	Second generation: Cefuroxime, Cefoxitin
Third generation: Cefixime, Cefpodoxime proxetil, Cefdinir	Third generation: Ceftriaxone, Cefoperazone, Cefotaxime
Fourth generation: Cefepime, Cepriome	

Adverse reaction

- Pain at the site of (i.m.) injection.
- Diarrhoea and hypersensitivity reaction like penicillins.
- Nephrotoxicity is highest with cephaloridine.
- Platelet dysfunction and bleeding.
- Disulfiram like reaction.

Uses

- In the penicillin producing staphylococcal infections

  E.g., cephalothin.
- In the gonorrhea caused by penicillinase producing organism; E.g., cefuroxime and cefotaxime.
- Septicemias caused by gram negative organism.

Monobactams

Aztreonam

- It is a monocyclic novel β–lactam antibiotic which has
- resistance to β–lactamase. It is active against gram neg-ative bacilli, H. influenza and Pseudomonas but does not affect gram positive cocci.
- It is used in the patient allergic to penicillin or cephalosporins.

Adverse effect: hypersensitivity reactions and thrombophlebitis.

Carbapenems
Imipenem, Meropenem and Ertapenem

- Penicillin like, but sulphur atom of thiazolidine ring is replaced with a carbon atom. These are potent and very broad spectrum, β–lactam antibiotic. It is resistant to β–lactamase.
- Unlike Meropenem and Ertapenem, Imipenem is rapidly inactivated by dehydroxypeptidase. For this reason, imipenem combined with dehydroxypeptidase inhibitor called cilastatin, which has similar pharmacokinetics with imipenem (t1/2 of both = 1h).
- Probencid inhibits tubular secretion of imipenem like penicillins.
- Carbapenem exerts cross sensitivity with penicillins. Cephalosporins and other beta lactams and should not be administered to patients who are allergic to these drugs.
- Contraindicated in epileptic patients, higher dosage can produce convulsions.

Chloramphenicol

Chloramphenicol is broad spectrum antibiotics with bacteriostatic activity and wide spectrum of activity but currently a backup drug for infections due to Salmonella typhi, B. fragilis, Rickettsia, and possibly in bacterial meningitis.

It was initially obtained from Streptomyces vanezualae

- **Chloramphenicol palmitate** Prodrug designed for masking the bitter taste.

- **Chloramphenicol succinate** Prodrug designed for increase water solubility.

Mechanism of Action

Chlormphenicol binds with 50S ribosome → blocks the transfer of aminoacyl t–RNA to the acceptor site for amino acid incorporation → inhibits protein synthesis.

Adverse Effects

- Dose-dependent *bone marrow suppression is common;* aplastic anemia is rare (1 in 35, 000).
- *Gray baby syndrome in neonates (decreases glucuronysyl* transferase) and optic neuritis in children.
- **Superinfection Results**

  Inhibits metabolism of phenytoin, sulfonylureas, and warfarin.

  Hepatic failure requires dose adjustment of chloramphenicol.

Tetracycline

- Tetracyclines are bacteriostatic and broad spectrum antibiotics obtained from soil actinomycetes and having a nucleus of four cyclic rings. These are water unstable and concentrated in liver and spleen and bind to the connective tissued of bones and teeth.

Mechanism of Action:

- Binds to the 30S ribosome and inhibit aminoacyl tRNA attachment to the acceptor site → inhibits protein synthesis.
- Used in Granuloma inguinale due to Calymm granuloma, Atypiacl pneumonia, cholera, Brucellosis, Plague and rickettsial infection and prolonged therapy in the acne.

Aminoglycoside Antibiotics

- Aminoglycosides are natural products or semisynthetic derivatives of compounds produced by a variety of soil actinomycetes. These are a group of natural and semisynthetic antibiotics having polybasic amino groups linked glcosidically to two or more amino sugars [streptidine (found in streptomycin), 2–deoxy streptamine (found in all other available aminoglycosides), garosamine) residues.
- They are water-soluble, stable in solution, and more active at alkaline than at acid pH.
- Aminoglcosides are active against aerobic gram negative bacilli and gives bactericidal action irreversible inhibition of protein synthesis.

Mechanism of action

Antibiotics penetrate the cell wall → bind with 30S –50S subunit (Streptomycin with 30S and other amino glycosides 50S ribosomes) of ribosome → interfere with the initiation of peptide formation, interfere with polysome formation and misreading of mRNA → irreversibly protein synthesis inhibition → death of cell.

Mechanism of resistance Microorganisms produce a transferase enzyme or that inactivate the aminoglycoside by adenylation, acetylation, or phosphorylation. Impaired the entry of aminoglycosides into the cell. Mutation in the 30S ribosomal subunit receptor protein.

Adverse Effects:

- Nephrotoxicity
- Ototoxicity
- Neuromuscular blockade

Interactions

- Concurrent use with loop diuretics (E.g., Ethacrynic acid, furosemide) and other nephrotoxic drugs (E.g.Amphotericin B, vancomycin and cisplatin) → potentiate nephrotoxicity.
- Concurrently used with muscle relaxant and neuromuscular blockers → muscular weakness.
- Avoid during pregnancy: risk of foetal ototoxicity.

Macrolides and others Antibiotics

- The macrolides are a group of closely related compounds characterized by a macrocyclic lactone ring (usually containing 14 or 16 atoms) to which deoxy sugars are attached. These are acid unstable so are administered in enteric coated formulation.

- **Mechanism of Action:**

  Binds with 50s ribosomal RNA → inhibits the amino acyl translocation and formation of initiation compex → inhibits, protein synthesis.

Erythromycin

- Obtained from *Streptomyces erythreus and has 14* membered macrocyclic rings with deoxy sugars.
- Erythromycin is used for infections caused by *gram-positive cocci (not MRSA), atypical organisms* (Chlamydia, Mycoplasma, and Ureaplasma species), Legionella pneumophila, *Campylobacter jejuni and Bordetella pertussis. First choice drug for whooping* cough and Chancroid.
- Erythromycin (estolate is best absorbed in oral form)- wide distribution into tissue and is eliminated mainly via biliary excretion.

- Adverse reaction and Interaction:

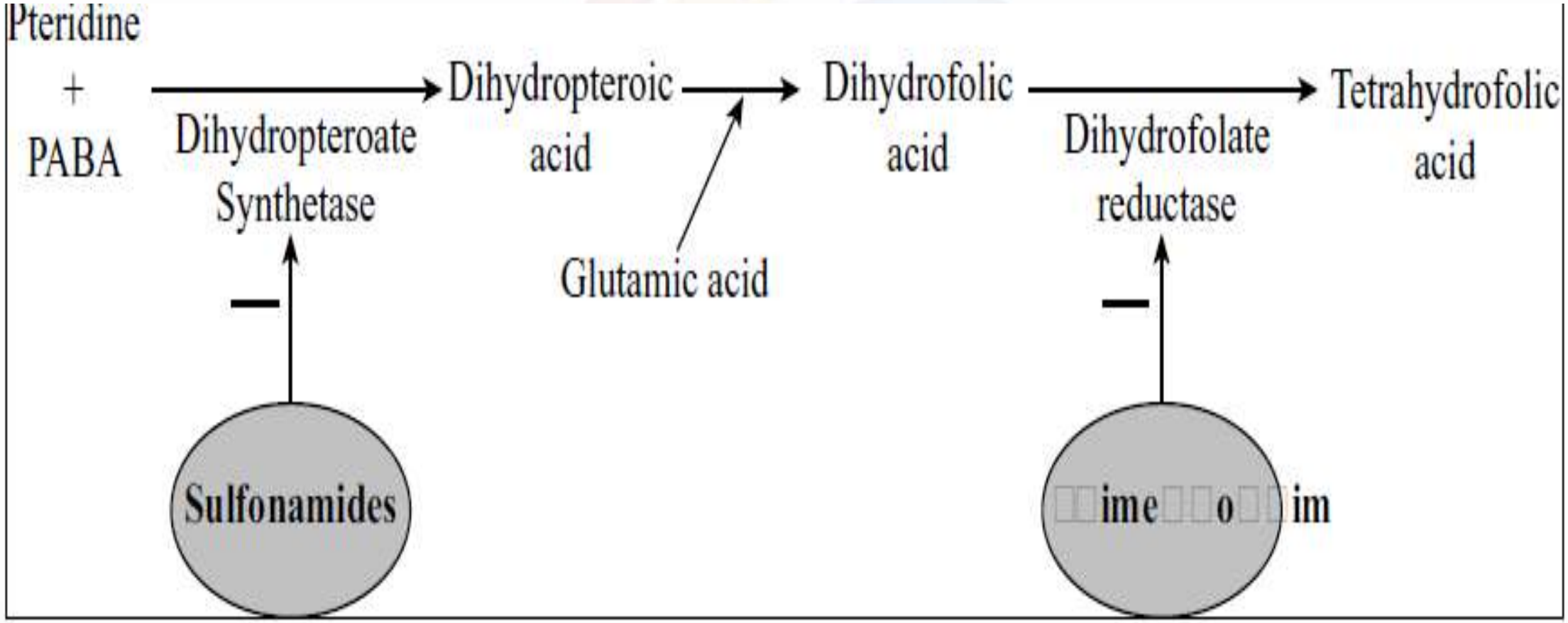
  gastrointestinal irritation (common), skin rashes, and eosinophilia. Hypersensitivity based–acute cholestatic hepatitis may occur with erythromycin estolate.

- Erythromycin inhibits several forms of hepatic cytochrome P450 → increase the plasma levels of anticoagulants, carbamazepine, cisapride, digoxin and theophylline. Cardiac arrhythmias occurred when erythromycin was administered to patients taking astemizole or terfenadine (the two antihistaminic drugs have been discontinued in the USA).

Sulfonamides

- The sulfonamide drugs were the first effective chemotherapeutic agents to be employed systemically for the prevention and cure of bacterial (pyogenic bacterial) infections in humans. Sulfonamide can be considered as derivatives of para-aminobenzenesulfonamide (sulfanilamide).

Mechanism of Action



Drugs	Adverse effect
Short acting: Sulfadiazine	Nausea, vomiting, crystalurea
Intermediate acting: Sulfamethoxazole	photosensitization,
Long acting: sulfadoxine	*Stevention–Johnson syndrome and exfoliative* dermatitis.
Special purpose sulfonamides: Sulfasalazine, Mefenide, Silver sulfadiazine	Hepatitis, haemolysis. **Kernicterus in new* born

Cotrimoxazole

- Sulfamethoxazole (5) + Trimethoprim (1) [Combination based on similar t1/2= 10hours.
- **Adverse effects** Megaloblastic anaemia due to folic acid deficiency and other sulfonamide's adverse effects.
- **Interactions** Diuretics with Cotrimoxazole produce higher incidence of thrombocytopenia.
- **Uses** Used in urinary tract infection and prostatitis, respiratory tract infections, typhoid, Chancroid-bacterial diarrhea and dystentry and Pneumonia due to *Pneumocystis carinii*

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