COURSE: B.PHARMACY SUBJECT: PHARMACOLOGY-III, CODE: BP602 Module 02 CHEMOTHERAPY

COURSE: B.PHARMACY

SEMESTER: 6TH

SUBJECT: PHARMACOLOGY-III

CODE: BP602T

SUBJECT TEACHER: MS. KIRAN SAINI

- Chemotherapy
- General principles of chemotherapy.
- Sulfonamides and cotrimoxazole.
- Antibiotics- Penicillins, cephalosporins, chloramphenicol, macrolides, quinolones and
- fluoroquinolins,
- tetracycline and aminoglycosides

General principles of chemotherapy

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.' The basis of selective microbial toxicity is the action of the drug on a component of the microbe (e.g. bacterial cell wall) or metabolic processes (e.g. folate svnthesis) that is not found in the host, or high affinity for certain microbial biomolecules (e.g. trimethoprim for bacterial dihydrofolate reductase). Due to analogy between the malignant cell and the pathogenic microbes, treatment of neoplastic diseases with drugs is also called 'chemotherapy'.

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

Antimicrobial agent (AMA) to designate synthetic as well as naturally obtained drugs that attenuate microorganisms.

CLASSIFICATION

Antimicrobial drugs can be classified in many ways:

A. Chemical structure

1. Sulfonamides and related drugs: Sulfadiazine and others, Sulfones-Dapsone (DDS), Paraaminosalicylic acid (PAS) .

2. Oiaminopyrimidines: Trimethoprim, Pyrimethamine.

3. Quinalones: Nalidixic acid, Norfloxacin,Ciprofloxacin, Gatifloxacin, etc.

4. □-Lactam antibiotics: Penicillins, Cephalosporins, Monobactams, Carbapenems.

5. Tetracyclines: Oxytetracycline, Doxycycline,etc.

6. Nitrobenzene derivative: Chloramphenico:

?. Aminog/ycosides: Streptomycin, Gentamycin,Amikacin, Neomycin, etc.

8. Macrolide antibiotics: Erythromycin, Clanthromycin,Azithromycin, etc.

9. Lincosamide antibiotics: Lincomycin, Clindamycin.

10. Glycopeptide antibiotics: Vancomycir Teicoplanin.

1 1 . Oxazolidinone: Linezolid.

1 2. Polypeptide antibiotics: Polymyxin-B, Col□tin,Bacitracin, Tyrothricin.

13. Nitrofuran derivatives: Nitrofurantoin, Furc: zolidone.

14. Nitroimidazoles: Metronidazole, Tinidazole etc.

1 5 . Nicotinic acid derivatives: Isoniazid, Pyrczinamide,Ethionamide.

1 6 . Polyene antibiotics. Nystatin, Amphotericin-B, Hamycin. 1 7. Azote derivatives: Miconazole, Clotrimoxzole, Ketoconazole, Fluconazole.

18. Others: Rifampin, Spectinomycin, Cycloserine, Viomycin, Ethambutol,

Thiacetazone, Clofazimine, Griseofulvin.

B. Mechanism of action

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

2. Cause leakage from cell membranes: Poly-peptides-Polymyxins, Colistin, Bacitracin, Polyenes-Amphotericin B, Nystatin, Hamycin.

3. Inhibit protein synthesis: Tetracycline, Chloramphenicol, Erythromycin, Clindamycin, Linezolid.

4. Cause misreading ofm-RNA code and affect permeability: Aminoglycosides-Streptomycin, Gentamicin, etc.

Inhibit DNA gyrase: Fluoroquinolones Ciprofloxacin and others.

Interfere with DNA function: Rifampin, Metronidazole.

- Interfere with DNA synthesis: Acyclovir, Zidovudine.

- Interfere with intermediary metabolism: Sulfonamides, Sulfones, PAS, Trimethoprim, Pyrimethamine, Ethambutol.

 Type of organisms against which primarily active

1 . Antibacterial: Penicillins, Aminoglycosides, Erythromycin, etc.

2. Antifungal: Griseofulvin, Amphotericin B,

Ketoconazole, etc.

3. Antiviral: Acyclovir, Amantadine, Zidovudine,

etc.

4. Antiprotozoal: Chloroquine, Pyrimethamine, Metronidazole, Diloxanide, etc.

5. Anthelmintic: Mebendazole, Pyrantel, Niclosamide, Diethyl carbamazine, etc.

D. Spectrum of activity

Narrow-spectrum

Penicillin G, streptomycin

Broad-spectrum

Tetracyclines

Chloramphenicol

Hypersensitivity reactions

Practically all AMAs are capable of causing hypersensitivity reactions. These are unpredictable and unrelated to dose. The whole range of reactions from rashes to anaphylactic shock can be produced. The more commonly involved AMAs are-penicillins, cephalosporins, sulfonamides, fluoroquinolones.

Drug resistance

It refers to unresponsiveness of a microorganismto an AMA, and is akin to the phenomenon of tolerance seen in higher organisms.

Natural resistance Some microbes have always been resistant to certain AMAs. They lack the metabolic process or the target site which is affected by the particular drug.

Acquired resistance It is the development of resistance by an organism (which was sensitive before) due to the use of an AMA over a period of time.

Superinfection (Suprainfection) infection occurring after or on top of an earlier infection, especially following treatment with broad-spectrum antibiotics This refers to the appearance of a new infection as a result of antimicrobial therapy.

Use of most AMAs causes some alteration 1:· the normal microbial flora of the body. The normal flora contributes to host defence elaborating substances called bacteriocins which inhibit pathogenic organisms. Further pathogen has to compete with the normal flora for nutrients, etc. to establish itself

Superinfections are more common when the defence is compromised.

• Corticosteroid therapy

• Leukaemias and other malignancies, especially when treated with anticancer drugs

• Acquired immunodeficiency syndrome (AIDS

• Agranulocytosis

• Diabetes, disseminated lupus erythematosus

Sulfonamides and cotrimoxazole

SULFONAMIDES

Sulfonamides were the first antimicrobial agents (AMAs) effective against pyogenic bacterial

infections. Sulfonamido-chrysoidine (Prontosil Red) was one of the dyes included by Domagk to treat experimental streptococcal infection in mice and found it to be highly effective. A large number of sulfonamides were produced and used extensively in the subsequent years, but because of rapid emergence of bacterial resistance and the availability of many safer and more effective antibiotics, their current utility is limited, except in combination with trimethoprim (as cotrimoxazole) (for malaria).

All sulfonamides may be considered to derivatives of sulfanilamide (p-aminobenzene sulfonamide).

1 . Short acting (4-8 hr): Sulfadiazine

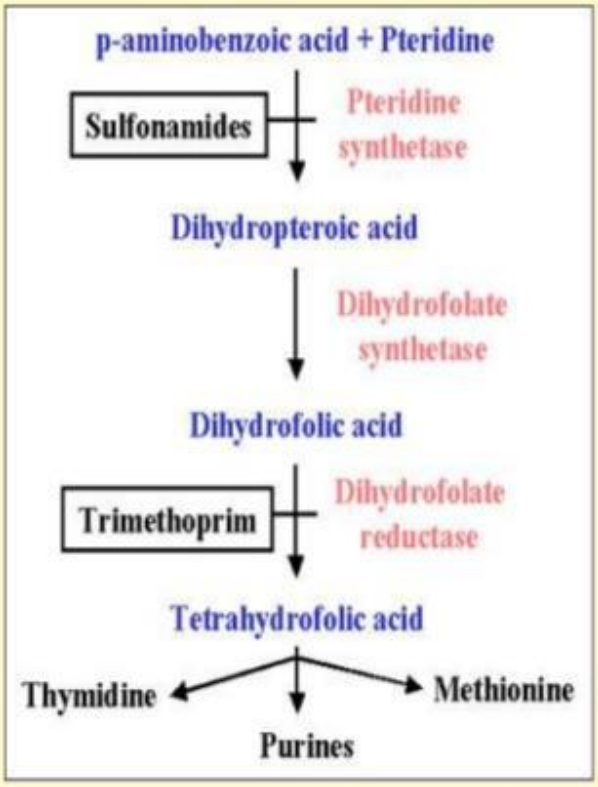
2. Intermediate acting (8-12 hr): Sulfamethoxazole

3. Long acting (-7 days): Sulfadoxine, Sulfamethopyrazine

4. Special purpose sulfonamides: Sulfacetamide sod., Mafenide, Silver sulfadiazine, Sulphsalazine

Mechanism of Sulfonamide

- Sulfonamide molecular structure is similar to p-Amino benzoic acid (PABA) which is needed in bacteria organisms as a substrate of the enzyme dihydro pteroate synthetase for the synthesis of Tetra Hydro Folic acid (THF).
- Folic acid - synthesized from PABA, pteridine and glutamate.
- All sulfonamides are analogs of PABA.
- All sulfa drugs are bacteriostatic.



COTRIMOXAZOLE

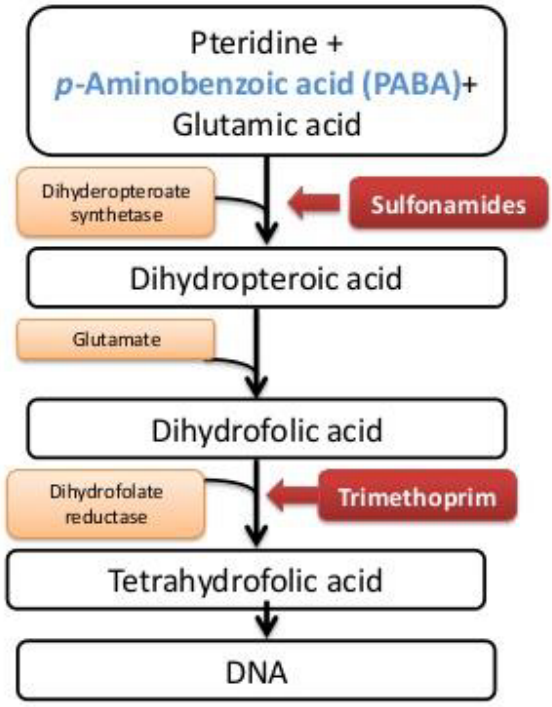
The fixed dose combination of trimethoprim and sulfamethoxazole is called cotrimoxazole.Trimethoprim is a diaminopyrimidine related to the antimalarial drug pyrimethamine which selectively inhibits bacterial dihydrofolate reductase (DHFRase).

Thus, human folate metabolism is not interfered at antibacterial concentrations of trimethoprim. Individually, both sulfonamide and trimethoprim are bacteriostatic, but the combination becomes cidal against many organisms.

Sulfamethoxazole was selected for combining with trimethoprim because both have nearly the same t hal f(- 10 hr). Optimal synergy in case of most organisms is exhibited at a concentration ratio of sulfamethoxazole 20 : trimethoprim 1, the MIC of each component may be reduced by 3-6 times. This ratio is obtained in the plasma when the two are given in a dose ratio of 5 : 1, because trimethoprim enters many tissues, has a larger. Cotrimoxazole volume of distribution than sulfamethoxazole and attains lower plasma concentration. However, the concentration ratio in many tissues is less than 20 : 1 . Trimethoprim adequately crosses blood-brain barrier and placenta, while sulfamethoxazole has a poorer entry. Moreover, trimethoprim is more rapidly absorbed than sulfamethoxazole--concentration ratios may vary with time. Trimethoprim is 40% plasma protein bound, while sulfamethoxazole is 65% bound. Trimethoprim is partly metabolized in liver and excreted in urine.

Cotrimoxazole

- Sulfamethoxazole was selected for combining with trimethoprim because both have nearly the same $t_{1/2}$ (~10 h).
- Optimal synergy in case of most organisms is exhibited at a concentration ratio of sulfamethoxazole: trimethoprim (20:1), the MIC of each component may be reduced by 3-6 times.



Uses

1 . Urinary tract infections

2. Respiratory tract infections

3. Typhoid

4. Bacterial diarrhoeas and dysentery

5. Pneumocystis

6. Chancroid

QUINOLONES

These are synthetic antimicrobials having a quinolone structure that are active primarily against gram-negative bacteria, though newer fluorinated compounds also inhibit gram-positive ones. The first member Nalidixic acid introduced in mid-1960s had usefulness limited to urinary and g.i. tract infections because of low potency, modest blood and tissue levels, limited spectrum and high frequency of bacterial resistance. at position 7 resulting in derivatives called

fluoroquinolones with high potency, expanded spectrum, slow development of resistance, better tissue penetration and good tolerability.

Nalidixic acid

It is active against gram-negative bacteria, especially coliforms: E. coli, Proteus, Klebsiella, Enterobacter, Shigella but not Pseudomonas.

It acts by inhibiting bacterial DNA gyrase and is bactericidal. Resistance to nalidixic acid develops rather rapidly.

Nalidixic acid is absorbed orally, highly plasma protein bound and partly metabolized in liver: one of the metabolites is active. It is excreted in urine with a plasma t half -8 hrs. Adverse effects These are relatively infrequent, consist mostly of g.i. upset and rashes. Most important toxicity is neurological-headache, drowsiness, vertigo, visual disturbances, occasionally seizures (especially in children).

Use

1 . Nalidixic acid is primarily used as a urinary antiseptic, generally as a second line drug in recurrent cases or on the basis of sensitivity reports.

2. It has also been employed in diarrhoea caused by Proteus, E. coli, Shigella or Salmonella, and has special place in ampicillin resistant Shigella enteritis.

FLUOROQUINOLONES

These are quinolone antimicrobials having one or more fluorine substitutions. The 'first generation' fluoroquinolones (FQs) introduced in 1980s have one fluoro substitution. In the 1990s, compounds with additional fluoro and other substitutions have been developed-further extending antimicrobial activity to gram-positive cocci and anaerobes, and/ or confering metabolic stability (longer Ph). These are referred to as'second generation' FQs.

Norfloxacin

Ciprofloxacin

Lomefloxacin

Levofloxacin

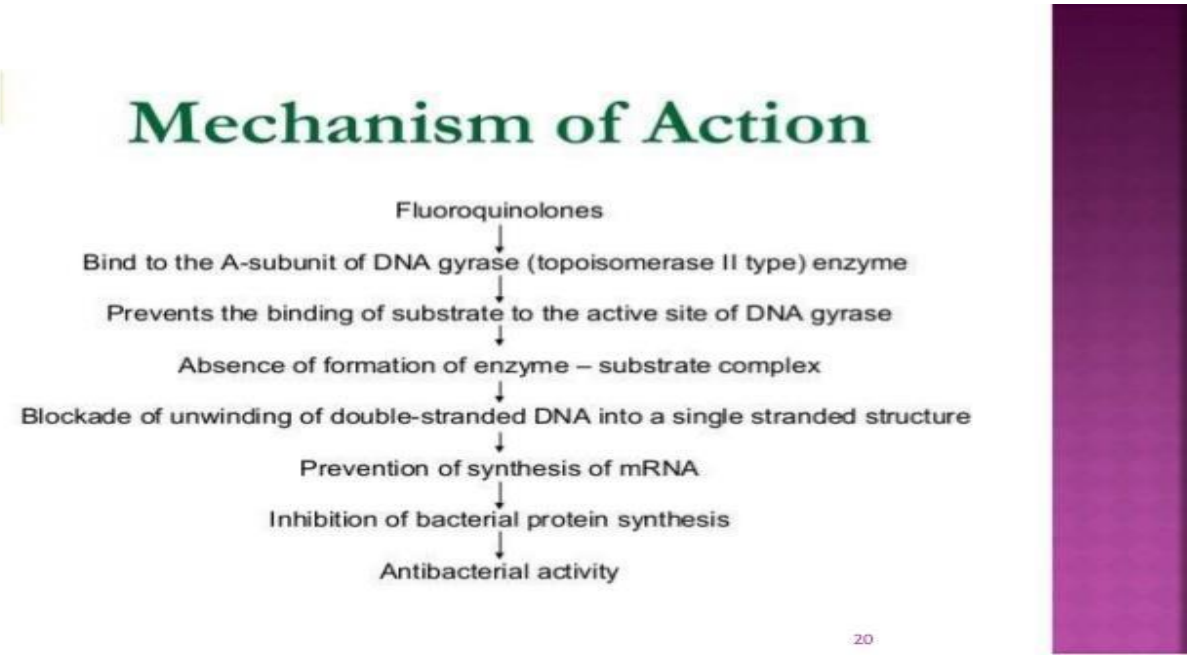
Ofloxacin

Pefloxacin

Sparfloxacin

Gatifloxacin

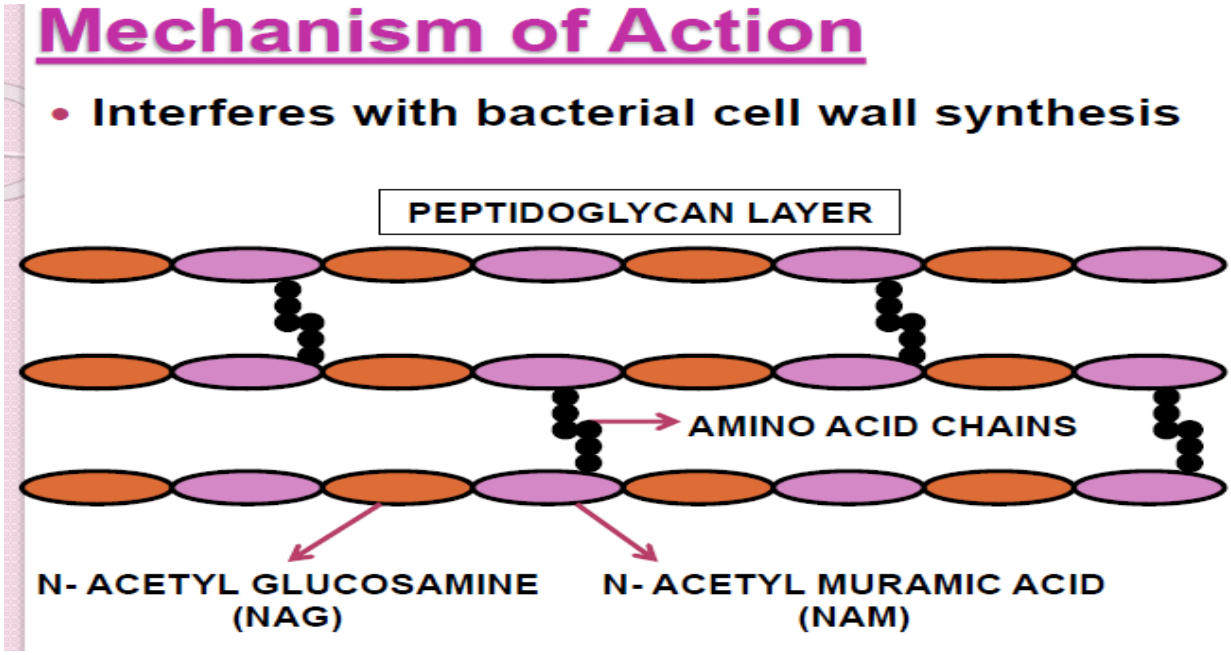
Moxifloxacin



Penicillin

Scottish biologist and pharmacologist

After World War I elected **Professor of Bacteriology** at the University of London in 1928



Fleming received the **Nobel Prize in 1945** Accidentally discovered Penicillin while studying **properties of Staphylococci**

Described the mould as being from the **genus Penicillium**

Named the substance released as Penicillin

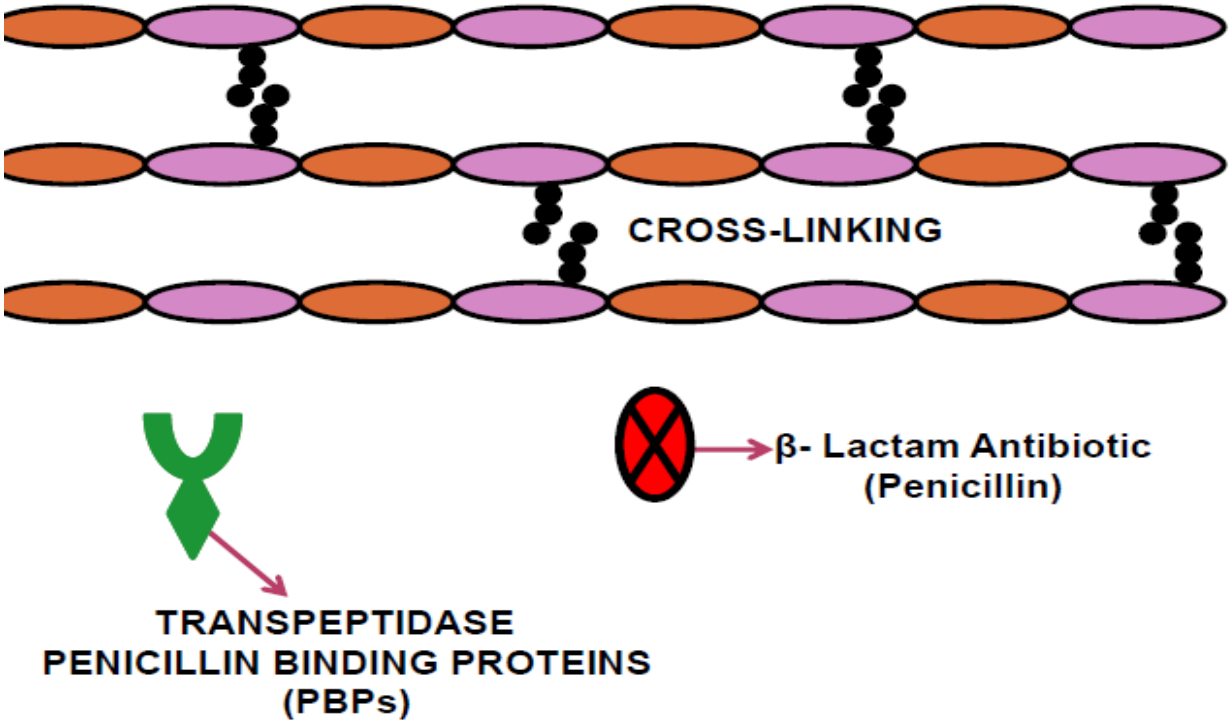
PENICILLIN WAS BORN 7TH MARCH, 1929

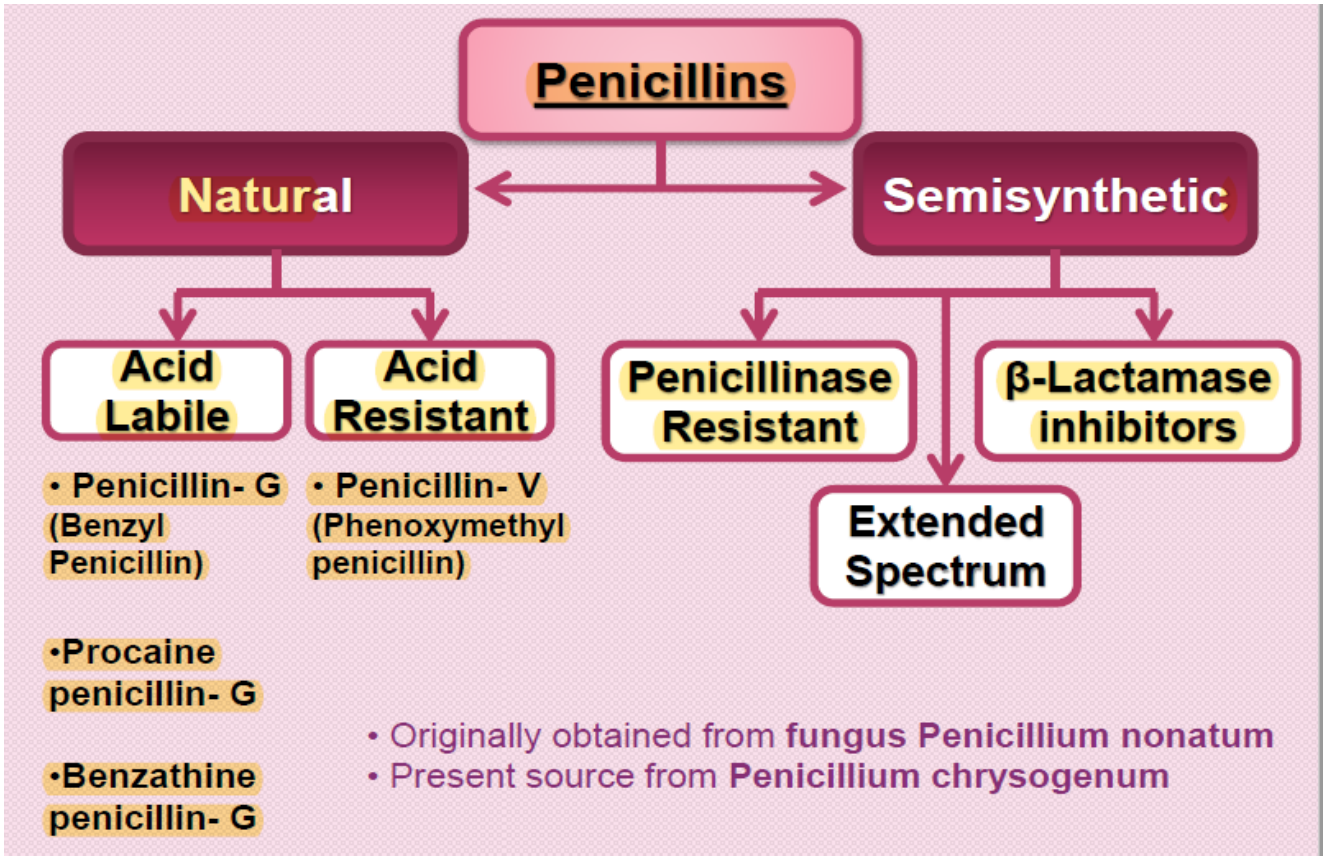
History

Mass production of the new drug for use in World War II

Penicillin saved many lives during the war that may have been lost due to infected wounds Penicillin was also said to treat **diphtheria, gangrene, pneumonia, syphilis and tuberculosis** Penicillin- **first antibiotic** to be used clinically

Penicillin was the first antibiotic to be used clinically in 1941 . It is a miracle that the least toxic drug of its kind was the first to be discovered.It was originally obtained from the fungus Penicillium notatum, but the present source is a high yielding mutant of P. chrysogenum. C hemistry and properties The penicillin nucleus consists of fused thiazolidine and β-lactam rings to which side chains are attached through an amide linkage. Penicillin G (PnG), having a benzyl side chain atR (benzyl penicillin:is the original penicillin used clinically.


CROSS-LINKING
β- Lactam Antibiotic
(Penicillin)
TRANSPEPTIDASE
PENICILLIN BINDING PROTEINS
(PBPs)


Penicillins
Natural
Semisynthetic
Acid Labile
Acid Resistant
Penicillinase Resistant
β-Lactamase inhibitors
Extended Spectrum
• Penicillin- G (Benzyl Penicillin)
• Penicillin- V (Phenoxymethyl penicillin)
•Procaine penicillin- G
•Benzathine penicillin- G
• Originally obtained from fungus Penicillium nonatum
• Present source from Penicillium chrysogenum

SEMISYNTHETIC PENICILLINS

Semisynthetic penicillins are produced by chemically combining specific side chains (in place of benzyl side chain of PnG) or by incorporating specific precursors in the mould cultures. Thus, procaine penicillin and benzathine penicillin are salts of PnG and not semisynthetic penicillins. The aim of producing semisynthetic penicillins has been to overcome the shortcomings of PnG, which are:

1 . Poor oral efficacy.

2. Susceptibility to penicillinase.

3. Narrow spectrum of activity.

4. Hypersensitivity reactions (this has not been overcome in any preparation).

CLASSIFICATION

1 . Acid-resistant alternative to penicillin G Phenoxymethyl penicillin (Penicillin V).

2. Penicillinase-resistant penicillins Methicillin, Cloxacillin.

3. Extended spectrum penicillins

(a) Aminopenicillins: Ampicillin, Bacampicillin, Amoxicillin.

(b) Carboxypenicillins: Carbenicillin, Ticarcillin.

(c) Ureidopenicillins: Piperacillin, Mezlocillin.

□-/actamase inhibitors Clavulanic acid Sulbactam, Tazobactam

BETA-LACTAMASE INHIBITORS

beta-lactamases are a family of enzymes produced by many gram-positive and gram-negative bacteria that inactivate β -lactam antibiotics by opening the β -lactam ring. Different β -lactamases differ in their substrate affinities. Three inhibitors of this enzyme clavulanic acid, sulbactam and tazobactam are available for clinical use.

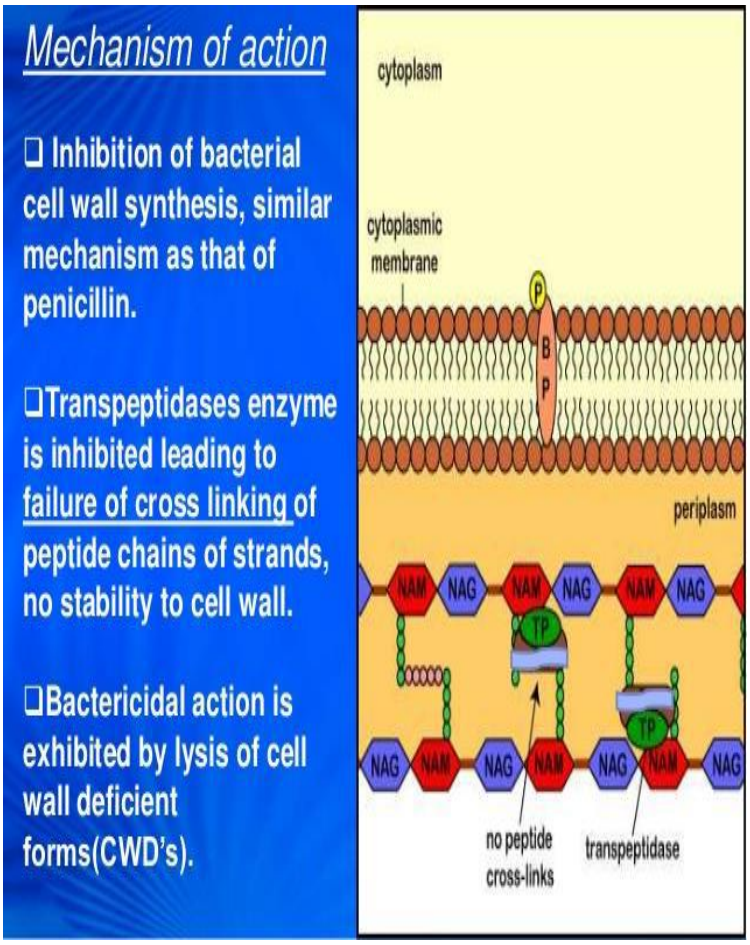
Clavulanic acid Obtained from Streptomyces clavuligerus, it has a β -lactam ring but no antibacterial activity of its own. It inhibits a wide variety (class II to class V) of β -lactamases (but not class I cephalosporinase) produced by both gram-positive and gram-negative bacteria. Clavulanic acid is a 'progressive' inhibitor : binding with □-lactamase is reversible initially, but becomes covalent later-inhibition increasing with time. Called a 'suicide' inhibitor, it gets inactivated after binding to the enzyme. It

CEPHALOSPORINS

These are a group of semisynthetic antibiotics derived from 'cephalosporin-C' obtained from a fungus Cephalosporium. They are chemically related to penicillins; the nucleus consists of a P-lactam ring fused to a dihydrothiazine ring, (7-aminocephalosporanic acid). By addition of different side chains at position 7 of [3-lactam ring (altering spectrum of activity) and at position 3 of dihydrothiazine ring (affecting pharmacokinetics), a large number of semisynthetic comp ounds have been produced.

Generations of Cephalosporin

Oral	Parentral
1st generation	
Cephalexin	Cephalothin
Cephradine	Cefazolin
Cefadroxil	
2nd generation	
Cefaclor	Cefuroxime
Cefuroxime axetil	Cefoxitin
3rd generation	
Cefixime	Cefotaxime
Cefdinir	Ceftizoxime
Ceftibuten	Ceftriaxone
Ceftamer pivoxil	Ceftazidime
4th generation	
	Cefepime
	Cefpirome



First generation: The first-generation cephalosporins act as *penicillin G* substitutes. They are resistant to the staphylococcal penicillinase and also have activity against Proteus mirabilis, E. coli, and Klebsiella pneumonia

Second generation: The second-generation cephalosporins display greater activity against three additional gram-negative organisms: H. influenzae, Enterobacter aerogenes, and some Neisseria species, whereas activity against gram-positive organisms is weaker [Note: The exception to this generalization is the structurally related cephamycin, *cefoxitin* which has little activity against H. influenzae yet is effective against the anaerobe Bacteroides fragilis

Third generation: These cephalosporins have assumed an important role in the treatment of infectious disease. Although inferior to first-generation cephalosporins in regard to their activity against gram-positive cocci, the third-generation cephalosporins have enhanced activity against gram-negative bacilli, including those mentioned above, as well as most other enteric organisms plus Serratia marcescens. *Ceftriaxone* [sef-trye-AKS-own] or *cefotaxime* [sef-oh-TAKS-eem] have become agents of choice in the treatment of meningitis. *Ceftazidime* [sef-TA-zi-deem] has activity against P. aeruginosa.

Fourth generation: *Cefepime* is classified as a fourth-generation cephalosporin and must be administered parenterally. *Cefepime* has a wide antibacterial spectrum, being active against streptococci and staphylococci (but only those that are *methicillin*-susceptible). *Cefepime* is also effective against aerobic gram-negative organisms, such as enterobacter, E. coli, K. pneumoniae, P. mirabilis, and P. aeruginosa.

C. Pharmacokinetics

Administration: Many of the cephalosporins must be administered IV or IM. because of their poor oral absorption.

1. **Distribution:** All cephalosporins distribute very well into body fluids. However, adequate therapeutic levels in the CSF, regardless of inflammation, are achieved only with the third-generation cephalosporins. For example, *ceftriaxone* or *cefotaxime* are effective in the treatment of neonatal and childhood meningitis caused by H. influenzae. *Cefazolin* [se-FA-zo-lin] finds application as a single prophylaxis dose prior to surgery because of its 1.8-hour half-life and its activity against penicillinase-producing S. aureus. However, additional

intraoperative *cefazolin* doses may be required if the surgical procedure lasts longer than 3 hours. *Cefazolin* is effective for most surgical procedures, including orthopedic surgery because of its ability to penetrate bone. All cephalosporins cross the placenta.

2. **Fate:** Biotransformation of cephalosporins by the host is not clinically important. Elimination occurs through tubular secretion and/or glomerular filtration). Therefore doses must be adjusted in cases of severe renal failure to guard against accumulation and toxicity. *Ceftriaxone* is excreted through the bile into the feces and, therefore, is frequently employed in patients with renal insufficiency

Adverse effects

Cephalosporins are generally well tolerated, but
are more toxic than penicillin.

1. Pain after i.m. injection occurs with many. This is so severe with cephalothin as to interdict i.m. route, but many others can be injected i.m. (seeindividual compounds). Thrombophlebitis of injected vein can occur.

2. Diarrhoea due to alteration of gut ecology or irritative effect is more common with oral cephradine and parenteral cefoperazone (it is significantly excreted in bile).

3. Hypersensitivity reactions caused by cephalosporins are similar to penicillin, but incidence is lower. Rashes are the most frequent manifestation, but anaphylaxis, angioedema, asthma and urticaria have also occurred. About 10% patients allergic to penicillin show cross reactivity with cephalosporins. Those with a history of immediate type of reactions to penicillin should better not be given a cephalosporin. Skin tests for sensitivity to cephalosporins are unreliable. A positive Coombs' test occurs in many, but haemolysis is rare.

4. Nephrotoxicity is highest with cephaloridine, which consequently has been withdrawn.

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5. Bleeding common inpatients with cancer, intra-abdominal infection or renal failure.

6. Neutropenia and thrombocytopenia are rareadverse effects reported with ceftazidime and some others.

7. A disulfiram-like interaction with alcohol hasbeen reported with cefoperazone.

Uses

1 . As alternatives to PnG;

2. Respiratory, urinary and soft tissue infections

3. Penicillinase producing staphylococcal infections.

4. Septicaemias

5. Surgical prophylaxis:

6. Meningitis:

7. Gonorrhoea

8. Typhoid:

9. Mixed aerobic-anaerobic infections in cancer Patients.

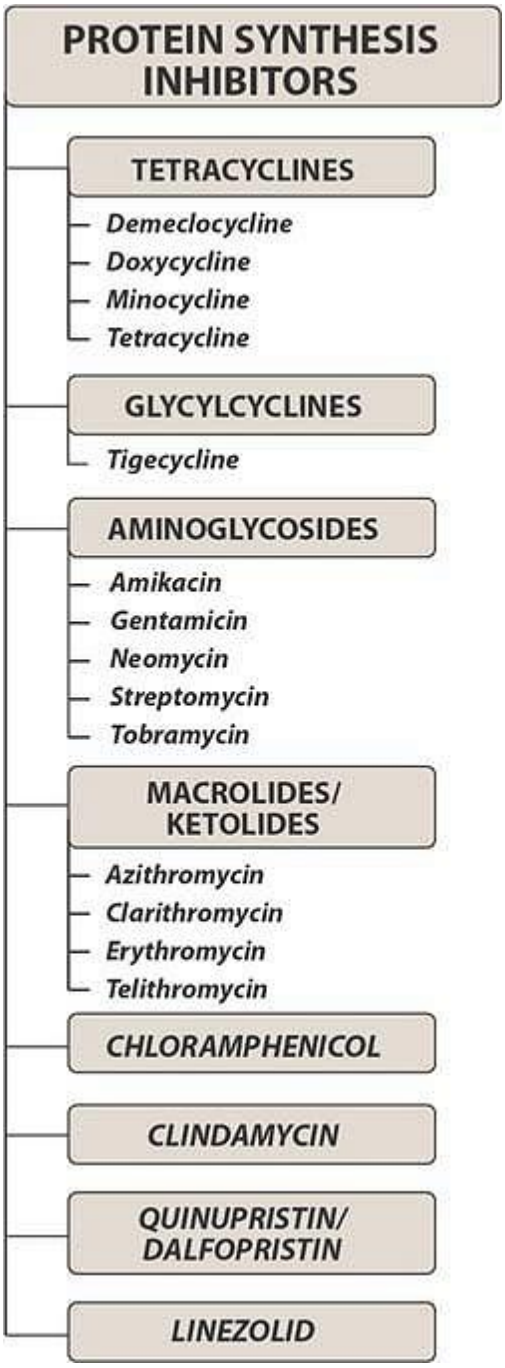
TETRACYCLINES

INTRODUCTION • Obtained from soil actinimycetes. • Introduced in 1948 by Benjamin Minge Duggar (chlortetracycline, aureomycin). • Tetracyclines is broad spectrum antibiotic having four cyclic ring nucleus. • All tetracyclines are slightly bitter solids, weakly water soluble, their hydrochlorides are more soluble. • Aqueous solutions are unstable.

Tetracyclines available in India for clinical use:- Tetracycline, Oxytetracycline, Demeclocycline, Doxycycline, Minocycline.

MECHANISM OF ACTION • Tetracyclines are primarily bacteriostatic. • Inhibit protein synthesis by binding to 30s ribosome in susceptable organism. • Inhibit binding of aminoacyl tRNA to the acceptor site of mRNA peptide chain fails to grow

Entry of these agents into susceptible organisms is mediated both by passive diffusion and by an energy-dependent transport protein mechanism unique to the bacterial inner cytoplasmic membrane.



D. Pharmacokinetics

Absorption: All tetracyclines are adequately but incompletely absorbed after oral ingestion. However, taking these drugs concomitantly with dairy foods in the diet decreases absorption due to the formation of nonabsorbable chelates of the tetracyclines with calcium ions. Nonabsorbable chelates are also formed with other divalent and trivalent cations (for example, those found in magnesium and aluminum antacids and in iron preparations). [Note: This presents a problem if a

patient self-treats the epigastric upsets caused by tetracycline ingestion with antacids Doxycycline and minocycline are almost totally absorbed on oral administration. Currently, doxycycline is the preferred tetracycline for parenteral administration.
Typical therapeutic applications of tetracyclines.

Distribution: The tetracyclines concentrate in the liver, kidney, spleen, and skin, and they bind to tissues undergoing calcification (for example, teeth and bones) or to tumors that have a high calcium content (for example, gastric carcinoma). Penetration into most body fluids is adequate. Although all tetracyclines enter the cerebrospinal fluid (CSF), levels are insufficient for therapeutic efficacy, except for minocycline. Minocycline enters the brain in the absence of inflammation and also appears in tears and saliva. Although useful in eradicating the meningococcal carrier state, minocycline is not effective for central nervous system infections. All tetracyclines cross the placental barrier and concentrate in fetal bones and dentition.

Fate: All the tetracyclines concentrate in the liver, where they are, in part, metabolized and conjugated to form soluble glucuronides. The parent drug and/or its metabolites are secreted into the bile. Most tetracyclines are reabsorbed in the intestine via the enterohepatic circulation and enter the urine by glomerular filtration. Obstruction of the bile duct and hepatic or renal dysfunction can increase their half-lives. Unlike other tetracyclines, doxycycline can be employed for treating infections in renally compromised patients, because it is preferentially excreted via the bile into the feces.

E. Adverse effects

Effect of antacids and milk on the absorption of tetracyclines.

Gastric discomfort: Epigastric distress commonly results from irritation of the gastric mucosa and is often responsible for noncompliance in patients treated with these drugs. The discomfort can be controlled if the drug is taken with foods other than dairy products.

1. Effects on calcified tissues: Deposition in the bone and primary dentition occurs during calcification in growing children. This causes discoloration and hypoplasia of the teeth and a temporary stunting of growth.

2.Fatal hepatotoxicity: This side effect has been known to occur in pregnant women who received high doses of tetracyclines, especially if they were experiencing pyelonephritis.

3. Phototoxicity: Phototoxicity, such as severe sunburn, occurs when a patient receiving a tetracycline is exposed to sun or ultraviolet rays. This toxicity is encountered most frequently with tetracycline.

4. Vestibular problems: These side effects (for example, dizziness, nausea, and vomiting) occur particularly with minocycline, which concentrates in the endolymph of the ear and affects function. Doxycycline may also cause vestibular effects.

5. Pseudotumor cerebri: Benign, intracranial hypertension characterized by headache and blurred vision may occur rarely in adults. Although discontinuation of the drug reverses this condition, it is not clear whether permanent sequelae may occur.

6. Superinfections: Overgrowths of Candida (for example, in the vagina) or of resistant staphylococci (in the intestine) may occur. Pseudomembranous colitis due to an overgrowth of Clostridium difficile has also been reported.

AMINOGLYCOSIDES

Aminoglycoside antibiotics had been the mainstays for treatment of serious infections due to aerobic gram-negative bacilli. However, because their use is associated with serious toxicities, they have been replaced to some extent by safer antibiotics, such as the third- and fourth-generation cephalosporins, the fluoroquinolones, and the carbapenems. Aminoglycosides that are derived from Streptomyces have -mycin suffixes, whereas those derived from Micromonospora end in -micin. The terms oeaminoglycosid stem from their

Structure two amino sugars joined by a glycosidic linkage to a central hexose (aminocyclitol) nucleus. Their polycationic nature precludes their easy passage across tissue membranes. All members of this family are believed to inhibit bacterial protein synthesis by the mechanism determined for *streptomycin* as described below.

A. Mechanism of action

Susceptible gram-negative organisms allow aminoglycosides to diffuse through porin channels in their outer membranes. These organisms also have an oxygen-dependent system that transports the drug across the cytoplasmic membrane. The antibiotic then binds to the 30S ribosomal subunit prior to ribosome formation. There, it interferes with assembly of the functional ribosomal apparatus and/or can cause the 30S subunit of the completed ribosome to misread the genetic code. Polysomes become depleted, because the aminoglycosides interrupt the process of polysome disaggregation and assembly.

B. Antibacterial spectrum

The aminoglycosides are effective in the empirical treatment of infections suspected of being due to aerobic gram-negative bacilli, including Pseudomonas aeruginosa. To achieve an additive or synergistic effect, aminoglycosides are often combined with a Î²-lactam antibiotic, or *vancomycin*, or a drug active against anaerobic bacteria. All aminoglycosides are bactericidal. The exact mechanism of their lethality is unknown because other antibiotics that affect protein synthesis are generally bacteriostatic. [Note: The aminoglycosides are effective only against aerobic organisms because strict anaerobes lack the oxygen-requiring drug transport system.]

C. Resistance

Resistance can be caused by 1) decreased uptake of drug when the oxygen-dependent transport system for aminoglycosides or porin channels are absent and 2) plasmid-associated synthesis of enzymes (for example, acetyl transferases, nucleotidyltransferases, and phosphotransferases) that modify and inactivate aminoglycoside antibiotics.

D. Pharmacokinetics

Administration: The highly polar, polycationic structure of the aminoglycosides prevents adequate absorption after oral administration. Therefore, all aminoglycosides (except *neomycin* must be given parenterally to achieve adequate serum levels

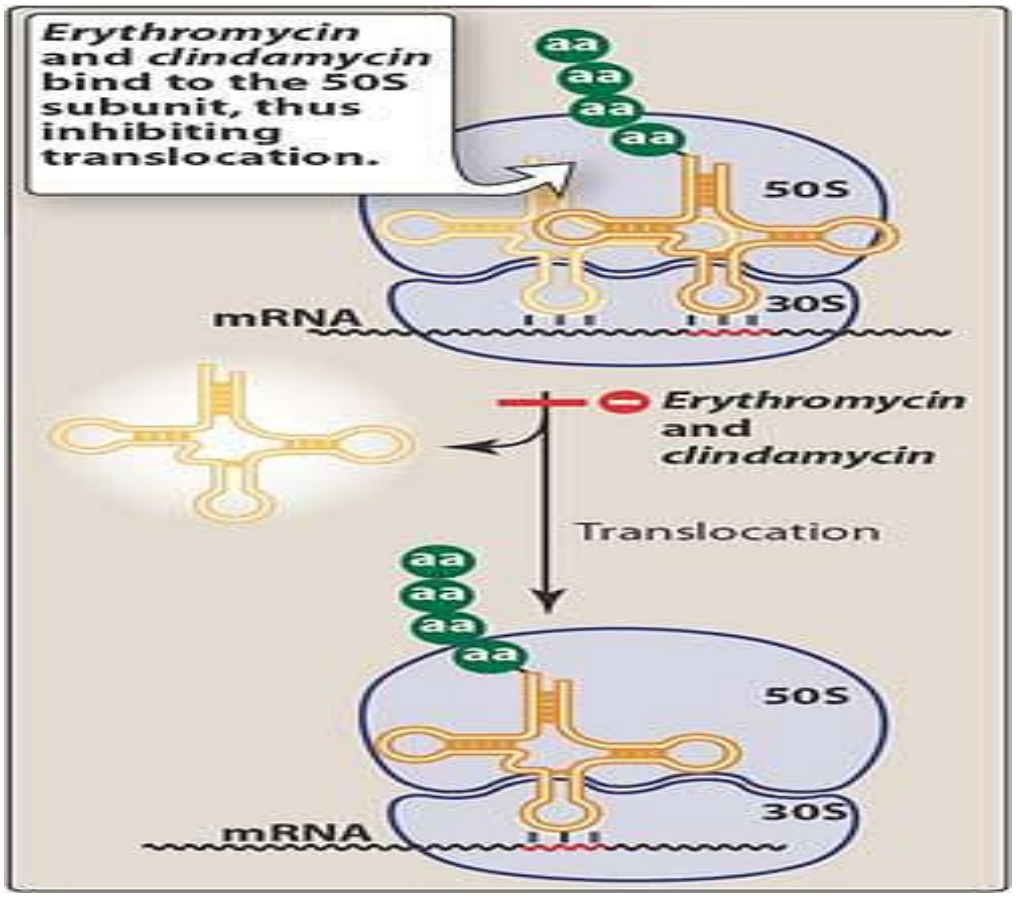
E. Adverse effects

Ototoxicity: Ototoxicity (vestibular and cochlear) is directly related to high peak plasma levels and the duration of treatment. The antibiotic accumulates in the endolymph and perilymph of the inner ear, and toxicity correlates with the number of destroyed hair cells in the organ of Corti.

Nephrotoxicity: Retention of the aminoglycosides by the proximal tubular cells disrupts calcium-mediated transport processes, and this results in kidney damage ranging from mild, reversible renal impairment to severe, acute tubular necrosis, which can be irreversible.

Neuromuscular paralysis: This side effect most often occurs after direct intraperitoneal or intrapleural application of large doses of aminoglycosides. The mechanism responsible is a decrease in both the release of acetylcholine from prejunctional nerve endings and the sensitivity of the postsynaptic site. Patients with myasthenia gravis are particularly at risk. Prompt administration of *calcium gluconate* or *neostigmine* can reverse the block.

Allergic reactions: Contact dermatitis is a common reaction to topically applied *neomycin*.



MACROLIDES

The macrolides are a group of antibiotics with a macrocyclic lactone structure to which one or more deoxy sugars are attached. *Erythromycin* [er-ith-roe-MYE-sin] was the first of these drugs to find clinical application, both as a drug of first choice and as an alternative to *penicillin* in individuals who are allergic to Î²-lactam antibiotics. The newer members of this family, *clarithromycin* (a methylated form of *erythromycin*) and *azithromycin* (having a larger lactone ring), have some features in common with, and others that improve on, *erythromycin*.

A. Mechanism of action

The macrolides bind irreversibly to a site on the 50S subunit of the bacterial ribosome, thus inhibiting the translocation steps of protein synthesis. They may also interfere at other steps, such as transpeptidation. Generally considered to be bacteriostatic, they may be bactericidal at higher doses. Their binding site is either identical or in close proximity to that for *clindamycin* and *chloramphenicol*.

B. Antibacterial spectrum

Erythromycin: This drug is effective against many of the same organisms as *penicillin G* therefore, it is used in patients who are allergic to the penicillins.

Clarithromycin: This antibiotic has a spectrum of antibacterial activity similar to that of *erythromycin*, but it is also effective against Haemophilus influenzae. Its activity against intracellular pathogens, such as Chlamydia, Legionella, Moraxella, and Ureaplasma species and Helicobacter pylori, is higher than that of *erythromycin*.

3. **Azithromycin:** Although less active against streptococci and staphylococci than *erythromycin, azithromycin* is far more active against respiratory infections due to H. influenzae and Moraxella catarrhalis. *Azithromycin* is now the preferred therapy for urethritis caused by Chlamydia trachomatis. It also has activity against Mycobacterium avium-intracellulare complex in patients with acquired immunodeficiency syndrome and disseminated infections.

4. **Telithromycin:** This ketolide drug has an antibacterial spectrum similar to that of *azithromycin*. Moreover, the structural modification within ketolides neutralizes the most common resistance mechanisms (methylasemediated and efflux-mediated) that make macrolides ineffective.

C. Resistance

Resistance to *erythromycin* is becoming a serious clinical problem. For example, most strains of staphylococci in hospital isolates are resistant to this drug. Several mechanisms have been identified: 1) the inability of the organism to take up the antibiotic or the presence of an efflux pump, both of which limit the amount of intracellular drug; 2) a decreased affinity of the 50S ribosomal subunit for the antibiotic, resulting from the methylation of an adenine in the 23S bacterial ribosomal RNA; and 3) the presence of a plasmid-associated *erythromycin* esterase. Both *clarithromycin* and *azithromycin* show cross-resistance with *erythromycin*, but *telithromycin* can be effective against macrolide-resistant organisms.

Administration: The *erythromycin* base is destroyed by gastric acid. Thus, either enteric-coated tablets or esterified forms of the antibiotic are administered. All are adequately absorbed upon oral administration. *Clarithromycin*, *azithromycin*, and *telithromycin* are stable to stomach acid and are readily absorbed.

Food interferes with the absorption of *erythromycin* and *azithromycin* but can increase that of *clarithromycin*. *Azithromycin* is available for intravenous infusion, but intravenous administration of *erythromycin* is associated with a high incidence of thrombophlebitis.

Distribution: *Erythromycin* distributes well to all body fluids except the CSF. It is one of the few antibiotics that diffuses into prostatic fluid, and it has the unique characteristic of accumulating in macrophages. All four drugs concentrate in the liver. Inflammation allows for greater tissue penetration. Similarly, *clarithromycin*, *azithromycin*, and *telithromycin* are widely distributed in the tissues. Serum levels of *azithromycin* are low; the drug is concentrated in neutrophils, macrophages, and fibroblasts. *Azithromycin* has the longest half-life and largest volume of distribution of the four drugs.

Fate: *Erythromycin* and *telithromycin* are extensively metabolized and are known to inhibit the oxidation of a number of drugs through their interaction with the cytochrome P450 system Interference with the metabolism of drugs such as *theophylline* and *carbamazepine* has been reported for *clarithromycin. Clarithromycin* is oxidized to the 14-hydroxy derivative, which retains antibiotic activity.

Excretion: *Erythromycin* and *azithromycin* are primarily concentrated and excreted in an active form in the bile. Partial reabsorption occurs through the enterohepatic circulation. Inactive

metabolites are excreted into the urine. In contrast, *clarithromycin* and its metabolites are eliminated by the kidney as well as the liver, and it is recommended that the dosage of this drug be adjusted in patients with compromised renal function.

Adverse effects

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Epigastric distress: This side effect is common and can lead to poor patient compliance for *erythromycin*. *Clarithromycin* and *azithromycin* seem to be better tolerated by the patient, but gastrointestinal problems are their most common side effects

Cholestatic jaundice: This side effect occurs especially with the estolate form of *erythromycin*, presumably as the result of a hypersensitivity reaction to the estolate form (the lauryl salt of the propionyl ester of *erythromycin*). It has also been reported for other forms of the drug.

Ototoxicity: Transient deafness has been associated with *erythromycin*, especially 3. at high dosages.

CHLORAMPHENICOL

Chloramphenicol is active against a wide range of gram-positive and gram-negative organisms. However, because of its toxicity, its use is restricted to life-threatening infections for which no alternatives exist.

A. Mechanism of action

The drug binds to the bacterial 50S ribosomal subunit and inhibits protein synthesis at the peptidyl transferase reaction. Because of the similarity of mammalian mitochondrial ribosomes to those of bacteria, protein synthesis in these organelles may be inhibited at high circulating *chloramphenicol* levels, producing bone marrow toxicity.

B. Antimicrobial spectrum

Chloramphenicol, a broad-spectrum antibiotic, is active not only against bacteria but also against other microorganisms, such as rickettsiae. Pseudomonas aeruginosa is not affected, nor are the chlamydiae. *Chloramphenicol* has excellent activity against anaerobes. The drug is either bactericidal or (more commonly) bacteriostatic, depending on the organism.

C. Resistance

Resistance is conferred by the presence of an R factor that codes for an acetyl coenzyme A transferase. This enzyme inactivates *chloramphenicol.* Another mechanism for resistance is associated with an inability of the antibiotic to penetrate the organism. This change in permeability may be the basis of multidrug resistance.

D. Pharmacokinetics

Chloramphenicol may be administered either intravenously or orally.It is completely absorbed via the oral route because of its lipophilic nature, and is widely distributed throughout the body. It readily enters the normal CSF. The drug inhibits the hepatic mixed-function oxidases. Excretion of the drug depends on its conversion in the liver to a glucuronide, which is then secreted by the renal tubule. Only about 10 percent of the parent compound is excreted by glomerular filtration. *Chloramphenicol* is also secreted into breast milk.

E. Adverse effects

The clinical use of *chloramphenicol* is limited to life-threatening infections because of the serious adverse effects associated with its administration. In addition to gastrointestinal upsets, overgrowth of Candida albicans may appearon mucous membranes.

Anemias: Hemolytic anemia occurs in patients with low levels of glucose 6-phosphate dehydrogenase. Other types of anemia occurring as a side effect of *chloramphenicol* include reversible anemia, which is apparently dose-related and occurs concomitantly with therapy, and aplastic anemia, which although rare is idiosyncratic and usually fatal.

Gray baby syndrome: This adverse effect occurs in neonates if the dosage regimen of *chloramphenicol* is not properly adjusted. Neonates have a low capacity to glucuronylate the antibiotic, and they have underdeveloped renal function. Therefore, neonates have a decreased ability to excrete the drug, which accumulates to levels that interfere with the function of mitochondrial ribosomes. This leads to poor feeding, depressed breathing,

cardiovascular collapse, cyanosis and death. Adults who have received very high doses of the drug can also exhibit this toxicity.