1. INTRODUCTION

1.1 Antibiotic Definition:
Antibiotics are similar to antibacterial agents that are used to kill or inhibit growth of microorganisms particularly to bacteria and may be bactericidal or bacteriostatics as per the concentration of the antibiotics. Antibiotics also acts against other microbes for examples virus, protozoan, fungi etc. these are mainly two types narrow spectrum and broad spectrum of activity against microbes. These antibiotic are useful against a number of infective diseases that are caused by various gram negative & gram positive bacterias, viruses, protozoans and fungi.
The antibiotic word is genereated by Greek word anti means against and bios means life or life of bacterias or microbes. The word coined by the scientist Selman Waksman in 1942 he explained that antibiotics are produced by microorganism and dilute solution of these substance can inhibit or kill the growth of microbes or these are the antimetabolites of microorganisms that are very useful to inhibit the growth of microorganisms including bacteria, fungi, virus and protozoans. These antibiotics do not include the juice that destroy the bacteria but can not produce by thems for example gastric juice and hydrogen peroxides. Gastric hydrochroric acid kills the bacteria in the stomach and hydrogen peroxide in the wound. Antibiotics also do not includes synthetic substances for example sulphonamides and their related substances. These antibiotics are low molecular weight substances their molecular weights are less than 2000. A large number of antibiotics are produced every year.
These antibiotics are useful as antibacterial agents and effective agents many causative organisms to treat various types of diseases. The bacteria causes many infections for examples mycobacteria tubercle cause tuberculosis, salmonella typi causes typhoid fever, treponema palladium causes syphilis, nesseria gonorreea causes gonorrea, streptococcus pneumoniaea causes pneumonia, clostridium tetani causes tetanus, vibrio cholera causes cholera, escherechia coli causes urinary tract infection etc. these all infections are treated by various types of antibiotics. The first antibiotics was penicilllin produced by Alexander Flamming in 1943. Other penicillin related antibiotic
such as ampicillin, amoxicillin, cloxacillin, dicloxacillin, carbecillin are produced by semisenthetic method and all are useful for treating gram positive bacteria induced diseases and extended spectrum antibiotics are also useful to treat gram negative bacteria induced disorders. These antibiotic are produced on industry scale by slant and media using fermentation techniques.

1.2 Antibiotic History
The disease before 20\textsuperscript{th} century were treated by the folklore medicines that are obtained from the forests or mountains or hilly regions. The extracts were obtained from different plants or molds. These extract are also prepared from ayurvedic drugs to treat the patients from various ailments. The tincture of various parts of plants like bark, leaf, root, stem etc were prepared in alcohol or aqueous solvents. These extracts are stored in cold places for preventing deterioration of the extract. Peasents were used warm soil to treat infections. More recently antibiotics are tested in laboroty to check the antibacterial activity against various diseases.

Observation of Louis Pasteur says that if we intervene the antagonism between bacteria and antimetabolites are best options for the discovery and invention of many antibiotics. Antibiotic history can be divided into two parts.

1.2.1 Early History:
From the old age & ancient time
a) Indians and Greeks were used moulds and other various plants extract to prevent disease and infections.

b) Serbia & Greece was found to use breads with mould to treat infections & wounds caused by various organisms traditionally.

c) The people of Russia used warm oil to treat wounds from microorganism,

d) Beer soup mixed with turtle shell and snake skin were used by Sumerian people to treat the patients.

e) Mixture of sure milk and frog bile was used to treat the eye infection from Babylonian doctors.

f) Oil cake or sweetmeat was used by Sri Lanka’s Doctors as decicant and antibacterial agent.
After that in 1940 to 1950 various classes of antibiotics were discovered. In this the first were pencillins and cefalosporins. After that Selman Waksman discovered the streptomycin from the fungus streptomyces griseus. After that a number of aminoglycosides have been discovered from various scientists for example gentamicillin was prepared from purpurea fungal species. aneomycin from streptomyces fradae. Other related aminoglycosides are tobramycin, netilamycin, amikacin. These antibiotics are effective against gram negative bacteria. The streptomycin was specially used against mycobacterium tubercle and was found to be very effective. These drugs are poorly absorbed from the gastro intestinal tract so intra muscular injections are available for the treatments. These drugs have some common side effects like nephrotoxicity, neutopathy and ototoxicity with neuromuscular blockage. These antibiotics have bactericidal effect against gram negative bacteria and narrow spectrum antibiotics. The antibiotics inhibit protein biosynthesis in bacteria. Other antibiotics are macrolides in which erythromycin is the prototype drug that was produced from streptomyces erythrus. The other drugs are roxithromycin and azithromycin that are most widely used in the market. These antibiotics are effective against gram positive bacteria and alternate for beta lactam antibiotics as penicillins and cephalosporins. The some patients are allergic to pencillins that can be treated with macrolide antibiotics. These antibiotics are most effective in spectroccocal pneumonia and lower respiratory tract infections. Azithromycin have a good penetration power so useful in deep fungal infection that are easily treatables. These drugs inhibit protein biosynthesis in last phase or post translational effects. Next generation of antibiotics is tetracyclines. These antibiotics are also generated from various fungal like streptomyces terrus. The antibiotics have four ring in the structure so known as tetracyclins. These antibiotics have bacteriostatics effect and known as broad spectrum antibiotic can be used against gram positive and gram negative baterias. These antibiotics have some side effects like teratogenicity and complexation with diary products or calciums, heamitinics or iron or calium tonics. Other antibiotic is chloramphenicol that is prepared from escherechia coli and have broad spectrum of activity. This drug is effective in typhoid fever and many infections whose causative organism is not known.
Newer synthetic antibiotics are floroquinolins and sulphonamides. The floroquinolones are synthetic antibiotics and produced by synthetic route. The floroquinolones are ciprofloxacin, norfloxacin, sparfloxacin, levofloxacin, gatifloxacin, oflaxaicin, lomefloxacin etc. these antibiotics are specially effective against gram negative bacteria and with narrow spectrum of activity. The drugs are very useful to treat various type of diseases.

**Sulfonamides**

**Sulfonamide (Antibacterial Agents)**

![Chemical structures of sulfonamides](image)

Sulfonamides:
- First antimicrobial drug to be used for pyogenic bacterial infections.

**Classified as:**
1) Short acting (4-8 hrs) – sulfadiazine.
2) Intermediate acting (8-12 hrs) – sulfamethoxazole, sulfamoxole.
3) Long acting (7 days) – sulfadoxine, sulfamethopyrazine.
4) Special purpose sulfonamides – sulfacetamide sodium, sulfasalazine, silver sulfadiazine

**Spectrum:**
• Bacteriostatic for many Gm +ve and Gm –ve bacteria
• Sensitive organisms – streptococcus pyogenes, H. influenzae, H. ducreyi, C. granulomatosi, V. cholerae, gonococci, meningococcal, E. coli, Chlamydia, LGV, nocardia and toxoplasma.

**Sulfonamides and DHFR inhibitors**

![Schematic Diagram of Sulphonamides & DHFR](image)

**Mechanism of action**

• Bacteria synthesize their own FA. PABA is a precursor of bacterial folic acid.
• Sulfonamides are structural analogs of PABA, they competitively inhibit dihydropteroate synthase, so prevents formation of dihydrofolic acid; an essential step in the production of purines & the synthesis of nucleic acid;
• They inhibit growth (bacteriostatic) by reversibly blocking folic acid synthesis.
• Trimethoprim (TPM) prevents the reduction of dihydrofolate to tetrahydrofolate by inhibiting dihydrofolate reductase.
• Synergistic combination cause sequential blockage of bacterial folic acid synthesis.
**Resistance:** Due to:
- Decreased intracellular accumulation of drug.
- Increased production of bacterial PABA.
- Decreased sensitivity of the folic acid metabolizing enzymes to drugs.

**Pharmacokinetics**
- Weak acids.
- Solubility decrease in acidic pH (precipitation of drug or metabolites in renal tubules. (this is less with triple sulfa).
- Some preparations are well absorbed from small intestine.
- Some preparations are poorly absorbed; unabsorbed part is excreted in the feces & partly in milk & bile.
- Binds to plasma proteins (albumin) at sites shared by bilirubin & other drugs (interactions)
- Distributed all over the body & pass BBB (the best is sulfadiazine).
- Sulfonamides are degraded in the liver by acetylation, oxidation & conjugation with glucoronic acid.
- Both parent drug & metabolites are excreted in the urine (so they are useful for urinary tract infection).

**Clinical uses**
1) Meningococcal meningitis (sulfadiazine achieves therapeutic concentrations in cerebrospinal fluid).
2) Acute uncomplicated urinary tract infection (sulfisoxazole & triple sulfa; sulfadiazine, sulfamerazine & sulfamethazine).
3) Nocardiasis (1st choice).
4) Chlamydia infections (not 1st choice).
5) Prophylaxis against streptococcal infections.
6) Poorly absorbed sulfonamides are used in shigellosis, bacillary dysentery, summer diarrhea & sterilization of colon before surgery.
7) Topically in ocular infections (sulfacetamide).
8) Burns infections (mafenide, silver sulfadiazine – pseudomonal).
9) Sufadiazine used in ulcerative colitis.

**Trimethoprim**

- broad spectrum, active against many Gm+ve, Gm-ve aerobic organism (except enterococci and pseudomonas aeruginosa)
- rapid emergence of resistance.
- Useful in susceptible organisms in
- Urinary and respiratory tract infections.

**Adverse effects:**

1) Mild nausea, vomiting & headache.
2) Crystallurea – due to precipitation of acetyl form or sulfonamides themselves in renal tubules at acidic pH – colics. Hematuria, oligouria & even enuria. Fluid intake should be such to ensure a daily urine volume of at least 1200 ml (in adults). Alkanization of the urine may be desirable if urine volume of pH is unusually low, since the solubility of the drug decreases greatly with slight elevation of pH.
3) Hypersensitivity and allergic reactions; erythma multiform, Stevens-Johnson syndrome. There is cross hypersensitivity with chemically related drugs (OHA, thiazides).
4) Granulocytopenia, thrombocytopenia and aplastic anemia, bone marrow depression.
5) Compete with warf and methotraxate for PPB – may increase toxicity. Kernicterus is NB if used during last trimester/ displace bilirubin.
6) Suprainfections.

**TRIMETHOPRIM**

- Weak base, so attain high concentration in acidic medium (prostate & vagina).
- Largely excreted unchanged in urine
- It inhibits dihydrofolate reductase, so prevents conversion of dihydrofolic acid into tetrahydrofolic acid essential for purine and pyrimidine synthesis.
- Broad spectrum antimicrobial, bacteriostatic.
- Active against many Gm+ve & Gm-ve aerobic organism (except enterococcal and p aeruginosa).

**Adverse effects and toxicity of Trimethoprim**

- Megoblastic anemia (give folic acid)
- Should not be used in pregnancy (teratogenic due to folate deficiency).
**Sulfonamide combination**

1) **Co-trimoxazole: (SMZ + TMP)**
- It is fixed dose combination of trimethoprim & sulfamethoxazole (1:5 of S:T)
- It is bactericidal combination.
- Less bacterial resistance.
- More broader spectrum than sulfonamide only.
- Salmonella, shigella, staphylococci, proteus, E. coli.
- Both have similar pKa, half life is around 10 hrs, 80% excreted in urine.
- Dose to be reduced in renal dysfunction.
- Additional organism covered are S. typhi, serratia, keleibsella, enterobacter, y. enterocolitica, Pn carinii and sulfonamide R stains of SA, Spy, shigella, H. influenza, EPEC, gonococci & meningococci.

**Uses of cotrimoxazole**
1. Respiratory tract infection, ear & sinus infection due to H. influenza.
3. Uncomplicated (4 tablets single dose) & complicated UTI & prostatitis. (3-10 days).
5. Salmonella infection (enteric fever).
7. Gonococcal urethritis.
2) **Fansidar** (sulfadoxine + pyremethamine) for ttt of chloroquine resistance malaria.
3) Sulfadiazine + pyremethamine for ttt of toxoplasmosis.
4) Salfasalazine (5-amino salysilic acid + sulfapyridine) – ulcerative colitis and rematoid arthritis.

**Fluoroquinolones**

Quinolones:
- Quinolones have quaniline ring with ketone group. The oldest member of this class is nalidixic acid that is particularly useful in urinary tract infections. The quanolones are synthetic antibacterial agents with specially active against gram negative bacteria. The
drug nalidixic acid inhibit the enzyme DNA gyrase or topo isomerase II to impair genetic control of the microorganism. Other drugs are cinoxacin, ciprofloxacin and norfloxacin.

- Novel introduction of fluoroquinolones are sparfloxacin, gatifloxacin, ofloxacin, levofloxacin, moxifloxacin have broad spectrum of activity. These fluoroquinolones are effective against gram negative bacteria as well as gram positive bacteria. The third and fourth generation fluoroquinolones are more effective against gram positive bacteria as compared to gram negative bacteria.

**FQs are Classified as:**

1) First Generation – Norfloxacin, Ofloxacin, Ciprofloxacin.
2) Second Generation – Lomefloxacin, Sparfloxacin, Levofloxacin, Gatifloxacin, Moxifloxacin.
3) Third Generation – Zenfloxacin.
4) Fourth Generation –

**Spectrum:**

- Highly active against Gm–ve bacilli.
- The prototype drug is ciprofloxacin – aerobic Gm-ve bacilli, especially enterbacteria, neisseria.
- Highly susceptible organisms are – E. coli, kleibsella, neisseria, enterbacter, H. influenzae, S. typhi, shigella, proteus, campylobacter, yersinia, etc.
- Moderately susceptible – staph (+MRSA), pseudo, legionella, brucella, mycobacteria, etc.
- Low sensitivity – strep pyogenes, strep fecalis, strep pneumoniae, mycoplasma, chamydia, MAC, M. kansassii.

**Distinct Features:**

- Rapid activity, high potency.
- Long post antibiotic effect.
- Less propensity to develop plasmid type resistance.
- No interference with gut flora.
- Active against many beta lactam and AG R bacteria.

**Mechanism of action**
• Quinolones enter the cell by passive diffusion. Intracellularly, they inhibit the synthesis of bacterial DNA by interfering with the action of DNA gyrase (DNA topoisomerase IV, mammalian cells possess topoisomerase II – low affinity for Fluoroquinolones).

• Topoisomerase II or DNA gyrase cuts the DNA double strand and insert negative supercoils and ligase the nicked part of DNA.

• Necessary to prevent excessive positive supercoiling of the strands during replication.

• Damaged DNA produces more exonucleases – which leads to digestion of DNA and exert its bactericidal action.

**Resistance**
- Due to chromosomal mutation producing a DNA gyrase with less affinity to fluoroquinolones. Or due to decreased influx mechanism.
- |Salmonella| staphylococcus| pseudomonas| gonococci and pneumococci|

**Pharmacokinetics**
- Absorption of fluoroquinolones are better from gastrointestinal tract after oral dosage (Fuloroquinolones show good biavailability generally 50% and other some fluoroquinolones exhibit more than ninety five percentage for severals) and are widely distributed in body tissue.
- High tissue penetrability – lung, sputum, muscle, bone, prostate and phagocytes, low levels in CSF and AH.
- Some quinolones are partially metabolized. Parent drugs and their metabolites are into the urine. But the route of elimination differs among the quinolones. Ciprofloxacin excreted unchanged in urine.

**Clinical uses**
2) Bacterial diarrhea caused by shigella. Salmonella, toxigenic E. coli or campylobacter.
3) Infections of soft tissue, bones & joints & intra-abdominal & respiratory tract infections (except norfloxacin because it doesn’t achieve adequate systemic concentration). Clindamycin/metronidazole used to cover anaerobes.
4) Gonococcal infection, including disseminated disease (ciprofloxacin & ofloxacin)
5) Ciprofloxacin is effective for chlamydial urethritis or cervicitis. Ciprofloxacin 500 mg SD in gonorrhea. 500 mg days for chancroids.

6) Ciprofloxacin is second line for legionellosis.

7) TB (ciprofloxacin or ofloxacin).

8) Eradication of meningococci for carriers or for prophylaxis of infection in neutropenic patients.

9) Levofloxacin, sparfloxacin, gatifloxacin, moxifloxacin (respiratory quinolones). – they have enhanced gram positive activity & active against atypical pneumonia agents (Chlamydia, mycoplasma & legionella) are used increasingly ttt of upper & lower respiratory tract infections.

10) Typhoid fever:
- First choice drug.
- 500 – 750 mg BD 10 days, or 200 mg IV 12 hourly.
- Also prevents carrier state.

**Adverse effects:**
- Well tolerated. In few points:
  1) Gastrointestinal distress is the most common side effects.
  2) CNS problem: headache, dizziness, restlessness, anxiety, insomnia, etc.
  3) Phototoxicity.
  4) Tendonitis and tendon rupture – may cause cartilage damage in weight bearing joints.
  5) Cardiac arrhythmia: Sparfloxacin prolongs QT interval.

**Interactions:**
- NSAIDs may enhance CNS toxicity of fluoroquinolones.
- Plasma concentration of theophylline, caffeine, warfarin is increased by ciprofloxacin, norfloxacin due to inhibition of their metabolism.
- Better avoided in pregnancy, lactation and in patients under 18 years (to avoid damaging of growing cartilage & arthropathy).

1) Norfloxacin:
- Less potent than ciprofloxacin.
- Excreted unchanged in urine.
Used for urinary and genital tract infections.

- 200 – 400 mg tablets

2) Pefloxacin:
- Derivative of norfloxacin, more lipid soluble.
- Preferred for meningeal infections – better BBB penetration
- 400 mg/ day

3) Ofloxacin:
- Intermediate activity against Gm-ve bacilli.
- Active against Chlamydia and mycoplasma.
- Inhibits M. tuberculosis and M. leprae
- Excreted largely unchanged in urine,
- 200-400 mg/day.

4) Levofloxacin:
- Levo isomer of ofloxacin.
- Better activity against streptococcal pneumoniae.
- Oral bioavailability is nearly 100%.
- Does not interfere with metabolism of warfarin, theophylline, etc.
- Used for CAP, exacerbation of chronic bronchitis.
- Also for sinusitis, pyelonephritis, skin and soft tissue infections.
- 500 mg OD.

5) Lomefloxacin:
- Second generation fluoroquinolones.
- More active and potent for Gm-ve bacilli.
- Long half life and better tissue persistence – OD dosing.
- Uses similar to levo and ofloxacin.
- 400 mg OD.

6) Sparfloxacin:
- Second generation.
- Enhanced activity against Gm-ve bacilli and other anaerobes.
- Major indications – pneumonia, exacerbations of chronic bronchitis, sinusitis & ENT infections.
- MAC infections in AIDS patients.
- More likely to cause photosensitivity.
- May rarely cause prolongation of QT interval.
- Should not be used with cisapride, tricyclic amines, etc.
- 200-400 mg/day.

7) Gatifloxacin:
- 2nd generation activity against strep pneumoniae, Chlamydia, etc.
- Also against Gm-ve cocci.
- Used for Cap, exacerbations of chronic bronchitis, sinusitis, UTI, gonorrhea.
- 400 mg day, 200-400 mg OD.
- May cause tachycardia and prolong QT interval.

8) Moxifloxacin:
- Long acting 2nd generation.
- Highly active against Stre pneumoniae.
- Used for pneumonia, bronchitis, sinusitis, otitis media, etc.
- Precipitates seizures and QT prolongation.
- 400 mg OD.

Urinary Antiseptics:
- These antimicrobial agents which attain therapeutic concentration in urinary tract and inhibit bacterial replication in the urinary tract.
- Lack systemic antibacterial activity but may cause toxicity on absorption.

5-nitro furanylamo 2,4 imidazoline dione derivative

\[
\text{Nitrofurantoin} \\
\text{Furazolidone}
\]

\[
\text{1-((((5-nitrofuran-2-yl)methyl)amino)imidazolidine-2,4-dione}
\]

\[
\text{3-(((5-nitrofuran-2-yl)methyl)amino)-1,3-oxazolidin-2-one}
\]
- It is used to treat urinary tract infections that are caused by particularly gram negative *Escherechia coli*. This not effective against *pseudomonas* and *proteus* bacteria.
- Activity greatly enhanced at pH < 5.5.
- Single daily doses can prevent recurrent UTIs.
- Active orally \(\rightarrow\) excreted so rapidly in urine via filtration and secretion (RF – insufficient urine levels and toxic blood levels.

**Adverse Effect:**
1. Anorexia, nausea & vomiting (main)
2. Neuroleptics and hemolysis in G 6PD.
3. Skin rashes and phototoxicity.

2. **Nalidixic Acid:**
   - First quinolones drug act on many G-ve (not proteus or pseudomonas) by Inhibiting DNA gyrase or Topoisomerase II or acidification.
   - Emergence of resistance is very fast.
   - Active orally \(\rightarrow\) excreted rapidy in urine partly unchanged and partly ad inactive glucorinide.
   - Now is obsolete.

3. **Methinamine:**
   - methamine mandelate and methinamine hippurate.
   - methinamine \(\rightarrow\) release of antibacterial formaldehyde
   - mandelate or hippurate \(\rightarrow\) bacterial in urine to G-ve
   - proteus resistant (release ammonia \(\rightarrow\) strongly alkaline urine.
   - formaldehyde + sulfonamide \(\rightarrow\) insoluble complexes (should not be used together).

**Macrolides**
- Erythromycin, Roxithromycin, Clarithromycin, Azithromycin

- Delithromycin, telithromycin – Newer FDA approved.

**Clarithromycin:** It is 6-methyl ether of erythromycin. This group inhibits peroxide formation with 12-OH group in the macrolacton ring.

**Roxithromycin:** It is produced by reaction of substituted hydroxyl amine at C-9 of macrolide ketone to produce oxime that also inhibit formation of ketal

**Azithromycin:** It is prepared by Beckmann rearrangement inserting N-CH3 between 9 and 10-position of macrolide ring. It has 15 membered macrolactone ring.

**Telithromycin:** This is ketolide and not resistance to bacterial enzyme due to modified structure of the drug.

**Mechanism of action:**

- Macrolides binds to the 50 S (Sub risomal unit of protein) and inhibit the process of protein biosynthesis by inhibiting translocation.

- These drugs inhibit enzymes that catalyze the movement of new amino acid to the peptide chain– stop chain propagation in eukaryotic cell.

- Sensitive Gm +ve bacteria accumulate erythromycin intracellularly.

**Spectrum of Antibacterial Activity**

- Effective against same organisms as Penicillin G used as alternative in PCN allergic patients.

- These have been alternate for allergic to penicillin or strain that emerges resistance opposite to penicillins
- These antibiotics are most useful against gram positive bacilli and cocci bacteria. These agents also show good activity against gram negative diplococcus, particularly *Nesseria gonorrheae*.
- Macrolide antibiotics are effective against *Mycoplasma*, *Chlamydia*, *Camphylobacter* and *Leguinella* in comparison to β-lactam antibiotics.
- Clarithromycin and azithromycin are highly active against mycobacteria.
- Only bacteriostatics for most organisms.

**Mechanism of Resistance:**
- Active efflux mechanism in some bacteria.
- Methylase enzyme which modifies ribosomal target.
- Hydrolysis of macrocyclic antibiotics by esterases chromosomal.

**Pharmacokinetics**
- Macro cyclics are administered orally.
- i.v. preparations can cause phlebitis.
- Erythromycin is acid labile and destroyed by hydrochloric acid in the stomach so the formulation are enteric coated type to prevent degradation by gastric acid (HCl).
- Esters of erythromycin – stearic acid ester/ethylsuccinate are resistant to inactivation.
- Clarithromycin is less susceptible to acid.
- Undergoes extensive first pass hepatic metabolism.
- Roxithromycin and Azithromycin are well absorbed.
- All these antibiotics are widely distributed to tissues and fluids except CSF.
- Azithromycin accumulates in tissue fibroblasts – act as a reservoir
- Tissue concentrations > plasma level.

**Adverse effects**
- Epigastric distress
- Cholestatic jaundice
- Ototoxicity (transient, seen with high doses)
- Hypersensitivity hepatitis.

**Contraindications:** hepatic dysfunction.

**Drug Interactions**
- Interfere with cytochrome P450 clearance
- Theophylline, cyclosporine, cardiac digoxins cisapride – CYP3A4

**Uses**

- As an ALTERNATIVE to Pns:
- Streptococcal pharyngitis, tonsillitis, mastoiditis.
- Respi infections by pneumococcal and H. influenzae.
- Diphtheria, Tetanus, Syphilis and gonorrhea.

**As a FIRST LINE drug for**

- Atypical pneumonia caused by mycoplasma pneumonia.
- Whooping cough – 1-2 weeks of erythromycin.
- Chancroid – erythromycin 2g/day for 7 days

**As a SECOND Choice drug in:**

- Camphylobacter enteritis.
- Cegionairre,s pneumonia.
- Chlamydia trachomatities.
- Penicillin resistant staph infections. Not effective against MRSA.

**Roxithromycin**

- Long acting, acid stable macrolide.
- Spectrum similar to erythromycin, but more active against Branh catarhhalis, Gardenel gaginalis and legionella.
- Twice a day dosing adequate.
- May also interact with CYP3A4 and interact with terfenadine, cisapride, etc.
- It is an alternative to erythromycin for respiratory, ENT, skin and soft tissue infections.
- 150-300 mg BD 30 minutes before meals.

**Clarithromycin**

- Spectrum similar to erythromycin additionally include – MAC, atypical mycobacteria, M, leprae
- Indicated in URTI, LRTI, sinusitis, otitis media, atypical pneumonia, streptococcal skin infections.
- As a component of triple drut regimen for H. Pylori eradication.
- First line drug for MAC infections in AIDS patients.
- 250-500 mg BD – 7-14 days,
**Azithromycin**
- Expanded spectrum, more active against *H. influenzae*.
- Also against other respiratory pathogens – mycoplasma, *Chlamydia pneumoniae*, 
  legionella, moraxella, etc.
- Not effective against erythromycin resistant bacteria.
- Rapid and near complete oral absorption.
- Attains high concentration in macrophages and fibroblasts.
- Used for legionaire’s pneumonia, *Chlamydia trachomatis*, bronchitis, skin and soft tissue 
  infections.
- 500 mg OD for 3 days.
- SE – mild gastric upset, abdominal pain, headach, dizziness.
- Does not inteact with CYP3A4.

**Clindamycin**: it is similar to macrolides and S isomer is more effective as compared to 
R isomer. This is effective against many gram negative bacteria and pencillin 
alternative.

![SN2 reaction](image)

**Lincomycin**

This antibiotic is obtained from lincomycin that is obtained from actinomycyes 
streptomycyes lincolnness. Pseudomembrane colitis is major side effect that is treated 
with vancomycin.

**Glycosides of Amino sugars (Amino-glycosides)**
Different Sources of antibiotics:-

1. Gentamicin  \( \text{Micromonospora purpurea} \)
2. Neomycin  \( \text{Streptomyces fradiae} \)
3. Streptomycin  \( \text{Streptomyces griseus} \)
4. Tobramycin  \( \text{Streptomyces tenebrarius} \)
5. Framycetin  \( \text{Streptomyces decaries} \)
6. Kanamycin  \( \text{Streptomyces kanamyceticus} \)
7. Amikacin  It is 1-L-(\(\text{-}\))-4-amino-2-hydroxybutyryl kanamycin

**Ribosomal Inhibitors**

A. The agents all bind to ribosomal subunits, interfering with one or more steps in translation
   - Initiation
   - Translocation
   - Extension

B. Most are bacteriostatic
   - These glycosides of amino sugars are bactericidal at peak levels.

C. Some are bactericidal to Gram Positive organisms.
   - Inhibitors of protein synthesis.
   - Streptomycin was the first member, followed by neomycin.
   - They are effective against aerobic Gram-negative bacilli and inhibit protein synthesis by acting on 30s ribosomal unit and are bactericidal, more active at alkaline \( \text{pH} \).
- They have relatively narrow margin of safety between therapeutic and toxic concentration, they are ototoxic and nephrotoxic.
- Not absorbed orally, do not penetrate BBB.
- Only partial cross resistance amongst them.
- Neomycin and framycetin are associated with high systemic toxicity and so only used topically.
- Effect of antibiotic after minimum concentration in the serum is known as post antibiotic effect. The concentration of the drug falls below the minimum level that is not effective but shows effect latter.
- High concentration in renal cortex & inner ear – Nephrotoxicity and Ototoxicity.

**Mechanism of action:**
- These antibiotics are bactericidal by tightly binding to a structure component of the 30s ribosomal subunit to inhibit protein synthesis.
- They get inactivated under anaerobic conditions and are non effective against anaerobic bacilli.
- They diffuse through the porin channels in outer coat of Gm-ve bacilli into the cytoplasm and bind to 30S, 50S or 30-50S interface.
- After binding they distort the mRNA codon recognition and result in misreading of the code.
- Wrong amino acid (AA) enters the peptide chains or peptide chains of abnormal lengths are produced.
- Inhibition of initiation complex of peptide formation.
- Breaking up of polysomes into nonfunctional monosomes.
- Also induce secondary changes in integrity of bacterial cell wall and exert their bactericidal action.
- Primarily active against Gm-ve bacilli.

**Mechanism of Resistance:**
A. Ribosome alteration:
   The drug has low affinity to bacterial ribosomes (E. coli to streptomycin)
B. Decreased permeation of the antibiotic: absence of alteration in the glycosides of amino sugar transport system, inadequate membrane potential can result in a cross
resistance to all glycosides of amino sugar. Passage of glycosides of amino sugar through the cytoplasmic membranes is depend on the oxygen, bacteria live without oxygen are thus resistance to amino-glycosides. E.g. Pseudomonas aeruginosa.

C. Microbial cell membrane enzyme can also deactivate the drug (acetyltransferases, phosphotransferases, adenylase are the three enzymes that inactivate the drugs by their cell membrane) these drug should be avoided by the resistance by inserting groups that are not substrate of the enzymes.

**Common Adverse Drug Reactions:**

1) **Ototoxicity:** it can be both cochlear (auditory) and vestibular.
   - Toxicity of Cochlear:- A pressure-piteched tinitusis probably the 1st characteristic of generating difficulty. The medicament is not stopped quickly, hearing problem may create some days latter. Deafness can be reversible or irreversible.
   - Neomycin, kanamycin and amikacin are more cochelotoxic.
   - Vestibular Toxicity:- headache, nausea, vomiting, (spontaneous nystagmus), dizziness, ataxia.
   - They accumulate in the inner ear particularly the concentration of drug in the plasma is high. These amino-glycosides have half life five to six time higher in the otic fluid to normal plasma fluid. The toxicity of drugs to the ear are high in the patients when the plama concentration is elevated.
   - Streptomycin and gentamicin are vestibulotoxic.
   - These antibiotics are found to disturb active transport of the system that is compulsory for ionic balance in the fluid and maintain it properly in the cell the impairment to normal concentration change ionic concentration to labrynthin fluid that causes impairment in nerve conduction and electrical conductivity. This destroys the hair cells irreversibly.

i. **Nephrotoxicity:**
   - Biochemical event: aminosugar glycosides are polycation, they bind to anion phospholipids of renal tubular cell membrane and inhibit phospholipases and damage intracellular organelles.
   - Mild reversible renal impairment:- on use for more than several days – moderate protein urea, appearance of casts (hgranular & hyaline) and reduction in G.F.R occurs.
- Severe damage of tubal may occur.
- Renal function may be impaired that is reversible because nearest tubule cells can regenerate.
- Reduced excretion if the drug, in turn leads to ototoxicity.
- The plasma concentration should be monitored mainly during long term therapy and high dosage.
- Neomycin is most nephrotoxic followed by gentamicin and tobramycin, streptomycin is least nephrotoxic.

ii. Neuromuscular blockage
- They may produce acute neuromuscular blockade and apnea.
- All aminoglycides reduce release of Acetyl choline from motor nerve endings and also interfere with mobilization of centrally located synaptic vesicals to fuse with terminal membrane (Ca++).
- Neomycin is most likely to produce this, followed by kanamycin, amikacin, gentamicin and tobramycin.
- Intrapleural or intraperitoneal instillation is more toxic than IV or IM injection.
- Mysthenic patients are more prone to this adverse effect.
- General anesthetics, hypocalcemia, hypermagnesemia also effect Neuromuscular blockade.
- Neuromuscular blockade is treated by IV calcium or edrophonium/neostigmine.

iii. Hypersensitivity
- In general, the glycosides of aminosugars have little allergenic potential;
- Hyper-sensitivity reactions are rare that include fever, angiedema, skin rashes angioedema, anaphylactic shock & exfoliative dermatitis are seen in some patients.

iv. Other effects
- Optic neuritis with streptomycin.
- Peripheral neuritis and paresthesia mostly periferi but also of hands and face with streptomycin.
- Radiculitis- on intraventricular or intrathecal gentamicin.

Precautions
- Don’t mix with any drug in the same syringe/infusion bottle.
- Avoid during pregnancy as there is risk of fetal ototoxicity.
- Avoid concurrent use of other ototoxic drugs like minocycline and loop diuretics.
- Avoid concurrent use of other nephrotoxic drugs like amphotericin B, vancomycin, cyclosporine and cisplatin.
- Cautious use in patients past middle age and in patients and kidney damage.
- Cautious use with muscle relaxants.

**Antibacterial spectrum of these antibiotics**

- amikacin, tobramycin, gentamicin & netilmicin are used mainly against to bacilli of aerobic gram negative (Pseudomonas, Proteus, Enterobacter, Klebsiella, Serratia, citrobacter)
- Streptococcal pneumonia & streptococcal pyogens are resistance.
- Streptomycin & gentamicins are effective to enterococci and streptococci viridans – when administered with penicillin.
- Tobramycin and gentamicin are effective against Staph. aureus and Staph. Epidermidis.
- Tobramycin is more active than gentamicin against Pseudomonas aeruginosa and proteus species.
- Organisms which are resistant to gentamicin, are also resistant to tobramycin but they respond to amikacin and netilmicin. Amikacin and netilmicin are used in nosocomial infection. Amikacin and netilmicin are effective against organisms producing amino-glycosides-inactivating enzymes.

1) **STM or Streptomycin:**

- Streptomycin (STM) is useful to treat tuberculosis (as second line agent).
- Since it can induce severe adverse reactions and is less active against aerobic gram-negative rods than other members of this class, it is generally used with other antibacterial agents in the treatment of endocarditis.
- Bacterial endocarditis – given with penicillin to produce a synergistic bactericidal effect against Strep. Viridans and Strep. Faecalis. Gentamicin – preferred because of irreversible vestibular toxicity produced by streptomycin.
- Tularemia – Tetracyclines are also highly effective.
- Plague – for all types. Tetra-cyclines and chloramphenicol are also beneficial.
- Brucellosis – doxycycline and rifampin are the drug of choice.

2) Aminoglycoside Gentamicin (GTM)
- Gram negative bacilli are killed by gentamicin so the drug of choice in gram negative bacillus disorders.
- Choice of drug amino-glycosides because of cheapness, the activity of drug is reliable due to longer application of drug.
- Used extrena of otitis, burn infections & pyelonephritis of acute type
- Trough plasma drugs concentration > microgram/milliliter – causes toxicity..
- Gentamicin produces predominantly vestibular toxicity, also cause nephrotoxicity more often than other members.
- Tobramycin, amikacin and gentamicin are used interchangeably for:
  1. Urinary tract infections (UTI)
     - the patient seriously suffered from pyelonephritis is treated with gentamicin alone or combination with beta lactam antibiotics. These drugs are very effective to treat the infection. If the micro-organism is isolated and sensitivity is identified then the combination of these drug offer broad and long coverage to the disease.
     - aminoglycosides can stoped for less toxic antibiotics.
  2. Pneumonitis
     - Pneumonia is mainly caused or produced by gram negative bacillus species are mainly found patient of hospitaly admited, patients with respirator or ventilator, patients those hearing system is impaired particularly granulocytopenia.
     - Amino-glycosides are widely used to treat this condition along with penicillin or cephalosporin.
     - Nor for community acquired pneumonia.
     - Intrathecal route being toxic – not recommended, 3rd generation cephalosporins are preferred.
  4. Bacterial endocarditis: gram-positive bacterial infections like enterococcal endocarditis is treated with penicillin and glycosides of aminosugars.
5. Other infections:
- Empirical therapy of sepsis in immunocompromised patients,
- Acute salpingitis –(PID)-given with doxycycline and clindamycin, intraabnormal infection secondary to penetrating trauma, diverticulitis, chloangitis, appendicitis, peritonitis, post surgical wound infection-polymicrobial infection with –ve and anaerobes, osteomyelitis.

6. Topical application: Cream, ointment, solutions, infected burns, wounds, skin lesions, prevention of IV catheter, ophthalmic infections (keratitism conjunctivitis).

3) Tobramycin
- 2-4 times more active against pseudomonas and proteus than gentamicin.
- Used only as a reserved drug for pseudomonas and proteus infections.
- Osteomyelitis, pneumonia.
- 3-5mg/kg/day.
- Also as ophthalmic ointment and solutions.

4) Amikacin:
- Semisynthetic derivative of kanamycin.
- It has broadest antimicrobial activity in the group because it is resistant to aminoglycosides inactivating enzymes, hence used in infections due to gentamicin of tobramycin resistant strains.
  **Uses**
- Gram negative bacilli infection is found in hospitalized patients or nosocomial infections. This is best treated with the amikacin that is newer agent prepared from tobramycin.
- Also effective against Mycobacterium tuberculosis resistant of streptomycin and for certain disseminated atypical mycobacterial infection (avium, kansasii....) in AIDS patients.
- 15/mg/kg/day.

5) Sisomycin
- Natural glycosides of amino-sugar similar to gentamicin, it is more potent for pseudomonas, few other gram negative bacilli and beta-hemolytic streptococci.
- It is used with penicillin for SABE. It can be used interchangeably with gentamicin, through it offers no advantages over gentamicin.
- Susceptible to aminoglycosides inactivating enzymes.

6) **Netilmicin**
- Latest of the group.
- Antimicrobial activity similar to amikacin except for mycobacterium tuberculosis.
- Relatively resistant to aminosugar antibiotics inactivating enzymes.
- Distribution and elimination similar to gentamicin and tobramycin.
- Least ototoxic and nephrotoxic.
- Uses are similar to amikacin. Effective against serious infections due to gram negative bacilli and certain gentamicin resistant pathogens.

7) **Neomycin**
- Effective against various gram-negative (except pseudomonas) and positive microorganisms (except Strep.) and mycobacteria. Cross resistance seen between neomycin and kanamycin. Because of their use for preparation of bowel, resistant organisms have developed.

**Use**

I. **Topical:**
- As cream, ointment, solution, powder for infections of skin or mucous membranes, i.e., injected burns wounds, ulcers and infected dermatoses, injections into joints, pleural cavity, tissue spaces, abscess cavities.
- It is used alone or with other antibiotics like polymyxin B for bladder’s regular irrigation to stop bacteriuria & bacteremia found to catheters of indwelling type.

II. **Oral:**
- Neomycin with erythromycin is given orally for 1-2 days for preparation of bowel for surgery – reduces aerobic bowel flora. Reduces rate of postoperative wound infection.
- It is useful to hepatic coma treatment-to destroy colonic bacterial flora to prevent ammonia formation- nowadays lactulose is preffered.

**Adverse Reactions:**
- hypersensitivity reactions – skin rashes – on topical application – cross reactivity with others.
- Ototoxicity and nephrotoxicity on parenteral use-hence not used by this route.
- Respiratory paralysis is occurred with neuromuscular blockage due to wound irrigation & serosal cavities.
- On oral administration – a sprue like mal absorption syndrome and superinfection with overgrowth of candida in the intestine may occur.

8) Framycetin:
- Too toxic for systemic administration, only used topically on skin, eye, ear similar to neomycin.

**Tetracyclines**

Tetracycline, \( R = H, X = OH, Y = CH_3 \)
Demeclocycline, \( R = Cl, X = OH, Y = H \)
Minocycline, \( R = N(CH_3)_2, X = Y = H \)
Sanocycline, \( R = X = Y = H \)

Oxytetracycline, \( X = OH, Y = CH_3 \)
Methacycline, \( X = Y = CH_2 \)
Doxycycline, \( X = H, Y = CH_3 \)

**Tetracyclines:**
- These synthetic antimicrobial agents are older members. Specially

**Tetracyclines are Classified as:**
5) Group I – Tetracycline, oxytetracyclines.
6) Group II – Demeclocycline, methacycline, Lymecycline.
7) Group III – Doxycycline, minocycline.
8) Fourth Generation –

**Spectrum:**
- Spectrum: broad spectrum – including intracellular organisms.
- Most Gm +ve bacilli and cocci – many resistant now.
- Sensitive Gm –ve bacilli are – H. ducreyi, calymmatabacterium granulomatis, V. cholerae, Y. pestis, campylobacter, H. pylori.
- Others – Rickettsial diseases, Chlamydia trachomatis, and mycoplasma infection.
Malaria, Lyme, Bartonella, Brucella, coxiella, atypical mycobacteria.
**Drug action Mechanisms (MAOs)**

- Tetracyclins act by inhibiting the bacterial growth or bacteriostatics in nature. Protein biosynthesis process is inhibited by acting on 30 S bacterial ribosome & accessibility of aminoacyl t-RNA is prevented to acceptors (A) site of composition of ribosomes-mRNA. It stops insertion various AA (Amino-acids) to propagating polypeptide series.

- At high concentrations, tetra-cyclines also change bio-synthesis of proteins in mammalia cells although the mammal lost system of active transport (ATS).

**Resistance**

- Cross-resistance between members of this group is observed except for minocycline.

- Resistance is mediated by plasmids. This may be due to:
  - i) Decreased accumulation due to decreased incoming / development of outgoing pathway is depend on energy.
  - ii) reduced accessibility of tetracycline to the ribosomes due to the appearance of ribosomal protection protein.

- Enzyme inactivates tetracycline.

**Pharmacokinetics**

- Adequate but incomplete absorption of older tetracyclines.

- Doxycycline 95 % and mincycline 100%. Absorption of minocycline & doxycyclin is not interrupted by food and related materials.

- Absorption is decreased by concurrent administration of dairy products (milk etc) AlCl3 or chloride of aluminum, salts of Ca (calcium), Mg (magnesium), Fe (Iron) and Bi (bismuth) sub salicylate-due to chelation of divalent and trivalent cations.

**Distribution**

- Protein binding varies – 80-95% for doxycycline and 20-40% for oxytetracycline.

- All tetracyclines concentrate to the hepatic system & have been eliminated in intestine via biles. Enterohepatic circulation occurs.

- On I.V. – may appear in spinal fluid. They penetrate well into other tissues and fluids-synovial fluid and maxillary sinus. Minocycline reach concentrations in tears and saliva adequate to eradicate meningococcal carrier state. Minocycline is deposited in body fat.

- Are stored in RES of hepatic, bone marrow & spleen in bones. Dentine and enamale of unruptured teeth absorbs these antibiotics. This causes discoloration of teeth.
These drugs are teratogenic means crosses the placenta of pregnant ladies and concentrate in amniotic fluid. These antibiotics also enters blood circulation of new born fetus.

Relatively high concentration of drugs are found in breast milk.

**Metabolism**

- Minocycline and doxycycline are metabolized significantly in the liver.
- Doxycycline is excreted in feces as inactive conjugate or chelate. Since it is completely metabolized, it is preferred to treat extra renal infection in patients with renal failure.
- Enzyme inducers decrease their half lives.

**ADRs:**

1) **Toxic Effects:**

I. **Gasterointestinal**
   - Dose dependent GI irritation: epigastric burning and distress, abdominal discomfort, nausea and vomiting
   - Esophagitis and esophageal ulcer.
   - Pancreatitis
   - Diarrhea-irritative effect – differentiate from pseudomembranous enterocolitis.

II. **Photosensitivity**
   - Mainly demeclocycline and doxycycline and to a less extent others may produce sunburn
   - It may also be associated with onycholysis and pigmentation of the nails.

III. **Hepatic toxicity**
   - May occur after large oral or IV doses. Persons with preexisting liver disease and pregnant women are more susceptible-fatty infiltration of liver-may result in jaundice, azotemia, acidosis and irreversible shock.

IV. **Kidney toxicity**
   - May induce excretion of urea (uremia) kidney damaged patients by protein biosynthesis inhibition. Doxycycline is least nephrotoxic.
   - Nephrogenic diabetes insipidus may occur due to demeclocycline used in the treatment of chronic inappropriate secretion of ADH
- Fanconi syncrome – renal tubular acidosis-with use of outdated or degraded tetracyclines – damage to proximal renal tubule- is reversible.

V. Effect of calcified tissues.
- Long or short term therapy in children-brown discoloration of the teeth. Pigmentation of permanent dentition (ages of 2 months to 5 years). Dentine and enamel affected – increased caries. Pigmentation of milk teeth-from mid-pregnancy to 4-6 months postnatally.
- 40% decrease in bone growth-deposition in skeleton throughout gestation and childhood- reversible.

VI. Miscellaneous effects
- enhanced pressure to intracranial system & increase tension of bulging fontanel (pseudo-tumor cerebrii) in new born children.
- Vestibular toxicity (dizziness, ataxia, nausea, vomiting) with minocycline is seen more often in women.

2) Hypersensitivity reactions:
- Hypersensitivity reactions are more common with these antibiotic and cross sensitivity is major problem.

3) Biological effects other than allergic and toxic:
- Superinfection with clostridium difficile.
- Super-infection with the yeast and fungi- vaginal, oral, pharyngeal or even systemic Infection.

Precautions:
- Should not be used in pregnancy, lactation and in children. Unless there is no other choice.
- Use with caution in patients with renal or hepatic disease.
- Don’t use expired preparations.

Clinical uses
11) Rickettsia disorders: (typhus fever of epidemic, scrub typhus, Rockies mountains spotful fever, murine typhus, rickettsia poxes Qs illness). Chloramphenicol & tetracyclins have been most powrful & these can be useful to saving of patients in rickettsia diaorders.
12) Mycoplasma infection- therapy of mycoplasma pneumonias with either erythromycin or tetracyclins shortens the duration of illness.

13) Chlamydial infections:
   - Chlamydia pneumoniae- or sinusitis- tetracyclin therapy used for recurrent infections. macrolide are used to treat initial infection.
   - Psittacosis, Trachoma.
   - Inclusion conjunctivitis – topical and oral administration.
   - Nonspecific urethritis – due to Chlamydia trachoma – doxycycline for one week. However azithromycin 1 gm single dose is preferred-better compliance.
   - Sexually transmitted disease-because of associated Chlamydial infection.

14) Bacillary infections
   - Brucellosis-doxyycline + rifampin
   - Cholera – Doxyycline
   - Traveler’s diarrhea- doxyycline
   - tularemia

15) Coccal infection
   - Prophylaxis for meningococcal infection-minocycline.
   - 85% S. pneumonia are susceptible to tetracyclines- doxycycline is used for empirical therapy of community acquired pneumonia.

16) Other infections:
   - Actinomycosis – penicillin G is preferred.
   - Nocardiosis – minocycline + sulphonamide
   - Anthrax.
   - Spirochetes- Lyme’s disease, relapsing fever- doxycycline.
   - Atypical mycobacterial diseases including M. marinum respond to tetracycline.

17) Pustular acne- they inhibit propionibacteria which metabolize lipids into irritating free fatty acid in sebaceous follicles. Small doses of doxycycline or minocycline are used for a long period. Topical clindamycin is also effective.

18) In intestinal amebiasis – tetracycline is given with other drugs.

19) In chloroquine or multiple drug resistance P. falciparum infection – doxycycline.

20) Eradication of H. pylori – tetracycline.
21) Demeclocycline for syndrome of inappropriate secretion of ADH- inhibits the action of ADH on nephron.

**CHLORAMPHENICOL**

It contains nitrobenzene moiety in its structure.

**Mechanism of action**

- It is bacteriostatic. This can be cidal to specific known microorganisms like Haemophilous influenzae, Nesseria meningitides and S. pneumonia.
- It inhibits protein synthesis both in bacteria and in eucaryotics cells. It binds reversibly to 50 S ribosomal subunit and prevents binding of amino acyl tRNA to fifty S ribosome sub unit. Amino acid substrate & peptidyl transferase substrate interaction can’t obtain & thus formation of peptide bond is stopped. Inhibits transpeptidation reaction.
- It also inhibits mitochondrial protein synthesis by acting on 70 S ribosome. Mammalian erythropoitrict cells are particularly sensitive to the drug.

**Spectrum:**

- Gram positive and negative organisms and anaerobes.
- Broad spectrum (gram+ve and –ve and most anaerobes- these are effective against gram negative rod e.g. bacterial fragilis and gram positive anerobic cocci e.g. closterdium species as clostridium tetani, clostridium perifrigen.
- Susceptible organisms:- H. influenzae, N. meningitides, Salmonella typhi, Brucella species, Bordetella pertussis.
- V. cholerae and Shigella are largely susceptible.
- Tickettsia, Mycoplasma and Chlamydia.

**Resistance**

- Due to plasmid encoded acetyl transferase, which acetylates (inactivates) the drug. Acetylated drug fail to bind to bacterial ribosomes.
- Decreased permeability of the microorganisms (E. Coli).

**Pharmacokinetics**

- **Absorption**
  - Chloramphenicol is available orally in two forms: the inactive pro-drug and the active drug. Chloramphenicol palmitate (prodrug) is hydrolyzed in duodenum and then absorbed.
  - Chloramphenicol succinate is meant for IM or IV injection.

- **Distribution**
  - 50% is protein bound.
  - Distribute in body fluids- reaches therapeutic concentration in Cerebrospinal fluid (60%).

- **Metabolism**
  - It is mainly metabolized in the liver by glucuronidation. Its t1/2 is 4 hours
  - Enzyme inducer decrease its half life.

- **Excretion**
  - Excreted by GF and TS.
  - 90% as metabolite and 10% in active form. In cirrhosis, and neonate its metabolism is decreased.

**ADRs:**

1. hematological toxicity
   1) Idiosyncratic reaction (dose independent) – aplastic anemia; leucopenia, thrombocytopenia and aplasia of marrow – genetic predisposition (1:30,000). If aplasia is complete it is fatal and there is high suspetible of sharp myeloblastic ) increase in WBC) leukemia in patients that become healthy.
   2) A second dose related hematological most known and common to determine-suppression of bone marrow reversibly with concentration> 25 microgram/ml-characterized by anemia, leucopenia and thromobocytopenia.

2. Hypersensitivity reactions-skin rashes, fever, angioedema may occur.

3. Toxic and irritable effects:
   1) Chloramphenicol (CRP) fatal toxicities can occur in neonate particularly in immature children. This illness called “gray baby syndrome- stops feeding, occurrence of
vomiting, hypotonia, hypothermia, abdominal distention, irregular respiration, ashen gray cyanosis develops. May lead to CV collapse and death.

2) Due to failure of conjugation (lack of glucuronyl transferase in first 3-4 weeks of life, and decreased renal functions) - appears when plasma concentration exceeds 100 microgram/ml.

3) Optic neuitis – loss of ganglian cell symmetrically from retina & atropy to optic nerve.

**Interactions:**
- Irreversible inhibition of hepatic microsomal enzymes of cytochrome P 450 complex leads to increased half life of warfarin, phenytoin, tolbutamide, antiretroviral protease inhibitors and rifabutin.
- Enzyme inducers (rifampin, phenobarbitone) shorten the half life of chloramphenicol.

**Clinical uses**
- It should be never used for minor infections, or infections which could be treated by other drugs.

1) Typhoid fever: systemic salmonella infections – ciprofloxacin is now the drug of choice. Ceftriazone is one of the fastest acting bactericidal drug – good for multidrug resistant strains.

2) Bacterial meningitis: ceftriazone of 3rd generat^n cefalosporins & qciprofloxacin of fluoroquinolones are the drugs of best preference for the therapy & prevention of disease. i) it can act synergistically with ampicillin for H. influenzae. However excellent results have been obtained with ceftriaxone, cefotaxime, ceftizoxime. ii) An alternative medicine for meningitis due to N. meningitides. Strepto pneumonia in patients allergic to penicillin.

3) Anaerobic infection – brain abscess – effective against most anaerobes including B. fragilllis. It is used together with penicillin for brain abscess. Metronidazole and penicillin is also used.

4) Intraocular infection – endophthalmitis.

5) Topical use in conjunctivitis, and external ear infections.
6) Second choice drug in: a) Rickettsial infections: Tetracyclines are preferred, it may be used in
- Patients sensitized to tetracyclines
- Patients with reduced kidney working
- In babies, < 8 yrs of ages
- B) Brucellosis: in patient where tetracyclines are contraindicated.
- Chloramphenicol is also used in the treatment of eyes and it is broad category drug to all types of micro-organism so it can be used in epidemic of some contagious diseases.

**Antimicrobials**

- Antibiotics are the agents that are generated from the micro-organisms and their dilute solution of antimetabolites inhibit the growth of bacteria or kill the microbes.
- e.g. penicillin, streptomycin, etc.
- Antimicrobial agent includes antibiotics as well as synthetic antimicrobial agent includes antibiotics as well as synthetic antimicrobial compounds – quinilones, sulfonamides.

**Classification:**

1. **According to spectrum of activity:**
   a) **Broad spectrum** have wider limits of biological-activities including both G-negative and gram positive organisms e.g. tetracyclines, chloramphenical, 3rd generation cephalosporins.
   b) **Narrow spectrum** has limited antimicrobial activity, e.g., penicillin G, streptomycin, erythromycin, nafcillin etc.

2. **According to chemical structure:**
   a) Sulfonamides and related drugs – sulfadiazine, dapsone, PAS, sulfadoxine, sulfamethoxazole, sufisoxazole, sulfasalazaline, sulfapyridine, sulfamerazine.
   b) Diaminopyrimidines – trimethoprim, pyremethamine.
   c) Quinolones – Nalidixic acid, norfloxacin, ciprofloxacin, ofloxacin, sparfloxacin.
   d) β-lactam antibiotics – penecillins, cephalosporins, monobatams, carbapenams.
e) Tetracyclines – oxytetracycline, doxycycline, minocycline, demeclocycline.

f) Nitrobenzene derivatives - Chloramphenicol.

g) Aminoglycosides – streptomycin, gentamicin, neomycin, amikacin, kanamycin

h) Macrolides – erythromycin, azithromycin, roxithromycin, clarithromycin

i) Polypeptides – polymyxin B, bacitracin.

j) Glycopeptides – vancomycin

k) Oxazolidinone – Linezolid

l) Nitrofuran derivatives - nitrofurantoin, furazolidone.

m) Nitroimidazoles – metronidazole, tinidazole.

n) Nicotinic acid derivatives – INH, Pyrazinamide, ethionamide.

o) Polyene antibiotics – nystatin, amphotericin B.


q) Others – rifampin, clindamycin, lincomycin, ethambutol, etc.

3. According to type of action:

a) Primarily bacteriostatic, e.g., sulfonamides, tetracyclines, erythromycin, chloramphenicol, ethambutol.

b) Primarily bactericidal – penicillin, cephalosporins, aminoglycosides, vancomycin, quinolines, isoniazid (INH), rifampin, nalidixic acid.

4. According to mechanism of action:

a) Agents that inhibit the synthesis bacterial cell wall e.g. penicillin, cephalosporin, cycloserine, vancomycin, bacitracin, imidazole group of antifungal agents like ketoconazole. etc.

b) Agents that affect cell membrane permeability leading to leakage of intracellular compounds, e.g. polymyxin, polyene antifungal agents like nystatin, amphotericin B.

c) Agents that affects ribosomes, inhibit protein synthesis in a reversible way (bacteriostatics), e.g. chloramphenicol, clindamycin and erythromycin affects 50 S ribosomes whereas tetracyclines affects 30S ribosomes.

d) Agents that affect nucleic acid metabolism:

a. Those that affect DNA dependent RNA polymerase, e.g. rifampin.
b. Those that inhibit DNA supercoiling and DNA synthesis (inhibit DNA gyrase), e.g. quinolines.

e) Agents that bind 30S ribosomal subunit, after protein synthesis in such a way that leads to cell death (bactericidal), e.g. aminoglycosides.

f) Antimetabolites block specific metabolic steps that are essential to microorganisms e.g. trimethoprim and sulfonamides.

g) Nucleic acid analogues – agents bind to viral enzymes that are essential for DNA synthesis and thus stop their replication. e.g. acyclovir........

h) 

5. Type of organism against which primarily active:

a) Antibacterial – penicillins, aminoglycosides, erythromycin, etc.

b) Antifungal – griseofulvin, amphotericin B, ketoconazole, etc.

c) Antiviral – acyclovir, amantidine, zidovudine, etc.

d) Antiprotozoal – chloroquine, pyremethamine, metronidazole, etc.

e) Anthelmintics – mebendazole, DEC, etc.

6. According to their source:

a) Fungi – penicillin, cefalosporins, griseofulvin.

b) Bacteria – polymyxin B, aztreonam, colistin, bacitracin.

c) Actinomycetes – aminoglycosides, tetracyclines, macrolides, chloramphenicol.
1.2 problem on hand:

**Bacterial resistance to antimicrobial agents:**

Acquired resistance.

Microbes generate chemical substance that catalyst of organic nature that inactivate drug moiety responsible for action, e.g.:

- Staphylococcus resistance to penicillins G (Benzylic pencillin) produce a $\beta$-lactam ring inactivating beta lactamase, which destroy medicament.
- Gram negative bacteria resistant to aminoglycosides produce adenylating, phosphorylate, or acetylate enzyme that inactivate the medicament.
- Gram-negative bacteria may be resistant to chloramphenicol if they produce a chloramphenicol acetyltransferase.

**Microbes alter their penetration to medicament: e.g.**

- Tetracycline antibiotics assimilate in micro-organism though not in resistance microbes (altered porin structure)
- Amino-glycosides have problem in penetration to streptococcal bacteria due to interfere with active transport system. It can be overcome by using penicillin in combination.

**Microbes can create a structural change by alteration in cell wall by mutation e.g.**

- Microbes resistance to glycosides of aminosugars have be obtained by microsomal mutation to 30 S ribosomal protein biosynthesis alteration in the structure of micro-organism.
- Microbes resistant to erythromycin developed altered structure of 50 S ribosomal unit that is required for protein biosynthesis and make change to 23 S ribosomal RNA

**Microbes that develop alternate path to the metabolic process to inactivate the medicaments e.g.:**
- Few sulpha drugs do not use PABA for the biosynthesis of folic acid for genetic materials like mammals it directly utilize folic acid from the diet to synthesize genetic material.

**Table 1: Mechanism of action of antimicrobial agents**

<table>
<thead>
<tr>
<th>Mechanism of action</th>
<th>Antimicrobial agents</th>
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<tbody>
<tr>
<td>Bacterial cell wall syntheses inhibitors</td>
<td>Cephalosporins, Penicillin, Imopenem meropenam, aztreonam, vancomycins</td>
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<tr>
<td>Bacteria Protein Biosynthesis Inhibitors</td>
<td>Macrolides, Chloramphenicol, aminoglycosides, tetracyclines, streptogramin, linezolid,</td>
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<tr>
<td>Nucleic acid synthesis Inhibitors</td>
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<tr>
<td>Folic acid syntheses Inhibitors</td>
<td>Sulf drugs, trimethoprim &amp; pyremethamine</td>
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<tr>
<td>Disruption of cell membrane function</td>
<td>Azoles and antifungal polyene antibiotics</td>
</tr>
</tbody>
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**OBJECTIVE OF RESEARCH WORK**

1. To develop & provide a process for preparing key intermediate of cephalosporin
antibiotics, and the use of the intermediate in the process of cephalosporin antibiotics.

2. To provide high purity and more yield of cephalosporin antibiotics by providing simple, cost-effective method for preparation.

3. To make a process which is less time consuming for preparation of cephalosporin antibiotics.

1.3 Scope of Research Work
The scope of research work is to semi synthesize the cephalosporin antibiotics from different types of cefalosporins obtained from fungal species after fermentation. Cephalosporins are obtained from cephalosporium fungus species by fermentation in the industry on large scale. The media is prepared according to requirement of fungal growth that can optimize the yield of the antibiotics. The fungal species is kept on the optimum media and provide the essential requirements to increase the amount of antibiotics. It is under general observation of the pharmacists. The drug is then collected in the large tank and then purified from the tank and recrystalize.

In the present research the focus is given on third generation cephalosporins because these are most widely used antibiotics at present in the emergency for the treatment of complicated disease such as typhoid, meningities, septicemia and other severe infections. In the present investigation there are four drugs (cefprozil, cefpodoxime proxetil, cefotaxime sodium, cefetamet sodium) have been selected for the process development. The process of third generation cephalosporins are very lengthy and costly. In the present work it is try to reduce time and cost and increase the yield of the cephalosporins.

The methods are developed on the basis of optimuized conditions and other catalysts that can increase the yield of third generation cephalosporins. There are number of cephalosporins that can be used to develop the process and can increase the yield and reduce the time. The latest technology and latest & sophisticated instruments are used to increase the yield of the products. Old process and procedures are very tedious, slow, costly and time consuming as compared to newers which are fast, cheap, quick, sensitive and latest by technology.

The drug cefprozil is first generation cephalosporin and cefotaxime sodium, cefpodoxime proxetil and cefetamet sodium are third generation cephalosporin antibiotics. These are specially active against gram negative bacteria and also to gram positive bacteria. These drugs also penetrate to ceberspinal fluid to treat CNS disorders.

**Beta lactams**
<table>
<thead>
<tr>
<th>Penicillins</th>
<th>Cephalosporins</th>
</tr>
</thead>
<tbody>
<tr>
<td>First generation</td>
<td>Second generation</td>
</tr>
<tr>
<td>Narrow spectrum</td>
<td>Wider spectrum</td>
</tr>
<tr>
<td>Third generation</td>
<td>Fourth generation</td>
</tr>
<tr>
<td>β-lactamase Resistant</td>
<td></td>
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</tbody>
</table>

Methicillin  
Nafacillin  
Oxacilline  
Cloxacillin  
Flucloxacinlin  
β-lactamase Susceptible  
Penicillin G  
Penicillin V  

<table>
<thead>
<tr>
<th>Broad Spectrum</th>
<th>Antipseudomonal</th>
<th>other β-lactams</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>Carboxypenicillin</td>
<td>Ticarcillin</td>
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<tr>
<td>Amoxicillin</td>
<td></td>
<td></td>
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<tr>
<td>Bacampicillin</td>
<td>Uredioopenicillin</td>
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<table>
<thead>
<tr>
<th>Monobactam</th>
<th>Carbepenems</th>
<th>β-lactamase inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aztreonam</td>
<td>Impenem</td>
<td>Clavulanic acid</td>
</tr>
<tr>
<td>Piperacillin</td>
<td>Meropenem</td>
<td>Sulbactum</td>
</tr>
</tbody>
</table>

### Inhibitors of cell wall synthesis

**Penicillins:**
- These are antibiotics having β-lactam ring.
- Work by binding to penicillin proteins (PBPs) located on bacterial cell membrane, and inhibit transpeptidase enzymes which stops transfer of peptide & its reaction, that provide attachments in the last step or final step of cell wall synthesis.
- Attachment to PBP also carried out to release enzymes of autolysin types.
- In presence of β-lactam antibiotics cell wall deficient forms are produced and lead to bacterial lysis.
- Gm +ve cell wall is entirely made up of peptidoglycans, while Gm-ve cell wall is having alternating layers of lipoprotein and peptidoglycan.

**Classification:**
1) Natural penicillin – penicillin G  
2) Semisynthetic penicillins:
Penicillins:-

Penicillinase resistant Parenteral Penicillin

Penicillinase sensitive (Broad-Spectrum) Parenteral Penicillin

Beta-Lactamase Inhibitors:-

Penicillin G:
- Benzyl penicillin.
- Narrow spectrum primarily for Gm +ve bacteria

Spectrum:
- Cocci – streptococci, pneumonia, staphylococci, Gm –ve – Neisseria gonorrhoea & meningitidis. (R)
- Bacilli – Gm +ve – B. anthracis, C. diphtheriae, clostridia, listeria, spirochetes (treponema),
- Actinomyces – israelli

Resistance:
- Produce penicillinase(β-lactamase) – staphylococcus aureus
- Include structural change in PBPs – MRSA, Pn R pneumococci
- Change in porin structure – pseudomonas.
Pharmacokinetics:
- Acid labile, destroyed by gastric acid.
- Sodium Penicillin G Intra Muscular
- Widely distributed, penetration in CSF is poor.
- In presence of inflammation – adequate amount reaches the CSF.
- Renal excretion – active tubular secretion – blocked by probenecid.

Preparation and Dose:
- Sodium Penicillin G – crystalline Pn – 0.5-5 MU im/iv 6-12 hourly.
- Repository salts of Pn G in plasma. Procaine penicillin – 0.5-1 MU in 12-24 hrly.
  Fortified procaines Penicillin G – 3 lac U procaine penicilline + 1 lac U sodium pencillin G, benzathine penicillin G – 0.6-2.4 MU, every 2-4 weeks. Long acting, penicillin G.

Adverse effects: (most nontoxic antibiotics)
- May cause local irritation and direct toxicity – pain at IM site. Thrombophlebitis at injection site.
- Accidental iv injection of procaine penicillin – hallucinations and convulsions.
- Hypersensitivity – 1-10% incidence. Most common drug causing drug allergy.
- Manifested as fever, rash, itching and urticaria. May cause anaphylaxis in severe cases.
- Partial cross sensitivity exists
- H/O allergy must be elicited and intradermal test should be done before its use.
- Also very toxic if used topically – banned topically.
- Jarisch – hexheimer reaction – in secondary syphilis. Due to sudden release of spirochetal lytic products, 12-72 hrs.
- Does not recur and aspirin and sedation suffice.

Uses:
1) Streptococcal infections: pharyngitis, OM, RF, SABE.
2) Pneumococcal infections: Lobar pneumonia and meningitis.
3) Meningococcal infections: Rifampin is used for prophylaxis of MM.
4) Gonorrhea: unreliable due to resistance. Fluoroquinolones and ceftriaxone is used
5) Syphilis: Treponema Pallidum still sensitive to penicillin G and is the drug of choice (DOC). 2-4 MU 1-3 weekly doses for 4 weeks.
6) Diphtheria: procaine penicillin 1-2 MU im + antitoxin therapy.
7) Tetanus and Gas gangrene:

8) Drug of choice for anthrax, actinomyces, trench mouth, rat bite fever, and listeria and pasturella infections.

9) Prophylaxis in
   - Rheumatic fever – benzathine penicilline 1-2 Mu every 4 weeks till 18 years of age or 5 years after an attack, whichever more
   - Gonorrhea or syphilis
   - Bacterial endocarditis – dental extractions, endoscopies, catheterization, etc.
   - Agranylocytosis patients
   - Surgical infections – wound infections.

**Semisynthetic Penicillins:**
   - Better orally efficacy,
   - Some resistance to penicillinase.
   - Broad spectrum
   - β-lactamase inhibitors – not antibiotics augment activity of penicillin against β-lactamase producing organisms.

**Penicillin V:**
   - Acid stable – used orally.
   - Used for streptococcus pharyngitis, sinusitis, otitis media, RF, etc.
   - 250-500 mg 6 hourly.

**Penicillinase resistant penicillins:**
   - Additional side chains protect inner β-lactam ring by penicillinase.
   - Only used for penicillinase producing staphylococcus
   - Not resistant to Gm-ve β-lactamase.

**Methicillin:**
   - Penicillinase resistance, not acid resistance – given IV.
   - MRSA developed rapidly.
   - DOC – vancomycin, linezolid and ciprofloxacin.
   - ADR – hematuria, albuminiuria and interstitial nephritis.

**Cloxacillin:**
   - Active against penicillinase producing staphylococcus aureus, but not against MRSA.
- Can used orally 6 hourly.

**Extended Spectrum penicillin:**
- Broader spectrum of activity, not resistance to penicillinase.

**Aminopenicillins: (ampicillin, amoxicillin, bacampicillin)**

**Ampicillin:**
- All penicillin sensitive organisms + many Gm –ve – H. influenza, E. coli, proteus, salmonella, shigella.
- More active against – streptococcal viridans and enterococci, equally active against – pneumo, gonorrhea, and meningococci.
- Penicillinase producing staph are not affected.

**Pharmacokinetic:**
- Not degraded by gastric acid, food interferes with absorption.
- 0.5-2gm oral/iv/im. Every 6 hours.
- 250-500 mg caps.

**Adverse effects**
- Alteration of bacterial flora in gut – diarrheas.
- Hypersensitivity.
- May cause failure of conception with OCP because of interference with enterohepatic cycling.

**Uses:**
1) UTI – rapid resistance, fluoroquinolones and cotrimoxazole is used now.
2) RTI – bronchitis, sinusitis, otitis media.
3) Meningitis- usually combined with 3rd generation cephalosporin/chloramphenicol
4) Gonorrhea – drug of choice 3.5 gm ampicillin + 1 gm probenecid single dose
5) Typhoid fever – R
6) Bacillary dysentery – quinolones now.
7) Cholecystitis – because attains high concentration in bile.
8) SABE
9) Septicemia.

**Bacampicillin:**
- Prodrug to ampicillin,
- Better tissue penetration, high plasma concentration.
- Does not markedly interfere with GI flora.
- 400-800 mg BD

**Amoxicillin:**
- Similar to ampicillin except
- This shows better oral absorption & no interference with food.
- acute diarrhea is less
- Less active against shegella and H. influenza.
- Used for typhoid, bronchitis, UTI, SABE and gonorrhea.
- 0.25 – 1 g TDS oral.

**Carboxypenicillin: (Carbenicillin):**
- Active against Peudomonas aeruginosa and proteus.
- Penicillin G and aminopenicillin does not act on these.
- Neither penicillinase resistance nor acid resistance
- Only used for serious pseudomonas or proteus infections – burns, UTI, specticemias.

**Ticarcillin:** more potent than carbecillin.

**Ureidopenicillin: (Piperacillin)**
- More active than carbecillin.
- Has antipseudomonal activity
- Also active against kleibesella.
- Main use of this drug in neutropenia or immunocomperomised patient with Gm +Ve disorders & burn cases.
- 100-150 mg /kg/day.

**β-lactamase Inhibitors: (Clavulinic acid)**
- Obtained from clavuliferus, has β-lactam ring but no antibacterial activity.
- Inhibits all β-lactamase except cephalosporinase.
- It is a progressive or suicide inhibitor – binding with β-lactamase is reversible initially and becomes covalent later, gets inactivated after binding to the enzyme.
- Also inhibits β-lactamase of Gm-ve bacilli.

**Pharmacokinetics:** rapid orall absorption, combined with amoxicillin. (Co-amoxiclav)

**Uses:**
- Addition of CA to mox, reestablishes its activity against - β-lactamase producing staph aureus – but not MRSA, also against H. influenza, proteus, E.coli, klebsella, salmonella, shigella and B. fraglis.
- Co-Amoxiclav is indicated for:
- Skin and soft tissue infections, intraabdominal and gynec sepsis, UTI, RTI and bialary infection.
- Gonorrhea – single dose
- Augmentin 250 mg mox + 125 ng clavulanic acid tab.

**Sulbactum:**
- Also a progressive or suicidal inhibitor.
- Less potent than clavulanic acid.
- Given parenterally.
- Used for
  - PPNG gonorrhea
  - Mixed aerobic, anerobic infections.
  - Sulbain – ampicillin 1 gm + sulbactum 0.5 gm per vial.
- May cause pain and thrombophlebitis of injected vein.

**Tazobactam:**
- Also β-lactamase inhibitor, combined with piperacillin.

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**Cephalosporins**

Beta lactams

- Penicillins
  - Narrow spectrum
  - β-lactamase Resistant
- Cephalosporins
  - First generation
  - Second generation
  - Wider spectrum
  - Third generation
  - Antipseudomonal
  - fourth generation
  - other β-lactams
  - Broad Spectrum
Oxacilline           Ampicillin                  Carboxypenicillin  
Cloxacillin          Amoxicillin                   Ticarcellin  
Flucloxacillin       Bacampicillin                **Urediopenicillin**
**β-lactamase Susceptible**         Azlocillin  
Penicillin G         Piperacillin

Penicillin V       **Monobactam**  **Carbepenems** **β-lactamase inhibitors**
                    Aztreonam                     Impenem                  Meropenem               Clavulanic acid  
                                      Sulbactum

These are similar to penicillin in pharmacologically and chemically. Also have a beta lactam ring and do inhibit bacterial cell wall synthesis. These are classified chronologically, spectrum varies with members of different groups.

### Table 2 Classification of beta lactam antibiotics with spectrum of activity & Route

<table>
<thead>
<tr>
<th>Generation</th>
<th>Spectrum</th>
<th>Parenteral</th>
<th>Oral</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>Staphy (Except MRSA)</td>
<td>Cefazoline</td>
<td>Cephalaxin</td>
</tr>
<tr>
<td></td>
<td>Strepto (not enterococci), E.coli, Proteus, Klebsella</td>
<td>Cefalothin</td>
<td>Cephradine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cefdroxil</td>
</tr>
<tr>
<td>Second</td>
<td>As 1st generation plus Haemophilus (<strong>β-lactamase producers</strong>)</td>
<td>Cefamandole</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cefuroxime</td>
<td></td>
</tr>
<tr>
<td>2nd</td>
<td>(Cephmycenes) As above + anaerobes(Bacteriosides)</td>
<td>Cefoxitin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cefotetan</td>
<td></td>
</tr>
<tr>
<td>Third</td>
<td>As 2nd generation plus most Gm-ve bacilli (except Pseudo), Gm-ve Cocci, Nesseriae, Morresilla</td>
<td>Cefoxatime (antipeneum)</td>
<td>Cefpodoxime</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ceftiazone (antipeneum)</td>
<td>Cefixime</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cefaperazone</td>
<td></td>
</tr>
<tr>
<td>3rd/fourth</td>
<td>As above + Peudomonas</td>
<td>Ceftazidime</td>
<td></td>
</tr>
</tbody>
</table>
1\textsuperscript{st} Generation Cefalosporins

The first generation includes cephalexin and cefprozil orally. These antibiotics are mainly effective against gram positive cocci. In emergency parenteral cephalosporins e.g. cefazoline, cepharadine and cefalothine are used. These antibiotics are also effective some gram negative bacteria such as klebsilla pneumonia, Escherichia coli, pseudomonas aeruginosa. These antibiotics also show resistance to beta lactamase that destroy the beta lactam ring and inactivate the antibiotics.

2\textsuperscript{nd} Generation cephalosporins

Second generation cefalosporins are more active against gram negative bacterica as compared to gram positive. The drug includes are cefclor, cefmandole, cefurixome and cefotan. Some second generation cefalosporins do not enter in cerebrospinal fluid as cefotan used in bacteroides virgulis and cefclor used in the treatment of H. influenza & moraxella catarrhalis.

3\textsuperscript{rd} Generation cephalosporins

Third generation cefalosporins are specially effective against gram negative cocci and gram negative rods as well as gram positive bacteria. The drug cefexime is used orally while cefpodoxime, cefotaxime, ceftriaxone, cefetamet, cefoperazone. These antibiotics have wider spectrum of activity and enters the brain (not cefoperazone) to treat the CNS disorders such as meningitis and sepsis. Ceftriazone choice of drug in meningitis and complicated typhoid in emergency cases and have a longer duration of action for better activity. Ceftizoxime is used in bacteroid fraglis treatments.

4\textsuperscript{th} Generation Cefalosporins
These are the latest cefalosproins & resistance to all types of beta lactmase enzymes. These show wider spectrum of activity with gram negative cocci & rods and gram positive cocci & rods – cefepime (IV) is the drug at this time used as fourth generation cephalosporin antibiotics into the market and the drug cefepime has broad spectrum of activity to treat different disorders.

These drugs shown above are cefapirin and cefclor. The drug cefapirin is first generation oral and parenteral antibiotics that can be given to hospitalized person. Thes drug cefapirin is important due to its both form drug can be started as parenteral and when patient is relieved from the hospital it can be given as oral tablet or capsule form so the patient can take itself not need of doctor or nursing staff. The drug cefclor is second generation oral antibiotic that is very useful to gram negative cocci and anerobic bacteria.

\[
\text{Cefapirin} \quad \text{Cefclor}
\]

The diagram shown below are cefuroxime, cefprozil and cefcapene which are also very important to treat the various types of infections. The drug cefuroxime is second generation parenteral cephalosporin antibiotics and useful to treat gram negative as well gram positive bacteria. The drug has quick on set of action and absorb rapidly after
intramuscular and intravenous injection. Cefprozil is similar to cefuroxime in first generation cephalosporins and more useful in gram negative bacterial infections. The third generation cefalosporins such as ceftriaxone, cefotaxime, cefetamet, cefepime, cefexime are the utmost widely used in intensive care units, emergency, and top most severe diseases because these drug have a broad spectrum of activity with many dangerous bacteria. These drugs also penetrate to cerebrospinal fluid and can treat the severe disorders of the central nervous systems.

![Cefuroxime, Cefprozil, Cefcapene](image)

**Figure 2:** Examples of cephalosporin drugs from structurally different classes

**Pharmacokinetics:**
- Cefalosporins are administered parenterally and orally.
- Cefalosporins plasma protein binding vary from drug to drug for example cephalexin binds 10 to 15 percent to plasma protein binding while cefazolin binds 60% to plasma protein binding to various tissues.
- Hydrophilic penicillin and cephalosporin do not enter to the brain and are ineffective in treatment while third generation cephalosporin and cefuroxime are lipophilic and easily absorbed from the central nervous system.
- Almost cefalosporins and penicillins are excreted by kidney through active glomerular filtration and tubular secretion. Ceftriazone and cefoperazone are excreted in the bile.
- The excretion of penicillin and cefalosporins are interfered by probenecid and increase the concentration of these drugs.
- Ceftriazone has longer half life of 5 to 7 hrs.
- 1\textsuperscript{st} and 2\textsuperscript{nd} generation except cefuroxime don’t reach CSF.
- 3\textsuperscript{rd} and 4\textsuperscript{th} generation including cefuroxime enter BBB.

1) **Cephalexin:**
   - Oral 1\textsuperscript{st} generation.
   - Less active against penicillase producing staphylococcus aureus and H. influenza.
   - Less PPB and high concentration in bile.
   - Can be combined with probenecid – Prolong duration of action.
   - 0.25-1 gm 6-8 hourly.

2) **Cefadroxil:**
   - Oral 1\textsuperscript{st} generation
   - More sustained action at site of infection.
   - 12 hourly dosing despite short half life.
   - Spectrum similar to cephalexin.
   - 0.5 – 1 gm BD.
   - Droxyl.

3) **Cefuroxime:**
   - It is effective against Gram negative bacteria and resistant to beta lactmase.
   - Parenteral 2\textsuperscript{nd} generation, cefuroxime axetil – oral.
   - Highly active against PPNG and ampicillin resistant H. influenza.
- Attains high level in CSF.
- Used in meningitis, pneumo and H. influenza meningitis and single dose treatment for PPNG gonorrhoea.
- 0.75-1.5 gm im/iv 8 hourly.
- 250-500 mg BD cef axetil – ceftum.

4) Cefotaxime:
- prototype 3rd generation cephalosporin – parenteral.
- It is effective against Aerobic Gm –ve and some GM +ve bacilli.
- It is not effective against anaerobes, staphylococcus and pseudomonas.
- Can cross BBB.
- Used for Gm –ve meningitis, HAI, and infections in immunity compromised host
- 1-2 gm im/iv, 6-12 hrly.

5) Ceftriaxone:
- longer duration of action
- wide spectrum – resistant cases of bacterial meningitis, typhoid, complicated UTI, septicemias.
- May cause hypotrombinemia and bleeding.

6) Ceftazidine:
- Antipseudomonal cephalosporin
- Febrile neutropenia, hematological malignancies, burns, etc.
- 0.5 -2 gm im/iv 8 hourly.

7) Cefixime:
- Orally active 3rd generation.
- Active against entrobactriaceae, H. influenza, streptococcal pyogenes, streptococcal pneumonia, resistance to many β lactamase.
- Not active against staphylococcuse and pseudomonas.
- Used for respiratory, biliary and urinary infections.
- 200 -400 mg BD.

8) Cefepime:
- 4th generation parenteral.
- Highly resistant to beta lactamases.
- Reserved only for severe R cases of hospital acquired pneumonia, febrile neutropenia, bacteremia, septicemia.
- 1-2 gm iv 8-12 hrly.

**Drugs adverse effect (ADR)**
- Hyper sensitivity rxns – the maximum occurrence, 2% incidence.
  - Ana-phylaxis, bronchospasm, urticarias, mucopapular skin-rashes.
  - Cross reactivity to acute penicillin allergy.
- Nephrotoxicity – cephaloridine – withdrawan.
- Pain on IM injection, thrombophlebitis on i.v. administration.
- Superinfections, neutropenia and thrombocytopenia – rare.
- Diarrhea – oral cephalosporins, cefoperazone, ceftriazone.
- Ceftriazone and cefperazone may cause
  - Emesis due to intake of alcohol
  - Disorders of blood, increase heart rate and reddening of face.

**Uses**
1) If patient shows allergic reaction to pencillin can be treated with cefalosporins.
2) Ear deafness and URTI can be treated with (especially by Gm-ve): cefotaxime, cefuroxime axetil and ceftriazone.
3) Septicemia caused by gram negative bacterial microbes (Pseudomonas auruginosa): A penicillin (e.g. ticarcillin or piperacillin) + glycosides of amino sugar or cefalosporins and amino-glycosides.
4) Third generation oral cefexime and second generation cefuroxime parenteral are useful in urinary tract infections.
5) Ceftazidime is used prophalaxis in surgery & operation of appendix due to anerobic bowel syndrome. Gynecological & obstetrical, orthopodic and urological, etc. are caused by staphyllococcus aureus & staphy epidermidis and treated with the drug cephalozline.
7) Gonococcal infections: ceftiazone
8) Multidrug R typhoid – alternative to FQs.

9) Infections by odd organisms and R HIAs, 3rd – 4th Generation.

10) Prophylaxis and treatment of neutropenic patients.

**Monobactams:**
- Effective only against aerobic gram-negative organisms: enteric bacilli and H. influenza at very low concentrations.
- Resistant to gram negative & beta lactmases.
- Have no activity against Gram-positive cocci or anaerobes.
- Chief indications are – HIA originating from Urinary, biliary, GI and female genital tract.
- Lacks cross sensitivity with other beta lactams.
- 0.5-2 gm im or iv 6-12 hrly.

**Carbapenems: (Imipenem, Meropenem)**
- have the broadest bacterial coverage of the β-lactam antibiotics.
- These are used against most infections with gram positive, gram negative enteronacteriaceae, Peudomonas auruginosa, listeria and anaerobic bacteria – closteridia and bacteria fragilis.
- Only carbepenam class of β-lactam antibiotics exhibits concentration-dependent killing-maximal activity occurs at 4-5 times the minimum inhibitory concentration (MIC) of the organism
- Of all β-lactam agents, only the carbapenams have postantibiotic effect.
- Is inactivated by an enzyme present on the renal brush border, dehydropeptidase I
- Cilatatin is dehydropeptidase inhibitor administered along with imipenem to prevent subtherapeutic levels of the antibiotic in urine.
- 0.5 gm iv 6 hrly –serious HIAs, in neutropenic, AIDS and cancer patients.
- May precipitate seizures at high doses in susceptible patients.

**Vancomycin:**
- It is glycopeptide.
- Antibacterial activity: Gram-positive cocci especially MRSA (synergism with gentamicin or tobramycin)
- Staphylococcus epidermidis, streptococcal pyogenes, streptococcal pneumoniae, streptococcal viridans.
- For streptococcal faecalis (not bactericidal but exerts synergism with gentamycin or streptomycin)
- Other organisms susceptible are Corynebacterium, Actinomyces, nesseria & clostridium.

**Drugs mechanism action (MOA)**
- The drug inhibits biosynthesis of cell wall by attaching to terminal dipeptide Dextro-aladextro-alasequence of peptidoglycan units and preventing its release from the carrier so that assembly and cross linking does not take place. It is bactericidal to dividing microorganisms.

**Mechanism of Resistance:**
- VRSA and VRE develop due to structural modification in terminal dipeptide target.

**ADME**
- Poor absorption after oral administration given IV.
- Crosses CSF if meninges are inflamed.
- Up to 90% is excreted by glomerular filtration, dosages adjustment is required in renal failure.
- Its half life is 6 hours

**Adverse effects:**
- Hypersensitivity reactions.
- Phlebitis and pain at site of injection.
- A shock like state (red neck or red man syndrome, due to flushing) may develop during rapid IV infusion, due to release of histamine.
- Ototoxicity – it is significant adverse reaction – worsened by simultaneous administration of aminoglycosides and high ceiling diruretics.
- It may produce nephrotixicity, hence, should not be used with other nephrotoxic drugs (aminoglycosides)

**Therapeutic uses:** (only to treat serious infections particularly)
- Infection due to MRSA- empyemas, endo-carditis, pneumonia osteimyelitis & absceses of soft tissue & in serious staphylococcus disorders in allergic patients to penicillin & cefalosporins.
- Localized disorder of shunt or dissiminated staph. Diseases.
- Endocarditis due to streptococcal Faecalis, it is administered along with gentamicin.
- Orally – antibiotiv associated colitis due to Clostridium difficlle and Staphylococcus aureus. 125-500 mg 6 hourly.
- To treat meningitis due to penicillin resistant Streptococcal pneumonia – used with ceftriazone/cefotaxime/rifampin
- Systemically 500 mg 6 hourly infused iv slowly.