General consideration

Chemotherapy
- Chemotherapy is the treatment of infectious diseases or malignancy with drugs that destroy microorganisms or cancer cells preferentially with minimal damage to host tissues.
- The infection may be due to bacteria, virus, fungi, protozoa or helminths.

Antibiotics
- Antibiotics are chemical substances obtained from microorganisms that kill or suppress growth of other microorganisms at a very low concentration.

Bactericidal agents
- They kill or destroy microorganisms, e.g. penicillins, cephalosporins, aminoglycosides, etc.

Bacteriostatic agents
- They inhibit the growth and multiplication of microorganisms, e.g. sulphonamides, tetracyclines, chloramphenicol, erythromycin, etc.
- At high concentration, some of the ‘static’ drugs may produce ‘cidal’ effect; for example, chloramphenicol is a bacteriostatic drug, but it may be bactericidal against Haemophilus influenzae, Neisseria meningitidis and Streptococcus pneumoniae.

Antimicrobial agents
- Antimicrobial agents (AMAs) are synthetic as well as naturally obtained drugs that act against micro-organisms.

Minimum inhibitory concentration
- Minimum inhibitory concentration (MIC) is the minimum concentration of an antimicrobial agent that prevents visible growth of a microorganism.
Resistance to Antimicrobial Agents

Resistance is defined as the unresponsiveness of a microorganism to an antimicrobial agent (AMA).

The resistance may be natural or acquired.

- **The natural resistance** is genetically determined, e.g. normally, gram-negative bacilli are not affected by penicillin G.

- In acquired resistance, microbes that initially respond to an AMA later develop resistance to the same AMA by mutation or gene transfer, e.g. gonococcal resistance to penicillins.

The transfer of genes for drug resistance occurs by the following mechanisms

**Transduction**

- There is transfer of DNA carrying a gene for resistance from one bacterium to another through bacteriophage
- e.g. resistance of strains of Staphylococcus aureus to antibiotics is mediated via transduction.

**Transformation**

- The resistance carrying genetic material that is released into the environment by resistant bacteria is taken up by other sensitive bacteria,
- e.g. penicillin G resistance in pneumococci.

**Conjugation**

- Conjugation is the transfer of genetic material carrying resistance between bacteria by direct contact through sex pilus
- e.g. Escherichia coli resistance to streptomycin.

Mechanism of development of resistance to antimicrobial agents

The important mechanisms are:

1. **Production of inactivating enzymes:**
   - For example, staphylococci, gonococci, E. coli, etc. produce β-lactamases that can destroy some of the penicillins and cephalosporins.
2. An efflux pump mechanism
   - It is a mechanism that prevents the accumulation of the drug in the microorganism
   - e.g. resistance of gram-positive and gram-negative bacteria to tetracyclines, chloramphenicol, macrolides, etc.

3. Alteration of the binding site
   - For example, change in penicillin-binding proteins (PBPs) in case of certain pneumococci with decreased affinity for penicillins.

4. Absence of metabolic pathway
   - For example, sulphonamide-resistant bacteria can utilize preformed folic acid without the need for the usual metabolic steps.

Cross-resistance
   - Organisms that develop resistance to an antimicrobial agent may also show resistance to other chemically related AMAs.
   - The cross-resistance among AMAs could either be one-way or two-way.

Among tetracyclines and sulphonamides is usually ‘two-way’.
Tetracycline------ Doxycycline (tetracyclines)
Sulphadiazine ------- Sulphadoxine (sulphonamides)

The ‘one-way’ resistance is seen between neomycin and streptomycin.
   - Neomycin-resistant organisms are resistant to streptomycin but streptomycin-resistant organisms may be sensitive to neomycin.

Prevention of development of resistance to antimicrobial agents
It is done by:
1. Selecting right antimicrobial agent.
2. Giving right dose of the AMA for proper duration.
3. Proper combination of AMAs,
   - e.g. in tuberculosis (TB), multidrug therapy (MDT) is used to prevent development of resistance to antitubercular drugs by mycobacteria.
Superinfection (Suprainfection)

It is defined as the appearance of a new infection due to antimicrobial therapy.

- The causative organism of superinfection should be different from that of the primary disease.
- Most of the AMAs—especially broad-spectrum antibiotics (tetracyclines, chloramphenicol), clindamycin, ampicillin, etc.—alter the normal bacterial flora.
- As a result of which the host-defence mechanism is impaired.
- Hence, pathogenic organisms invade the host, multiply and produce superinfection.
- The causative organism may be fungi or bacteria.

Pathogenesis

The sites involved in superinfection are those body cavities that have direct communication with the exterior, i.e. rectum, oral cavity, vagina, lower urinary tract, upper respiratory tract.
SULPHONAMIDES

The sulphonamides were the first effective antimicrobial agents used in the treatment of bacterial infections in man.

- They are derivatives of sulphanilamide (para-aminobenzene sulphonamide) and are synthetic compounds

Mechanism of action

- Para-aminobenzoic acid (PABA) is a precursor of folic acid, which is essential for the growth and multiplication of many bacteria.
- Sulphonamides, being structurally similar to PABA, competitively inhibit folate synthetase enzyme and prevent the formation of folic acid thereby producing bacteriostatic effect.
- Sulphonamides are not effective in the presence of pus as it is rich in PABA, purines and thymidine.
- Mammalian cells do not synthesize folic acid, but utilize folic acid present in the diet, hence are unaffected by sulphonamides.
Bacterial resistance to sulphonamides
Most of the bacteria have developed resistance to sulphonamides. It could be due to:
1. **Decreased affinity** of folate synthetase for the drug.
2. **Efflux of the drug** by bacteria.
3. **Development of alternate metabolic pathway** for folate synthesis.

Pharmacokinetics
- All systemic acting sulphonamides are well absorbed from the gut.
- They are **bound to plasma proteins, particularly albumin**.
- Sulphonamides are distributed in almost all the tissues of the body including CSF.
- They **cross placental barrier and reach foetal circulation**;
- They are **metabolized in liver mainly by acetylation**.

Adverse effects
1. The **acetylated products of sulphonamides** are poorly soluble in acidic urine and may cause **crystalluria, haematuria** or even **obstruction to urinary tract**.
   - This may be avoided by **taking plenty of water and alkalinizing the urine**.
2. **Hypersensitivity reactions** include skin rashes, itching, drug fever and exfoliative dermatitis.
   - **Stevens–Johnson syndrome** is the most severe type of hypersensitivity reaction
3. In patients with **G6PD deficiency**, sulphonamides may cause acute haemolytic anaemia.
4. Rarely cause **hepatitis and suppression of bone marrow**.
5. Use of sulphonamides in neonates, especially in **premature babies**, may cause **displacement of bilirubin from plasma proteins**.
   - The free bilirubin can cross the blood–brain barrier and get deposited in the basal ganglia resulting in **kernicterus**.

**Drug interactions**
Sulphonamides **potentiate the effect** of
- **phenytoin**,  
- **methotrexate**,  
- **oral anticoagulants** and  
- **oral hypoglycaemic agents (sulfonylureas)**
by inhibiting their metabolism and displacing them from plasma protein binding sites.

**Therapeutic uses**
**Not used alone**
They are used in combination with other antimicrobial agents.

1. **Sulphadoxine and pyrimethamine** can be used in combination with **artesunate** in the treatment of **mefloquine-resistant Plasmodium falciparum malaria**.

2. Sodium salt of sulphacetamide is used topically for the treatment of **ophthalmic infections**.

3. **Silver sulphadiazine and mafenide** are used **topically for preventing infection of burn wound**.
   - Silver sulphadiazine is not effective in the presence of pus and tissue fluid.
COTRIMOXAZOLE

Cotrimoxazole is a World Health Organization (WHO)-approved fixed-dose combination of sulphamethoxazole and trimethoprim in the ratio of 5:1.

Cotrimoxazole (sulphamethoxazole and trimethoprim) produces sequential blockade, i.e., two drugs interfere with two successive steps in the same metabolic pathway; hence, their combination produces supra-additive effect.

Sulphamethoxazole inhibits folate synthetase whereas trimethoprim inhibits folate reductase enzyme.

The pharmacokinetic properties of these two drugs match each other almost closely; hence they are selected for combination. Optimum synergistic effect is seen at a concentration ratio of 20:1 (sulphamethoxazole to trimethoprim) in blood and tissues.

The advantages of this combination are:
1. Individually, both are bacteriostatic but the combination has a cidal effect.
2. Chances of development of bacterial resistance are also greatly reduced.

Pharmacokinetics

Cotrimoxazole is well absorbed after oral administration and is also available for parenteral use.
Adverse effects

- Cotrimoxazole is well tolerated in most patients. **Most of the adverse effects are same as that of sulphonamides.**
- The common adverse effects are skin rashes and gastrointestinal (GI) disturbances.
- **Exfoliative dermatitis**, erythema multiforme and Stevens–Johnson syndrome are rare.
- The GI symptoms include **nausea, vomiting, glossitis and stomatitis.**
- **Megaloblastic anaemia** due to folate deficiency may occur.
- **Bone marrow suppression** with leukopaenia, neutropaenia and thrombocytopaenia occurs rarely.
- **Cotrimoxazole is contraindicated in pregnancy.**

Therapeutic uses

1. **Urinary tract infection:**
   - Cotrimoxazole is effective for the treatment of acute, chronic and recurrent lower urinary tract infections (UTIs) due to gram-negative organisms such as E. coli, Proteus.
   - The usual dose is **800 mg sulphamethoxazole plus 160 mg of trimethoprim daily for 3 days.**

2. **Bacterial respiratory tract infections**
   - Cotrimoxazole is effective for acute and chronic bronchitis due to S. pneumoniae and H. influenzae.
   - It is also useful for acute maxillary sinusitis and otitis media.

3. **Bacterial diarrhoeas**
   - Cotrimoxazole may be used for GI infections due to shigella, E. coli and Salmonella spp. **But fluoroquinolones are the preferred agents.**

4. **Typhoid fever**
   - Cotrimoxazole may also be effective.

5. **P. jiroveci infections**
   - Cotrimoxazole is useful for the treatment as well as prophylaxis of P. jiroveci pneumonia.

7. **Chancroid-** Cotrimoxazole is effective.
Fluoroquinolones

Classification

➢ First generation FQs
  o Norfloxacin
  o Ofloxacin
  o Pefloxacin
  o Ciprofloxacin

Note: Remember as NOP Cipro

➢ Second generation FQs
  o Levofloxacin
  o Lomefloxacin
  o Moxifloxacin
  o Gemifloxacin
  o Sparfloxacin

Note: Remember as Levo Lome Moxi Gem Spark

Mechanism of Action

➢ The FQs enter the bacterium by passive diffusion through porins in the outer membrane
➢ Once inside the cell, they inhibit replication of bacterial DNA by interfering with the action of DNA gyrase (Topoisomerase II) in gram negative bacteria and Topoisomerase IV in gram positive bacteria
➢ DNA gyrase is the enzyme that change the configuration of DNA by a ‘nicking, formation of negative supercoils and resealing DNA’ mechanism.
➢ Binding of quinolone to the enzyme and inhibits the resealing step, and can cause cell death by inducing the cleavage of the DNA
➢ It is more occurring in gram Negative bacteria

The second site blocked by FQs– Topoisomerase IV–
• It is required by bacteria for cell division.
• It is helpful for separation of daughter DNA strands after replication
It is more occurring in gram positive bacteria

Uses
- **Urinary tract infections:**
  - High cure rates, even in complicated cases or those with indwelling catheters or prostatitis
  - Chronic Pseudomonas infections respond less completely

- **Gonorrhoea:**
  - Single dose of Ciprofloxacin - 500 mg was nearly 100% curative in PPNG (PPNG: Penicillinase Producing Neisseria Gonorrhoeae)
  - as well as non-PPNG infections, but the cure rates have declined due to emergence of resistance and it is no longer a first line drug

- **Chanchroid:**
  - Ciprofloxacin 500 mg BD for 3 days – second line alternative drug to Ceftriaxone/ Azithromycin

- **Bacterial gastroenteritis:**
  - Use is reserved for severe cases of diarrhoea due to EPEC, Shigella, Salmonella, Campylobacter jejuni infections
  - Can reduce stool volume in cholera
Pharmacology

- **Typhoid:**
  - One of the 1st choice drugs in typhoid fever
  - Ciprofloxacin 750 mg BD for 10 days is recommended or 200 mg i.v 12 hourly till oral therapy can be instituted
  - The advantages of Ciprofloxacin are:
    - quick defervescence: fever usually subsides in 4-5 days
    - Early abetment of symptoms, low incidence of complications and relapse
    - Prevention of carrier state due to cidal action
  - Ciprofloxacin can be used to treat typhoid carrier (750 mg BD for 4-8 weeks). This has been found to achieve 92% eradication rate

- **Bone, soft tissue, gynaecological and wound infections:**
  - High cure rate have been obtained in osteomyelitis and joint infections but prolonged treatment with high doses (6-8 weeks with 750 md BD) is required

- **Respiratory infections:**
  - Not a primary drug because Streptococci and Pneumococci have low susceptibility
  - However, RT infections due to Mycoplasma, Legionella, H.influenzae respond

- **Tuberculosis:**
  - One of the drugs in multidrug regimens used for resistant TB
  - Also useful in atypical mycobacterial infections

- **Gram negative septicaemias:**
  - Parenteral Ciprofloxacin may be combined with 3rd generation cephalosporin or an aminoglycoside

- **Prophylaxis:**
  - Prophylactic use for infections in neutropenic or cancer patients and other susceptible patients

- **Conjunctivitis:**
- Topical therapy is effective

- **Meningitis:**
  - Though penetration in CSF is not very good, it has been successfully used in Gram negative bacterial meningitis especially that occurring in immunocompromised patients or those with CSF shunts

- ** Anthrax **
  - Ciprofloxacin is used for treatment and prophylaxis of anthrax

**Adverse effects**

Fluoroquinolones have good safety record: side effects occur in ~10% patients, but are generally mild, withdrawal needed only in 1.5%

- **GIT:**
  - Nausea, vomiting, anorexia, bad taste
  - Does not affect gut anaerobes – hence diarrhoea is infrequent

- **CNS:**
  - Headache, dizziness, restlessness, anxiety, insomnia, impairment of concentration and dexterity
  - Tremor and seizures are rare: occur at high doses or when predisposing factors are present

- **Skin/hypersensitivity:**
  - Rash, pruritus, photosensitivity, urticaria, swelling of lips etc.
  - Serious cutaneous reactions are rare

- **Tendinitis and tendon rupture:**
  - Risk of tendon damage is higher in patients above 60 yrs age and in those receiving corticosteroids
  - FQs should be stopped at the first sign of tendinitis

**Contraindicated during pregnancy**
<table>
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<th>Fluoroquinolone</th>
<th>Routes of Administration</th>
<th>Oral Bioavailability</th>
<th>Antibacterial Spectrum and Uses</th>
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</table>
| Norfloxacin     | Oral, topical (eye)      | 30–40%               | Mainly against gram-negative organisms, but not *Pseudomonas*  
U ses: It is used mainly in the treatment of urinary tract infections and bacterial diarrhoeas | Inhibits metabolism of theophylline and warfarin |
| Ciprofloxacin   | Oral, i.v. infusion, topical (eye) | 70%                 | (See pp. 306 and 308)          | Inhibits metabolism of theophylline and warfarin |
| Pefloxacin      | Oral, i.v. infusion      | Almost 100%          | Similar to ciprofloxacin, also effective against *Mycobacterium leprae*   
U ses: Typhoid, gonococcal infection, UTI, bacterial diarrhoeas and leprosy | Inhibits metabolism of theophylline and warfarin |
| Ofloxacin       | Oral, i.v. infusion, topical (eye) | Almost 100%          | Effective against gram-negative organisms, gram-positive organisms and some anaerobes; has activity against *Chlamydia, Mycoplasma*  
and mycobacteria  
U ses: Tuberculosis (TB), leprosy | Inhibits the metabolism of theophylline, but to a lesser extent |
| Moxifloxacin    | Oral, i.v. infusion, topical (eye) | 90%                 | More active against gram-positive bacteria including *S. pneumoniae, M. tuberculosis* and some anaerobes (*Bacteroides fragilis*)  
U ses: Community-acquired pneumonia, chronic bronchitis and sinusitis. It is useful in odontogenic infection as it has activity against gram-positive and some of the anaerobes. | — |
| Levofloxacin    | Oral, i.v., topical (eye drops) | 100%                | Increased activity against *S. pneumoniae*; effective against gram-negative bacteria and anaerobes.  
U ses: Community-acquired pneumonia, sinusitis, chronic bronchitis, etc. | — |
Beta Lactam Antibiotics

It consisting of penicillins, cephalosporins, carbapenems, Monobactams.

Que. Penicillins

Classification

1. Natural penicillins
   - Penicillin G
   - Procaine penicillin G
   - Benzathine Penicillin

2. Acid-resistant alternative to penicillin G
   - Phenoxyethyl penicillin (Penicillin V).

3. Penicillinase-resistant penicillins
   - Methicillin, Cloxacillin.

4. Extended spectrum penicillins
   (a) Aminopenicillins: Ampicillin, Bacampicillin, Amoxicillin.
   (b) Carboxypenicillins: Carbenicillin, Ticarcillin.
   (c) Ureidopenicillins: Piperacillin, Mezlocillin.

5. β-lactamase inhibitors
   - Clavulanic acid
   - Sulbactam
   - Tazobactam

Mechanism of action of penicillin

- The cell wall completely surrounds the cytoplasmic membrane, maintains cell shape and integrity and prevents cell lysis from high osmotic pressure.
- The cell wall is composed of a complex cross-linked polymer of polysaccharides and polypeptides, peptidoglycan (murein, mucopeptide).
- The polysaccharide contains alternating amino sugars, N-acetylglucosamine, and N-acetylmuramic acid.
- A five-amino-acid peptide is linked to the N-acetylmuramic acid sugar.
- This peptide terminates in D-alanine-D-alanine.
Penicillin-binding protein (PBP, an enzyme) removes the terminal alanine in the process of forming a cross-link with a nearby peptide.

- Cross-links give the cell wall its structural rigidity.
- Beta lectams are structural analogue of D-alanine.
- Beta-lactam antibiotics covalently bind to the active site of PBPs.
- This inhibits the transpeptidation reaction, stopping peptidoglycan synthesis, and the cell dies.
- Beta-lactams kill bacterial cells only when they are actively growing and synthesizing cell wall.

Bactericidal activity of penicillin is more against Gram positive.
Uses
Penicillin G is the drug of choice for infections caused by organisms susceptible to it

1. Streptococcal infections
   - pharyngitis, otitis media, scarlet fever, rheumatic fever respond to ordinary doses of PnG given for 7–10 days.
   - For subacute bacterial endocarditis (SABE) high doses along with gentamicin given for 2–6 weeks is needed.

2. Pneumococcal infections
   - PnG is not used now because many strains have become highly penicillin resistant.
   - It is drug of choice if organism is sensitive.

3. Meningococcal infections
   - It is treated with high doses intravenous injection.

4. Gonorrhoea
   - PnG not used due to spread of resistant strains.

5. Syphilis
   - PnG is the drug of choice.
   - Early and latent syphilis is treated either with daily injection of 1.2 MU of procaine penicillin for 10 days or
   - 1–3 weekly doses of 2.4 MU benzathine penicillin.

6. Diphtheria
   - Antitoxin therapy given primarily
   - Procaine penicillin 1–2 MU daily for 10 days has adjuvant value and prevents carrier state.

7. Tetanus and gas gangrene
   - Antitoxin used primarily
   - PnG 6–12 MU/day is used to kill the causative organism and has adjuvant value.

8. Penicillin G is the drug of choice for rare infections like
   - anthrax,
   - actinomycosis
   - Listeria infection

9. Prophylactic uses
(a) Rheumatic fever:
  ➢ Benzathine penicillin 1.2 MU every 4 weeks till 18 years of age or 5 years after an attack, whichever is more.

(b) Bacterial endocarditis:

(c) Agranulocytosis patients:
  ➢ It is used to prevent respiratory and other acute infections.

Adverse effects
Penicillin G is one of the most nontoxic antibiotics; up to 100 MU (60 g) has been injected in a day without any direct toxicity.
  ➢ Pain at i.m. injection site,
  ➢ nausea on oral ingestion
  ➢ thrombophlebitis
  ➢ mental confusion, muscular twitchings, convulsions and coma, when very large doses are used.

Hypersensitivity
  ➢ PnG is the most common drug causing allergy
  ➢ rash, itching, urticaria and fever. Wheezing, angioneurotic edema
  ➢ Anaphylaxis

Superinfections
  ➢ These are rare with PnG because of its narrow spectrum.
  ➢ GIT, respiratory and cutaneous microflora does undergo changes.

Acid-stable Penicillins- penicillin V
  ➢ It is The oral form of penicillins
  ➢ Indicated only in minor infections because of their relatively poor bioavailability, weaker antimicrobial activity
  ➢ Need for dosing many times
  ➢ Narrow antimicrobial spectrum.

Penicillinase-resistant penicillins
Methicillin, oxacillin, cloxacillin and dicloxacillin)
  ➢ They are the drugs of first choice for treating infections of the penicillase-producing bacteria.
  ➢ But penicillin-susceptible strains of streptococci and pneumococci are also susceptible
  ➢ Enterococci and methicillin-resistant strains of staphylococci are resistant to these penicillins
Aminopenicillin
This group of penicillin has an amino substitution in the side chain

Ampicillin
- It is active against all organisms sensitive to PnG;
- In addition, many gram-negative bacilli, e.g. H. influenzae, E. coli, Proteus, Salmonella and Shigella are inhibited.
- However, due to widespread use, many of these have developed resistance
- Ampicillin is more active than PnG for Strep. viridans and enterococci;
- Ampicillin is not degraded by gastric acid;
- Food interferes with absorption

Uses
1. Urinary tract infections:
   - Ampicillin has been the drug of choice for most acute infections
   - Fluoroquinolones are now more commonly used

2. Respiratory tract infections
   - Bronchitis, sinusitis, otitis media, etc. are usually treated with ampicillin.

3. Meningitis:
   - Ampicillin has been a first line drug.

4. Gonorrhoea:
   - It is one of the first line drugs for oral treatment

5. Typhoid fever:
   - Due to emergence of resistance it is now rarely used.

6. Bacillary dysentery
7. Cholecystitis:
   - Ampicillin is a good drug because high concentrations are attained in bile.

9. Subacute bacterial endocarditis:
10. Septicaemias and mixed infections:
    - Injected ampicillin may be combined with gentamicin or one of the third generation cephalosporins.

ADR
- Diarrhoea is more frequent
- Rashes
Amoxicillin

It is a close congener of ampicillin similar to it in all respects except:

- Oral absorption is better; food does not interfere with absorption; higher and more sustained blood levels are produced.
- Incidence of diarrhoea is lower.
- It is less active against Shigella and H. influenzae.
- Many physicians now prefer it over ampicillin for bronchitis, urinary infections, SABE and gonorrhoea.

BETA-LACTAMASE INHIBITORS

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

Clavulanic acid

- It has a β-lactam ring but no antibacterial activity of its own.
- It inhibits a wide variety of β-lactamases
- It’s an example of suicide inhibition
- It is combined with Amoxicillin

Sulbactam

- It’s a semisynthetic beta lactmase inhibitor
- It is combined with Ampicillin
CEPHALOSPORINS

These are a group of **semisynthetic antibiotics** derived from ‘cephalosporin-C’

- It is obtained from a **fungus Cephalosporium**.
- They are **chemically related to penicillins**

Classification

**First generation cephalosporins**

*Parenteral*
- Cephalothin*
- Cefazolin

*Oral*
- Cephalexin
- Cephradine
- Cefadroxil

**Second generation cephalosporins**

*Parenteral*
- Cefuroxime
- Cefoxitin*

*Oral*
- Cefaclor
- Cefuroxime axetil

**Third generation cephalosporins**

*Parenteral*
- Cefotaxime
- Ceftizoxime
- Ceftriaxone
- Ceftazidime
- Cefoperazone

*Oral*
- Cefixime
- Cefpodoxime proxetil
- Cefdinir
- Ceftibuten
- Ceftamet pivoxil

**Fourth generation cephalosporins**

*Parenteral*
- Cefepime
- Cefpirome

MOA

- All cephalosporins are **bactericidal and have the same mechanism of action as penicillin**
- **inhibition of bacterial cell wall synthesis**.
- However, they bind to different proteins than those which bind penicillins.

**FIRST GENERATION CEPHALOSPORINS**
They have **high activity against gram-positive** but weaker against gram-negative bacteria.

**Cefazolin** This prototype first generation cephalosporin.

**Antibacterial Spectrum**

- It is active against most PnG sensitive organisms, i.e. *Streptococci, gonococci, meningococci, C. diphtheriae, H. influenzae, clostridia and Actinomyces*.
- Activity against Klebsiella and E. coli is relatively high

**Use**

- It is the preferred **parenteral first generation cephalosporin, especially for surgical prophylaxis**.

**Cephalexin**

- It is an **orally effective** first generation cephalosporin
- **Antibacterial spectrum is similar to cefazolin**, but less active against penicillinase producing Staphylococci and H. influenzae.
- **It is one of the most commonly used cephalosporins.**

**SECOND GENERATION CEPHALOSPORINS**

They are more active against **gram-negative organisms**

- Some drugs active against anaerobes, but none inhibits P. aeruginosa.
- Clinically, they have been largely replaced by the 3rd generation agents that are more active.

**Cefuroxime**

- It is resistant to **gram-negative β-lactamases**:
- It has high activity against organisms producing these enzymes including **PPNG and ampicillin-resistant H. influenzae**
- It has significant activity on **gram-positive cocci and certain anaerobes**.
- It is well tolerated by i.m. route and attains relatively higher CSF levels,
- It has been employed for **single dose i.m. therapy of gonorrhoea due to PPNG**.
THIRD GENERATION CEPHALOSPORINS

They are **highly effective against gram-negative Enterobacteriaceae**;
- some inhibit Pseudomonas as well.
- All are **highly resistant to β-lactamases** from gram-negative bacteria.
- They are **less active on gram-positive cocci and anaerobes**.

**Cefotaxime**
- It is the prototype of the third generation cephalosporins;
- It exerts potent action on **aerobic gram-negative as well as some gram positive bacteria**,;
- It is not active on anaerobes, Staph. aureus and Ps. aeruginosa.

**indications**
- Meningitis
- Life-threatening resistant hospital-acquired infections
- Septicaemias and
- Infections in **immunocompromised patients**.

**Ceftriaxone**
- Ceftriaxone has shown **high efficacy in a wide range of serious infections**
  **Active against**
  - bacterial meningitis
  - multiresistant typhoid fever
  - complicated urinary tract infections
  - abdominal sepsis and septicaemias.
  - gonorrhoea including PPNG
  - chancroid.
- Hypoprothrombinaemia and bleeding are specific adverse effects.
  Haemolysis is reported

**Ceftazidime**
- **Highly active against pseudomonas infection**
- Used in hematological malignancy and burn patients

**Cefoparazone**
- Stronger effect against pseudomonas
- Used in Biliary, respiratory, skin-soft tissue infection, meningitis and septicemia
Cefixime
- Orally active third generation cephalosporin
- Highly active against Enterobacteria, H.influenzae
- Used in dose of 200 to 400 mg BD for Biliary, Respiratory and urinary infection

Fourth generation cephalosporins
- Antibacterial spectrum is same as 3rd generation
- They are reserved drugs for hospital acquired resistant infections

Adverse effects
Cephalosporins are generally well tolerated, but are more toxic than penicillin.
1. Pain after i.m. injection
2. Diarrhoea
3. Hypersensitivity - Rashes
4. Nephrotoxicity
5. Bleeding
This is due to hypoprothrombinaemia caused by the same mechanism as warfarin
6. Neutropenia and thrombocytopenia are rare
7. disulfiram-like interaction with alcohol has been reported with cefoperazone.

Uses
Cephalosporins are now extensively used antibiotics.
Their indications are
1. As alternatives to PnG; particularly in allergic patient
2. Respiratory, urinary and soft tissue infections
3. Penicillinase producing staphylococcal infections
4. Septicaemias caused by gram-negative organisms
5. Surgical prophylaxis: the first generation cephalosporins are popular drugs.
6. Meningitis
For empirical therapy before bacterial diagnosis,
- i.v. cefotaxime/ceftriaxone is generally combined with ampicillin or vancomycin.
- Ceftazidime + gentamicin is the most effective therapy for Pseudomonas meningitis.
7. Gonorrhea
   - ceftriaxone is a first choice drug for single dose therapy of gonorrhea

8. Typhoid:
   - Currently, ceftriaxone and cefoperazone injected i.v. are the fastest acting
   - They are alternative to fluoroquinolones

9. Mixed aerobic-anaerobic infections
   - in cancer patients
   - those undergoing colorectal surgery,
   - obstetric complications

10. Hospital acquired infections
11. Prophylaxis and treatment
   - infections in neutropenic patients
   - ceftazidime or another third generation compound, alone or in combination with an aminoglycoside.

**MONOBACTAMS**

**Aztreonam**
It is a β-lactam antibiotic in which the other ring is missing (hence monobactam).
   - It inhibits gram-negative enteric bacilli, H. influenzae and Pseudomonas
   - It does not inhibit gram-positive cocci or faecal anaerobes.
   - Thus, it is a β-lactam antibiotic with a spectrum resembling aminoglycosides.
   - It is resistant to gram-negative β-lactamases.

**The main indication**
   - Hospital acquired infections originating from urinary, biliary, gastrointestinal and female genital tracts.
   - Rashes and rise in serum aminotransferases are adverse effects.
CARBAPENEMS

Imipenem
It is an extremely potent and broad-spectrum β-lactam antibiotic
Antibiotic spectrum
➢ gram positive cocci, Enterobacteriaceae, Ps. aeruginosa, Listeria
➢ anaerobes like Bact. fragilis and Cl. difficile.
It is resistant to most β-lactamases; inhibits penicillinase producing staphylococci and some MRSA.

➢ It is hydrolysed by the enzyme dehydropeptidase I located on the brush border of renal tubular cells.
➢ It is combined with cilastatin which is reversible inhibitor of dehydropeptidase I
➢ Imipenem-cilastatin has proved effective in a wide range of serious hospital acquired infections including those in neutropenic, cancer and AIDS patients.

Meropenem
➢ This newer carbapenem is not hydrolysed by renal peptidase; does not need to be protected by cilastatin.
➢ Meropenem is a reserve drug for the treatment of serious nosocomial infections like septicaemia, febrile neutropenia, intra abdominal and pelvic infections.

Faropenem
➢ Carbapenem β-lactam antibiotic that is orally active against many grampositive as well as gram-negative bacteria,
➢ It has been mainly used in respiratory, ENT and genitourinary infections.
TETRACYCLINES

These are a class of antibiotics having a nucleus of four cyclic rings.

Mechanism of action

The tetracyclines are bacteriostatic

- Tetracycline binds with 30S ribosomes
- So aminoacyl-t-RNA cannot attach to mRNA-ribosome complex
- peptipe chain fails to grow
- Protein synthesis is inhibited.

The sensitive organisms have an energy dependent active transport process.

- It concentrates tetracyclines intracellularly.
- In gram negative bacteria tetracyclines diffuse through porin channels also.
- The more lipid-soluble members (doxycycline, minocycline) enter by passive diffusion also
- This is partly responsible for their higher potency

Why host cells are not affected by tetracyclines?

- The carrier involved in active transport of tetracyclines is absent in the host cells.
- Protein synthesizing apparatus of host cells is less sensitive to tetracyclines.

These two factors are responsible for the selective toxicity of tetracyclines for the Microbes and not affecting host cells.

Antimicrobial spectrum

Tetracyclines inhibited practically all types of pathogenic microorganisms except fungi and viruses; hence the name ‘broad-spectrum antibiotic’.

- Gradually narrowed the field of their usefulness.

1. Cocci

- All gram-positive and gram-negative cocci were originally sensitive,
- Strep. pyogenes, Staph. aureus and enterococci have become resistant.
- now active against few N. gonorrhoeae and N. meningitidis.

2. Most gram-positive bacilli

- Clostridia, Listeria, Corynebacteria, B. anthracis are inhibited
  Mycobacteria not inhibited

3. Sensitive gram-negative bacilli
V. cholerae, Yersinia pestis, Helicobacter pylori, Brucella
Enterobacteriaceae are now largely resistant.

4. Spirochetes - T. pallidum and Borrelia are sensitive.
5. All rickettsiae and chlamydiae are sensitive.
6. Mycoplasma and Actinomycetes are moderately sensitive.
7. Entamoeba histolytica and Plasmodia are inhibited at high concentrations.

Resistance occurs due to...
- Tetracycline concentrating mechanism becomes less efficient
- The bacteria acquire capacity to pump it out.
- Another mechanism is plasmid mediated synthesis of a ‘protection’ protein which protects the ribosomal binding site from tetracycline.
- Nearly complete cross resistance is seen among different members of the tetracycline group.

Uses
1. Empirical therapy
- Tetracyclines are used when the nature and sensitivity of the infecting organism cannot be guessed.
- They may also be used for initial treatment of mixed infections.

2. Tetracyclines are the first choice drugs
(a) Venereal diseases:
• Chlamydial nonspecific urethritis/endocervicitis
• Lymphogranuloma venereum
(b) Atypical pneumonia: due to Mycoplasma
(c) Cholera
(d) Brucellosis
(e) Plague: Tetracyclines are highly effective in both bubonic and pneumonic plague.
(f) Relapsing fever: due to Borrelia recurrentis
(g) Rickettsial infections

3. Tetracyclines are second choice drugs:
- Tetanus
- Anthrax
- Gonorrhea
 Syphilis
 leptospirosis
 Chlamydia pneumoniae.

4. Other situations in which tetracyclines may be used are:
(a) Urinary tract infections
(b) Community-acquired pneumonia
(c) Amoebiasis
(d) As adjuvant to quinine or sulfadoxinepyrimethamine for chloroquine-resistant P. falciparum malaria
(e) Acne vulgaris:
(f) Chronic obstructive lung disease

Adverse effects
 Epigastric pain, nausea, vomiting and diarrhoea
 Liver damage - Fatty infiltration of liver
 Kidney damage - renal failure.
 Phototoxicity - A sunburn-like
 Chelating property - deposited in developing teeth and bone.
 **Antianabolic effect** - Tetracyclines reduce protein synthesis
 Increased intracranial pressure is noted in some infants.
 **Diabetes insipidus**
 **Vestibular toxicity** - ataxia, vertigo and nystagmus
 **Hypersensitivity** - Skin rashes, urticaria, glossitis
 **Superinfection** Tetracyclines are the **most common antibiotics responsible for superinfections**, because they cause marked suppression of the resident flora.
 Mouth, skin or vagina may be involved
 **intestinal superinfection by Candida albicans is most prominent**

The tetracycline should be discontinued at the first sign of superinfection and appropriate therapy instituted.

Precautions
Tetracyclines should not be **used during pregnancy, lactation and in children.**
 They should be **avoided in patients on diuretics**
 They should be used cautiously in **renal or hepatic insufficiency.**
 Do not mix injectable tetracyclines with penicillin—**inactivation occurs.**
CHLORAMPHENICOL

Mechanism of action
- It binds with 50 s ribosome
- It inhibit transfer of elongating peptide to newly attached aminoacyl t-rna
- It prevents formation of peptide bonds.
- Thus inhibiting protein synthesis in bacteria.
- At high doses, it can inhibit mammalian mitochondrial protein synthesis as well. Bone marrow is more susceptible.

Antimicrobial spectrum
It is a broad-spectrum antibiotic, active against nearly the same range of Organisms as tetracyclines.
Notable differences between these two are:
- Chloramphenicol was highly active against Salmonella
- It is more active than tetracyclines against H. influenza, B. pertussis, Klebsiella, N. meningitides
- It is less active against gram-positive cocci, spirochetes, certain Enterobacteriaceae

Uses
(a) Never use chloramphenicol for minor infections or those of undefined etiology.
(b) Do not use chloramphenicol for infections treatable by other safer antimicrobials.
(c) Avoid repeated courses
Indication are...
1. Enteric fever
2. Pyogenic meningitis
3. Anaerobic infections - wound infections, pelvic and brain abscesses
4. Intraocular infections - endophthalmitis
5. As second choice drug...
   - Brucellosis and rickettsial infections
   - Whooping cough.
6. Urinary tract infections
7. Topically In conjunctivitis
Adverse effects

 **Bone marrow depression**- aplastic anaemia, agranulocytosis, thrombocytopenia or pancytopenia.

 **Hypersensitivity reactions**- Rashes, fever, angioedema

 **Nausea, vomiting, diarrhoea, pain on injection.**

 **Superinfections**

 **Gray baby syndrome**
  - It occurred when **high doses were given prophylactically to neonates, especially premature.**
  - The baby stopped feeding, vomited, became hypotonic and hypothermic, abdomen distended, respiration became irregular
  - **Gray cyanosis develop** followed by **cardiovascular collapse and death.**
  - It occurs because of inability of the newborn to adequately metabolize and excrete chloramphenicol.
  - At higher concentration, **chloramphenicol blocks electron transport chain.**
**Aminoglycoside antibiotics**

- Obtained from Actinomycetes

  **Common properties**
  - Bactericidal antibiotics
  - Interfere with protein synthesis
  - Used to treat aerobic Gram –ve bacteria
  - Resemble each other in MOA, pharmacokinetic therapeutic and toxic properties
  - Relatively low margin of safety
  - Exhibit ototoxicity and nephrotoxicity

  **Classification**

  **Systemic**
  - Streptomycin
  - Gentamicin
  - Kanamycin
  - Amikacin
  - Sisomicin
  - Tobramycin

  **Topical**
  - Neomycin
  - Framycetin

  **Mechanism of action**
  - Initially they **penetrate bacterial cell wall**, to reach periplasmic space through **porin channels (passive diffusion)**
  - Further transport across cytoplasmic membrane takes place by **active transport by proton pump; an oxygen-dependent process**
  - Bind 30S ribosomal subunits and interfere the initiation complex
  - Induce **misreading of genetic code on mRNA**
  - Breakup of polysomes into monosomes
  - Aminoglycosides exhibit **concentration dependent killing**.
They also having significant Post-antibiotic effect.

**Mechanism of resistance**

- Synthesis of plasmid mediated bacterial transferase enzyme which inactivates aminoglycosides
- ↓ transport into bacterial cytosol
- **Deletion/alteration of receptor protein on 30 S ribosomal** unit by mutation: prevents attachment

**Antibacterial spectrum**

- **Primarily against Gm –ve aerobic bacilli**
  - Proteus, pseudomonas
  - E.Coli, enterobacter
  - Klebsiella
  - Shigella
- **Only few Gm +ve cocci:**
  - staph aureus, strepto viridans
- **Not effective against Gm +ve bacilli, Gm-ve cocci and anaerobes**

**Pharmacokinetics**

- **Highly polar basic drugs**: poor oral BA
- **Administered parenterally or applied locally**
- Poorly distributed and poorly protein bound
- Do not **undergo any significant metabolism**
- **Nearly all IV dose is excreted unchanged in urine**
- Dose adjustment is needed in renal insufficiency
Uses

- Gram –ve bacillary infection
  - Septicaemia, pelvic & abdominal sepsis
- Bacterial endocarditis – enterococcal, streptococcal or staphylococcal infection of heart valves
- Pneumonias, Tuberculosis
- Tularemia
- Plague, Brucellosis
- Topical – Neomycin, Framycetin.
- Infections of conjunctiva or external ear
- To sterilize the bowel of patients who receive immunosuppressive therapy, before surgery & in hepatic coma

Adr

Ototoxicity
- Impairment of VIII cranial nerve function
- Hearing loss and tinnitus - More with Neomycin, amikacin and kanamycin
- Vertigo, ataxia, loss of balance - More with Streptomycin, gentamycin
- Tobramycin has both types of toxicity
- Netilimycin claimed to have low ototoxicity

Nephrotoxicity
- Gentamicin, amikacin and tobramycin are more toxic than streptomycin
- Responsible for 10-15% of all renal failure cases
- Reversible if drug promptly discontinued
- ↓ GFR, ↑ sr creatinine
- ↓ clearance of antibiotic → ↑ ototoxicity
Neuromuscular blockade
• Cause N-M junction blockade by
  – Displacing Ca\(^{2+}\) from NM junction
  – By blocking post synaptic N\(_{\text{M}}\) receptors
  – Inhibiting Ach release from motor nerve
• Neomycin & streptomycin: more propensity
• Tobramycin least likely to produce it
• Myasthenic weakness ↑by these drugs

Precautions / Contraindications
• Pregnancy: foetal ototoxicity
• With other ototoxic drugs: furosemide, minocycline
• With nephrotoxic drugs: vancomycin ,cisplatin
• Elderly patients
• Those with kidney disease
• Cautious use of muscle relaxants
• Do not mix with any other drug in same syringe

Streptomycin
• Ribosomal resistance develops fast
• Limited usefulness as single agent
• Plague, tularemia and brucellosis
  – In combination with tetracycline
• SABE: due to Streptococcus Viridans & faecalis
  – With penicillin but gentamicin preferred
• Reserve first line drug for tuberculosis used only in combination

Gentamicin
• Obtained from Micromonospora purpurea
• Most commonly used aminoglycoside
  – More potent than Streptomycin
– Broad spectrum: pseudomonas, proteus, E.coli, klebsiella, enterobacter, serratia
– Low cost, reliability of use, long experience
– Acts synergistically with ampicillin, penicillin G, Ticarcillin, ceftriaxone, Vancomycin

• Ineffective against M.tuberculosis
• Relatively more nephrotoxic

Use
➢ restricted to serious Gm-ve bacillary infections
• Septicaemia, sepsis, fever in immunocompromised patients
  – Used with penicillins
• Pelvic infections: with metronidazole
• SABE: with Penicillin G or ampicillin or vancomycin
• Coliform infection: with ampicillin or ceftriaxone
• Pseudomonal infections: with ticarcillin
• Meningitis by Gm-ve bacilli: III generation cephalosporin alone or with gentamicin

Tobramycin
• Identical to gentamicin
• Used in pseudomonas and proteus infections
• Ototoxicty and nephrotoxicity probably lower

Amikacin
• Less toxic semisynthetic derivative of kanamycin
• Resistant to enzymes that inactivate gentamicin and tobramcyin
• Widest spectrum of activity
• Uses:
  – Same as gentamicin
  – Reserve drug for hospital acquired Gm-ve bacillary infections
  – Multidrug resistant TB along with other drugs
Neomycin

- wide spectrum active against Gm-ve bacilli and some gm+ve cocci
- Pseudomonas and strep.pyogenes not sensitive
- Too toxic for parenteral use, limited to topical use
- Topically used in skin, eye and external ear infections combined with bacitracin or polymyxin-B to widen antibacterial spectrum and to prevent emergence of resistant strains
- **Orally**
  - Preparation of bowel before surgery
  - **Hepatic coma**: Supresses ammonia forming coliforms prevents encephalopathy (Lactulose more preferred)
- Bladder irrigation along with polymyxin B

Framycetin

- Very similar to neomycin
- Too toxic for systemic administration
- Used topically on skin, eye ear
Macrolides

- The Macrolides are a group of closely related compounds characterized by a macrocyclic lactone ring to which deoxysugars are attached.

CLASSIFICATION

MACROLIDES
- ERYTHROMYCIN
- CLARITHROMYCIN
- AZITHROMYCIN
- ROXITHROMYCIN
- SPIRAMYCIN

MECHANISM OF ACTION

- Inhibits protein synthesis by reversibly binding to the 50S ribosomal subunit
- Suppression of RNA-dependent protein synthesis by inhibition of translocation of mRNA.
  - After peptide bond formation newly synthesized chain translocated to P site and make A site free for other T-rna
  - It is prevented and ribosome fails to move on mRNA
- Typically bacteriostatic activity and at high dose bactericidal activity.

SPECTRUM OF ANTIBACTERIAL ACTIVITY

Bactericidal at high concentrations against very susceptible organisms
- Macrolides are similar to Penicillins regarding their spectrum of activity.
- They are effective against Penicillin-resistant strains.

BACTERIAL RESISTANCE

- Methylation of a guanine residue on ribosomal RNA leads to lower affinity toward Macrolides
An active efflux system
Presence of a plasmid-associated Erythromycin esterase.
Clarithromycin and Azithromycin show cross-resistance with Erythromycin, Against Macrolide-resistant organisms.
Lack of cell wall permeability to Macrolides is the reason why G(-) bacteria are resistant to antibacterial effects of these agents.

THERAPEUTIC USES OF ERYTHROMYCIN
It is used to treat
1. The upper part of the respiratory tract infections
2. Soft tissue infections
3. Diphtheria
4. Tetanus
5. Syphilis
6. Urethritis caused by (MRSA, Ureaplasma Urealyticum)
7. Mycoplasma pneumonia caused pneumonia, Campylobacter jejuni -- Enteritis,
8. Chlamydia infections
   Trachomatis - (may result in Urethritis, epididymitis, cervicitis, pelvic inflammatory disease (PID) and other conditions. )
9. C. Pneumonia – causes respiratory illness (prolonged cough, bronchitis, and pneumonia as well as a sore throat, laryngitis, ear infections, and sinusitis)
10. Gonorrhoea caused by Nesseria gonorrhoea
11. Treatment and prophylaxis of ophthalmic infections and also neonatal conjunctivitis
12. To treat acne
13. Pelvic inflammatory disease due to susceptible organisms (e.g., Streptococcus Pneumoniae, Streptococcus pyogenes, Haemophilus influenzae, Chlamydia, Legionella, Mycoplasma, Nesseria gonorrhoeae, Treponema)

Pharmacology
ADVERSE EFFECTS

GASTROINTESTINAL EFFECTS:

✓ Anorexia, nausea, vomiting, and diarrhoea occasionally accompany oral administration.
✓ Gastrointestinal intolerance, which is due to a direct stimulation of gut motility, is the most common reason for discontinuing Erythromycin and substituting another antibiotic.

LIVER TOXICITY:

✓ Erythromycins, particularly the estolate, can produce acute cholestatic hepatitis (fever, jaundice, impaired liver function), probably as a hypersensitivity reaction.
✓ Most patients recover from this, but hepatitis reoccurs if the drug is re-administered.

❖ Macrolides get deposited in perilymph and causes ototoxicity and hearing impairment.
❖ Other allergic reactions include fever, eosinophilia, and rashes.
❖ Prolong QT WAVE

AZITHROMYCIN

✓ It has an extended spectrum compared to Erythromycin.
✓ It is acid stable, rapid oral absorption
✓ High tissue distribution and intracellular penetration
✓ High concentration attained in side macrophages and fibroblasts

Because of higher efficacy and better gastric tolerance it’s convenient for once daily dosing

It has a higher activity against

➢ Chlamydia trachomatis, Mycoplasma pneumoniae, Nesseria gonorrhoeae, toxoplasma gondii.
- **Campylobacter jejuni** (It is among the most common bacterial infections of humans, often a foodborne illness.)
- **H. Influenza** (Bacteremia, Meningitis, Epiglotittis, Cellulitis, Infectious arthritis).
- **Moraxella catarrhalis** (can cause infection of the respiratory system, middle ear, eye, central nervous system)

**Use**
- It is used for acute bacterial infection
- Single dose treatment for mild to moderate sinusitis
- **Chancroid** (STD; Caused by haemophilus ducreyi)
- **Chlamydia trachomatis**
- To treat non gonococcal infections (urethritis, cervicitis)
- **Donovanosis**
- **Pharyngitis, Tonsilitis, sinusitis, otitis media, bronchitis**
- **Streptococcal and staphylococcal skin and soft tissue infection**
- Prophylaxis and treatment of **MAC in Aids**
- **Typhoid, Toxoplasmosis, Malaria**

**ADVERSE REACTIONS:**
- Pseudomembranous colitis,
- Abdominal pain, Nausea/Vomiting,
- Rash
Classification of anti tubercular Drugs

Clinically the anti-TB drugs can be divided into:

**First line**: These drugs have **high antitubercular efficacy** as well as **low toxicity**; are used routinely.

**Second line**: These drugs have either low antitubercular efficacy or high toxicity or both; are used in special circumstances only.

**First line drugs**
1. Isoniazid (H)
2. Rifampin (R)
3. Pyrazinamide (Z)
4. Ethambutol (E)
5. Streptomycin (S)

**Second line drugs**
1. Thiacetazone (Tzn)
2. Paraaminosalicylic acid (PAS)
3. Ethionamide (Etm)
4. Cycloserine (Cys)
5. Kanamycin (Kmc)
6. Amikacin (Am)
7. Capreomycin (Cpr)

**Newer drugs**
1. Ciprofloxacin
2. Ofloxacin
3. Clarithromycin
4. Azithromycin
5. Rifabutin
Isoniazid (Isonicotinic acid hydrazide, H)

Isoniazid is the antitubercular drug

Mechanism of action of INH

- It can inhibit the synthesis of mycolic acids which are unique fatty acid component of mycobacterial cell wall.
- The sensitive mycobacteria concentrate INH
- Catalase peroxidase in bacteria convert INH into an active metabolite
- Active metabolite interacts with the inh A gene.
- A gene inh makes a fatty acid synthase enzyme
- This gene is inhibited so fatty acid synthesis is inhibited
- It is primarily tuberculocidal.
- Fast multiplying organisms are rapidly killed.
- It acts on extracellular as well as on intracellular TB
- It is equally active in acidic and alkaline medium.
- It is one of the cheapest antitubercular drugs.

Mechanism of INH resistance

- By mutation of the catalase-peroxidase gene So that the bacilli do not generate the active metabolite of INH.
- TB bacilli lose the active INH concentrating process.

- Combined with other drugs, INH has good resistance preventing action.
- No cross resistance with other antitubercular drugs occurs.

Pharmacokinetics

- INH is completely absorbed orally and penetrates all body tissues, tubercular cavities, placenta and meninges.
- It is extensively metabolized in liver metabolites are excreted in urine.

Interactions

- INH inhibits phenytoin, carbamazepine, diazepam and warfarin metabolism

Adverse effects

- INH is well tolerated by most patients.
- Peripheral neuritis and a variety of neurological manifestations (paresthesias, numbness, mental disturbances, rarely convulsions)
These are due to interference with utilization of pyridoxine and its increased excretion in urine.

Pyridoxine given prophylactically (10 mg/day) prevents the neurotoxicity.

INH neurotoxicity is treated by pyridoxine 100 mg/day.

- Hepatitis
- Rashes, fever, acne and arthralgia.
Rifampin (Rifampicin, R)

It is a semisynthetic derivative of rifamycin B obtained from *Streptomyces mediterranei*.

**MOA**
- repoB gene forms Rna polymerase
- rifampin inhibit RNA Polymerase
- So DNA dependent RNA synthesis is inhibited.
- Mammalian RNA polymerase does not bind rifampin.
- **Rifampin is bactericidal to M. tuberculosis** and many other gram-positive and gram-negative bacteria like *Staph. aureus, N. meningitidis, H. influenzae, E. coli, Klebsiella, Pseudomonas, Proteus and Legionella*.

- Against TB bacilli, it is as efficacious as INH and better than all other drugs.
- The bactericidal action covers all subpopulations of TB bacilli
- Acts best on **slowly or intermittently dividing ones, as well as on many atypical mycobacteria**.
- Both extra- and intracellular organisms are affected.
- It has good sterilizing and resistance preventing actions.

**Rifampin resistance is due to mutation in the repoB gene**
- Reducing RNA polymerase affinity for the drug.

**Pharmacokinetics**
- It is well absorbed orally, widely distributed in the body penetrates cavities, caseous masses, placenta and meninges.
- It is metabolized in liver
- It is excreted mainly in bile, some in urine also.

**Rifampin is a microsomal enzyme inducer**
- It increasing its own metabolism as well as that of many drugs including warfarin, oral contraceptives, corticosteroids, sulfonylureas, digitoxin, steroids, theophylline, metoprolol, fluconazole, ketoconazole, etc.

**Adverse effects**
- **Hepatitis**, development of jaundice
Pharmacology

- **Respiratory syndrome**: breathlessness, shock
- Purpura, haemolysis, shock and renal failure.
- ‘**Cutaneous syndrome**’: flushing, pruritus + rash,
- Redness and watering of eyes.
- **Flu syndrome** with chills, fever, headache, malaise and bone pain.
- ‘**Abdominal syndrome**’: nausea, vomiting, abdominal cramps with or without diarrhoea.
- **Urine and secretions may become orange-red— but this is harmless.**

**Other uses of rifampin**

1. Leprosy
2. Prophylaxis of Meningococcal and H. influenzae meningitis.
4. Combination of **doxycycline and rifampin** is the **first line therapy of brucellosis.**
Pyrazinamide (Z)

Chemically similar to INH.
Mechanism of antimycobacterial action of Z resembles INH;

- pncA gene which encodes for the enzyme generating the active metabolite of Z.
- Active metabolite of Z interacting with a fatty acid synthase encoding gene.
- Thus it inhibits mycolic acid synthesis

- It is weakly tuberculocidal
- More active in acidic medium.
- It is more lethal to intracellularly located bacilli and to those at sites showing an inflammatory response
- It is highly effective during the first 2 months of therapy when inflammatory changes are present.
- By killing the residual intracellular bacilli it has good ‘sterilizing’ activity.
- By its use TB regimens to be shortened and risk of relapse to be reduced.

Resistance to Z develops
- due to mutation in the pncA gene which encodes for the enzyme generating the active metabolite of Z.

- Pyrazinamide is absorbed orally, widely distributed, has good penetration in CSF
- Metabolized in liver and excreted in urine;

ADR
- Hepatotoxicity - It is contraindicated in patients with liver disease.
- Hyperuricaemia is common and is due to inhibition of uric acid secretion in kidney
- Gout can occur.
- Arthralgia, flushing, rashes, fever and loss of diabetes control.
Ethambutol (E)

Ethambutol is selectively tuberculostatic and clinically as active as S.

The mechanism of action of E is not fully understood

- It has been found to inhibit arabinosyl transferases involved in arabinogalactan synthesis
- It interfere with mycolic acid incorporation in mycobacterial cell wall.
- Fast multiplying bacilli are more susceptible
- Added to the triple drug regimen of RHZ
- It prevents development of resistance.

Resistance to E develops

- Due to alteration in the drug target gene.

It is distributed widely but penetrates meninges incompletely

- It is excreted in urine by glomerular filtration and tubular secretion
- Limited use in patients with renal disease.

ADR

- Patient acceptability of E is very good and side effects are few.
- Loss of visual acuity/colour vision due to optic neuritis
  young children may be unable to report early visual impairment, it should not be used below 6 years of age.
  - With early recognition and stoppage of therapy, visual toxicity is reversible.
  - nausea, rashes, fever, neurological changes
  - Hyperuricemia is due to interference with urate excretion.

It is a commonly used antitubercular drug.
Streptomycin (S) as Antitubercular Drug

- It was the first clinically useful antitubercular drug.
- It is tuberculocidal, but less effective than INH or rifampin.
- It acts only on extracellular bacilli (because of poor penetration into cells).
- It penetrates tubercular cavities, but does not cross to the CSF, and has poor action in acidic medium.

Resistance developed rapidly when streptomycin was used alone in tuberculosis

- In case of S-resistant infection, it must be stopped at the earliest because of chances of S-dependence—the infection flourishing when the drug is continued.
- Popularity of S in the treatment of tuberculosis had declined due to need for i.m. injections and because of ototoxicity and nephrotoxicity like side effects.

Tuberculosis Therapy

<table>
<thead>
<tr>
<th>Category</th>
<th>Intensive phase</th>
<th>Continuation phase</th>
<th>Duration (months)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>I New patient</td>
<td>2ª HRZE daily</td>
<td>4ª HR daily</td>
<td>6ª</td>
<td>Optimal</td>
</tr>
<tr>
<td></td>
<td>2 HRZE daily</td>
<td>4 HR thrice weekly</td>
<td>6</td>
<td>Acceptable if DOT ensured</td>
</tr>
<tr>
<td></td>
<td>2 HRZE thrice weekly</td>
<td>4 HR thrice weekly</td>
<td>6</td>
<td>Acceptable if DOT ensured and no HIV coinfection or its risk</td>
</tr>
<tr>
<td>II Previously treated patients pending DST result</td>
<td>2 HRZES daily + 1 HRZE daily</td>
<td>5 HRE daily</td>
<td>8</td>
<td>For patient with low/medium risk of MDR-TB (failure, default, etc.)</td>
</tr>
<tr>
<td>Empirical* (standardized) MDR-regimen</td>
<td>Empirical (standardized) MDR-regimen</td>
<td>18–24 or till DST result</td>
<td>For patient with high risk of MDR-TB (failure, 2nd default contact of MDR-TB, etc.)</td>
<td></td>
</tr>
</tbody>
</table>

DST—Drug sensitivity testing; DOT—Directly observed therapy
H, R, Z, E, S—Standard codes for isoniazid, rifampin, pyrazinamide, ethambutol and streptomycin, respectively.
$—The numerals indicate duration of a phase/total duration in months.
*—Empirical (Standardized) MDR regimen is country specific depending upon local data and situation (Indian regimen on p.776)
Antileprotic Drugs

CLASSIFICATION
1. **Sulfone** - Dapsone (DDS)
2. **Phenazine derivative** - Clofazimine
3. **Antitubercular drugs** - Rifampin, Ethionamide
4. **Other antibiotics** - Ofloxacin, Minocycline, Clarithromycin

**Que. Dapsone (DDS)**

It is diamino diphenyl sulfone (DDS)
- It is the simplest, oldest, cheapest, most active and most commonly used.

**Activity and mechanism**

Dapsone is chemically related to sulfonamides and has the same mechanism of action
- inhibition of PABA incorporation into folic acid
- Folic acid synthesis is inhibited

- It is leprostatic at low concentrations
- At higher concentrations **arrests the growth of many other bacteria sensitive to sulfonamides.**

**Adverse effects**

Dapsone is generally well tolerated at doses 100 mg/day or less.

**Mild haemolytic anaemia** is common.
- **Patients with G-6-PD deficiency** are more susceptible; doses > 50 mg/day produce haemolysis in them.

**Gastric intolerance**
- nausea and anorexia are frequent in the beginning, decrease later.

**Other side effects are**
- **methaemoglobinaemia, headache, paresthesias, mental symptoms and drug fever.**
- **Cutaneous reactions** - allergic rashes, hypermelanosis, phototoxicity and exfoliative dermatitis.
- Hepatitis and agranulocytosis
- Lepra reaction and sulfone syndrome
Contraindications

- Dapsone **should not be used in patients with severe anaemia with Hb < 7g%**,
- **G-6-PD deficiency** and in those showing hypersensitivity reactions.

Other use

- In combination with pyrimethamine, **dapsone can be used for chloroquine-resistant malaria.**

**Clofazimine (Clo)**

*It is a dye with leprostatic and anti-inflammatory properties;*

**MOA**

- It acts by **interfering with template function of DNA** in *M. leprae.*

When used alone, resistance to clofazimine develops in 1–3 years.

- Dapsone-resistant *M. leprae* respond to clofazimine, but apparently after a lag period of about 2 months.
- Clofazimine is orally active.
- **It accumulates in many tissues, especially in fat**
- However, **entry in CSF is poor.**

**Use**

- Clofazimine is used as a **component of multidrug therapy of leprosy.**
- Because of its antiinflammatory property, **it is valuable in lepra reaction.**

**Adverse effects**

- In the doses employed for multidrug therapy (MDT), **clofazimine is well tolerated.**
- Reddish-black discolouration of skin
- Discolouration of hair and body secretions
- Dryness of skin and itching
- Acneform eruptions and phototoxicity
- Conjunctival pigmentation
- Enteritis with intermittent loose stools, nausea, abdominal pain
- The early syndrome occurs due to irritant effect of the drug—**subsides with dose adjustment and by taking the drug with meals.**
A late syndrome occurring is due to deposition of clofazimine crystals in the intestinal submucosa.
Clofazimine is to be avoided during early pregnancy and in patients with liver or kidney damage.

Rifampin (R) in Leprosy

It is an important antitubercular drug; also bactericidal to M. leprae; Rapidly makes leprosy patients noncontagious.
- Up to 99.99% M. leprae are killed in 3–7 days.
- However, it is not satisfactory if used alone—some bacilli persist even after prolonged treatment—resistance develops.

USE
- It has been included in the multidrug therapy of leprosy: shortens duration of treatment.
- The 600 mg monthly dose used in leprosy is relatively nontoxic and does not induce metabolism of other drugs.
- It should not be given to patients with hepatic or renal dysfunction.

TREATMENT OF LEPROSY

Leprosy is a chronic granulomatous infection caused by Mycobacterium leprae; primarily affecting skin, mucous membranes and nerves.
- It is more prevalent among the lowest socio-economic strata.
- Two polar types—lepromatous (LL) and tuberculoid (TT)
- 4 intermediate forms—borderline (BB), borderline lepromatous (BL), borderline tuberculoid (BT) and indeterminate (I)

Important features of two polar types of leprosy
Tuberculoid leprosy
- Anaesthetic patch
- Cell mediated immunity (CMI) is normal
- Lepromin test—positive
- Bacilli rarely found in Skin and mucous membrane biopsies
**Lepromatous leprosy**
- Diffuse skin and mucous membrane infiltration, nodules
- CMI is absent
- Lepromin test—negative
- Skin and mucus membrane lesions loaded with bacilli
- Progresses to anaesthesia of distal parts
- Atrophy, exacerbations ulceration, absorption of digits, etc.

**Paucibacillary leprosy (PBL) (Non-infectious):** This includes TT, BT, I and polyneuritic.

**Multibacillary leprosy (MBL) (Infectious):** This includes LL, BL and BB.

Subsequently the definition of MBL has been widened to include **any active patient with > 5 lesions irrespective of results of skin smear tests**.

Treatment therapy is described below.

---

### Multidrug therapy (MDT) of leprosy

<table>
<thead>
<tr>
<th></th>
<th>Multibacillary</th>
<th>Paucibacillary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rifampin</strong></td>
<td>600 mg once a month supervised</td>
<td>600 mg once a month supervised</td>
</tr>
<tr>
<td><strong>Dapsone</strong></td>
<td>100 mg daily self administered</td>
<td>100 mg daily self administered</td>
</tr>
<tr>
<td><strong>Clofazimine</strong></td>
<td>300 mg once a month supervised</td>
<td>50 mg daily self administered</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>12 months</td>
<td>6 months</td>
</tr>
</tbody>
</table>

Doses to be reduced suitably for children.
Reactions in leprosy

Lepra reaction
- These occur in LL, usually after starting of chemotherapy
- It is a Jarish Herxheimer (Arthus) type of reaction due to release of antigens from the killed bacilli.
- It may be mild, severe or lifethreatening (erythema nodosum leprosum).
- Lepra reaction is of abrupt onset; existing lesions enlarge, become red, swollen and painful;
- Several new lesions may appear.

Treatment
- Temporary discontinuation of dapsone is recommended only in severe cases.
- Clofazimine (200 mg daily) is highly effective in controlling the reaction
- Other drugs used are—analgesics, antipyretics, antibiotics, etc. according to need.
- Corticosteroids should be used only in severe cases.

Sufone syndrome
- It is the reaction which develops 4–6 weeks after dapsone treatment
- It consists of fever, malaise, lymph node enlargement, desquamation of skin, jaundice and anaemia.

Reversal reaction
- This is seen in TT Leprosy
- It is a manifestation of delayed hypersensitivity to M. leprae antigens.
- Cutaneous ulceration, multiple nerve involvement with pain and tenderness occur suddenly even after completion of therapy.
- It is treated with clofazimine or corticosteroids.
Que. ANTIAMOEBIC DRUGS

CLASSIFICATION

Tissue amoebicides

For both intestinal and extraintestinal amoebiasis:
- Metronidazole, Tinidazole, Secnidazole, Ornidazole
- Emetine, Dehydroemetine

For extraintestinal amoebiasis only - Chloroquine

Luminal amoebicides - Diloxanide furoate

Antibiotics - Tetracyclines

Metronidazole

It is the prototype nitroimidazole

Metronidazole is selectively toxic to anaerobic and microaerophilic microorganisms.

MOA
- It enters the micro organism
- It generates nitro group
- Nitro group is reduced and converted to a highly reactive nitro radical group
- It competes with the biological electron acceptors.
- The energy metabolism of anaerobes disrupted.
- Anaerobes are killed.

[Diagram showing the mechanism of action of Metronidazole]
Uses

1. **Amoebiasis**
   - Metronidazole is a first line drug for all forms of amoebic infection.
2. **Giardiasis**
   - It is highly effective in a dose of 400 mg TDS for 7 days.
3. **Trichomonas vaginitis**
   - It is the drug of choice. 2.0 g single dose is preferred.
4. **Anaerobic bacterial infections**
   - Metronidazole is an effective drug for these and is generally used in combination with gentamicin or cephalosporins.
5. **Pseudomembranous enterocolitis**
6. **Acute necrotizing ulcerative gingivitis (ANUG)**
   - Metronidazole/tinidazole are the drugs of choice for ANUG which is caused by anaerobes like spirochetes and bacteroides.
7. **Helicobacter pylori gastritis/peptic ulcer**
   - Metronidazole 400 mg TDS or tinidazole 500 mg BD are combined with amoxicillin/clarithromycin and a proton pump inhibitor.

Adverse effects

Side effects of metronidazole are relatively frequent

- Anorexia
- Metallic taste
- Abdominal cramps
- Looseness of stool
- Headache
- Itching, rashes
- Peripheral neuropathy and CNS effects
- Seizures
- Metronidazole is contraindicated in neurological disease and during first trimester of pregnancy
Tinidazole
- Most of the features are similar to metronidazole.
- Tinidazole has a longer duration of action and better tolerability than metronidazole.

Secnidazole
- Like metronidazole, secnidazole is a nitroimidazole derivative.
- The spectrum, side effects and mechanism of action of secnidazole are similar to metronidazole.

Ornidazole and Satranidazole
- Both of these are nitroimidazoles with longer duration of action and better tolerability than metronidazole.
- Satranidazole does not have interaction with alcohol
Anthelmintic Drugs

Mebendazole
It is a benzimidazole.
- It’s having the broad-spectrum anthelmintic activity

The immobilizing and lethal action of mebendazole on worms is slow: takes 2–3 days to develop.

- Mebendazole acts on microtubular protein ‘β-tubulin’ of the parasite.
- It binds to β-tubulin with high affinity and inhibits its polymerization.
- *Intracellular microtubules in the cells of the worm are gradually lost.*
- In addition, it *blocks glucose uptake in the parasite* and *depletes its glycogen stores.*
- Hatching of nematode eggs and their larvae are also inhibited.

**Adverse effects**
- Mebendazole is well tolerated even by patients in poor health.
- **Diarrhoea, nausea and abdominal pain**
- **Incidents of expulsion of Ascaris** from mouth or nose have occurred, probably due to starvation of the parasite and their slow death.
- **Allergic reactions, loss of hair and granulocytopenia**
- Safety of mebendazole during pregnancy is not known, but it is contraindicated.

**Uses and administration**
Mebendazole is available as: MEBEX, WORMIN 100 mg chewable tab and 100 mg/5 ml suspension.

Useful in...
- Roundworm
- Hookworm
- Whipworm
- Pin worm
- Trichinosis
- Hydatid disease
- Guinea worm
Albendazole

- It is a subsequently introduced congener of mebendazole:
- retains the broad-spectrum activity and excellent tolerability
- It has the advantage of single dose administration in many infestations.
  One dose treatment has

ZenTel, Alminth, Albezole, Combantrin-A 400 mg tab, 200 mg/5 ml suspension.

Uses

- **Ascaris, hookworm, Enterobius** and Trichuris: a single dose of 400
- Tapeworms and strongyloidosis: 400 mg daily for 3 consecutive days.
- **Trichinosis**: Three day treatment
- **Neurocysticercosis**: 8–15 days course of 400 mg BD
- **Cutaneous larva migrans**: Albendazole 400 mg daily for 3 days
- **Hydatid disease**: 400 mg BD for 4 weeks, repeat after 2 weeks (if required)
- **Filariasis**: Added to diethylcarbamazine (DEC) or ivermectin, Albendazole has adjuvant value in treating lymphatic filariasis.

Side effects

- Albendazole is well tolerated;
- **Only gastrointestinal side effects** have been noted.
- Few patients have felt dizziness, headache, fever, alopecia, jaundice and neutropenia.
Malaria is a protozoal infection caused by genus Plasmodium and transmitted to man by the infected female Anopheles mosquito.

- The species of malarial parasites are Plasmodium vivax, Plasmodium ovale, Plasmodium malariae and Plasmodium falciparum.
- In India, P. vivax and P. falciparum are common.

### Classification

**Chemical classification**

- **4-Aminoquinoline:** Chloroquine
- **8-Aminoquinoline:** Primaquine
- **Quinoline methanol:** Mefloquine
- **Alkaloids:** Quinine, quinidine
- **Antifolates:** Pyrimethamine, sulphadoxine
- **Antibiotics:** Doxycycline
- **Qinghaosu compounds:** Artemisinin, artemether, artesunate.

### 4-Aminoquinoline

**Chloroquine**

- Chloroquine is a 4-aminoquinoline.
- It is very effective against P. vivax, P. ovale, P. malariae and chloroquine-sensitive strains of P. falciparum.

### Mechanism of action

- Chloroquine is a basic drug, which is taken up by the acidic food vacuoles of susceptible plasmodia.
- Haemoglobin Heme (toxic) Hemozoin (non-toxic)
- Chloroquine (weak base) Concentrated in acidic vacuole of parasite binds to heme
- It inhibits the conversion of heme to hemozoin.
- The ‘drug–heme’ complex is toxic and kills the parasite.

### Pharmacokinetics

- Chloroquine is commonly administered by oral route, but it can also be given by i.m. and slow i.v. routes.
It is well absorbed after oral and parenteral administration.
- It gets concentrated in liver, spleen, kidney, lungs, skin, etc.
- Chloroquine is metabolized in the liver and slowly excreted in urine.

Adverse effects and contraindications
- Chloroquine in antimalarial doses may cause nausea, vomiting, skin rashes, itching, headache and visual disturbances.
- Parenteral administration can cause hypotension, confusion, cardiac arrhythmias, convulsions and even cardiac arrest.
- It can also cause ototoxicity, retinopathy, myopathy, neuropathy and rarely psychiatric disturbances.
- It is safe in pregnancy.

Uses
1. Malaria
   - Chloroquine is the drug of choice for the treatment of acute attack of malaria
2. Other uses are as follows:
   a. Amoebiasis—hepatic.
   b. Lepra reaction.
   c. Rheumatoid Arthritis.
   d. Infectious mononucleosis.
   e. Autoimmune disorder—discoid lupus erythematosus.

Note: Uses of chloroquine: Mnemonic – MALARIA
Treatment of uncomplicated Malaria

<table>
<thead>
<tr>
<th>Pharmacology</th>
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<tbody>
<tr>
<td>Treatment of uncomplicated Malaria</td>
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</table>

A. Vivax (also ovale, malariae) malaria
1. Chloroquine 600 mg (10 mg/kg) followed by 300 mg (5 mg/kg) after 8 hours and then for next 2 days (total 25 mg/kg over 3 days) + Primaquine 15 mg (0.25 mg/kg) daily × 14 days
   In occasional case of chloroquine resistance
2. Quinine 600 mg (10 mg/kg) 8 hourly × 7 days + Doxycycline 100 mg daily × 7 days or
   + Clindamycin 600 mg 12 hourly × 7 days
   + Primaquine (as above)
   or
   Artemisinin-based combination therapy (see below)
   + Primaquine (as above)

B. Chloroquine-sensitive falciparum malaria*
1. Chloroquine (as above) + Primaquine 45 mg (0.75 mg/kg) single dose (as gametocidal)

C. Chloroquine-resistant falciparum malaria
1. Artesunate 100 mg BD (4 mg/kg/day) × 3 days +
   Sulfadoxine* 1500 mg (25 mg/kg) + Pyrimethamine 75 mg (1.25 mg/kg) single dose
   or
2. Artesunate 100 mg BD (4 mg/kg/day) × 3 days +
   Mefloquine* 750 mg (15 mg/kg) on 2nd day and 500 mg (10 mg/kg) on 3rd day.
   or
3. Artemether 80 mg + Lumefantrine 480 mg twice daily × 3 days (child 25–35 kg BW ¾ dose;
   15–25 kg BW ½ dose; 5–15 kg BW ¼ dose)
   or
4. Arterolane (as maleate) 150 mg + Piperaquine 750 mg once daily × 3 days
   or
5. Quinine 600 mg (10 mg/kg) 8 hourly × 7 days
   + Doxycycline 100 mg daily × 7 days or + Clindamycin 600 mg 12 hourly × 7 days

*First line ACT under NVBDCP
*Sulfadoxine-pyrimethamine (S/P) alone and mefloquine alone are also used, but should preferably be combined with artesunate.
*In India (including under NVBDCP) all P.f. cases, irrespective of CQ-resistance status, are treated with artemisinin-based combination therapy (ACT).
Treatment of Complicated Malaria

1. Artesunate: 2.4 mg/kg i.v. or i.m., followed by 2.4 mg/kg after 12 and 24 hours, and then once daily for 7 days. Switchover to 3 day oral ACT inbetween whenever the patient can take and tolerate oral medication.

or

2. Artemether: 3.2 mg/kg i.m. on the 1st day, followed by 1.6 mg/kg daily for 7 days. Switchover to 3 day oral ACT inbetween whenever the patient is able to take oral medication.

or

3. Arteether: 3.2 mg/kg i.m. on the 1st day, followed by 1.6 mg/kg daily for the next 4 days. Switchover to 3 day oral ACT inbetween whenever the patient is able to take oral medication.

or

4. Quinine diHCl: 20 mg/kg (loading dose) diluted in 10 ml/kg 5% dextrose/dextrose-saline and infused i.v. over 4 hours, followed by 10 mg/kg (maintenance dose) i.v. infusion over 4 hours (in adults) or 2 hours (in children) every 8 hours, until patient can swallow. Switchover to oral quinine 10 mg/kg 8 hourly to complete the 7 day course.

*Arteether (i.m.) is slower acting than artesunate (i.v.), and appears to be less efficacious. It is used only in India.

1. Volume of fluid for i.v. infusion of quinine should be reduced in patients with volume overload/pulmonary edema.
2. If possible, oral quinine should be substituted by 3 day oral ACT, or doxycycline 100 mg daily should be combined with it.
3. Chloroquine HCl i.v. to be used only if none of the above is available and only in adults.
ANTIVIRAL AGENTS

Classification

 Drugs used against herpetic infection (antiherpes agents):
  - Acyclovir, valacyclovir, famciclovir, penciclovir, ganciclovir, foscarnet, idoxuridine.

 Anti-influenza agents
  - Amantadine, rimantadine, oseltamivir, zanamivir.

 Other antiviral agents
  - Interferons and ribavirin.

Drugs used against HIV infection (antiretroviral agents)

a. Nucleoside reverse transcriptase inhibitors:
   - Zidovudine,
   - stavudine,
   - lamivudine,
   - didanosine,
   - zalcitabine, abacavir, emtricitabine, tenofovir.

b. Non-nucleoside reverse transcriptase inhibitors:
   - Nevirapine,
   - efavirenz,
   - delavirdine.

c. Protease inhibitors:
   - Saquinavir,
   - indinavir,
   - ritonavir,
   - nelfinavir,
   - amprenavir, lopinavir

d. Entry inhibitors:
   - Enfuvirtide, maraviroc.

e. Integrase inhibitor: Raltegravir.
**Antiherpes Agents**

**Acyclovir**
- It is a synthetic, purine nucleoside analogue that has antiherpes activity.
- It is more effective against HSV-1 and HSV-2 than Varicella zoster virus (VZV) infections.

**Mechanism of action**

- Acyclovir is selectively taken up by the herpes virus infected cells and activated to triphosphate derivative, which inhibits viral DNA synthesis.
- It is available for oral, topical and i.v. administration.
- It is a highly potent antiherpes drug.
It has high therapeutic index with low toxicity to host cells.
- Its oral bioavailability is poor.
- It is poorly bound to plasma proteins, widely distributed in the body, freely crosses BBB and is excreted in urine.

**Uses**

**Mucocutaneous HSV:**
- Acyclovir is used orally or topically in the treatment of gingivostomatitis, herpes labialis and ulcers in mouth (200–800 mg orally five times daily).
- It is used intravenously in immunocompromised patients.

**Other uses**
- genital herpes,
- herpetic encephalitis,
- herpes simplex keratitis,
- chickenpox and herpes zoster.

**Adverse effects**
- Acyclovir is usually **well tolerated**.
- Nausea, vomiting, diarrhoea and headache are the other side effects.
- High doses may cause **neurotoxicity with tremor, confusion, disorientation and convulsions**.
- On topical use, it can cause **irritation and burning**.
Valacyclovir
- Valacyclovir is a **prodrug of acyclovir**.
- Valacyclovir is *converted to acyclovir* in liver after oral administration.
- It produces **greater oral bioavailability** than acyclovir.

Famciclovir
- Famciclovir is a prodrug of penciclovir.
- Famciclovir is administered orally, well absorbed and converted to penciclovir in liver.
- The mechanism of action of valacyclovir and famciclovir are similar to acyclovir.
- Famciclovir has activity against hepatitis-B virus.

Penciclovir
- Penciclovir is administered through topical and i.v. routes.
- It is used in the treatment of genital herpes and herpes zoster infections.

Ganciclovir
- The structure and mechanism of action of ganciclovir is similar to acyclovir.
- Ganciclovir is reserved for the treatment and **prophylaxis of severe CMV infections**—retinitis, pneumonia, gastroenteritis, etc. in immunocompromised individuals.
Anti-influenza Agents

Amantadine
- It is an antiviral drug that has antiparkinsonian effect as well.
- **It inhibits viral replication.**
- Amantadine is used orally for the prophylaxis and treatment of influenza-A virus infection.

Oseltamivir
- It selectively **inhibits influenza A and B virus neuraminidases**, thus **interfering with the release of virus from infected cells.**
- It is used orally in the treatment and prevention of influenza A (avian influenza or bird flu) and B virus infections.
- Adverse effects are **nausea, vomiting and abdominal discomfort.**

Zanamivir
- The mechanism of action and uses are similar to oseltamivir.
- Oral bioavailability is low.
- **It is administered by inhalation.**
- Adverse effects are **bronchospasm, headache and dizziness.**
- It should be avoided in patients with airway disease.
ANTIRETROVIRAL AGENTS

Nucleoside reverse transcriptase inhibitors, protease inhibitors and integrase inhibitors are effective against both HIV-1 and HIV-2.

- **Non-nucleoside reverse transcriptase inhibitors** and **entry inhibitors** are active against HIV-1.
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)
- These drugs, after entering the HIV-infected cells,
- They are converted to their active triphosphate forms by cellular kinases
- Then, competitively inhibit HIV reverse transcriptase.
- They get incorporated into the growing viral DNA and cause termination of chain elongation of proviral DNA

Zidovudine [Azidothymidine (AZT)]
Zidovudine was the first antiretroviral drug approved for the treatment of HIV infection.
- It is the prototype drug of NRTIs.
- Zidovudine is effective against HIV-1 and HIV-2.
- It protects the uninfected cells from HIV, but has no effect on HIV-infected cells.
- Zidovudine is orally effective.

Pharmacokinetic
- It is well absorbed from GI tract, metabolized in liver by glucuronide conjugation and excreted in urine.
- It crosses placenta and BBB, and is also secreted in milk.

Adverse reactions
- Bone marrow suppression, anaemia and neutropaenia are the common side effects.
- Nausea, vomiting, abdominal discomfort, headache and insomnia are commonly seen during the initial stages of therapy.
- Long-term therapy may cause hepatotoxicity, myopathy with fatigue and lactic acidosis.

Use
- Zidovudine is used in combination with other antiretroviral drugs for the treatment of AIDS.
- It is also used for post-exposure prophylaxis (PEP) and to prevent vertical transmission of HIV.
1. Zidovudine _paracetamol:
   • Both are metabolized by glucuronide conjugation.
   • Paracetamol competes and interferes with glucuronide conjugation of zidovudine.
   • This leads to a rise in the plasma concentration of zidovudine and its toxicity.

2. Azoles _zidovudine:
   ➢ Azole antifungal agents are hepatic microsomal enzyme inhibitors.
   ➢ They inhibit the metabolism of zidovudine and increase its blood level resulting in its toxicity.

3. Zidovudine and stavudine:
   ➢ They should not be combined together because they compete for intracellular phosphorylation.

Didanosine, Stavudine, Emtricitabine and Lamivudine

They are effective orally.

Didanosine, Stavudine, Zalcitabine, Lamivudine, Emtricitabine

Transported into cells and activated to respective triphosphate forms

Inhibit HIV reverse transcriptase

DNA chain termination

➢ The adverse effects are peripheral neuritis, pancreatitis, gastrointestinal disturbances, lactic acidosis, skin rashes, etc
➢ Lamivudine is a commonly used agent in antiretroviral therapy because of its efficacy and low toxicity.
Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

- NNRTIs are highly active against HIV-1 but have no effect on HIV-2.
- There is no cross-resistance with the NRTIs.
- They are used in combination with NRTIs in the treatment of AIDS.

Adverse effects
- Skin rashes, fever, nausea, pruritus
- CNS disturbances like headache, confusion, insomnia, bad dreams, amnesia, etc.

Protease Inhibitors (PIs)

MOA
- They competitively inhibit the HIV protease enzyme
- Prevent cleavage of viral polyproteins to the final functional, structural and enzymatic components of HIV
- So, immature and noninfectious viral particles are produced.

Cross-resistance is common among the PIs,
- But there is no cross-resistance with reverse transcriptase inhibitors.
- PIs are used orally with reverse transcriptase inhibitors in patients with AIDS.
- PIs are extensively metabolized in liver.

ADR
- Nausea, vomiting and diarrhoea are common side effects.
- They also produce skeletal muscle wasting
- lipodystrophy, insulin resistance, diabetes, etc.
Other Drugs
Entry or Fusion Inhibitors: Enfuvirtide and Maraviroc
- Enfuvirtide and maraviroc prevent viral entry into the cell.
- They are used as add on drugs in patients who are not responding to ongoing antiretroviral therapy (ART).

Treatment of HIV Infection
Objectives of anti-HIV therapy
1. To suppress HIV replication and improve immune status of the patient.
2. To prevent the emergence of drug-resistant virus.
3. To prevent or treat opportunistic infections.

Principles of therapy
- Antiretroviral therapy (ART) regimen is used to achieve the above objectives.
- In ART regimen, drugs with different mechanism of action should be used so that they produce synergistic effect.
- It usually consists of a combination of two NRTIs with an NNRTI or a PI (two NRTIs +one NNRTI, two NRTIs +one PI).

Criteria for anti-HIV treatment
- ART is initiated for all HIV patients with CD4 count of < 350 cells/mm$^3$
- And for those with WHO clinical stage 3 or 4

Preferred regimen
1. Lamivudine + Zidovudine + Nevirapine

Alternative regimens
1. Lamivudine + Zidovudine + Efavirenz
2. Lamivudine + Stavudine$^1$ + Efavirenz
3. Lamivudine + Stavudine + Nevirapine

Other options
1. Lamivudine + Tenofovir$^2$ + Nevirapine
2. Lamivudine + Tenofovir$^2$ + Efavirenz
3. Lamivudine$^3$ + Zidovudine + Tenofovir
Prophylaxis of HIV infection (postexposure prophylaxis)

- Doctors, nurses, technicians and other healthcare workers who have had accidental exposure to HIV infection with surgical instruments, blood transfusion or needle-prick injury require prophylactic therapy.

- The need for postexposure prophylaxis (PEP) depends on the degree of exposure to HIV and the HIV status of the exposure source.

Depending on risk of HIV, either a basic regimen or an expanded regimen can be used (National AIDS Control Organization, NACO, India).

<table>
<thead>
<tr>
<th>Basic (2 drug) regimen (for low risk)*</th>
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<tbody>
<tr>
<td>Zidovudine 300 mg + Lamivudine 150 mg</td>
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<table>
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<tr>
<th>Expanded (3 drug) regimen (for high risk)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zidovudine 300 mg + Lamivudine 150 mg + Indinavir 800 mg</td>
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</tbody>
</table>

*Low risk
- When the source is HIV positive, but asymptomatic with low HIV-RNA titre and high CD4 cell count.
- Exposure is through mucous membrane, or superficial scratch, or through thin and solid needle.

*High risk
- When the source is symptomatic AIDS patient with high HIV-RNA titre or low CD4 count.
- Exposure is through major splash or large area contact of longer duration with mucous membrane or abraded skin or through large bore hollow needle, deep puncture, visible patient’s blood on the needle.
Basic regimen
- Zidovudine 300 mg + Lamivudine 150 mg, each BD for 4 weeks

Expanded regimen
- Zidovudine 300 mg + Lamivudine 150 mg, each BD + Indinavir 800 mg TDS for 4 weeks

In HIV-positive pregnant women
- **Zidovudine therapy** is required to prevent vertical transmission to the offspring
- And it should be continued in the newborn for 6 weeks
Antifungal Drugs

Classification based on structure

- **ANTIBIOTICS**
  - Polyene: Amphotericin B, nystatin, hamycin
  - Heterocyclic benzofuran: griseofulvin
- **ANTIMETABOLITE**: Flucytosine
- **AZOLES**
  - **Imidazoles**: Ketoconazole, clotrimazole, oxiconazole, miconazole,
  - **Triazoles**: Fluconazole, itraconazole, voriconazole,
- **ALLYLAMINES**
  - Terbinafine, butenafine
- **OTHER TOPICAL AGENTS**
  - Tolnaftate, Undecyclinic acid, benzoic acid

Classification based on mechanism of action

1. Fungal cell wall synthesis inhibition: Caspofungin.
2. Bind to fungal cell membrane ergosterol: Amphotericin–B, Nystatin.
3. Inhibition of ergosterol + lanosterol synthesis: Terbinafine, Naftifine, Butenafine.
4. Inhibition of ergosterol synthesis: Azoles
5. Inhibition of nucleic acid synthesis: 5–Flucytosine.
6. Disruption of mitotic spindle and inhibition of fungal mitosis: Griseofulvin.
7. Miscellaneous:
   - Ciclopirox, Tolnaftate, Haloprogin, Undecylenic acid, Topical azoles.
Que. Amphotericin B

- Obtained from Streptomyces Nodosus
- Amphoteric in nature

Mechanism of action

- Amphotericin B binds ergosterol in fungal cell membrane
- Form pores in cell membrane
- Cell contents leak out and cell death occurs

Broader spectrum of action
Fungicidal at high & static at low conc

Antifungal spectrum
- Aspergillus
- Blastomyces dermatitidis
- Candida albicans
- Cryptococcus neoformans
- Coccidioides immitis
- Histoplasma capsulatum
- Mucor spp.

Also active against Leshmania

Mechanism of resistance
- Resistance:
  - Replacement of ergosterol by other sterols in fungal plasma membrane.

Uses
- Useful drug in nearly all life threatening mycotic infections
- Treatment of invasive aspergillosis
- Rapidly progressive Blastomycosis & Coccidiomycosis
- Cryptococcus neoformans
• Mucormycosis.
• Disseminated rapidly progressing Histoplasmosis
• Reserve drugs for resistant kala azar
• Topical uses

**Adverse Reactions**

- **Acute reaction:**
  - Chills, fever, headache, pain all over, nausea, vomiting, dyspnoea lasting 2-5 hrs because of release of IL & TNF
  - can be treated with hydrocortisone 0.6mg/kg
- **Long term toxicity**
  - **Nephrotoxicity:** Azotemia, Hypokalemia, acidosis, ↓ GFR
  - anemia
- **CNS toxicity:** intrathecal administration, headache, vomiting, nerve palsies
- **Hepatotoxicity** rarely

**Que. Nystatin**

- Obtained from S.Noursei
- **Similar to AMB in antifungal properties, high systemic toxicity so used locally only**
- Poorly absorbed from mucus membrane
- Available as ointment, cream, powder, tablet

**Uses**

- Intestinal moniliasis
- Vaginitis
- Prevention of oral candidiasis
- Can be used in oral, cutaneous, conjunctival candidiasis

**Adverse events**

- Gastointestinal disturbances with oral tablets
Hamycin
- Isolated from S. Pimprina
- Developed by Hindustan antibiotics at pimpri
- More water soluble, fraction absorbed orally but unreliable in systemic infections
- Topical use in thrush, cutaneous candidiasis, trichomonas & monilial vaginitis, otomycosis by aspergillus

Natamycin
- Similar to nystatin, broad spectrum
- Used topically 1%, 3% ointment
- Fusarium solani keratitis, trichomonas & monilial vaginitis

Que. Griseofulvin
- One of early antibiotics from penicillium griseofulvum

Mechanism of action:
- Griseofulvin interacts with polymerized microtubules and disrupts the mitotic spindles thus arresting fungal mitosis
- Fungistatic, systemic drug for superficial fungal infections
- Active against most dermatophytes
- Dermatophytes concentrate it actively hence selective toxicity

Resistance due to loss of concentrating ability

Uses
- Systemically only for dermatophytosis, ineffective topically
- Systemic azoles more effective and preferred
- Duration of treatment depends on site, thickness of keratin and turnover of keratin.
- Treatment must be continued till infected tissue is completely replaced by normal skin, hair, nail.
- Dose: 125-250 mg QID
Duration of treatment

- Body skin = 3 weeks
- Palm, soles = 4- 6 weeks
- Finger nails = 4- 6months
- Toe nails = 8 – 12 months
- Griseofulvin should be reserved for nail hair or larger body surface involvement

Adverse Drug reaction

- Headache most common
- GIT disturbances
- CNS symptoms: confusion, fatigue, vertigo
- Peripheral neuritis
- Rashes, photoallergy
- Transient leukopenia, albuminuria

Interactions

- Induce Warfarin and OCP metabolism
- Disulfiram like reaction

SQ Flucytosine

- Prodrug, pyrimidine analog, antimetabolite
- Converted to 5 FU
- Human cells cant convert it to 5FU

Adverse events:
- Bone marrow toxicity, GIT, Alopecia, skin rashes, itching, rarely hepatitis

Uses:
- In combination with AMB in cryptococcal meningitis
- Narrow spectrum of action
Azoles

- Synthetic antifungals
- Broad spectrum
- **Fungistatic or fungicidal depending on conc of drug**
- Most commonly used

Classified as imidazoles & triazoles

- **Imidazoles**: Two nitrogen in structure
  - Topical: econazole, miconazole, **clotrimazole**
  - Systemic: **ketoconazole**
  - Newer: **butaconazole**, oxiconazole, sulconazole

- **Triazoles**: Three nitrogen in structure
  - **Fluconazole**, **itraconazole**, voriconazole
  - Terconazole: Topical for superficial infections

- Both these groups are
  - Structurally related compounds
  - Have same mechanism of action
  - Have similar antifungal spectrum

**Mechanism of action**

- Imidazoles and triazoles **Inhibit ergosterol synthasis**
- Membrane abnormalities accours
- And Fungus growth is inhibited
Miconazole & clotrimazole

- **Topical use:**
  - Miconazole 2% and clotrimazole 1% applied BD for 2 weeks in pityriasis versicolor, 4 weeks in cruris, capitis and corporis

- **Uses:**
  - Dermatophyte infections
  - Candida: oral pharyngeal, vaginal, cutaneous

- **Adverse events:**
  - Local irritation, itching or burning
  - Miconazole shows higher incidence of vaginal irritation & pelvic cramps

Ketoconazole

- **First orally effective broad spectrum antifungal**
- Effective against - Dermatophytosis, Deep mycosis, Candidiasis

- **Uses**
  - **Dermatophytosis:** conc in stratum corneum
  - **Monilial vaginitis:** 5-7 days
  - **Systemic mycosis:** blastomycosis, histoplasmosis, coccidiodomycosis
    - Less efficacy than AMB & slower response
    - ↓Efficacy in immunocompromized and meningitis
    - Lower toxicity than AMB higher than triazoles
  - **High dose used in cushings syndrome**
  - **Topical:** T.pedis, cruris, corporis, versicolor

- **Adverse events**
  - Nausea, vomiting, anorexia, Headache, paresthesia, alopecia
  - ↓ steroid, testosterone & estrogen synthesis
    - Gynaecomastia, oligospermia, loss of libido & impotence in males
    - Menstrual irregularities & amenorrhoea in females
  - **Elevation of liver enzymes**
  - **Hypersensitivity reaction** - skin rashes, itching
Fluconazole

- Newer water soluble triazole
  - Oral, IV as well as topical
  - Broad spectrum antifungal activity
    - Candida, cryptococcosis, coccidiodomycosis
    - Dermatophytosis
    - Blastomycosis
    - Histoplasmosis
    - Sporotrichosis
    - **Not effective against aspergillosis & mucormycosis**

**Uses**
- **Candida:**
  - 150 mg oral dose can cure vaginal candidiasis
  - **Oral candidiasis** - 2 weeks treatment required
- **Tinea infections & cutaneous candidiasis:** 150 mg weekly for 4 weeks, *tinea unguim* : 12 months
- Systemic fungal infections: Disseminated candidiasis, cryptococcal, coccidiodal meningitis 200-400 mg / day for 4-12 weeks or longer
- **Meningitis:** preferred drug
- **Eye drops for fungal keratitis**

**Adverse events**
- GIT upset
- **Headache, alopecia, skin rashes, hepatic necrosis**
- **Teratogenic effect**
- CYP450 Enzyme inhibiting property less Interactions:
  - Effects hepatic drug metabolism to lesser extent than Ketoconazole
  - H2 blockers & PPI do not affect its absorption
- **No anti androgenic & other endocrine effects**
**Itraconazole**

**Broader spectrum of activity also against aspergillus**
- Fungistatic but **effective in immunocompromised**
- Does not inhibit steroid hormone synthesis and no serious hepatotoxicity

**Uses**
- DOC for paracoccidomycosis & chromoblastomycosis
- DOC for histoplasmosis & blastomycosis
- Esophageal, oropharyngeal vaginal candidiasis
  - Not superior to fluconazole: 200 mg OD X 3 days
- **Dermatophytosis**: less effective than fluconazole
  - 100-200 mg OD X 15 days
- **Onychomycosis**: 200 mg / day for 3 months
  - Intermittent pulse regime 200 BD once a week / month for 3 months equally effective
- **Aspergillosis**: 200 mg OD/ BD with meals for 3 months or more

**Voriconazole**

- **II generation triazole**
- High oral bioavailability, low protein binding
- **Good CSF penetration**
- Metabolized by CYP2C19
- Doesn’t require gastric acidity for absorption
- T1/2= 6 hrs

**Uses:**
- **DOC for invasive aspergillosis**
- Most useful for **esophageal candidiasis**
- First line for moulds like fusarium
- Useful in **resistant candida infections**
Dose and Adverse effects

• Dose: 200 mg BD
• **Adverse drug reaction**
  – Transient visual changes like blurred vision, altered color perception & photophobia
  – Rashes in 5-6%
  – Elevated hepatic enzymes
  – Prolongation of QT

**Terbinafine**

- Orally & topically effective drug against candida & dermatophytes
- Fungicidal: shorter courses of therapy required & low relapse rates

**Mechanism of action**

- It is a non-competitive **inhibitor of squalene epoxidase**
- Ergosterol synthesis is inhibited
- Squalene is deposited within fungus and its responsible for fungicidal action
- Well absorbed orally and Highly keratophilic & lipophilic

**Uses**

- **Dermatophytosis**: topically/orally 2-6 weeks
- **Onychomycosis**: first line drug 3-12 months
- **Candidiasis**: less effective 2-4 weeks therapy may be used as alternative 250 mg OD

**Adverse Reaction:**

- Nausea, vomiting, Diarrhoea
- **Taste disturbances**
- Rarely hepatic dysfunction
- Topical: erythema, itching, dryness, urticaria, rashes