Program	B. Pharmacy
Semester	VI
Subject /Course	Pharmacology-III
Subject/Course ID	BP602T
Module No.	02
Module Title	Chemotherapy
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Learning Outcome of Module-2

LO	Learning Outcome (LO)	Course Outcome Code
LO1	Students understand the general principles of chemotherapy and pharmacology of microbial agents.	BP602.2
LO2	Students understand the basic concept regarding pharmacology and chemotherapy of various diseases.	BP602.2
LO3	Know about the different classes of the drugs with their mechanism of action, therapeutic uses and adverse effects.	BP602.2
LO4	To Understand the Pharmacokinetics and pharmacological action of different class of drugs.	BP602.2

Content Table

Topic
• General principles of chemotherapy • Sulfonamides and cotrimoxazole • Antibiotics: penicillins, • Cephelosporins • Chloramphenicol • Macrolides • Quinolones and fluoroquinolones • Tetracycline • Aminoglycosides

CHEMOTHERAPY

Cytotoxic chemotherapy agents are used to treat cancers, leukaemia's and lymphomas. There are over 50 such drugs, which can be used as single agents, or in combination, orally, IV and subcutaneously.

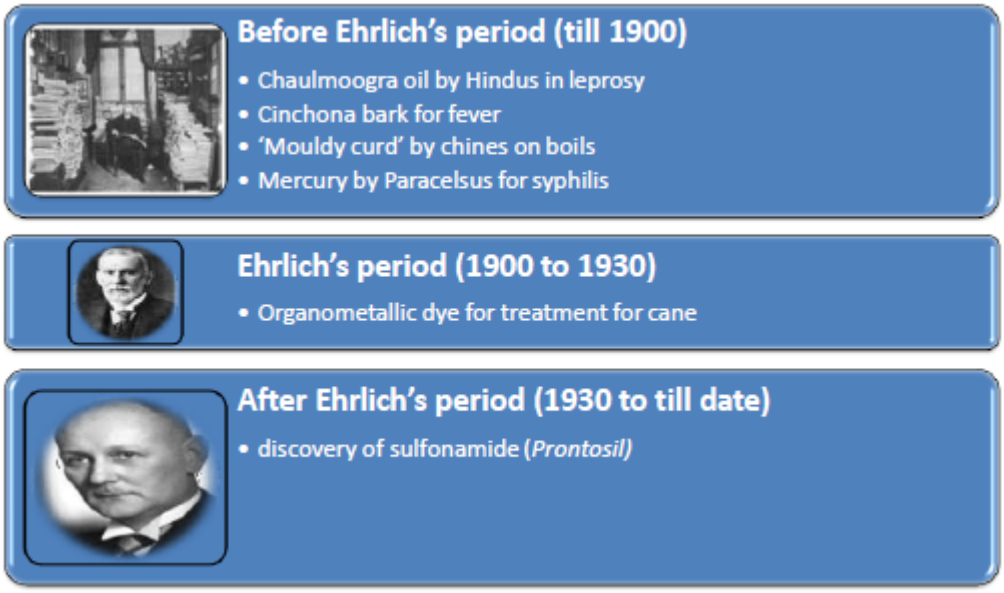
- Cytotoxic chemotherapy refers to agents whose mechanisms of action cause cell death or prevent cell growth, generally through inhibiting microtubule function, protein function, or DNA synthesis.
- Cytotoxic chemotherapy mechanisms of action may be cell cycledependent—arresting cancer cell growth at specific phases in the cell cycle.

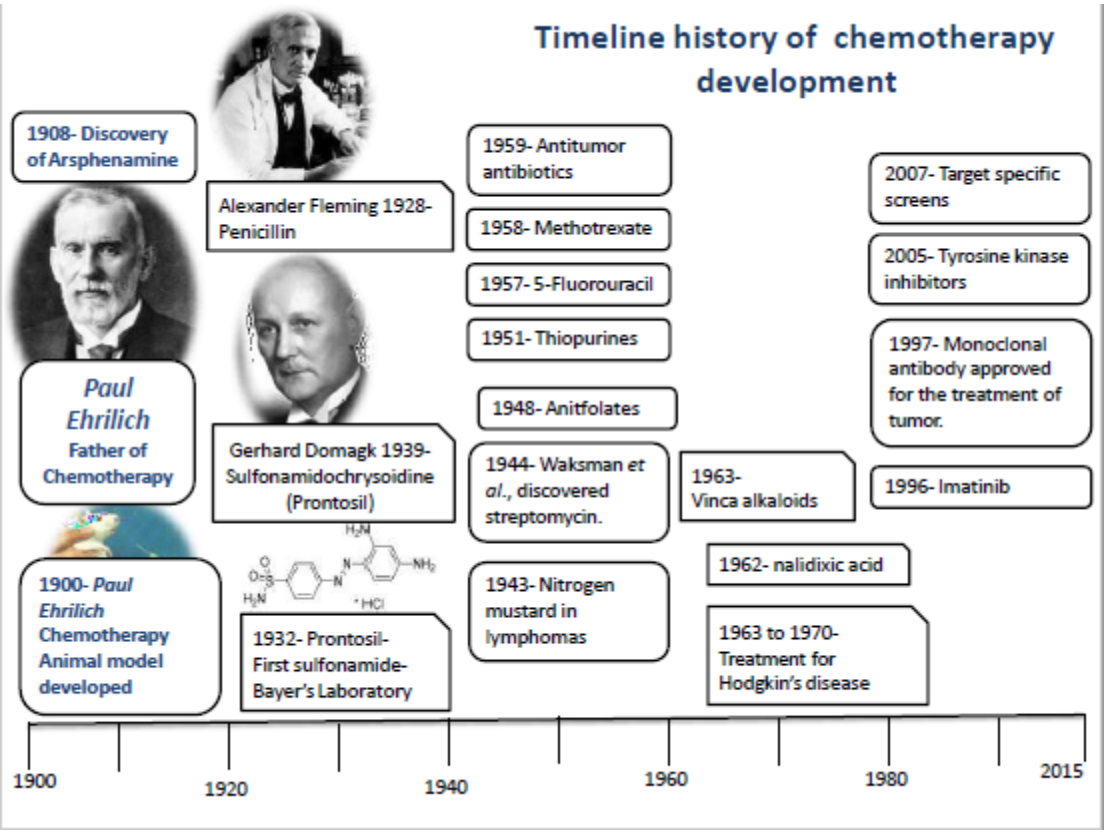
To fully understand chemotherapy it is important to have an understanding of the cell cycle.

The cell cycle comprises of four stages. The cell must progress through these in order to duplicate its chromosomes and divide. These are:

1) G0 –Normal functions
2) G1 phase (Gap 1) during this phase, the cell is growing and preparing to double its DNA.
3) S phase (DNA synthesis) this is the phase in which the amount of DNA is doubled.
4) G2 phase (Gap 2) the cell prepares for mitosis
5) M phase (mitosis) Division of the nucleus.

History of chemotherapy





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'.

Antibiotics and Antimicrobials

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

Antimicrobials: (chemotherapeutic agent + Antibiotics) Any substance of natural, synthetic or semisynthetic origin which at low concentrations kill or inhibits the growth of microorganisms but causes little or no host damage.

Principles of antimicrobial therapy

Diagnosis: Site of infection, responsible organism, sensitivity of drug

Decide- chemotherapy is necessary:

Acute infection requires chemotherapy whilst chronic infections may not. The chronic abscess respond poorly, although chemotherapy cover is essential if surgery is undertaken to avoid a flare-up of infection.

Select the drug: Specificity (spectrum of activity, antimicrobial activity of drug), pharmacokinetic factors (physiochemical properties of the drug) , patient related factors (allergy, renal disease)

Frequency and duration of drug administration: Inadequate dose may develop resistance, intermediate dose may not cure infection, optimize dose should be used for therapy.

Continue therapy: Acute infection treated for 5-10 days. But some of the bacterial infection exceptions to this. E.g.: Typhoid fever, tuberculosis and infective endocarditis (after clinical cure, the therapy is continued to avoid relapse).

Test for cure: After therapy, symptoms and signs may disappear before pathogen eradicated.

Prophylactic chemotherapy: To avoid surgical site infections.

CLASSIFICATION

Antimicrobial drugs can be classified in many ways:

1) Chemical structure

2) Mechanism of action

3) Type of organisms (against which primarily active)

4) Spectrum of activity

5) Type of action (bacteriostatic and bactericidal)

6) Source of antibiotics

1) Chemical structure

Sulfonamides and related drugs: Dapsone (DDS), Sulfadiazine, Paraaminosalicylic acid (PAS)

•Diaminopyrimidines: Trimethoprim, Pyrimethamine

•Quinolones: Nalidixic acid, Norfloxacin, Ciprofloxacin

•Beta lactam antibiotics: Penicillins, Cephalosporins

•Tetracyclines: Oxytetracycline, Doxycycline

•Nitrobenzene derivative: Chloramphenicol

•Aminoglycosides: Streptomycin, Gentamycin, Amikacin, Neomycin

•Macrolides antibiotics: Erythromycin, Clanthromycin, Azithromycin

•Lincosamide antibiotics: Clindamycin

•Glycopeptide antibiotics: Vancomycin

•Polypeptide antibiotics: Polymyxin-B, Bacitracin, Tyrothricin

•Nitrofuran derivatives: Nitrofurantoin

•Nitroimidazoles: Metronidazole, Tinidazole

•Nicotinic acid derivatives: Isoniazid, Pyrczinamide, Ethionamide

•Polyene antibiotics: Amphotericin-B, Nystatin, Hamycin

•Azole derivatives: Miconazole, Clotrimazole, Ketoconazole, Fluconazole

•Others: Rifampin, Ethambutol, Griseofulvin

2) Mechanism of action

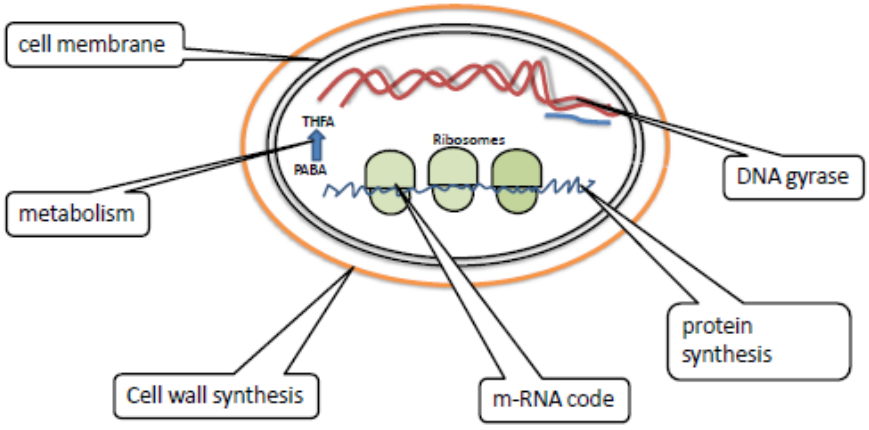


Figure 1: Mechanism of antimicrobials

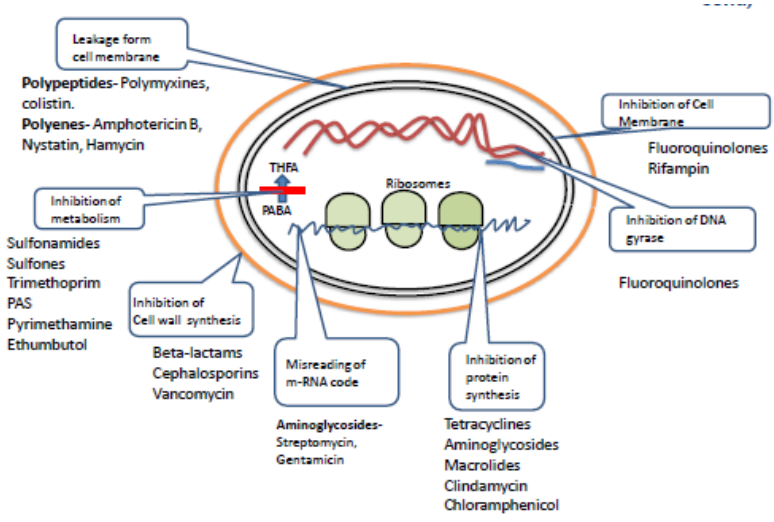


Figure 1.1

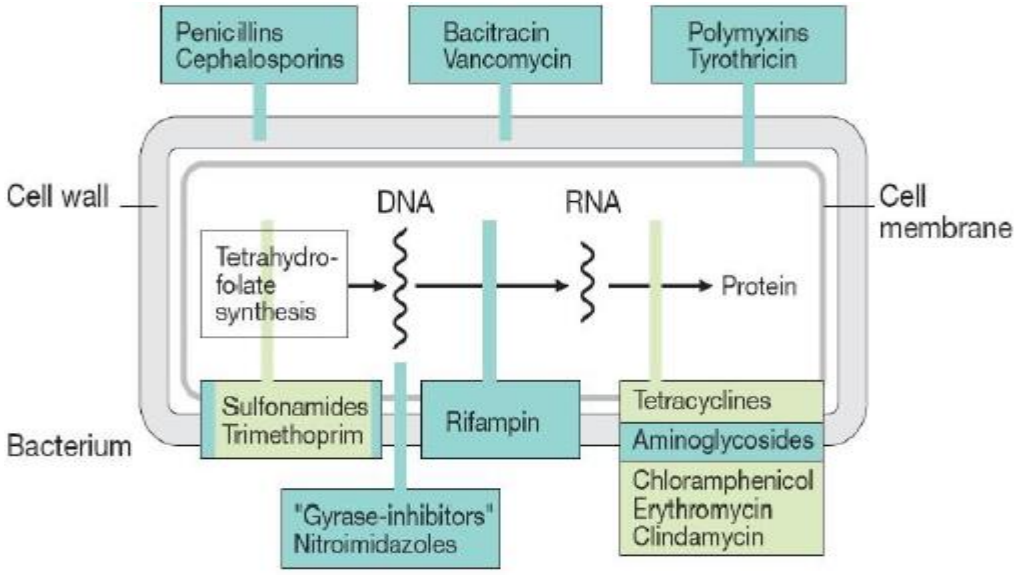


Figure: 1.3

3) Type of organisms (against which primarily active)

•Antibacterial*:* Penicillins, Aminoglycosides, Erythromycin etc.

•Antiviral*:* Acyclovir, Amantadine B, Zidovudine, etc.

•Antifungal*:* Griseofulvin, Amphotericin B, Ketoconazole, etc.

•Antiprotozoal*:* Chloroquine, Pyrimethamine, Metronidazole, etc.

•Anthelminthic*:* Mebendazole, Niclosamide, Diethyl carbamazine, etc.

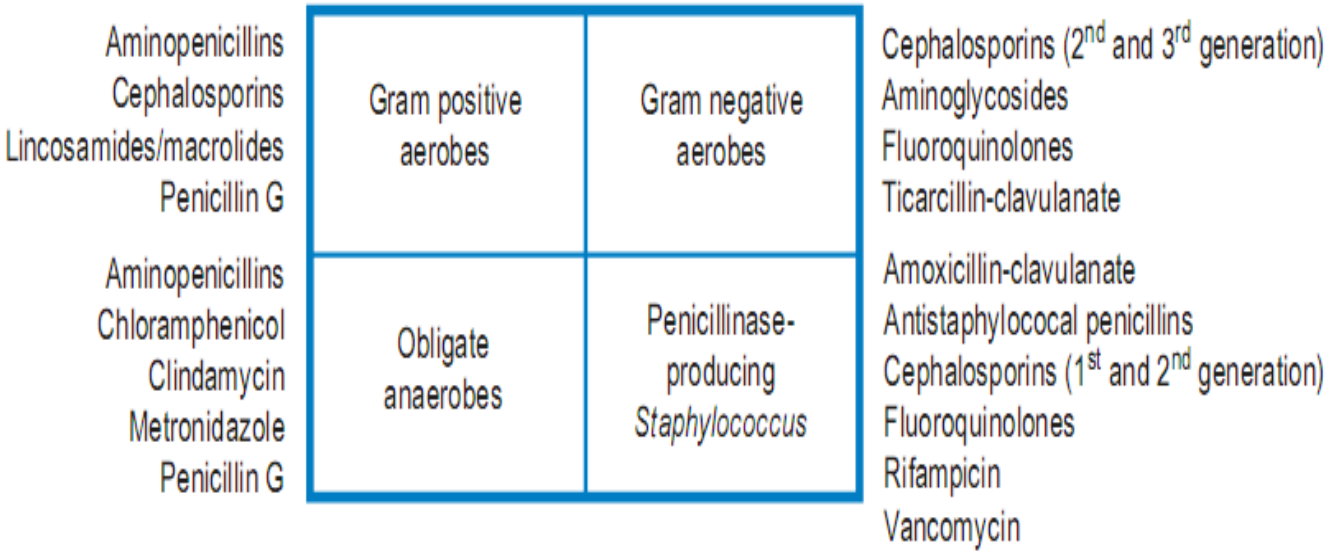


Figure 2

4) Spectrum of activity

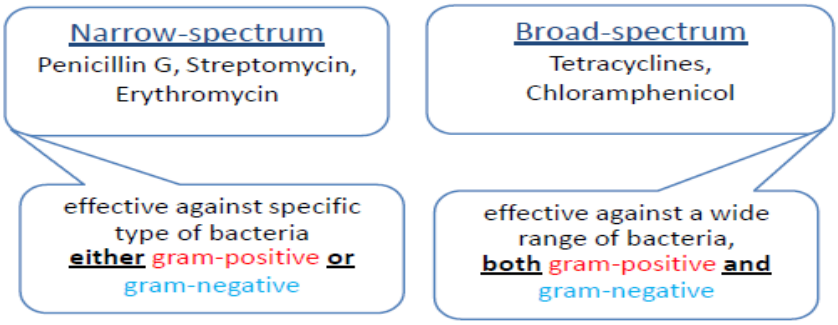


Figure: 3

5) Type of action (bacteriostatic and bactericidal)

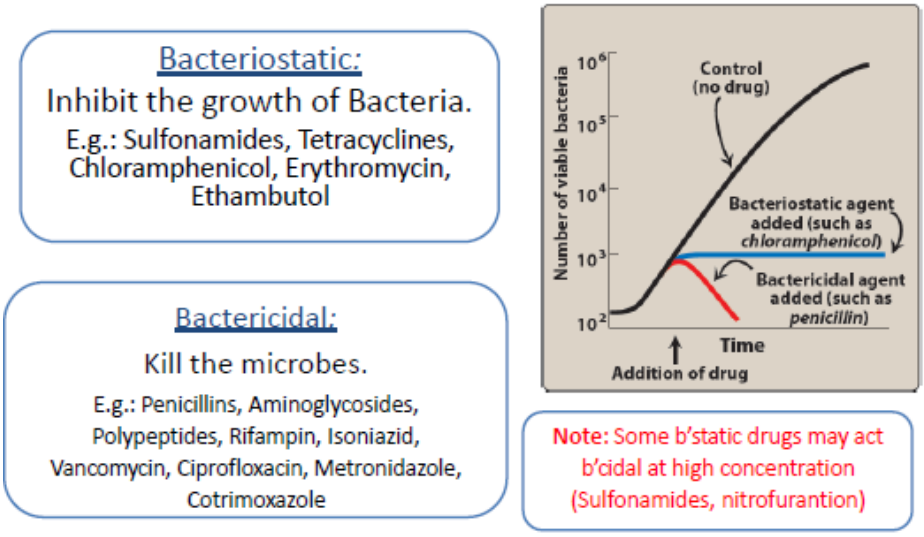


Figure: 4

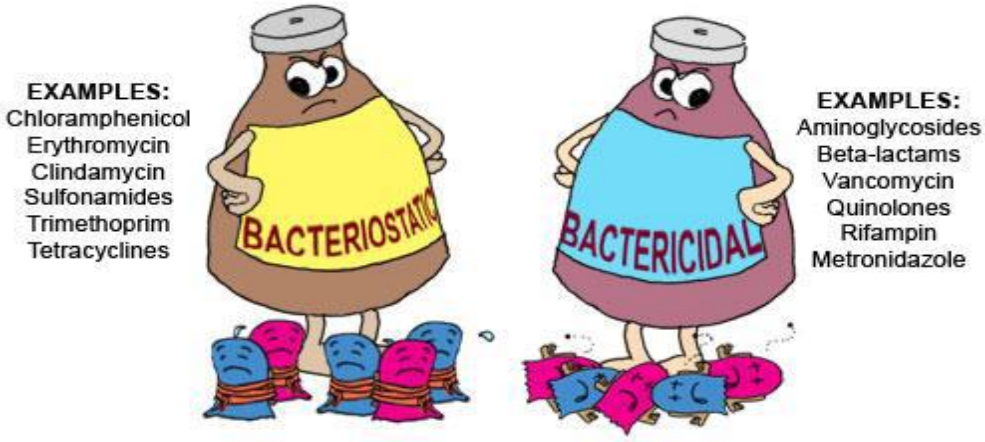


Figure: 4.1

Source of antibiotics

•Fungi*:* Penicillin, Griseofulvin, Cephalosporin

•Bacteria*:* Polymyxin B, Tyrothricin, Colistin, Aztreonam, Bacitracin

•Actinomycetes*:* Aminoglycosides, Macrolides, Tetracyclines, Polyenes, Chloramphenicol

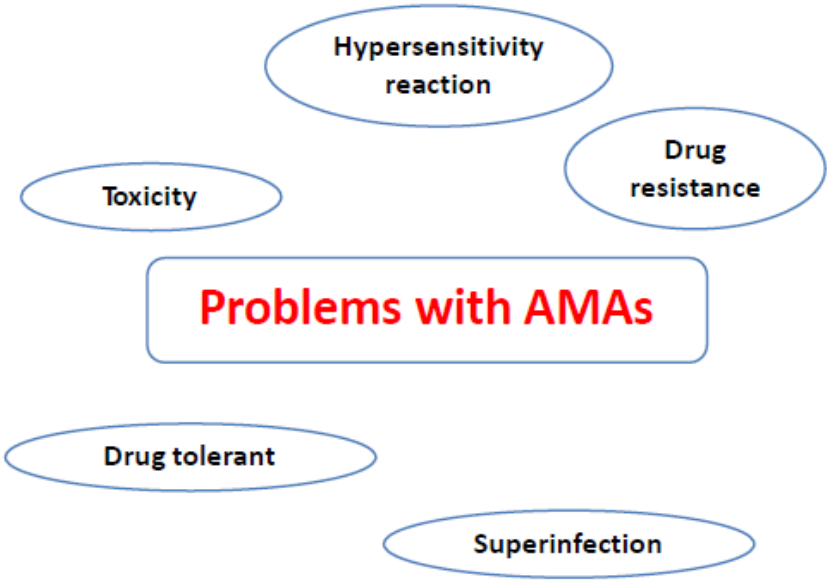


Figure: 5

Resistance

•Unresponsiveness of a microorganism to an AMA, and is similar to the phenomenon of drug tolerance.

–Natural resistance

–Acquired resistance

Natural resistance: Some microbes have resistant to certain AMAs. E.g.: Gram negative bacilli not affected by penicillin G; M. tuberculosis insensitive to tetracyclines.

Acquired resistance: Development of resistance by an organism (which was sensitive before) due to the use of AMA over a period of time. E.g.: Staphylococci, tubercle bacilli develop resistance to penicillin (widespread use for >50 yr). Gonococci quickly developed resistant to sulfonamides in 30 yr.

Development of resistance

•Resistance mainly developed by mutation or gene transfer.

•Mutation: Resistance developed by mutation is stable and heritable genetic changes that occur spontaneously and randomly among microorganism (usually on plasmids).

•Mutation resistance may be single step or multistep.

–Single gene mutation may confer high degree of resistance. E.g.: enterococci to streptomycin

–Multistep mutation may modify the more number of gene that will decreases the sensitivity of AMAs to pathogens.

•Development of resistance

•Gene transfer (Infectious resistance): From one organism to another organism.

–Conjugation

–Transduction

–Transformation

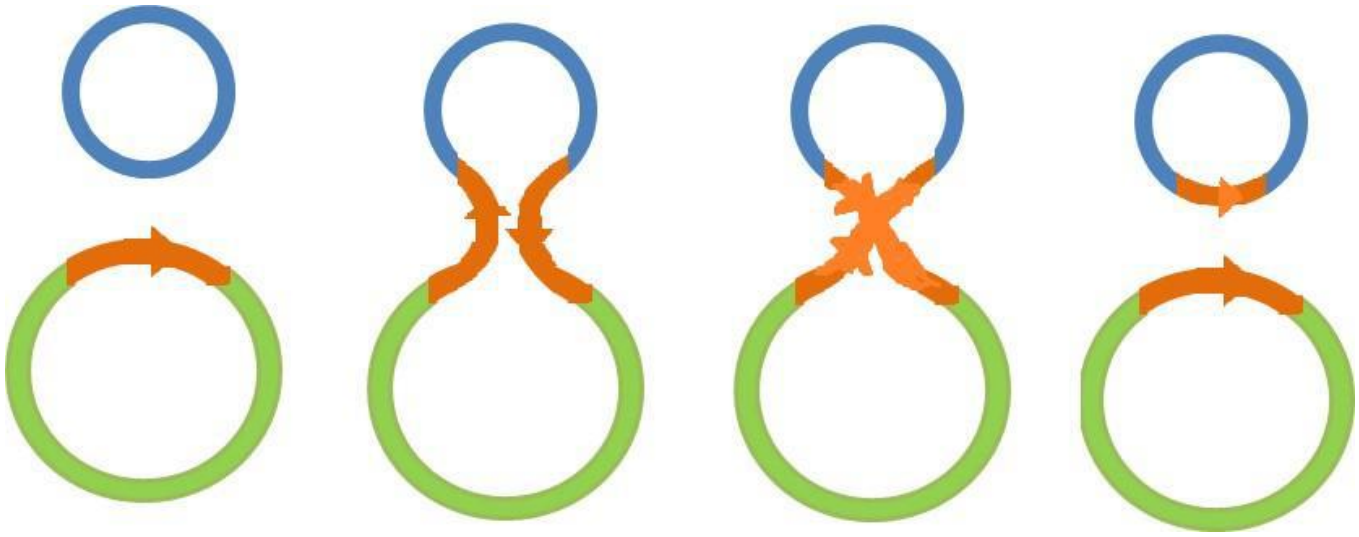


Figure 6*: Transfer of resistance genetic elements within the bacterium*

Development of resistance Gene transfer - Conjugation:

•cell-to-cell contact; transfer extrachromosomal DNA from one another through sex pili. The gene bacterium carrying of chromosomal or to the resistance or 'R' factor is transferred only if another "resistance transfer factor" (RTF) is present. This will frequently occurs in gram negative bacilli.

•The nonpathogenic organisms may transfer 'R' factor to pathogenic organisms, which may become wide spread by contamination of food and water.

•The multidrug resistance has occurred by conjugation.

- ✓ Chloramphenicol resistance to typhoid bacilli
- ✓ Penicillin resistance to *Haemophilus*, gonococci
- ✓ Streptomycin resistance to *E.coli*

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.

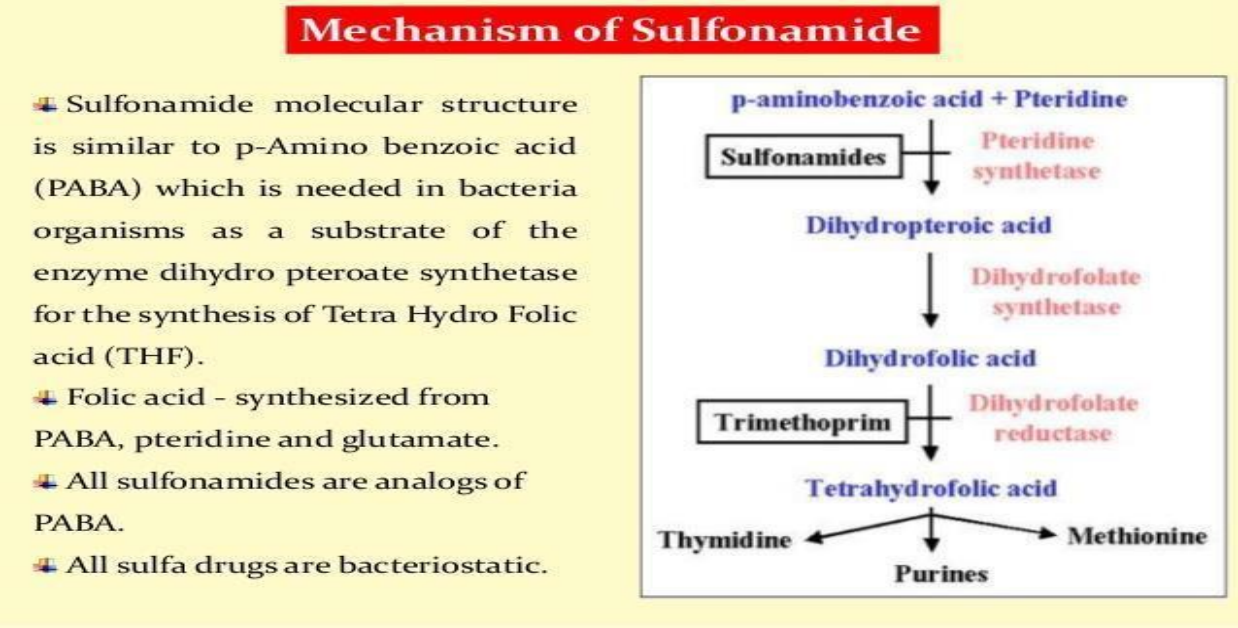


Figure 7: Mechanism of sulfonamide

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.

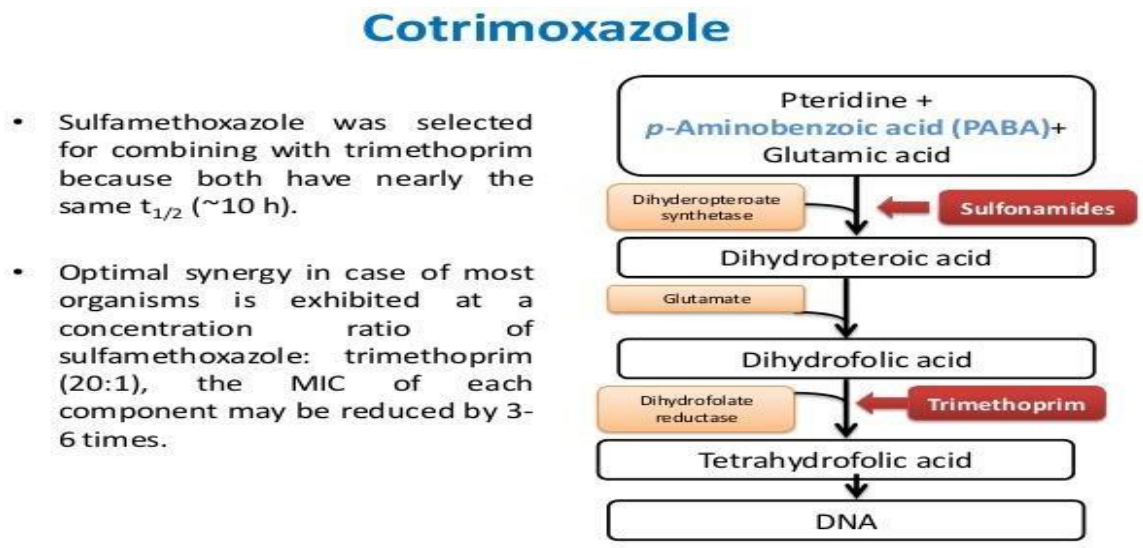


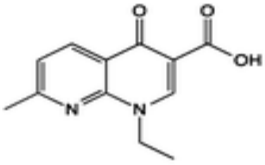
Figure: *mechanism of action of Cotrimoxazole*

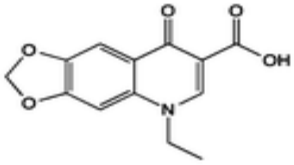
Uses

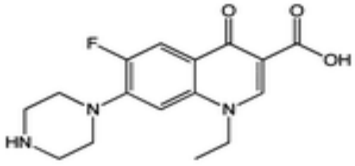
1. Urinary tract infections
2. Respiratory tract infections
3. Typhoid
4. Bacterial diarrhoeas and dysentery
5. Pneumocystis
6. Chancroid

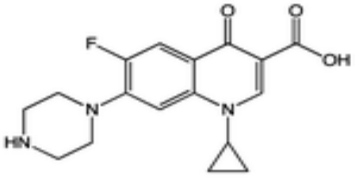
QUINOLONES

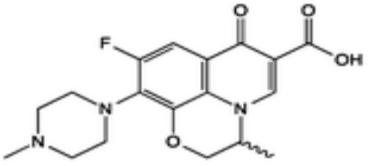
These are synthetic antimicrobials having a quinolone structure that are active primarily against gram-negative bacteria, though newer fluorinated compounds also inhibit gram-positive ones. The first member Nalidixic acid introduced in mid-1960s had usefulness limited to urinary and g.i. tract infections 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.

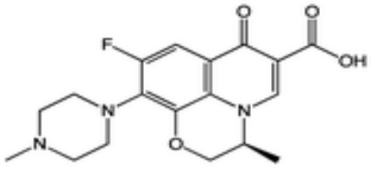

Nalidixic acid

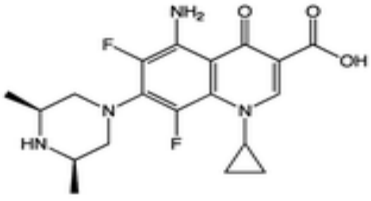

Oxolinic acid

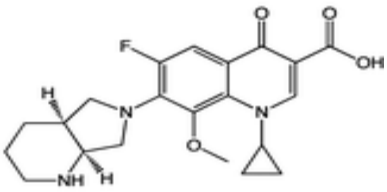

Norfloxacin


Ciprofloxacin


Ofloxacin


Levofloxacin


Sparfloxacin


Moxifloxacin

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.

MECHANISMS OF QUINOLONE RESISTANCE

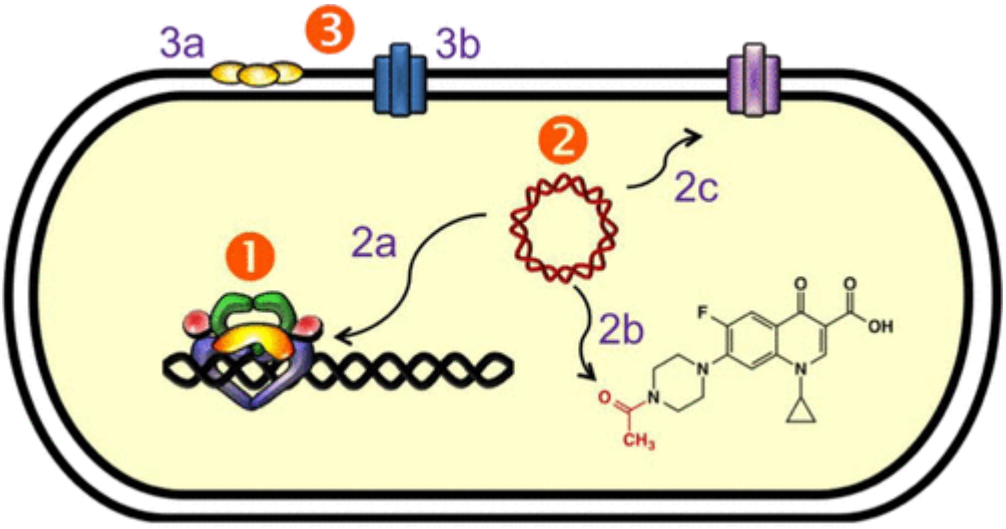


Figure: Mechanisms of quinolone resistance. (1) Target-mediated resistance. Mutations in gyrase and topoisomerase IV weaken quinolone–enzyme interactions. (2) Plasmid-mediated resistance. (2a) Qnr proteins (yellow) decrease topoisomerase–DNA binding and protect enzyme–DNA complexes from quinolones. (2b) Aac(6′)-Ib-cr is an aminoglycoside acetyltransferase that acetylates the free nitrogen on the C7 ring of ciprofloxacin and norfloxacin, decreasing their effectiveness. (2c) Plasmid-encoded efflux pumps decrease the concentration of quinolones in the cell. (3) Chromosome-mediated resistance. (3a) Underexpression of porins in Gram-negative species decreases drug uptake. (3b) Overexpression of chromosome-encoded efflux pumps decreases drug retention in the cell.

FLUOROQUINOLONES

These are quinolone antimicrobials having one or more fluorine substitutions. The 'first generation' fluoroquinolones (FQs) introduced in 1980s has 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 conferring metabolic stability (longer Ph). These are referred to as'second generation' FQs.

Classification

Generation	Drug	Characteristic features
First	Naldixic acid Oxolinic acid Pipemidic acid	Active against some Gram negative bacteria. Highly protein bound drugs. Short half life.
Second	Norfloxacin Enoxacin Ciprofloxacin Ofloxacin Lomefloxacin	Protein binding (50%). Longer half life than previous agents. Improved activity against Gram negative bacteria.
Third	Temafloxacin Sparafloxacin Grepafloxacin	Active against Gram negative bacteria. Also active against Gram positive bacteria.

Mode of Action:

The quinolones inhibit bacterial enzyme topoisomerases, including topoisomerase II (otherwise known as DNA gyrase) and topoisomerase IV. Bacterial DNA supercoils and then uncoils during replication. Supercoiling requires transient nicks that are subsequently sealed after DNA polymerase passes. Topoisomerase II allows for single strand nicks in the DNA that support coiling and uncoiling. Topoisomerase IV supports disentanglement of DNA as chromosomes separate. Inhibition of topoisomerases reduces supercoiling, resulting in disruption of the spatial arrangement of DNA, and reduces DNA repair. Mammalian topoisomerase enzymes fundamentally differ from bacterial gyrase and are not susceptible to quinolone inhibition. The quinolones are usually bactericidal; susceptible organisms lose viability within 20 min of exposure to optimal concentrations of the newer fluoroquinolones. Typically, clearing of cytoplasm at the periphery of the affected bacterium is followed by lysis, rendering bacteria recognizable only as “ghosts.”

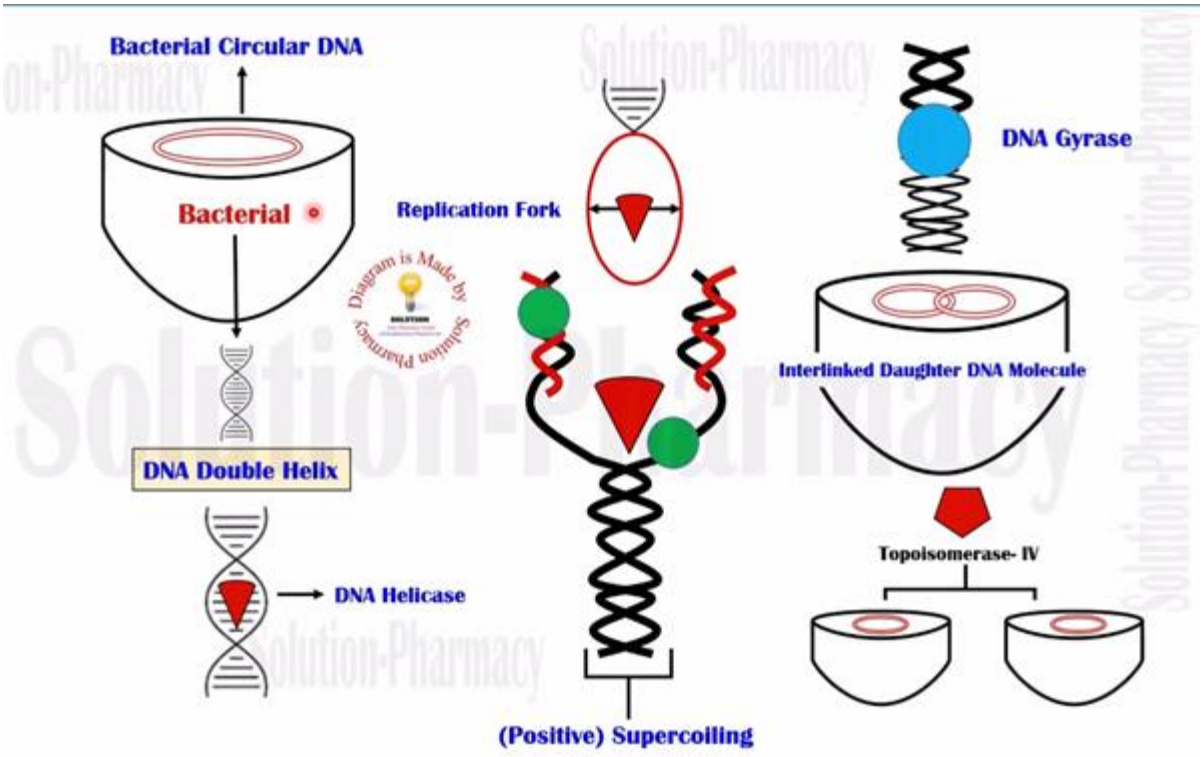


Figure: mechanism of action of fluoroquinolones

Bacterial Resistance:

Chromosomal mutational resistance to the original fluoroquinolones was considered to be low in frequency, and plasmid-mediated resistance nonexistent. However, resistance is increasingly being recognized, indicating that therapy based on culture and susceptibility is prudent. In general, cross-resistance should be anticipated among the more closely related members of this class.

Gram-negative bacteria more commonly target DNA gyrase; emerging resistance is more often associated with changes in the GyrA compared to the GyrB subunit. In contrast, the primary target of gram-positive organisms tends to be topoisomerase IV, with resistance mechanisms targeting it, followed by changes in DNA gyrase. Use of the drug selects for resistance. High-level resistance (3–4 times the breakpoint MIC) generally reflects a second-step mutation that leads to changes in the amino acid sequence of subsequent topoisomerase targets. However, even with this second step of resistance, MIC are often below the resistant breakpoint range on which susceptibility testing is based. With the second increase in MIC, mutations in efflux pump regulators also emerge, causing marked increase in expression. As a result, high-level, multidrug resistance emerges.

Another mechanism of resistance is the combined effect of increased efflux pumps and decreased porins that act in concert to reduce intracellular concentrations. Virulence of refractory mutants may not diminish.

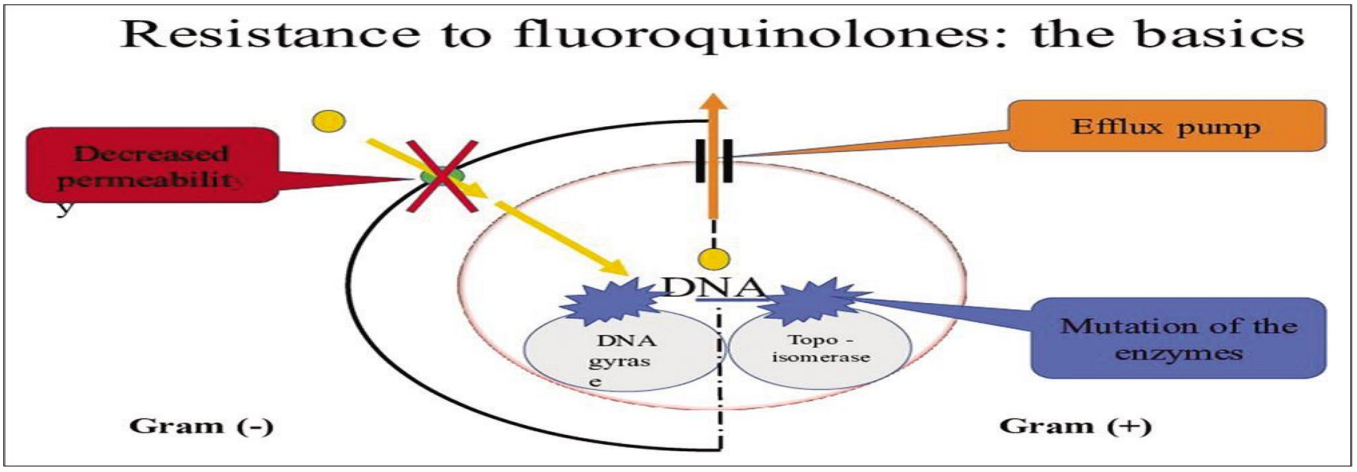


Figure: Resistance to fluroquinolones

PENICILLINS

INTRODUCTION TO PENICILLINS (known for˜80 years)

•Antibacterial agents which inhibit bacterial cell wall synthesis

•Discovered by Fleming from a fungal colony (1928)

•Shown to be non toxic and antibacterial

•Isolated and purified by Florey and Chain (1938)

•First successful clinical trial (1941)

•Produced by large scale fermentation (1944)

•Structure established by X-ray crystallography (1945)

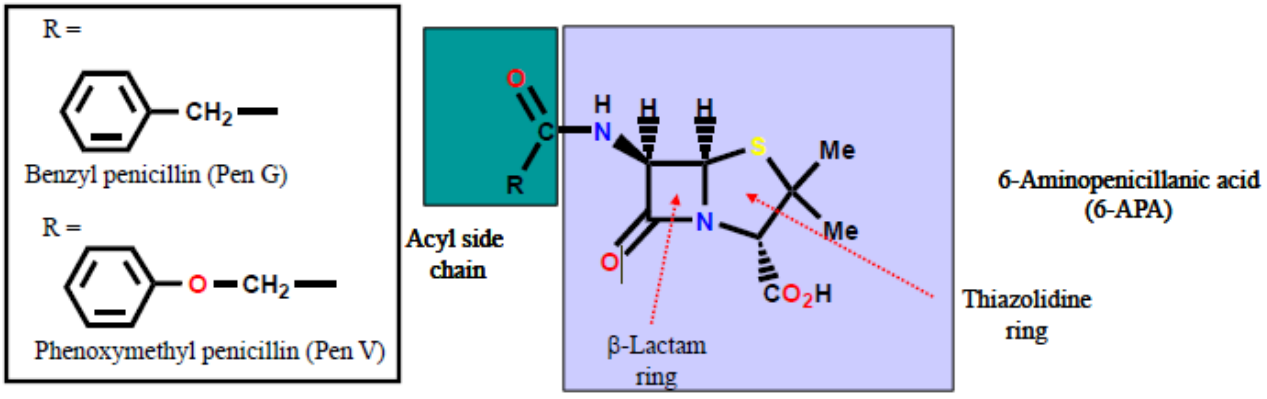
•Full synthesis developed by Sheehan (1957)

•Isolation of 6-APA by Beechams (1958-60) - development of semi-synthetic penicillins

•Discovery of clavulanic acid and β-lactamase inhibitors

The penicillins are among the earliest classes of antibacterial drugs. Penicillins are divided into subclasses based on chemical structure (eg, penicillins, monobactams, and carbapenems), spectrum (narrow, broad, or extended), source (natural, semisynthetic, or synthetic), and susceptibility to β-lactamase destruction. Manipulation of some drugs has improved the spectrum, resistance to β-lactamase destruction, or clinical pharmacologic characteristics that enhance efficacy.

STRUCTURE

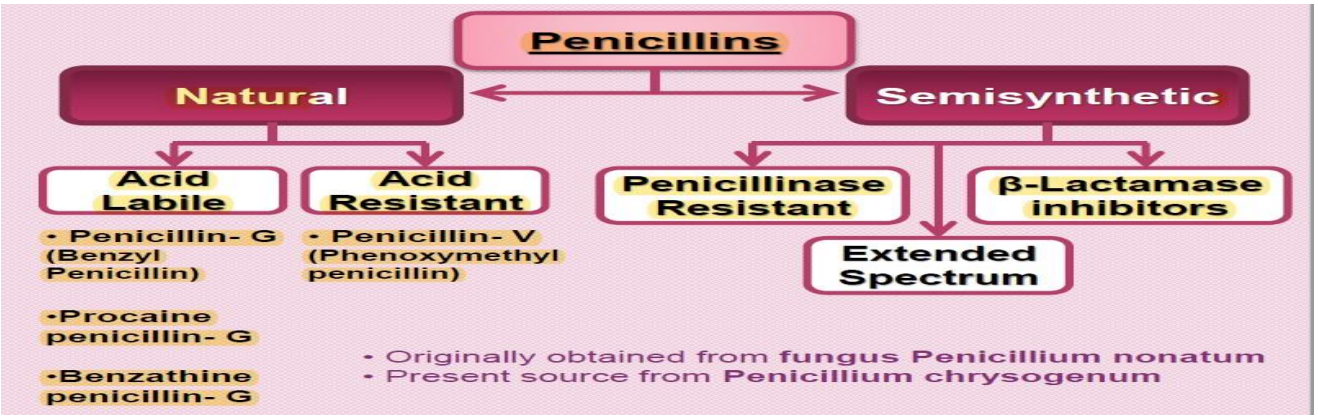


Classification by spectrum

All penicillins are ineffective toward cell wall–deficient microorganisms such as Mycoplasma or Chlamydia spp.

Narrow-spectrum β-Lactamase–sensitive Penicillins:

This group includes naturally occurring penicillin G (benzylpenicillin) in its various pharmaceutical forms and a few biosynthetic acid-stable penicillins intended for oral use (penicillin V



[phenoxymethyl-penicillin] and phenethicillin). Penicillins in this class are active against many gram-positive but only a limited number of gram-negative bacteria. These drugs are also effective against anaerobic organisms. They are, however, susceptible to β-lactamase (penicillinase) hydrolysis.Penicillin G and its oral congeners (eg, penicillin V) are active against both aerobic and anaerobic gram-positive bacteria and, with a few exceptions (*Haemophilus* and *Neisseria* spp and strains of *Bacteroides* other than *B fragilis*), are inactive against gram-negative organisms at usual concentrations. Organisms usually sensitive in vitro to penicillin G include streptococci, penicillin-

sensitive staphylococci, *Trueperella (Arcanobacterium) pyogenes*, *Clostridium* spp, *Erysipelothrix rhusiopathiae*, *Actinomyces bovis*, *Leptospira* Canicola, *Bacillus anthracis*, *Fusiformis nodosus*, and *Nocardia* spp.

Broad-spectrum β-Lactamase–sensitive Penicillins:

Penicillins in this class are derived semisynthetically and are active against many gram-positive and gram-negative bacteria. However, they are readily destroyed by the β-lactamases (produced by many bacteria). Many members of the group are acid stable and are administered either PO or parenterally. Of those used in veterinary medicine, aminopenicillins, eg, ampicillin and amoxicillin (which may also be produced naturally), are the best known. Several ampicillin precursors more completely absorbed from the GI tract also belong to this class (eg, hetacillin, pivampicillin, talampicillin).

A large number of gram-positive and gram-negative bacteria (but not β-lactamase–producing strains) are sensitive to the semisynthetic broad-spectrum penicillins (ampicillin and amoxicillin). Susceptible genera

include *Staphylococcus*, *Streptococcus*, *Trueperella*, *Clostridium*, *Escherichia*, *Klebsiella*, *Shigella*, *Salmonella*, *Proteus*, and *Pasteurella*. Although bacterial resistance is widespread, the combination of β-lactamase inhibitors and broad-spectrum penicillins markedly enhances the spectrum and efficacy against both gram-positive and gram-negative pathogens. Clavulanate-potentiated amoxicillin is an excellent example of such a synergistic association.

Mecillinam is less active than ampicillin against gram-positive bacteria but is highly active against many intestinal organisms (except *Proteus* spp) that do not produce β-lactamases.

Broad-spectrum β-Lactamase–sensitive Penicillins with Extended Spectra:

Several semisynthetic broad-spectrum penicillins are also active against *Pseudomonas aeruginosa*, certain *Proteus* spp, and even strains of *Klebsiella*, *Shigella*, and *Enterobacter* spp in certain cases. Examples of this class include carboxypenicillins (carbenicillin, its acid-stable indanyl ester, and ticarcillin), ureido-penicillins (azlocillin and mezlocillin), and piperazine penicillins (piperacillin).

The anti-*Pseudomonas* and other extended-spectrum penicillins are active against most of the usual penicillin-sensitive bacteria. They often have a degree of β-lactamase resistance and are usually active against one or more characteristic penicillin-resistant organisms. Yet, as a class, they remain susceptible to destruction by β-lactamases. Examples include the use of carbenicillin, ticarcillin, and piperacillin against *P aeruginosa* and several *Proteus* strains, and the use of piperacillin against P *aeruginosa*,several Shigella and Proteus strains,andsome *Citrobacter* and *Enterobacter* spp. *Streptoco*

ccus faecalis is often resistant to these new extended-spectrum penicillins. Imipenem and meropenem are relatively resistant to β-lactamase destruction. Their spectrum includes a wide variety of aerobic and anaerobic microorganisms, including most strains of *Pseudomonas*, streptococci, enterococci, staphylococci, and *Listeria*. Anaerobes, including *Bacteroides fragilis*, are highly susceptible.

B-Lactamase–protected Penicillins:

Several naturally occurring and semisynthetic compounds can inhibit many of the β-lactamase enzymes produced by penicillin-resistant bacteria. When used in combination with broad- or extended-spectrum penicillins, there is a notable synergistic effect because the active penicillin is protected from enzymatic hydrolysis—and thus is fully active against a wide variety of previously resistant bacteria. Examples of this chemotherapeutic approach include clavulanate-potentiated amoxicillin and ticarcillin as well as sulbactam-potentiated ampicillin and tazobactam-potentiated piperacillin.

Narrow-spectrum β-Lactamase–resistant Penicillins:

This group, through substitution on the penicillin nucleus (6-aminopenicillanic acid), is refractory to a greater or lesser degree to the effects of various β-lactamase enzymes produced by resistant gram-positive organisms, particularly *Staphylococcus aureus*. However, penicillins in this class are not as active against many gram-positive bacteria as penicillin G and are inactive against almost all gram-negative bacteria. Acid-stable members of this group may be given orally and include isoxazolyl penicillins, such as oxacillin, cloxacillin, dicloxacillin, and flucloxacillin. Methicillin and nafcillin are available as parenteral preparations. Temocillin is a semisynthetic penicillin that is β-lactamase stable but also active against nearly all isolates of gram-negative bacteria except *Pseudomonas* spp.

The semisynthetic β-lactamase–resistant penicillins, such as oxacillin, cloxacillin, floxacillin, and nafcillin, have spectra similar to those noted above (although often at higher MIC) but also include many of the β-lactamase–producing strains of staphylococci (especially *S aureus* and *S epidermidis*).

Carbapenems:

Imipenem and meropenem are among the most active drugs against a wide variety of bacteria. Imipenem is derived from a compound produced by *Streptomyces cattleya*. Aztreonam is a related (monobactam) compound but differs from other β-lactams in that it has a second ring that is not fused to the β-lactam ring.

Pharmacokinetic Features

The pharmacokinetics of the many penicillins differ substantially. The general guidelines below emphasize singularly significant aspects.

Absorption:

Most penicillins in aqueous solution are rapidly absorbed from parenteral sites. Absorption is delayed when the inorganic penicillin salts are suspended in vegetable oil vehicles or when the sparingly soluble repository organic salts (eg, procaine penicillin G and benzathine penicillin G) are administered parenterally. Although prolonged absorption results in longer persistence of plasma and tissue drug concentrations, peak concentrations may not be sufficiently high to be effective against organisms unless MICs are low. The penicillin G repositol salts should never be injected IV. Only selected penicillins are acid stable and can be administered PO at standard doses. Absorption from the upper GI tract differs markedly in amount and rate among the various penicillins. Penicillin V must be given at high oral doses. The aminopenicillins are orally bioavailable, although food impairs the absorption of ampicillin. Paracellular (as opposed to transcellular) transport may play a major role in oral absorption. The indanyl form of carbenicillin is orally bioavailable, but effective concentrations are likely to be achieved only in the urine. Serum concentrations of penicillins generally peak within 2 hr of PO administration. Penicillins may also be absorbed after intrauterine infusion. There is no information regarding bioavailability of human generic products when used off-label in veterinary patients.

Distribution:

After absorption, penicillins are widely distributed in body fluids and tissues. The volume of distribution tends to reflect extracellular compartmentalization, although some penicillins (including carbapenems) penetrate tissues quite well. Potentially therapeutic concentrations of the various penicillins are generally found in the liver, bile, kidneys, intestines, muscle, and lungs, but only very low concentrations are found in poorly perfused areas such as the cornea, bronchial secretions, cartilage, and bone. The diethylamino salt of penicillin G produces particularly high concentrations in pulmonary tissue. The penicillins usually do not readily cross the normal blood-brain, placental, mammary, or prostatic barriers unless massive doses are given or inflammation is present. Penicillins may be substrates for P-glycoprotein efflux from the CNS. Selected penicillins are able to penetrate nonchronic abscesses and pleural, peritoneal, or synovial fluids. Penicillins are reversibly and loosely bound to plasma proteins. The extent of this binding varies with particular penicillins and their

concentration, eg, ampicillin is usually ~20% bound, and cloxacillin may be ~80% bound. Pregnancy increases the volume of distribution, which has the effect of lowering the concentration of drug produced by a given dose.

Biotransformation:

Penicillins are generally excreted unchanged, but fractions of a given dose may undergo metabolic transformations by unknown mechanisms (usually <20% metabolized). Penicilloic acid derivatives that are formed tend to be allergenic.

Excretion:

Most (60%–90%) of a parenterally administered penicillin is eliminated in the urine within a short time (eg, up to 90% of penicillin G within 6 hr), which results in high concentrations in urine. Approximately 20% of renal excretion occurs by glomerular filtration and ~80% by active tubular secretion—a process that may be deliberately inhibited (to prolong effective concentrations in the body) by probenecid and other weak organic acids. Anuria may increase the half-life of penicillin G (normally ~30 min) to 10 hr. The biliary route also may be a major excretory pathway for the broad-spectrum semisynthetic penicillins. Clearance is considerably lower in neonates than in adults. Penicillins are also eliminated in milk, although often only in trace amounts in the normal udder, and may persist for up to 90 hr. Penicillin residues in milk also have been found after intrauterine infusion.

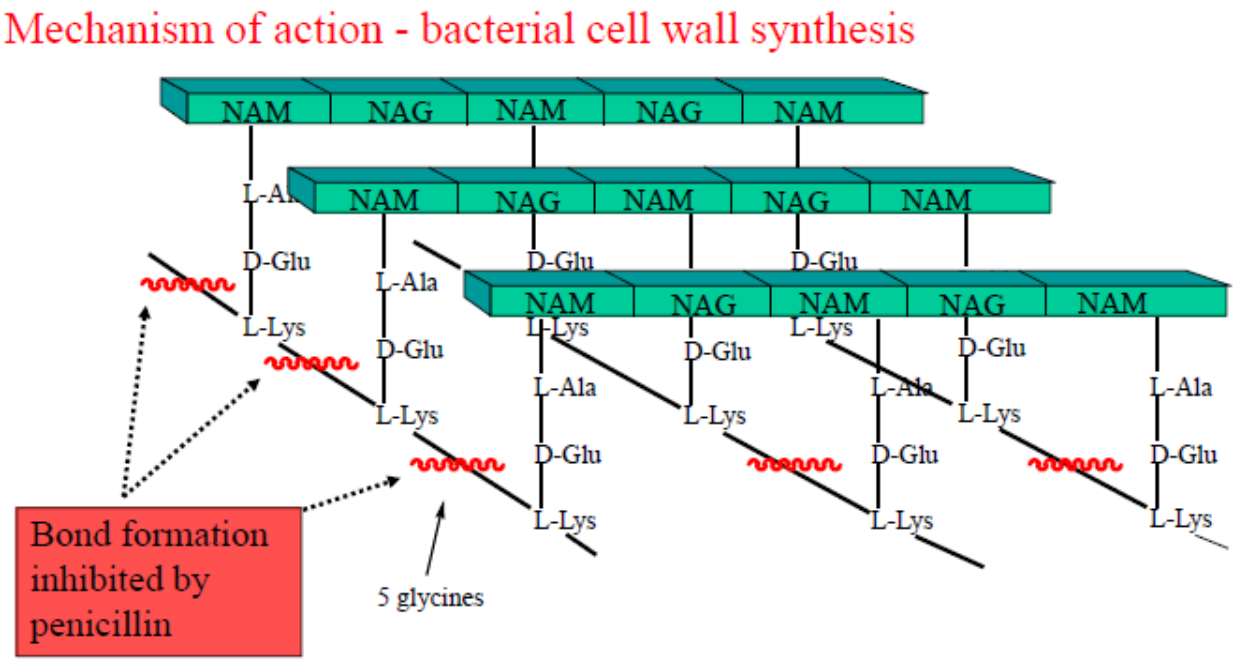
Pharmacokinetic Values:

Selected pharmacokinetic values for some penicillins in a few species are listed in Elimination, Distribution, and Clearance of Penicillins. Penicillins, in general, have very short elimination half-lives, which is problematic for time-dependent drugs. For example, ~90% of amoxicillin will be eliminated within 4 hr in dogs, suggesting that an 8-hr dosing interval is appropriate. Formulations that prolong absorption after IM administration are appropriate for time-dependent drugs, assuming peak concentrations surpass the MIC of the infecting microbes. Dosage modifications may be necessary because of age or disease. However, the general safety of β-lactams may negate the need for dose adjustment in all but profound renal disease.

Mechanism of action

- •Penicillins inhibit a bacterial enzyme called the transpeptidase enzyme which is involved in the synthesis of the bacterial cell wall
- •The β-lactam ring is involved in the mechanism of inhibition

- Penicillin becomes covalently linked y to the enzyme's active site by means of an ester link to a serine residue
- Penicillin is not split in two and acts as a steric shield to prevent access of substrate or water to the active site
- Results in irreversible inhibition



Mechanism of action - bacterial cell wall synthesis

Penicillin inhibits crosslinking stage of final cell wall synthesis

•It reacts with the transpeptidase enzyme to form an ester linkage with a serine residue

• The ring-opened penicillin acts as a steric shield

• Neither substrate nor water is capable of reaching the ester link

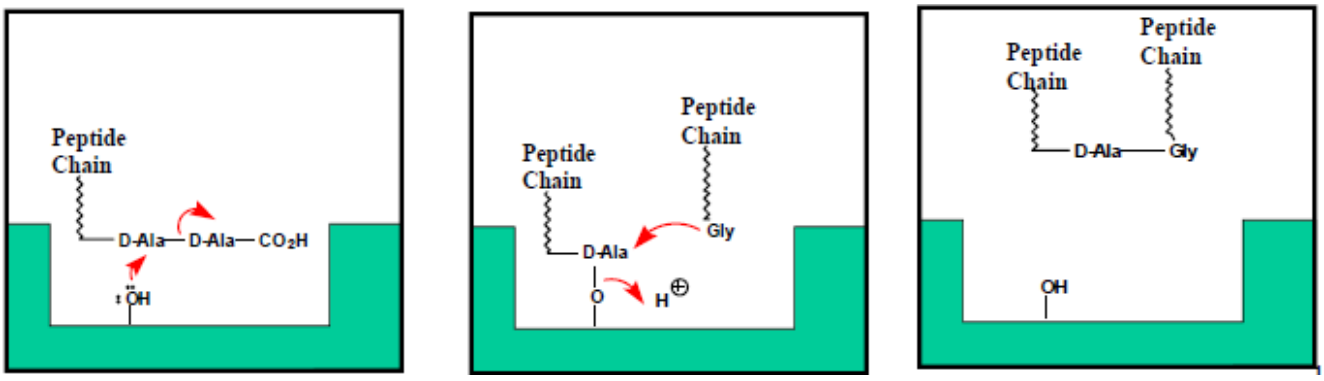
• Results in irreversible inhibition

•Inhibition of transpeptidase leads to a weakened cell wall

•Cells swell due to water entering the cell, and then burst (lysis)

•Penicillin thought to mimic *D*-Ala-*D*-Ala

Normal Mechanism



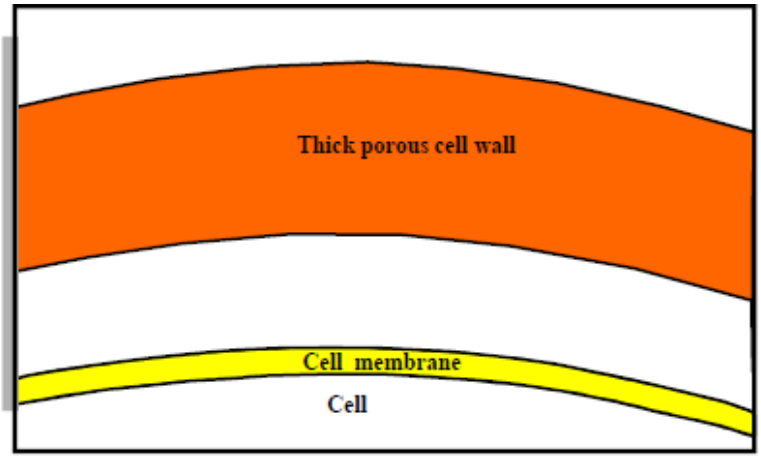
Gram positive and Gram negative cell walls

•Penicillins have to cross peptidoglycan layers in order to reach their target enzyme

•Peptidoglycan layers are porous and are not a barrier

•The peptidoglycan layers of Gram positive bacteria are thicker than Gram negative cell walls, but the former are more susceptible to penicillins.

Gram positive bacteria cell walls are thick



•Thick porous peptidoglycan cell wall
•No outer membrane
•Penicillins cross cell wall easily
•Gram positive more susceptible to penicillins

Gram negative bacteria cell walls are thinner, but have extra layers

•Thin peptidoglycan layer

•Hydrophobic outer membrane - acts as a barrier to penicillins

•Gram negative more resistant to penicillins

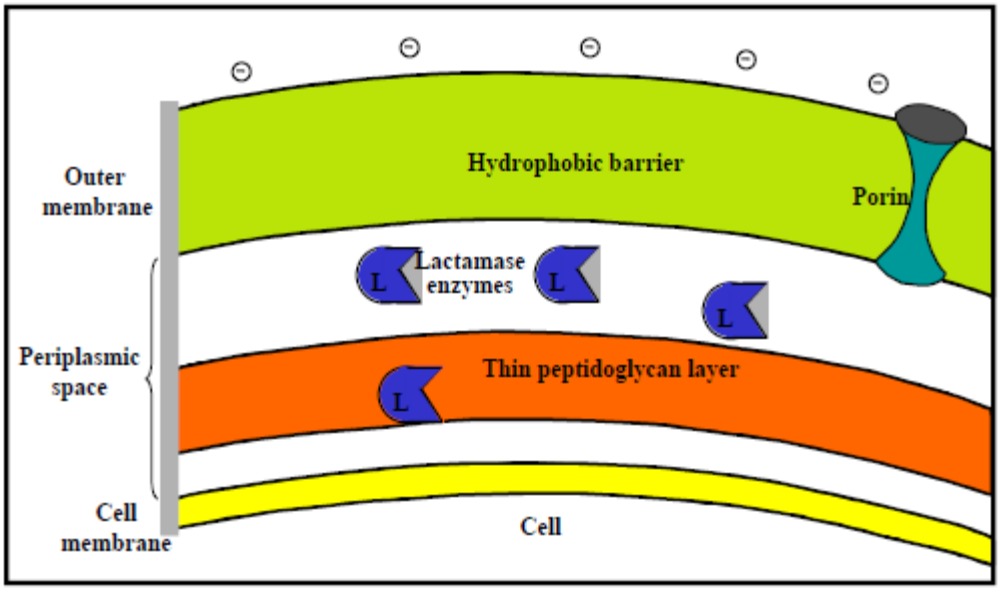


Figure: cell wall of Gram Positive bacteria

Resistance to Penicillins

Factors

- Gram negative bacteria have a lipopolysaccharide outer membrane preventing access to the periplasmic space. Penicillins can only cross via porins in the outer membrane
- Porins allow small hydrophilic molecules such as zwitterions to cross
- High levels of transpeptidase enzyme may be present
- The transpeptidase enzyme may have a low affinity for penicillins (e.g. PBP 2a for *S. aureus*)
- Presence and concentration of □-lactamases in the periplasmic space
- Efflux mechanisms pumping penicillins out of the periplasmic space
- Transfer of β-lactamases between strains
- Mutations

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.

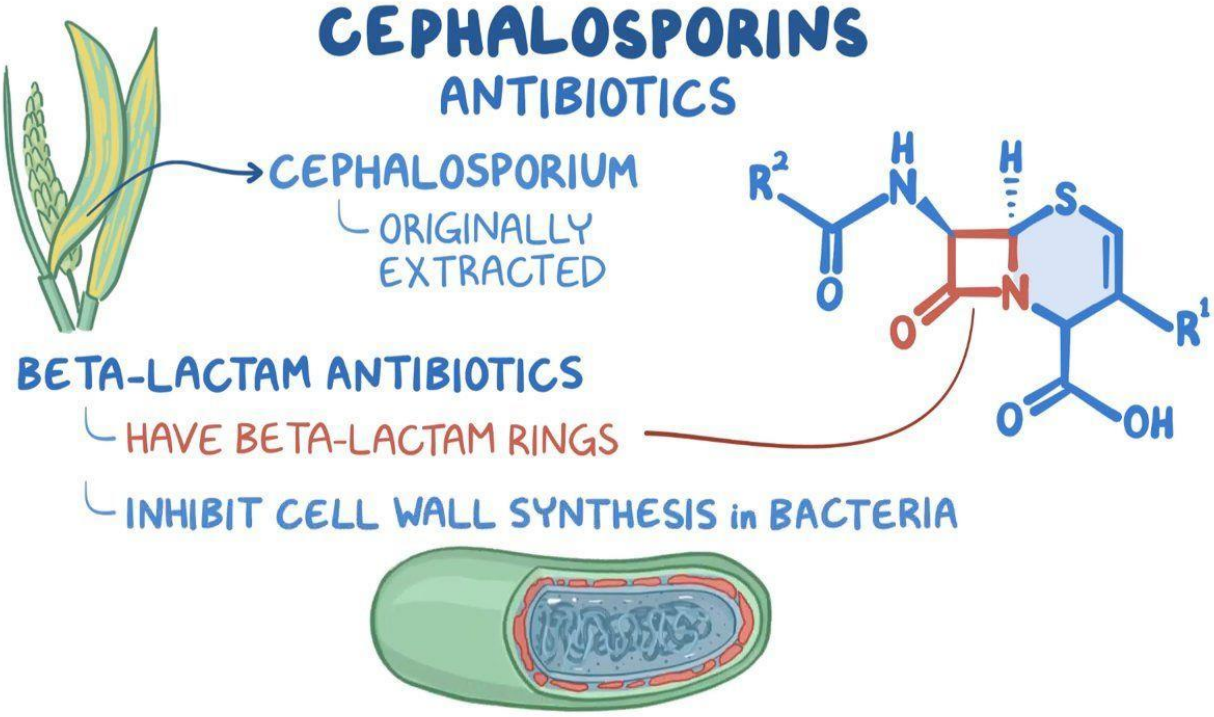
Clavulanic acid Obtained from Streptomyces clavuligerus, it has a β -lactam ring but no

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.

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.



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 Klebsiellapneumoni.

Second generation: The second-generation cephalosporins display greater activity against three

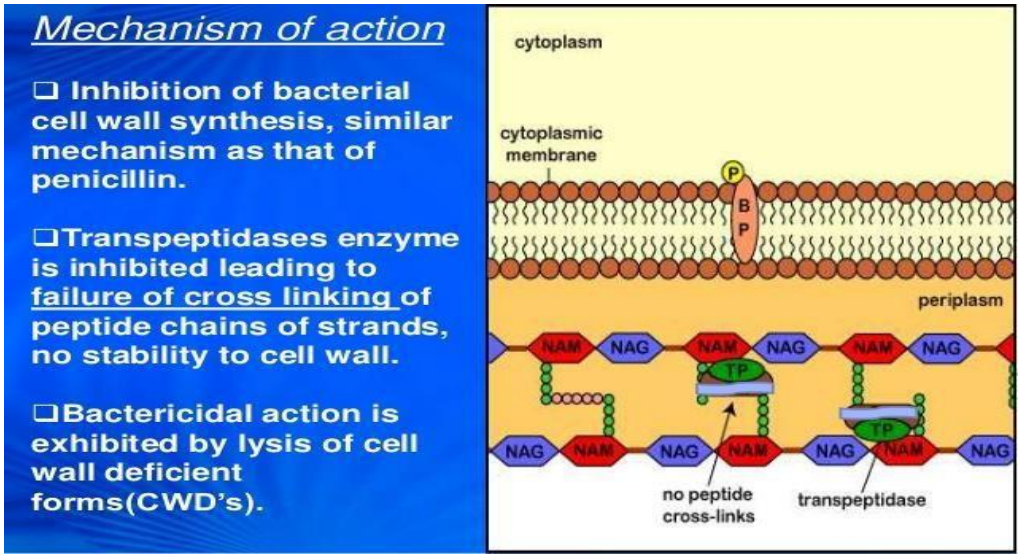
additional gram-negative organisms: H. influenzae, Enterobacter aerogenes, and some Neisseria species, whereas activity against gram-positive organisms is weaker [Note: The exception to this generalization is the structurally related cephamycin, *cefoxitin* which has little activity against H. influenzae 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.

Mechanism of action

Cephalosporins are bactericidal and, like other β-lactam antibiotics, disrupt the synthesis of the peptidoglycan layer forming the bacterial cell wall. The peptidoglycan layer is important for cell wall structural integrity. The final transpeptidation step in the synthesis of the peptidoglycan is facilitated by penicillin-binding proteins (PBPs). PBPs bind to the D-Ala-D-Ala at the end of muropeptides (peptidoglycan precursors) to crosslink the peptidoglycan. Beta-lactam antibiotics mimic the D-Ala-D-Ala site, thereby irreversibly inhibiting PBP crosslinking of peptidoglycan



Pharmacokinetics

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

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.

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.

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.

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).

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.

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

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

Neutropenia and thrombocytopenia are rareadverse effects reported with ceftazidime and some others. A disulfiram-like interaction with alcohol hasbeen reported with cefoperazone.

Uses

- As alternatives to PnG;
- Respiratory, urinary and soft tissue infections
- Penicillinase producing staphylococcal infections.
- Septicaemias
- Surgical prophylaxis:
- Meningitis:
- Gonorrhoea
- Typhoid:
- Mixed aerobic-anaerobic infections in cancer Patients.

Bacterial Resistance:

Resistance to the cephalosporins includes mechanisms described in general for β-lactams. Cephalosporins generally are stable against the plasmid-mediated β-lactamases produced by gram-positive bacteria such as *Staphylococcus aureus*. Several types of inducible β-lactamases produced by gram-negative organisms may be mediated by either plasmids or chromosomally and may hydrolyze either or both penicillins and cephalosporins (cross-resistance). Second- and particularly third-generation cephalosporins have greater stability against gram-negative β-lactamases. However, third- and fourth-generation drugs are susceptible to extended-spectrum β-lactamases, the presence of which

on susceptibility testing is indicated based on resistance to these drugs but susceptibility to clavulanic acid.

TETRACYCLINE

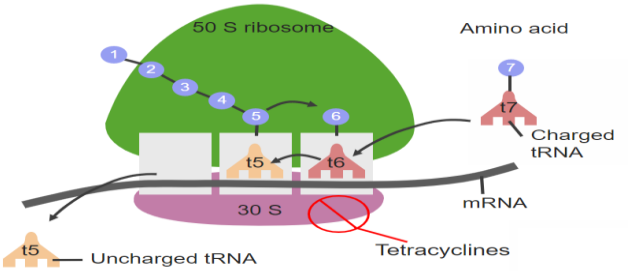
The tetracycline's are broad-spectrum antibiotics with similar antimicrobial features, but they differ somewhat from one another in terms of their spectra and pharmacokinetic disposition.

CLASSIFICATION

There are three naturally occurring tetracyclines (oxytetracycline, chlortetracycline, and demethylchlortetracycline) and several that are derived semisynthetically (tetracycline, rolitetracycline, methacycline, minocycline, doxycycline, lymecycline, etc). Elimination times permit a further classification into short-acting (tetracycline, oxytetracycline, chlortetracycline), intermediate-acting (demethylchlortetracycline and methacycline), and long-acting (doxycycline and minocycline). The newest class of tetracycline-related antimicrobials are the glycylcyclines, represented by tigecycline, which contains a bulky side chain compared with minocycline.

Mode of Action:

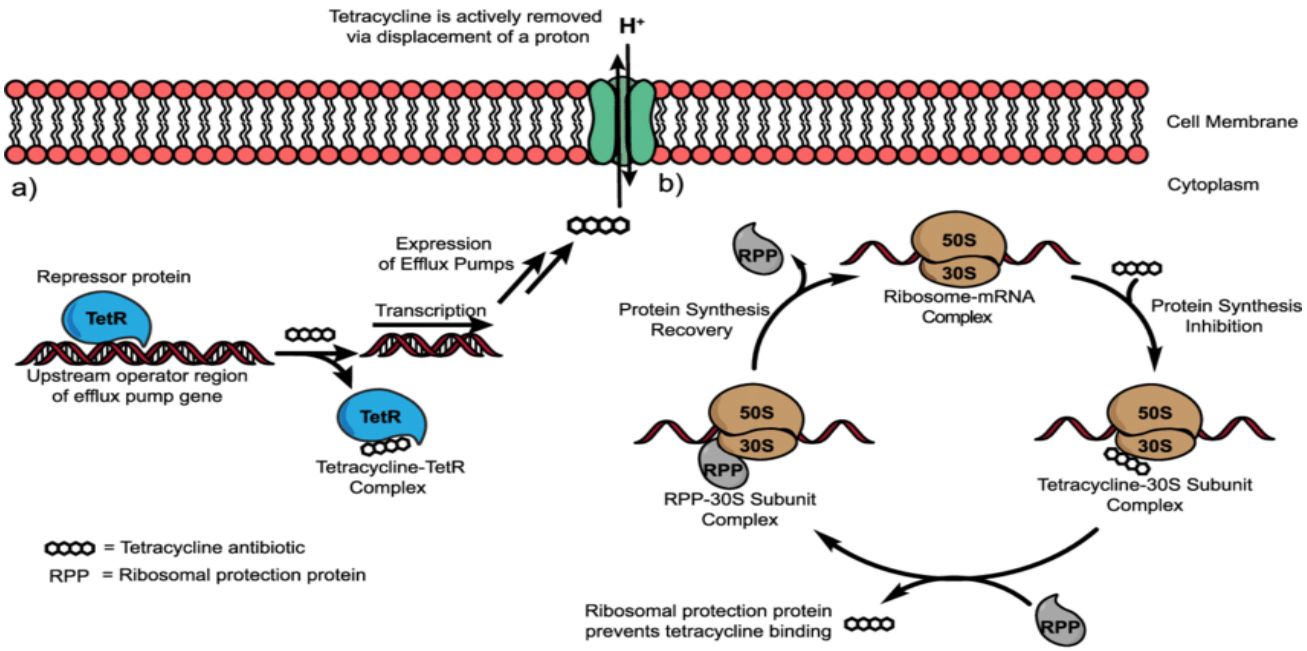
The antimicrobial activity of tetracyclines reflects reversible binding to the bacterial 30S ribosomal subunit, and specifically at the aminoacyl-tRNA acceptor ("A") site on the mRNA ribosomal complex, thus preventing ribosomal translation. This effect also is evident in mammalian cells, although microbial cells are selectively more susceptible because of the greater concentrations seen. Tetracyclines enter microorganisms in part by diffusion and in part by an energy-dependent, carrier-mediated system responsible for the high concentrations achieved in susceptible bacteria. The tetracyclines are generally bacteriostatic, and a responsive host-defense system is essential for their successful use. At high concentrations, as may be attained in urine, they become bactericidal because the organisms seem to lose the functional integrity of the cytoplasmic membrane. Tetracyclines are more effective against multiplying microorganisms and tend to be more active at a pH of 6–6.5. Antibacterial efficacy is described as time dependent.



Bacterial Resistance:

The most common mechanism by which microbes become resistant to tetracyclines is decreased accumulation of drug into previously susceptible organisms. Two mechanisms include 1) impaired uptake into bacteria, which occurs in mutant strains that do not have the necessary transport system, and 2) the much more common plasmid- or transposon-mediated acquisition of active efflux pumps. The genomes for these capabilities may be transferred either by transduction (as in *Staphylococcus aureus*) or by conjugation (as in many enterobacteria). A second mechanism of resistance is the production of a "protective" protein that acts by either preventing binding, dislodging the bound drug, or altering the negative impact of binding on ribosomal function. Among the tetracyclines, tigecycline is characterized by less resistance due to efflux or ribosomal protection. Rarely, tetracyclines can be destroyed by acetylation. Resistance develops slowly in a multistep fashion but is widespread because of the extensive use of low concentrations of tetracyclines.

Antimicrobial ***Spectra:***



All tetracyclines are about equally active and typically have about the same broad spectrum, which comprises both aerobic and anaerobic gram-positive and gram-negative bacteria, mycoplasmas, rickettsiae, chlamydiae, and even some protozoa (amebae). Tetracyclines generally are the drug of choice to treat rickettsiae and mycoplasma. Among the susceptible organisms is *Wolbachia*, a rickettsial-like intracellular endosymbiont of nematodes, including *Dirofilaria immitis*. Strains of *Pseudomonas aeruginosa*, *Proteus*, *Serratia*, *Klebsiella*, and *Trueperella* spp frequently are resistant, as are many pathogenic *Escherichia coli* isolates. Even though there is general cross-resistance among tetracyclines, doxycycline and minocycline usually are more effective against staphylococci.

Pharmacokinetics

Absorption:

After usual oral dosage, tetracyclines are absorbed primarily in the upper small intestine, and effective blood concentrations are reached in 2–4 hr. GI absorption can be impaired by sodium bicarbonate, aluminum hydroxide, magnesium hydroxide, iron, calcium salts, and (except for the lipid-soluble tetracyclines doxycycline and minocycline) milk and milk products. Oral bioavailability, however, can vary markedly among drugs, with chlortetracycline being the least and doxycycline the most orally bioavailable. Tetracyclines at therapeutic concentrations should not be administered PO to ruminants: they are poorly absorbed and can substantially depress ruminal microfloral activity. Specially buffered tetracycline solutions can be administered IM and IV. Through chemical manipulation (especially

choice of carrier and high magnesium content), the absorption of oxytetracycline from IM sites may be delayed, which produces a long-acting effect. Tetracyclines can also be absorbed from the uterus and udder, although plasma concentrations remain low.

Distribution:

Tetracyclines distribute rapidly and extensively in the body, particularly after parenteral administration. They enter almost all tissues and body fluids; high concentrations are found in the kidneys, liver, bile, lungs, spleen, and bone. Lower concentrations are found in serosal fluids, synovia, CSF, ascitic fluid, prostatic fluid, and vitreous humor. The more lipid-soluble tetracyclines (doxycycline and minocycline) readily penetrate tissues such as the blood-brain barrier, and CSF concentrations reach ~30% of the plasma concentrations. Doxycycline is the most extensively distributed. Because tetracyclines tend to chelate calcium ions (less so for doxycycline), they are deposited irreversibly in the growing bones and in dentin and enamel of unerupted teeth of young animals, or even the fetus if transplacental passage occurs. Drug bound in this fashion is pharmacologically inactive. Tetracyclines are bound to plasma proteins to varying degrees (eg, oxytetracycline, 30%; tetracycline, 60%; doxycycline, 90%).

Biotransformation:

Biotransformation of the tetracyclines seems to be limited in most domestic animals, and generally about one-third of a given dose is excreted unchanged. Rolitetracycline is metabolized to tetracycline. Doxycycline and minocycline may be more extensively biotransformed than other tetracyclines (up to 40% of a given dose).

Excretion:

Tetracyclines are excreted via the kidneys (glomerular filtration) and the GI tract (biliary elimination and directly). Generally 50%–80% of a given dose is recoverable from the urine, although several factors may influence renal elimination, including age, route of administration, urine pH, glomerular filtration rate, renal disease, and the particular tetracycline used. Biliary elimination is always significant, commonly being ~10%–20%, even with parenteral administration. Doxycycline appears to be eliminated through feces predominantly through intestinal cells, rather than bile. Only ~16% of an IV dose of doxycycline is eliminated unchanged in the urine of dogs. A portion of doxycycline is also renally excreted in active form in some species. For minocycline, bile appears to be the major route of excretion. Tetracyclines are also eliminated in milk; concentrations peak 6 hr after a parenteral dose, and traces are still present up to 48 hr later. Concentrations in milk usually attain ~50%–60% of the

plasma concentration and are often higher in mastitic milk. Tetracyclines also are excreted in saliva and tears.

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. 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.
3. 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.
4. 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.
5. 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.

CLASSIFICATION

Narrow-spectrum Aminoglycosides:

Included in this group are streptomycin and dihydrostreptomycin, which are mainly active against aerobic, gram-negative bacteria.

Expanded-spectrum Aminoglycosides:

Neomycin, framycetin (neomycin B), paromomycin (aminosidine), and kanamycin have broader spectra than streptomycin that includes many gram-negative aerobic bacteria, as well as synergistic activity toward selected gram-positive organisms. Gentamicin, tobramycin, amikacin (synthesized from kanamycin), sisomicin, and netilmicin are aminoglycosides with extended spectra that include *Pseudomonas aeruginosa*.

Miscellaneous Aminoglycoside Antibiotics:

The chemical structure of apramycin differs somewhat from that of the typical aminoglycosides but is similar enough to be included in this class. The structure of spectinomycin is unusual, but it is fairly comparable to other aminocyclitols with regard to its mechanism of action and antibacterial spectrum.

Mode of Action:

Aminoglycosides are more effective against rapidly multiplying organisms, and they affect and ultimately destroy bacteria by several mechanisms. They need only a short contact with bacteria to kill them and, as such, are concentration dependent in their actions. Their main site of action is the membrane-associated bacterial ribosome through which they interfere with protein synthesis. To reach the ribosome, they must first cross the lipopolysaccharide (LPS) covering (gram-negative organisms), the bacterial cell wall, and finally the cell membrane. Because of the polarity of these compounds, a specialized active transport process is required.

The first concentration-dependent step requires binding of the cationic aminoglycoside to anionic components in the cell membrane. The subsequent steps are energy dependent and involve the transport of the polar, highly charged cationic aminoglycoside across the cytoplasmic membrane, followed by interaction with the ribosomes. The driving force for this transfer is probably the membrane potential. These processes are much more efficient if the energy used is aerobically generated. The efficacy of the

aminoglycosides is markedly curtailed in an anaerobic environment. Aminoglycosides are associated with a postantibiotic effect in a number of bacteria, principally gram-negative (eg, *E coli*, *Klebsiella pneumoniae*, *P aeruginosa*). The effect generally lasts 2–8 hr after exposure and allows for dosing intervals longer than the half-lives of the drugs.

Several features of these mechanisms are of clinical significance: 1) The antibacterial activity of the aminoglycosides depends on an effective concentration of antibiotic outside the cell. 2) Anaerobic bacteria and induced mutants are generally resistant, because they lack appropriate transport systems. 3) With low oxygen tension, as in hypoxic tissues, transfer into bacteria is diminished. 4) Divalent cations (eg, calcium and magnesium) located in the LPS, cell wall, or membrane can interfere with transport into bacteria because they can combine with the specific anionic sites and exclude the cationic aminoglycosides. 5) Passive movement of aminoglycosides across bacterial cell membranes is facilitated by an alkaline pH; a low pH may increase membrane resistance more than 100-fold. 6) Changes in osmolality also can alter the uptake of aminoglycosides. 7) Some aminoglycosides are transported more efficiently than others and thus tend to have greater antibacterial activity. 8) Synergism is common when aminoglycosides and β-lactam antibiotics (penicillins and cephalosporins) are used in combination. The cell-wall injury induced by the β-lactam compounds allows increased uptake of the aminoglycoside by the bacteria because of easier accessibility to the bacterial cell membrane.

The intracellular site of action of the aminoglycosides is the ribosome, which is irreversibly bound by aminoglycosides, particularly at the 30 S but also the 50 S subunits (which comprise the 70 S subunit). Variability occurs between aminoglycosides with respect to their affinity and degree of binding. The number of steps in protein synthesis that are affected also varies. Spectinomycin cannot induce misreading of the mRNA and often is not bactericidal, in contrast to the other bactericidal members. However, at low concentrations, all aminoglycosides may be only bacteriostatic.

A cell-membrane effect also occurs with aminoglycosides. The functional integrity of the bacterial cell membrane is lost during the late phase of the transport process, and high concentrations of aminoglycosides may cause nonspecific membrane toxicity, even to the point of bacterial cell lysis.

Efficacy of aminoglycosides is enhanced if peak plasma or tissue drug concentrations exceed MIC by 10–12 times. Once-daily dosing has been used to enhance both efficacy and safety.

Bacterial Resistance:

Several mechanisms of resistance to the aminoglycoside antibiotics have been described. These may be plasmid or chromosomally mediated.

Impaired transport across the cell membrane is an inherent mechanism of nonplasmid-mediated resistance that occurs in anaerobic bacteria (eg, *Bacteroides fragilis* and *Clostridium perfringens*), because the transport process is active and oxygen-dependent. Facultative anaerobes (eg, enterobacteria and *Staphylococcus aureus*) are more resistant to the aminoglycosides when in an anaerobic environment. Impaired transport can be induced by exposure to sublethal concentrations of these antibiotics. Examples include streptomycin resistance among strains of *P aeruginosa*, low-level aminoglycoside resistance among enterococci, and gentamicin resistance in *Streptococcus faecalis*.

Impaired ribosomal binding may not be a clinically important form of single-step resistance, because generally the drugs bind to multiple sites on the ribosomes. Exceptions include *E coli* strains in which a single-step mutation prevents the binding of streptomycin to the ribosome. The same mechanism has been described in *P aeruginosa*.

Enzymatic modification of aminoglycosides may be either plasmid-encoded or chromosomally mediated. Enzymes occur in both gram-negative and gram-positive bacteria. More than 50 enzymes have been identified, with three major types, each including several subclasses: acetylating enzymes (acetyltransferases), adenylating enzymes (nucleotidyltransferases), and phosphorylating enzymes (phosphotransferases). The susceptibility of each aminoglycoside to specific enzymatic attack varies among each subclass. Although cross-resistance is common, there are differences in susceptibility patterns. Chemical modification stabilizes the drug, which decreases susceptibility to enzymatic destruction. For example, chemically modified kanamycin yields amikacin, which is more resistant to enzymatic hydrolysis.

Other mechanisms of resistance include

1) increased concentration of divalent cations (especially Ca^{2+} and Mg^{2+}), which act to repel ionized drug from the microbe, and 2) increased production by *P aeruginosa* mutants of the outer cell membrane protein, H1, resulting in resistance to gentamicin. Note that efficacy will be reduced in the presence of decreased pH (eg, acidic urine or abscesses), which increases resistance to relatively high concentrations of aminoglycosides.

Antibacterial Spectra:

Streptomycin and dihydrostreptomycin (no longer available in the USA) are characterized by narrow spectra, and efficacy is limited by bacterial resistance. Gram-negative bacilli are still susceptible, including strains of *Actinomyces bovis*, *Pasteurella* spp, *E coli*, *Salmonella* spp, *Campylobacter fetus*, *Leptospira* spp, and *Brucella* spp. *Mycobacterium tuberculosis* is also sensitive to streptomycin.

The spectra of neomycin, framycetin, and kanamycin are broader, with clinical use targeting gram-negative organisms, including *E coli* and *Salmonella*, *Klebsiella*, *Enterobacter*, *Proteus*, and *Acinetobacter* spp. Aminoglycosides with spectra that include *Pseudomonas aeruginosa* (gentamicin, tobramycin, amikacin, sisomicin, and netilmicin) are also often highly effective against a wide variety of aerobic bacteria. Because of their efficacy against *P aeruginosa*, aminoglycosides might be considered higher-tier drugs. Selected staphylococci are susceptible, but treatment should be based on synergistic effects, ie, combination with other antimicrobials (eg, β-lactams). With such combination therapy, generally low doses of aminoglycosides are used. Because oxygen is necessary for active transport of drug into the microbe, caution is recommended when treating facultative anaerobes in a low-oxygen environment. Obligate anaerobic bacteria and fungi are not appreciably affected; streptococci are usually only moderately sensitive or quite resistant.

MACROLIDE

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*

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*.

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*.

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.

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.

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

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.

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.

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.

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.

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.

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.

Very Short Answer Questions (2 marks)

1. Define chemotherapy.
2. Define becteriostatic and becteriocidal.
3. What is penicillin?
4. Write classification of penicillin.
5. What are cephalosporins?
6. Define antibiotics.
7. What are macrolides?
8. What are sulfonamides and name the drugs.
9. How toxicity of sulfonamides is reduced?
10. What are quinolones?
11. Name the ant malarial drugs.
12. Name the aminogycosides drugs.
13. Define suprainfection.
14. Define natural and acquired resistance.
15. Outline the reasons of drug resistance.
16. Classify sulfonamides.
17. Outline toxicity by penicillin.
18. Name broad spectrum penicillin.
19. What is thalidomide tragedy?
20. Whar are specific targets for chloramphenicol and quinolones?
21. Write MAO and side effects of cyclosporine.
22. What are β lactum antibodies?
23. What is bacterial resistance?
24. Write side effects of amphotericin.
25. What is grey baby syndrome?
26. Write the MAO of cotrimoxazole.
27. Give the MAO of erythromycin.
28. What are longer and short acting penicillin?
29. Give the MAO of tetracyclines.

30. What is nalidixic acid?

Short Answer Questions (5 marks)

1. Write a descriptive note on penicillin G.
2. Give a short note on cotrimoxazole.
3. Write the drugs and therapeutic uses of quinolones.
4. Write detailed note on floroquniolones.
5. Explain the general principles of chemotherapy.
6. Give the pharmacological actions of beta lactamase inhibitors.
7. Classify sulfonamides in detail.
8. Write the pharmacology of cephalosporins.
9. Write a note on synthetic penicillins.
10. Write a note on chemotherapy of amoxicillin.

Long Answer Questions (10 MARKS)

11. Describe the pharmacology of chloramphenicol and adverse effects.
12. Discuss in detail about aminoglycosides antibiotics and their side effects.
13. Discuss the pharmacology of macrolides in detail
14. Explain the mechanism of actions, uses and side effects of short acting sulfonamides.
15. Describe the pharmacology of tetracycline in deta