UNIT-3

Anti-tubercular Agents

These are the drugs that are used to treat tuberculosis (TB).

TB is a chronic granulomatous disease caused by Mycobacterium tuberculosis.

Granuloma → It is a tiny cluster of white blood cells and other tissue caused due to the infection of tuberculosis.

TB is characterized by formation of granulomas in the lungs.

Transmission: It is transmitted from an infected person to a healthy person by inhaling the droplets despersed in the air by the infected person during coughing or sneezing.

TB affects lungs primarily but also affects other organs like liver, kidney, spleen, uterus, etc.

→ BCG is the vaccine for TB.

Etiology (Causation)

1) Droplet Infection
2) Intake of Unpasteurised cow milk (M. bovis may be present in unpasteurised milk).
3) Diseased conditions: low immunity
4) Socioeconomic Factors:- Malnutrition, unhygienic living conditions, excess population, etc.

Signs and Symptoms

- Coughing with green, yellow or bloody sputum.
- weight loss, fatigue, fever, night sweats, chills, anorexia, chest pain, shortness of breath, loss of appetite.

classification

(A) First line drugs → These are most effective and least toxic for use in the treatment of TB.

1) Isoniazid
2) Rifampin
3) Pyrazinamide
4) Ethambutol
5) Streptomycin

B) Second-Line drugs → less effective, high toxicity and mor expensive.

1) Thiacetazone 2) p-Aminosalicylic acid
3) Ethionamide 4) Cycloserine 5) Kanamycin
6) Amikacin 7) Capreomycin

→ Second-line drugs strengthen the treatment in case of resistant bacteria.

Isoniazid

→ Most effective and cheapest primary anti-tubercular drug.
→ effective in both acidic and alkaline medium.
→ Tuberculocidal (kills bacteria) for rapidly multiplying bacilli. and tuberculostatic for resting bacilli.

MOA

Isoniazid is a prodrug activated by KatG. Active Isoniazid inhibit mycolic acid synthesis which is a component of bacterial cell wall (TB). This leads to the cell wall destruction (tuberculocidal).

Uses

- Mostly effective against M. tuberculosis.

Rifampicin

It is obtained from streptomyces mediferranei.
It is a semi-synthetic derivative of rifamycin B, well absorbed on oral administration.
→ It is highly effective as tuberoculocidal, and is a broad-spectrum drug.

MOA

Rifampicin binds with β-subunit of DNA dependent RNA polymerase and inhibit the synthesis of mRNA which is thus show tuberculocidal effect.

Therapeutic Uses

→ broad-spectrum antibiotic.
→ first-line drug for treatment of pulmonary tuberculosis.
→ Rifampicin acts as a bactericidal agent over M. leprae or M. lepromatosis.

Second-line drugs

1) Ethionamide → It blocks mycolic acid synthesis. It is administered via oral route only.
2) Capreomycin → It is obtained from Streptomyces capreolus. It inhibits peptide protein synthesis.
3) Cycloserine → It inhibits cell wall synthesis.
4) p-Aminosalicylic acid → It is a folate synthesis antagonist and is active against M. tuberculosis. It give rise to hypersensitivity reactions.
5) Kanamycin → It is used for treating TB caused by streptomycin resistant strains.
6) Amikacin → treat TB.

Newer Drugs

1) Ciprofloxacin & Ofloxacin → These are very effective in treating chronic mycobacterial diseases.
2) Clarithromycin → effective in combination with other anti-tuberculosis drugs.

Anti-leprotic Agents

Leprosy is also known as Hensen's Disease (HD). It is a chronic infectious disease caused by Mycobacterium lepra or Mycobacterium lepromatosis.

→ It is characterized by peripheral neuropathy with peripheral thickening of nerve and anaesthetic skin lesions.

→ The bacterium primary affects the peripheral nerves but also affects the skin, eyes, mucosa of upper respiratory tract, bone, muscles and testes.

Etiology

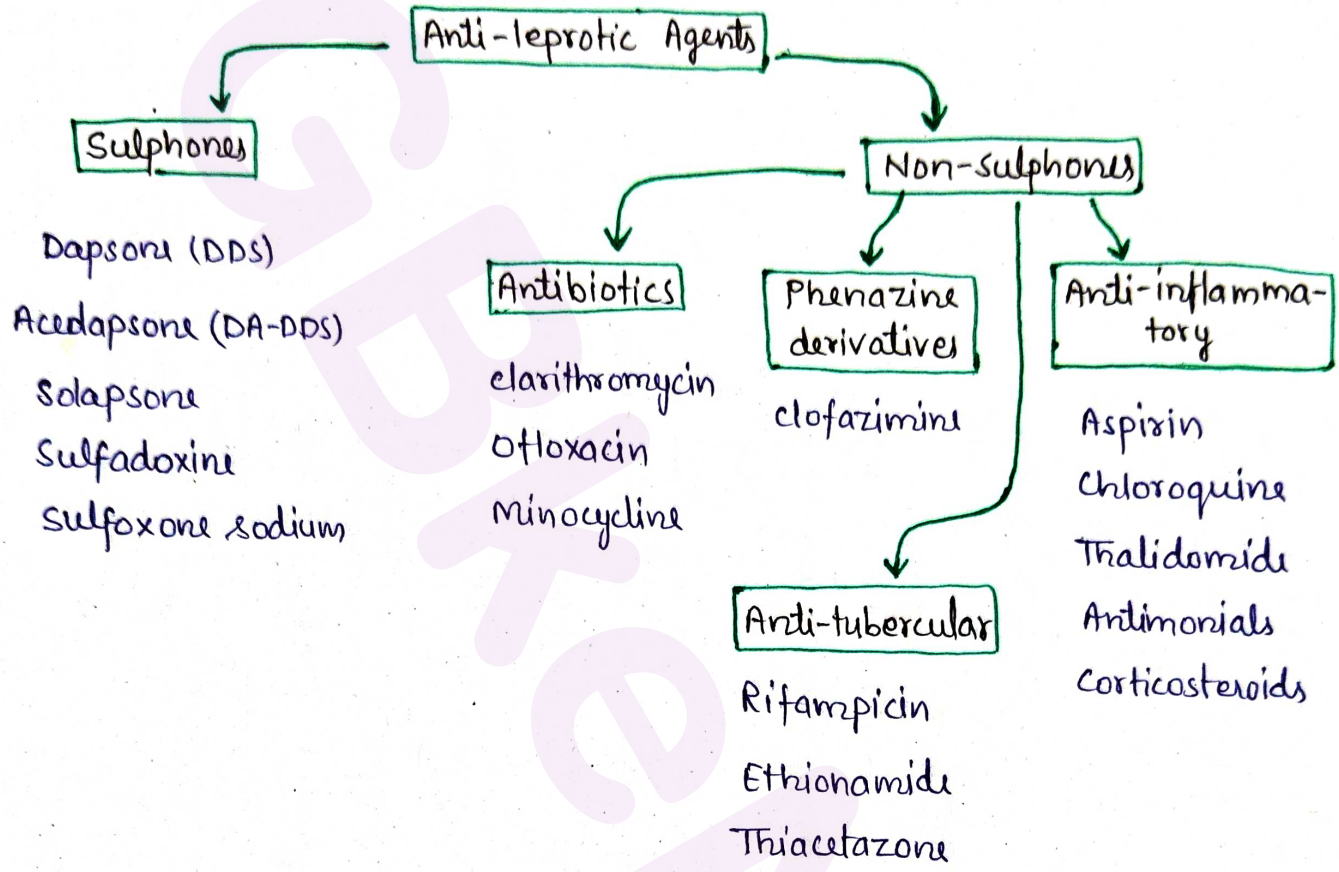
→ M. lepra is the primary cause of leprosy.

→ In humans, the disease spreads through respiratory route or broken skin.

→ Incubation period is 3 to 5 years.

Signs and Symptoms

Appearance of skin lesions, sensations like touch, pain, heat decreases, stuffy nose and nosebleeds, muscle weakness, eye problems, nerve enlargement.



Sulphones

They are considered as the first-line treatment for leprosy. They are chemically derivatives of 4,4-diaminodiphenylsulphone (DDS).

1) **Dapsone**
   - It is a synthetic compound chemically related to sulphonamides.
   - → It is a diaminodiphenylsulphone.
   - → It is bacteriostatic agent used to treat leprosy.

MOA:
It is similar to sulphonamides. It inhibit the synthesis of dihydrofolic acid.

2) **Sulfoxone sodium**
   It may be substituted for dapsone in patients who do not tolerate dapsone well. It is hydrolyzed in the gut to dapsone.

3) **Acedapsone** → DA-DDS
   Diacetyl-DDS is a long acting, oily, IM preparation. It is no longer in use today.

Non-sulphones

Non-sulphones which are used to treat leprosy are:

1) Rifampicin

It is bactericidal for M. lepraе and its action is more rapid than dapsone.

2) Clofazimine

It is a dye of phenazine derivative. It is bacteriostatic and used in patients with sulphone-resistant M. lepraе.

3) Thiacetazone

This drug is more tuberculostatic. It exerts greater effect on tuberculoid than on the lepromatous form of leprosy.

Antifungal Agents

These are the drugs used for superficial and deep fungal infections. (Deep means systemic)
Various types of fungi can cause the infections like rusts, moulds, mushrooms and yeasts.

→ Fungal infections are more common on skin but they may also occur in mouth, throat, lungs, urinary tract and many other parts.

→ Fungal infections thrive more in moist and hot conditions.

→ Symptoms depend upon the area or site of infection in the body.

For skin: dark skin, loss of colour, peeling, rashes or small bump.
Iching is the common symptom or problem.

Classification

Based on chemical nature:

1) Antibiotics
   a) Polyenes: Amphotericin B (AMB), Nystatin, Hamycin and Natamycin.
   b) Heterocyclic Benzofuran: Griseofulvin
2) Antimetabolite: Flucytocine (5-FC)
3) Azoles
   a) Imidazoles (Topical): clotrimazole, Econazole, Miconazole.
      (systemic): ketoconazole
   b) Triazoles (systemic):- Fluconazole, Itraconazole

Polyene Antibiotics

They belong to antimicrobial polyene class which target fungi. They are obtained from species of streptomyces bacteria. (Polyene = highly double bonded)

1) Amphotericin B

Amphotericin B is derived from streptomyces nodosus. It is amphoteric polyene macrolide antibiotic.

MOA

Amphotericin bind with ergosterol of fungal cell membrane and increases the cell permeability. This results in leakage of intracellular ions and other intracellular constituents in the extracellular fluid, resulting in death of fungal cells.

2) Herocyclic Benzofuran - Griseofulvin

One of the early antibiotics derived from Penicillium griseofulvum. However, due to lack of its antibacterial activity, little attention was paid to it.

It is orally given for treating dermatophytosis.

Azoles

Azoles are synthetic antifungal agents with a broad-spectrum anti-fungal activity.

Azoles are predominantly fungistatic.

MOA

Azoles partly act by blocking the synthesis of ergosterol of fungal cell membrane, thus increasing cell permeability.

Pharmacokinetics of azoles

1) Absorption → Ketoconazole, fluconazole, and itraconazole are absorbed well orally.
2) Distribution → Ketoconazole is highly protein bound (90%). But fluconazole passes into CSF in effective concentrations, therefore used in meningitis.
3) Metabolism → All azoles are metabolized in liver by microsomal enzymes.
4) Excretions → They are excreted in bile and urine.

Adverse effects

- Gastric upsets
- Hepatic impairment (Ketoconazole)
- Gynaecomastia with use of (Ketoconazole)

Antiviral Agents

Viruses are the ultimate expression of parasitism. They not only take nutrition from the host cells but also direct its metabolic machinery to synthesize new virus particles.

Antiviral agents are the drugs to treat viral infections.

Classification

1) Anti-Herpes virus : Idoxuridine, Acyclovir, Famciclovir, Valacyclovir, Penciclovir, Docosanol, Trifluridine, Ganciclovir and Foscarnet.
2) Anti-Retrovirus
   a) Nucleoside Reverse Transcriptase Inhibitors (NRTIs)
   Zidovudine (AZT), Didanosine, Zalcitabine, Stavudine, Lamivudine and Abacavir
   b) Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)
   Nevirapine, Efavirenz, Delavirdine
   c) Retroviral Protease Inhibitors
   Ritonavir, Indinavir, Nelfinavir, Saquinavir, Amprenavir, Lopinavir.
3) Anti-Influenza Virus : Amantadine, Rimantadine
4) Non-selective Antiviral Drugs : Ribavirin, Lamivudine and Interferon-α.

Anti-Herpes Virus Drugs

These drugs are made to act against herpes virus and used for the treatment of Herpes Simplex Virus (HSV) and Varicella Zoster Virus (VZV) infections.

1) Acyclovir

It is used to treat the symptoms of chickenpox, shingles, herpes virus infections of genitals, the skin, the brain, and mucous membranes.

MOA

→ It is first converted to the monophosphate derivative by the virus-specified thymidine kinase.
→ Then it is converted into its diphosphate derivative
→ Lastly into triphosphate compounds by host cell enzymes.
→ This acyclovir triphosphate inhibits viral DNA synthesis.

Uses

→ Genital Herpes simplex
→ Herpes simplex encephalitis
→ Chickenpox

2) Famciclovir

oral preparations of famciclovir are used for the first and recurrent genital herpes and acute zoster.

Anti-Retroviral Drugs

These are the drugs used for treating infections caused by retroviruses, mainly HIV.

Ⓐ NRTIs

1) Zidovudine → It is an analogue of deoxythiamidine.

MOA → Zidovudine gets incorporated into the developing viral DNA chain after getting phosphorylated. This leads to termination of DNA chain.

2) Lamivudine → It is a cytosine analogue. In combination with zidovudine, it increases the efficacy. It is also used in Hepatitis B infection.

3) stavudine → It is an analogue of thiamidine with high oral bioavailability.

Ⓑ NNRTIs → These are different from NRTIs as:

a) They do not require prior phosphorylation to be active.
b) They do not compete with nucleoside triphosphate.
c) Their viral binding site is different from NRTIs.

1) Efavirenz → It induces CYP3A4 enzyme which is also responsible for its metabolism. It should be avoided in pregnancy due to ADRs.

2) Nevirapine → Oral bioavailability is >90% and is food independent. It works well when given in combination therapy.

3) Delavirdine → Oral bioavailability is 85% which is reduced in presence of antacids. It does not pass CSF due to its plasma protein binding

© Retroviral Protease Inhibitors

Protease is essential for the production of mature infectious virus during HIV replication. Protease inhibitor prevent new waves of infection and are generally given in combination to avoid chances of resistance.

1) Saquinavir → It is extremely protein bound. Absorption of this drug is increased after a fatty meal.
2) Indinavir → oral bioavailability is 65%. It is a specific inhibitor of HIV-1 and HIV-2 proteases.
3) Nelfinavir → Bioavailability of the drug is increased if given with food.

Anti-Influenza Agents

1) Amantadine → It is a tricyclic primary amine.

MOA → Amantadine interferes with penetration of viruses into the host cells and also inhibits uncoating of viral nucleic acid inside the cells.

Uses.

→ Effective for the chemoprophylaxis of influenza A during an outbreak of an epidemic.
→ Also effective against rubella.
→ used in some cases of parkinsonism as it releases dopamine from dopaminergic nerve endings.

2) Rimantadine → It is orally administered and is used for certain type of flu viruses.

It inhibits replication of virus by preventing the uncoating of the virus's protective shells.

✱ Interferon-α

It is an antiviral agent which modulates the immune system functions. Production of interferons occurs in response to viruses and bacteria and their products.

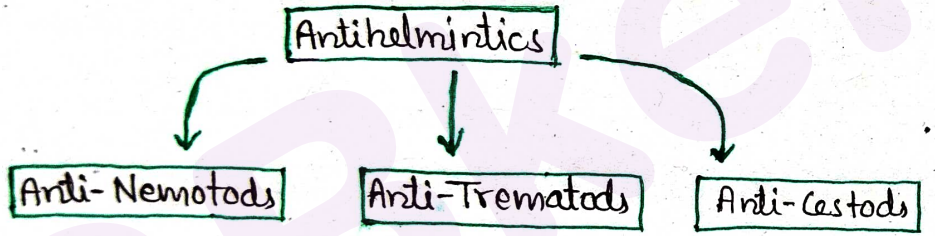
Antihelmintics

Three major groups of helminths (worms), nematods, tremalod and cestods infect humans.

Helminths generally invade the GIT of the hosts. They might cause damage to other organs as well.

The infection caused by helminths is known as Helmenthiasis.

The drugs used in the treatment of helmenthiasis are called antihelmintics.



1) Albendazole

It is a broad-spectrum anthelmintic administered orally. The active metabolites of albendazole are sulphoxide and sulfone which possess anthelmintic activity.

MoA → They act by binding with the free fungal B-tubulin, inhibiting its polymerisation and hyphal growth. They bind selectively with the spindle microtubules, thereby blocking the cell division.

Uses

→ used against the infection caused by Taenia solium.

→ Also against Echinococcus granulosus.

2) Mebendazole

It is highly effective against roundworms hookworms enterobius and trichuris infections.

MoA → similar to albendazole.

Both of the above drugs belong to a broader category of anthelmintics, Benzimidazoles.

3) Praziquantel

Broad-spectrum anthelmintic used against all the schistosomes species.

MOA→ It acts by increasing the nematode permeability for Ca^{2+} ions resulting in contraction of the muscles, followed by paralysis and death of the worm.

4) Piperazine

It is used against the infections caused by roundworm (A. lumbricoides) and the threadworm (E. vermicularis).

MOA→ It acts by reversibly inhibiting the neuromuscular transmission in the worm.

5) Ivermectin

It is derived from Streptomyces avermitilis. It is most effective drug in strongyloidiasis and onchocerciasis. It is also effective in filariasis.

MOA→ It paralyses the nematodes by GABA-ergic activation.

Antimalarial Drugs

Malaria is a protozoan disease caused by different Plasmodium species.

Malaria is the disease of red blood cells in which the cells become sticky and eventually burst out to cause blockage of small blood vessels.

→ It is transmitted by bite of an infected female Anopheles mosquito from one person to another.

→ The four species of Plasmodium which causes malaria in humans are:

1) Plasmodium falciparum
2) P. vivax
3) P. ovale
4) P. malariae

Malaria due to P. vivax is the most common and malaria due to P. falciparum is the most dangerous type and may be fatal.

The life cycle of malarial paracyte involves three stages:

1) Infecting an individual with sporozoites
2) Asexual reproduction in humans (liver)
3) Sexual reproduction in mosquito.

Signs and symtoms

Malaise, myalgis followed by fever, chills, high fever, headache, febrile seizures, rigors, cough, chest pain, diarrhoea.

→ signs of jundice, tachycardia, hypotension.

Classification of Antimalarial Drugs

1) 4-Aminoquinolones: Chloroquine, Amodiaquine, Piperaquine.
2) Quinoline-Methanol: Mefloquine
3) Cinchona alkaloid: Quinine and Quinidine
4) Biguanides: Proguanil & chloroproguanil
5) Diaminopyrimidines: Pyrimethamine
6) 8-Aminoquinolines: Primaquine & Bulaquine
7) Tetracyclines: Tetracycline and doxycycline
8) Sulfonamides and sulfones: Sufadoxine, dapsone and sulfamethopyrazine.
9) Sesquiterpene lactones: Artesunate, Artemether, Arteether
10) Amino Alcohols: Halfofantrine, Lumafantrine
11) Mannich Base: Pyronaridine
12) Naphthoquinone: Atovaquone

1) Chloroquine

It is a synthetic 4-aminoquinoline and a choice for the treatment of P. falciparum malaria.

MOA

1) Malarial parasite digest haemoglobin in their lysosomes to utilise amino acids.
2) chloroquine inhibits the polymerisation and detoxification of hematin and interferes with the degradation of host erythrocyte hemoglobin, preventing plasmodium growth.

Therapeutic uses

1) Malaria
2) suppressive prophylaxis in malaria

8) It is used alongwith metronidazole in extra-intestinal amoebiasis.

4) Giardiasis

2) **Mefloquine**

It is active and effective against chloroquine-sensitive and resistant plasmodia.

MOA → It binds with haem and the complex formed damages the parasites membrane

Its oral absorption is good but peak concentrations are achieved slowly.

Uses

→ Used for P. falciparum
→ for prophylaxis of malaria

3) **Quinine and Quinidine**

Quinine and quinidine interferes with the polymerization of heme, thereby resulting in the death of the erythrocytic form of the plasmodial parasite.

Therapeutic uses

1) Used to treat P. falciparum malaria resistant to chloroquine.
2) It relieves muscle spasm in myotonia congenita.

4) **Proguanil**

It inhibits the pre-erythrocytic stage of P. falciparum. On exposure to this drug, gametocytes do not develop properly in the mosquito.

5) **Primaquine**

It is an 8-aminoquinoline which eliminates the primary exoerythrocytic forms of P. falciparum and P. vivax.

MOA.

It destroys the sexual forms of all four plasmodia in the plasma and later prevents their maturation in mosquito, thus interrupts the disease transmission.

Uses.

1) falciparum malaria
2) vivax malaria

6) **Artemisinin**

Artemisinin is derived from the plant Artemisia annua.
It is used for treating severe, multi-drug-resistant P. falciparum malaria.

MOA

Artemisinin produce free radicals within the plasmodium food vacuole. It damage specific malarial parasite proteins.

Antiamoebic Agents

Amoebiasis, also called amoebic dysentery caused by the intestinal protozoan, Entamoeba hystolytica. It is an infectious disease which infects/affects both intestinal (primarily) and extraintestinal parts of the body including lungs, liver and brain. It affects different parts of colon.

common causes of spread of disease:
1) Faecal contamination of food and water
2) poor environmental sanitation

Classification

A) Tissue Amoebicides
1) For both intestinal and extraintestinal amoebiasis
   a) Nitroimidazoles: Metronidazole, Tinidazole, Secnidazole, ornidazole
   b) Alkaloids: Emetine and dehydroemetine
2) For extraintestinal amoebiasis only: Chloroquine

B) Luminal Amoebicides
1) Amides: Diloxanide furoate and nitazoxanide.
2) 8-Hydroxyquinolines: Quiniodochlor and Sodoquinol.
3) Antibiotics: Tetracyclines and Paramomycin.

1. **Metronidazole**

It is chemically a nitroimidazole derivative and a potent amoebicide.
It is less toxic and cost-effective in comparison to other antiamoebic agents.

MOA → It diffuses into the organism, inhibits protein synthesis by interacting with DNA and causes a loss of helical DNA structure and strand breakage.

2. **Emetin**

Emetin is an alkaloid obtained from the roots of Cephalis ipecacuanha. It is given parenterally as it induces vomitting on oral administration.

MOA → It kills the trophozoites of Entamoeba hystolytica that have invaded the intestinal wall or extra-intestinal tissues.

Therapeutic uses

→ Amoebic liver abscess
→ Also effective against other parasites like Balantidium coli, Fasiola hepatica.

3. **Chloroquine**

It is a 4-aminoquinoline derivative acting directly over the trophozoites of E. hystolytica. It is used only in hepatic amoebiasis as it concentrates significantly in the liver.

MOA → It inhibits the autophagy process in amoebae including E. hystolytica.

4) **Antibiotics**

Paromomycin is an aminoglycoside, not absorbed from GIT. It acts as a direct luminal amoebicide as well as acts indirectly by inhibiting the normal flora.
Adverse effects are diarrhoea, candidiasis, renal damage and ototoxicity.

Tetracycline and erythromycin act indirectly by altering the intestinal flora and acts as an adjuvant. Tetracycline should not be given to pregnant women and children below 8 years of age.