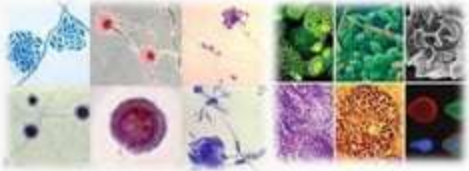
DR.D.Y.PATIL COLLEGE OF PHARMACY AKURDI

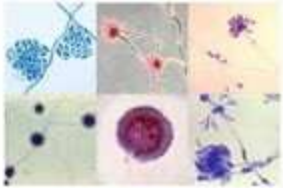
ANTIFUNGAL AND ANTI-TB DRUGS



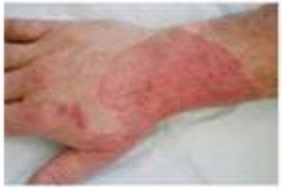
SUBJECT NAME – ADVANCE PHARMACOLOGY-II

PRESENTED BY – DHANASHRI PRAKASH SONAVANE

GUIDED BY- DR.D.S.SHIRODE



FUNGAL INFECTION AND ANTIFUNGAL DRUG



CONTENT:

1. Introduction
2. Define
3. Classification
4. Mechanism of action
5. Adverse effects
6. Interactions

INTRODUCTION

- Fungal infection:

It is an Infectious diseases caused by fungi are called mycoses, and they are often chronic in nature.

Fungal infectious occur due to :

1- Abuse of broad spectrum antibiotics

2- Decrease in the patient immunity

- They have rigid cell walls composed largely of a polymer of N-acetylglucosamine rather than peptidoglycan (a characteristic component of most bacterial cell walls).
- The fungal cell membrane contains ergosterol rather than the cholesterol found in mammalian membranes.
- These chemical characteristics are useful in targeting chemotherapeutic agents against fungal infections

- Types of fungal infections

A. Superficial : Affect skin – mucous membrane. e.g. Tinea versicolor

1. Dermatophytes : Fungi that affect keratin layer of skin, hair, nail. e.g. tinea pedis ,ring worm infection
2. Candidiasis : Yeast-like, oral thrush, vulvo-vaginitis , nail infections

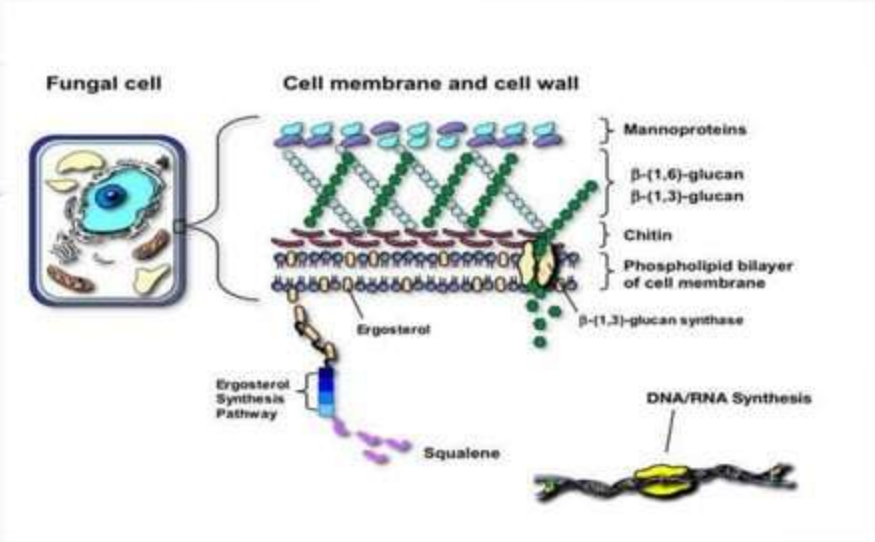
Deep infections Affect internal organs as : lung ,heart , brain leading to pneumonia , endocarditis , meningitis.

- DEFINE: Antifungals are **medicines that kill or stop the growth of fungi (the plural of fungus) that cause infections**. They are also called antimycotic agents.
- Fungi may be classified as…

- Yeasts: Blastomyces, candida, histoplasma, cryptococcus.
- Molds : Aspergillus spp. Dermatophytes, mucor
- Clinically classified as:

SYSTEMIC FUNGAL INFECTIONS:

- Cryptococcal meningitis, endocarditis
- Rhinocerebral mucormycosis
- Pulmonary aspergillosis Blastomycosis (pneumonitis, with dissemination)
- Histoplasmosis(cough, fever, multiple pneumon.ic infiltrates)
- Coccidiodomycosis
- Pnemocystis carinii pneumonia

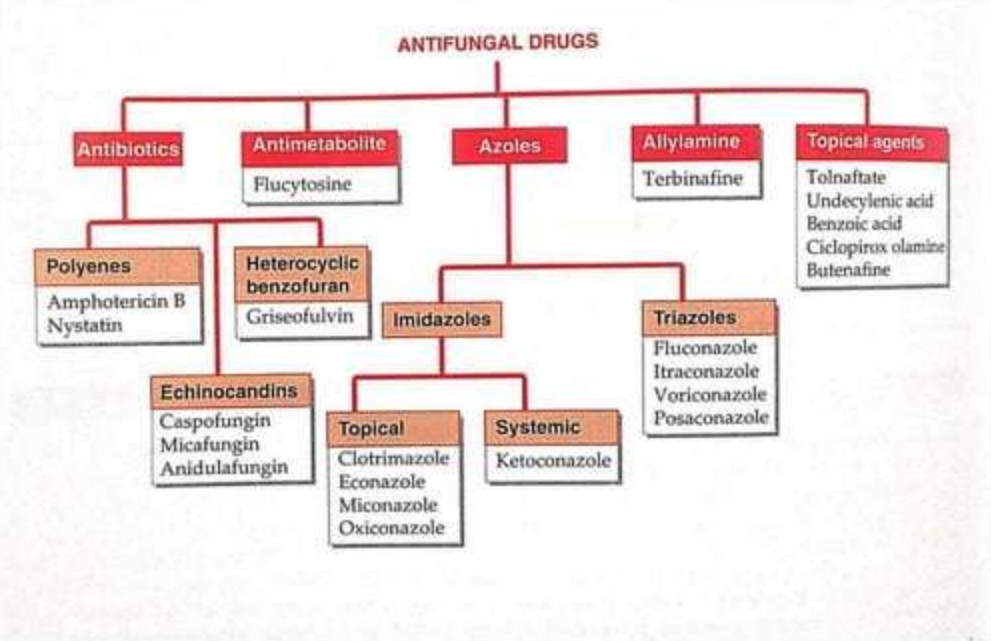

Fungal cell
Cell membrane and cell wall
Mannoproteins
β-(1,6)-glucan
β-(1,3)-glucan
Chitin
Phospholipid bilayer of cell membrane
Ergosterol
β-(1,3)-glucan synthase
Ergosterol Synthesis Pathway
Squalene
DNA/RNA Synthesis

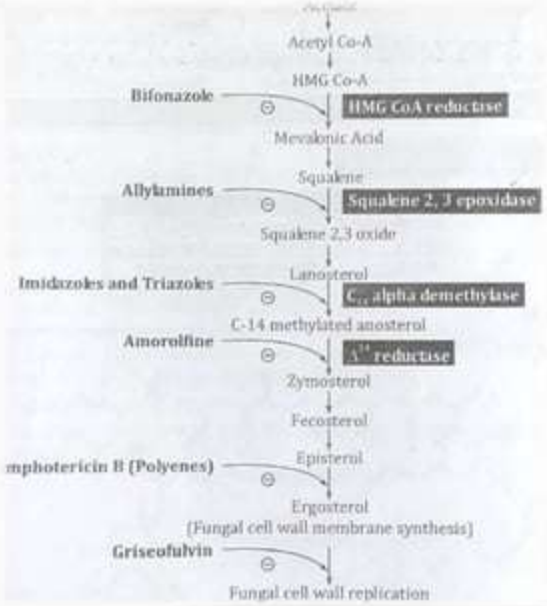
DRUGS USED TO TREAT FUNGAL INFECTIONS

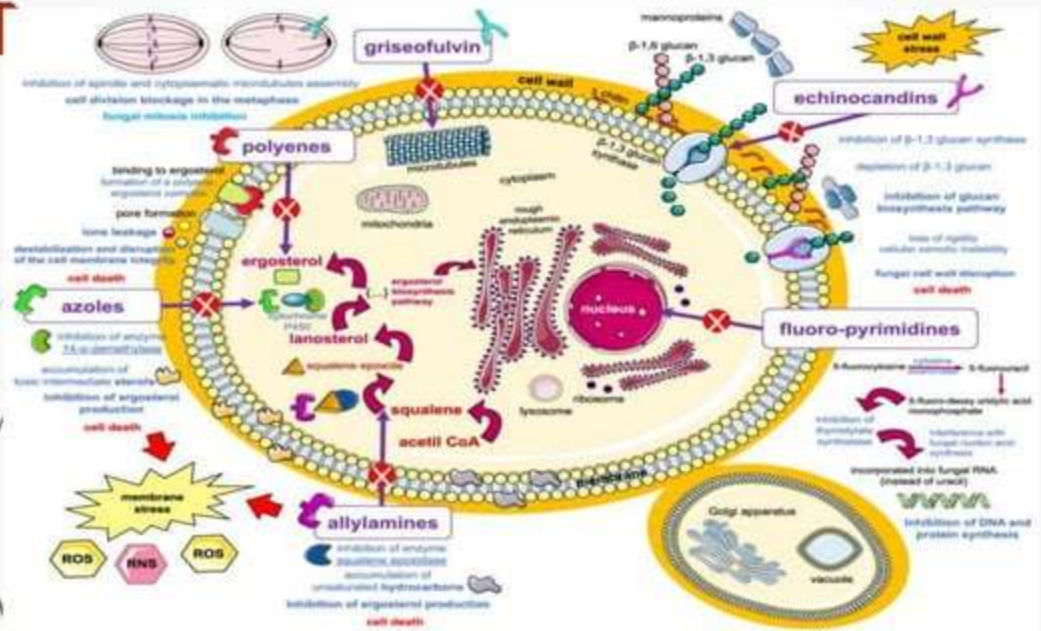
- The current therapeutic agents can be broadly classified into two groups:

1. first, the naturally occurring antifungal antibiotics such as the polyenes and echinocandins, and
2. second, synthetic drugs including azoles and fluorinated pyrimidines. Because many infections are superficial, there are many topical preparations. Many antifungal agents are quite toxic, and when systemic therapy is required these agents must often be used under strict medical supervision.

CLASSIFCATION




Acetyl Co-A
HMG Co-A
Bifonazole
HMG CoA reductase
Mevalonic Acid
Squalene
Allylamines
Squalene 2, 3 epoxidase
Squalene 2,3 oxide
Lanosterol
Imidazoles and Triazoles
C14 alpha demethylase
C-14 methylated anosterol
Amorolfine
Δ14 reductase
Zymosterol
Fecosterol
Episterol
mphotericin B (Polyenes)
Ergosterol
(Fungal cell wall membrane synthesis)
Griseofulvin
Fungal cell wall replication


griseofulvin
inhibition of spindle and cytoplasmatic microtubules assembly
cell division blockage in the metaphase
fungal mitosis inhibition
polyenes
binding to ergosterol
formation of a polyene-ergosterol complex
pore formation
ions leakage
destabilization and disruption of the cell membrane integrity
cell death
azoles
inhibition of enzyme 14-α-demethylase
accumulation of toxic intermediate sterols
inhibition of ergosterol production
cell death
membrane stress
ROS
RNS
ROS
allylamines
inhibition of enzyme squalene epoxidase
accumulation of unsaturated hydrocarbons
inhibition of ergosterol production
cell death
cell wall
β-1,6 glucan
β-1,3 glucan
mannoproteins
cell wall stress
echinocandins
inhibition of β-1,3 glucan synthase
depletion of β-1,3 glucan
inhibition of glucan biosynthesis pathway
loss of rigidity, cellular osmotic instability
fungal cell wall disruption
cell death
fluoro-pyrimidines
5-fluorouracil
5-fluorouracil
5-fluoro-deoxy uridylic acid monophosphate
inhibition of thymidylate synthetase
interference with fungal nucleic acid synthesis
incorporated into fungal RNA (instead of uracil)
inhibition of DNA and protein synthesis
cytoplasm
microtubules
mitochondria
rough endoplasmic reticulum
nucleus
ergosterol
ergosterol biosynthesis pathway
lanosterol
squalene epoxide
squalene
acetil CoA
ribosome
lysosome
plasma membrane
Golgi apparatus
vacuole

ANTIFUNGAL ANTIBIOTICS

A. AMPHOTERICIN

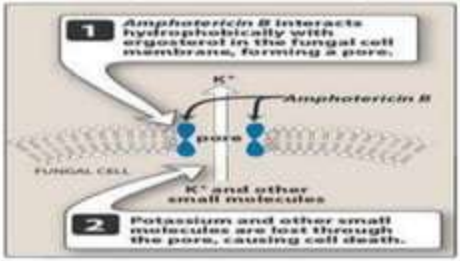
1. Amphotericin (also called amphotericin B) is a mixture of antifungal substances derived from cultures of Streptomyces.
2. Structurally, these are very large ('macrolide') molecules belonging to the polyene group of antifungal agents.

- **MECHANISM:**

1. It interferes with permeability and with transport functions. Its most important property is probably its ability to form large pores in the membrane.
2. Bind the ergosterol and forming ergosterol polyene complex→ pore formation →leakage of inner materials → cell die

PHARMACOKINETICS

1. Poorly absorbed orally , is effective for fungal infection of gastrointestinal tract.
3. For systemic infections given as slow I.V.I.
4. Highly bound to plasma protein .
5. Poorly crossing BBB, Metabolized in liver.
6. Excreted slowly in urine over a period of several days, Half-life 16 days.



ADVERSE EFFECT:

1. Fever, muscle spasm, vomiting, headache, hypotension.
2. Most serious is renal toxicity (nearly in all patients). Hypokalemia ,Hypomagnesaemia ,Impaired liver functions ,Thrombocytopenia, Anemia

CLINICAL USES

Has a broad spectrum of activity & fungicidal action. The drug of choice for life-threatening mycotic infections. For induction regimen for serious fungal infection. Also, for chronic therapy & preventive therapy of relapse. In cancer patients with neutropenia who remain febrile on broad –spectrum antibiotics.

B. NYSTATIN

1. It is a polyene macrolide ,similar in structure & mechanism to amphotericin B.
2. Too toxic for systemic use.
3. Used only topically.
4. It is available as creams, ointment , suppositories & other preparations.
5. Not significantly absorbed from skin, mucous membrane, GIT .

- **CLINICAL USES**

1. Prevent or treat superficial candidiasis of mouth, esophagus, intestinal tract.
2. Vaginal candidiasis
3. Can be used in combination with antibacterial agents & corticosteroids.

AZOLES

1. A group of synthetic fungistatic agents with a broad spectrum of activity . They have antibacterial , antiprotozoal anthelminthic & antifungal activity.

- Mechanism of Action

1. Inhibit the fungal cytochrome P450 enzyme, (αdemethylase) which is responsible for converting lanosterol to ergosterol (the main sterol in fungal cell membrane).
2. Inhibition of mitochondrial cytochrome oxidase leading to accumulation of peroxides that cause autodigestion of the fungus.
3. Imidazoles may alter RNA& DNA metabolism.

THEY ARE CLASSIFIED INTO :

A. IMIDAZOLE GROUP

1. Ketoconazole, Miconazole, Clotrimazole

MOA: Ketoconazole interacts with 14-α-sterol demethylase, a cytochrome P-450 enzyme necessary for the conversion of lanosterol to ergosterol.

USES:

1. Oral & vaginal candidiasis.
2. Dermatophytosis.
3. Systemic mycoses.

ADVERSE EFFECT: Nausea, vomiting ,anorexia ,Hepatotoxic, Gynacomestia

CONTRAINDICATED: Pregnancy , lactation ,hepatic dysfunction

B. TRIAZOLE GROUP

- Fluconazole ,Itraconazole ,Voriconazole

1. Selective
2. Resistant to degradation
3. Causing less endocrine disturbance

1. FLUCONAZOLE:

MOA: interruption of the conversion of lanosterol to ergosterol via binding to fungal cytochrome P-450 and subsequent disruption of fungal membranes..

USES: Oral & vaginal candidiasis ,Dermatophytosis, Systemic mycoses.

ADVERSE EFFECT: Nausea, vomiting ,anorexia ,Hepatotoxic, Gynacomestia

CONTRAINDICATED: Pregnancy, lactation ,hepatic dysfunction

Itraconazole

1. Has a broad spectrum activity
2. Given orally & IV
3. Food increases its absorption
4. Metabolized in liver to active metabolite
5. Highly lipid soluble ,well distributed to bone, sputum ,adipose tissues.
6. Can not cross BBB, Half-life 30-40 hours

- **Used** orally in dermatophytosis & vulvovaginal candidiasis, IV only in serious infections.
- **Side effects :** Nausea, vomiting, hypokalemia, hypertension, edema, inhibits the metabolism of many drugs as oral anticoagulants.

Anti-metabolite

A. Flucytosine

- Synthetic pyrimidine antimetabolite (cytotoxic drug) often given in combination with amphotericin B & itraconazole, Systemic fungistatic
- MECHANISM:

Converted within the fungal cell to 5- fluorouracil (Not in human cell), that inhibits thymidylate synthetase enzyme that inhibits DNA synthesis.

(Amphotericin B increases cell permeability , allowing more 5-FC to penetrate the cell, they are synergistic).

- Pharmacokinetic

Rapidly & well absorbed orally ,Widely distributed including CSF, Mainly excreted unchanged through kidney ,Half-life 3-6 hours.

- **CLINICAL USES:** Meningitis, For cryptococcal meningitis in AIDS patients.
- **ADVERSE EFFECT:**

Reversible neutropenia, thrombocytopenia, bone marrow depression , Alopecia, Nausea, vomiting , diarrhea, severe enterocolitis

- **CASPOFUNGIN (Echinocandins)**
- **MECHANISM:** Inhibits the synthesis of fungal cell wall by inhibiting the synthesis of β(1,3)-D-glucan, leading to lysis & cell death.
- Given by IV route only , Highly bound to plasma proteins , Half-life 9-11 hours , Slowly metabolized by hydrolysis & acetylation. ,Elimination is nearly equal between the urinary & fecal routes.
- **CLINICAL USES:** Effective in aspergillus & candida infections, Second line for those who have failed or cannot tolerate amphotericin B or itraconazole.
- **ADVERSE EFFECTS :**Flushing (release of histamine from mast cells), Nausea, vomiting

GRISEOFULVIN (HETROCYCLC BENZOFURAN)

- Fungistatic, has a narrow spectrum
- Given orally (Absorption increases with fatty meal)
- Half-life 26 hours
- Should be given for 2-6weeks for skin & hair infections to allow replacement of infected keratin by the resistant structure
- **MECHANISM:** Inhibits fungal mitosis by interfering with microtubule function
- **USES:** Used to treat dermatophyte infections (ring worm of skin, hair, nails). ,Highly effective in athlete, s foot.
- **ADVERSE EFFECTS:** Peripheral neuritis, mental confusion, fatigue, vertigo, GIT upset, enzyme inducer, blurred vision, Increases alcohol intoxication.

TOLNAFTATE

- Effective in most cutaneous mycosis.
- Used in tinea pedis (cure rate 80%), Used as cream, gel, powder, topical solution , Applied twice daily.

NAFTIFINE

Broad spectrum fungicidal .

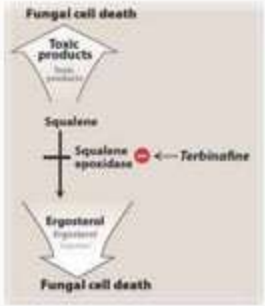
Available as cream or gel.

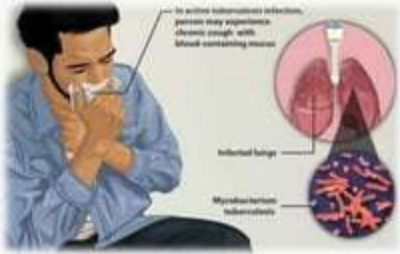
Effective for treatment of tinea cruris.

TERBINAFINE

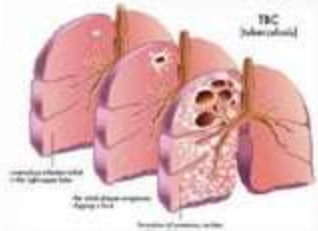
- **MECHANISM:** Inhibit ergosterol production. Inhibits fungal squalene epoxidase, decreases ,the synthesis of ergosterol .(Accumulation of squalene ,which is toxic to the organism causing death of fungal cell).

1. Drug of choice for treating dermatophytes (onychomycoses).
2. Well absorbed orally , bioavailability decreases due to first pass metabolism in liver.
3. Highly protein binding
4. Accumulates in skin , nails, fat.
5. Severely hepatotoxic, liver failure even death.
6. GIT upset (diarrhea, dyspepsia, nausea)
7. Taste & visual disturbance.





ANTI-TUBERCULOSIS:



INTRODUCTION:

- Tuberculosis is a chronic granulomatous disease and a major health problem in developing countries. About 1/3rd of the world's population is infected with Mycobact. tuberculosis.
- The main mycobacterial infections in humans are tuberculosis and leprosy, chronic infections caused by Mycobacterium tuberculosis and M. leprae, respectively.
- Tuberculosis generally affect the lung.
- All first line drug except ethambutol are bacteriostatic.
- All first line drug show hepatotoxicity except streptomycin and ethambutol
- First line drug used in pregnancy except streptomycin because it cause ototoxicity and which is contraindicated in pregnancy.

DRUGS USED TO TREAT TUBERCULOSIS

- India has a large load of HIV infected subjects (estimated2.1 million living with HIV in 2015), and these persons have 10% risk of developing TB every year. Moreover, they are especially vulnerable to severe forms of tubercular/MAC infection Emergence of multidrug resistant (MDR) TB which now accounts for 20% of previously treated, and 3.3% of new TB cases worldwide is a major challenge in antitubercular chemo- therapy. As per latest survey, in India-3% of new cases and 12-17% of previously treated patients have MDR TB.
- For centuries, tuberculosis was a major killer disease, but the introduction of **streptomycin** in the late 1940s followed by **isoniazid** and, in the 1960s, of **rifampicin** and **ethambutol** revolutionised therapy, and tuberculosis came to be regarded as an easily treatable condition.

- According to their clinical utility the anti-TB drugs can be divided into:

1. **First line:** These drugs have high antitubercular efficacy as well as low toxicity, are used routinely.
2. **Second line:** These drugs have either low antitubercular efficacy or higher toxicity or both and are used when first line drugs cannot be used, or to supplement them.

- Respiratory tuberculosis affected organs:

1. Pleural cavity
2. Mediastinal lymph mode
3. larynx

- To decrease the probability of the emergence of resistant organisms, compound drug therapy is a frequent strategy.
- This commonly involves:

• An initial phase of treatment (about 2 months) with a combination of isoniazid, rifampicin and pyrazinamide (plus ethambutol if the organism is suspected to be resistant).

- second, continuation phase (about 4 months) of therapy, with isoniazid and rifampicin; longer-term treatment is needed for patients with meningitis, bone/joint involvement or drug-resistant infection
- Two novel drugs, bedaquiline and delamanid have been recently approved. and bedaquiline is being used as reserve drug.

Antitubercular Drug

First line Drug

- Pyrazinamide
- Ethambutol
- Rifampicin
- Isoniazid
- Streptomycin

Second line Drug

Fluoroquinolone

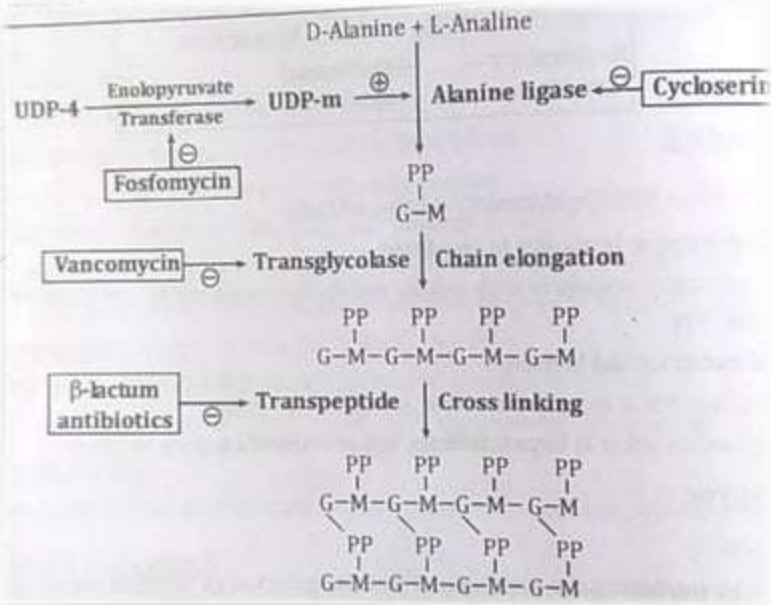
- Ofloxacin
- Levofloxacin
- Moxifloxacin
- Ciprofloxacin

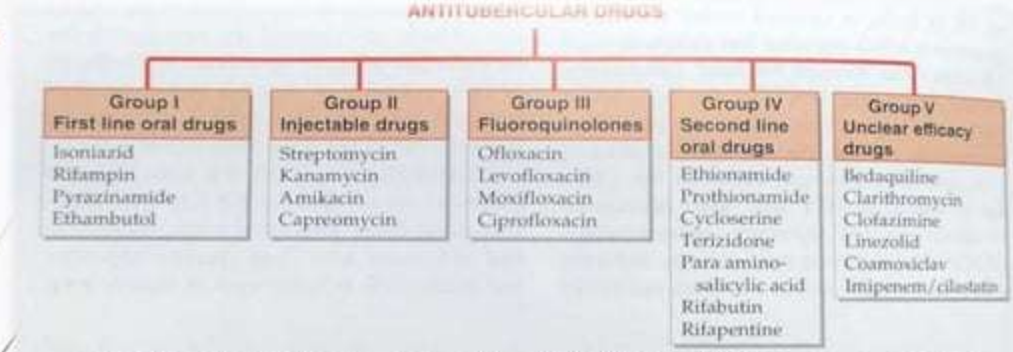
Other oral drugs

- Ethionamide
- Cycloserine
- Para amino salicylic acid
- Rifabutin
- Rifapentine
- Prothionamide

Injectable drug

- Kanamycin
- Amikacin
- capreomycin


D-Alanine + L-Analine
UDP-4
Enolopyruvate
Transferase
UDP-m
Alanine ligase
Cycloserin
Fosfomycin
PP
G–M
Vancomycin
Transglycolase
Chain elongation
PP PP PP PP
G–M–G–M–G–M–G–M
β-lactum
antibiotics
Transpeptide
Cross linking
PP PP PP PP
G–M–G–M–G–M–G–M
PP PP PP PP
G–M–G–M–G–M–G–M



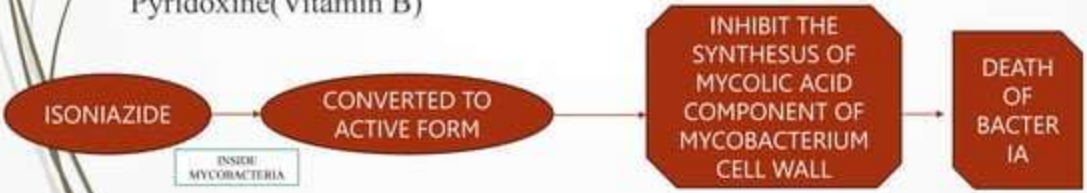
*Adopted from: Treatment of tuberculosis guidelines; WHO (2010) and RNTCP: Technical and operational guidelines for tuberculosis control (2016)

Group I: are the most potent and best tolerated oral drugs used routinely.
Group II: are potent and bactericidal, but injectable drugs.
Group III: includes fluoroquinolones (FQs) which are well tolerated bactericidal oral drugs; all patients with drug resistant TB should receive one FQ.
Group IV: are less effective, bacteriostatic/more toxic oral drugs for resistant TB.
Group V: are drugs with uncertain efficacy; not recommended for MDR-TB; may be used as reserve drugs, and in extensively resistant TB (XDR-TB).

First line drug :

1. Isoniazid [INH]

- It is a prodrug activated by catlase peroxidase (coded by KatG), Active metabolite Inhibits the enzyme ketoenoylreductase (coded by inh A) required for mycolic acid synthesis, an essential component of mycobacterial cell wall.
- It is the single dose important drug used in TB (Drug of choice for TB)
- It is the drug of choice for prophylaxis of tuberculosis.
- It cause peripheral neuritis that can be prevented and treated by Pyridoxine(Vitamin B)



- Isoniazid is restricted due to occurance of neurotoxicity.
- Isoniazid antitubercular drug that require pyridoxine supplement.
- **PHARMACOKINETICS**

1. It is widely distributed in the body including CSF.
2. It is effective orally and metabolized by Acetylation.
3. It is an essential component of multi-drug therapy.
4. PAS inhibits isoniazid metabolism and prolongs its action.
5. It caves peripheral neuritis that can be prevented and treated by pyridoxine.
6. It is also hepatotoxic and can cause hemolysis in G-6-PD deficient patients.
7. Essential component of MDT (Multi Drug Therapy)

8. PAS Inhibits INH metabolism and prolong its action.
9. Pyridoxine (Vitamin B6) given prophylactically prevents neurotoxicity.
10. Isoniazid is excreted in the urine partly as unchanged drug and partly in the acetylated or otherwise inactivated form.

- **DRUG INTERACTION:** Isoniazid inhibit metabolism of phenytoin are excreted in urine
- Unwanted effects depend on the dosage and occur in about 5% of individuals, the commonest being allergic skine ruptions

1. A variety of other adverse reactions have been reported, including fever, hepatotoxicity, haemato logical changes, arthritic symptoms and vasculitis.

- **ADVERSE EFFECTS** : involving the central or peripheral nervous systems are largely consequences of pyridoxine deficiency and are common in malnourished patients unless prevented by administration of this substance. Isoniazid may cause haemolytic anaemia in individuals with glucose 6-phosphatedehydrogenase deficiency, and it decreases the metabolism of the antiepileptic agents phenytoin, ethosuximide and carbamazepine, resulting in an increase in the plasma concentration and toxicity of these drugs.

2. RIFAMPICIN

- Rifampicin acts by binding to, and inhibiting, DNA dependent RNA polymerase in prokaryotic but not in eukaryotic cells . It is one of the most active antituberculosis agents known, and is also effective against leprosy (see below) and most Gram-positive bacteria as well as many Gram-negative species. It enters phagocytic cells and can therefore kill intracellular micro organisms including the tubercle bacillus. Resistance can develop rapidly in a one-step process and is thought to be caused by chemical modification of microbial DNA-dependent RNA polymerase, resulting from a chromosomal mutation.
- **Distribution:** Rifampicin is given orally and is widely distributed in the tissues and body fluids (including CSF), giving an orange tinge to saliva, sputum, tears and sweat. It is excreted partly in the urine and partly in the bile, some of it undergoing enterohepatic cycling.

PHARMACOKINETICS:

1. The metabolite retains antibacterial activity but is less well absorbed from the gastrointestinal tract. The half-life is 1–5 h, becoming shorter during treatment because of induction of hepatic microsomal enzymes.
2. Red orange discoloration of urine.
3. It is a derivative of Rifamycin (other derivatives are rifabutin and rifapentine)
4. Rifampicin + Doxycycline Treatment of Brucellosis.
5. Rifampicin is tuberculocidal for both dividing and nondividing mycobacteria.
6. Rifampicin is the most potent sterilizing antitubercular drug, Fastest to kill all bacilli in the lesion.
7. Safest drugs used in pregnancy and renal failure.

- Unwanted effects are relatively infrequent. The commone stare skin eruptions, fever and gastrointestinal disturbances. Liver damage with jaundice has been reported and has proved fatal in a very small proportion of patients, and liver function should be assessed before treatment is started. Rifampicin causes induction of hepatic metabolizing enzymes resulting in an increase in the degradation of warfarin, glucocorticoids, narcotic analgesics, oral antidiabetic drugs, dapsone and oestrogens, the last effect leading to failure of oral contraceptives
- ADVERSE EFFECTS:

1. Flu Syndrome
2. Cutanious syndrome
3. Abdominal syndrome
4. Respiratory syndrome

3. Ethambutol

- Ethambutol has no effect on organisms other than mycobacteria.It is taken up by the bacteria and exerts a bacteriostatic effect after a period of 24 h, although the mechanism by which this occurs is acts by inhibiting the synthesis of arabinogalactan (a component of cell wall) due to Inhibition of arabinosyl transferase.. Resistance emerges rapidly if the drug is used alone. Ethambutol is given orally and is well absorbed. It can reach therapeutic concentrations in the CSF in tuberculous meningitis. In the blood, itis taken up by erythrocytes and slowly released. Ethambutol is partly metabolized and is excreted in the urine.
- Unwanted effects are uncommon,

1. The most important being optic neuritis, which is dose related and is more likely to occur if renal function is decreased. It results in visual disturbances manifesting initially as red–green colour blindness (Eye toxicity)
2. The main adverse effect is retrobulbar neurosis, hyperuricemia and peripheral neuritis.

4. Pyrazinamide

- Pyrazinamide is inactive at neutral pH but tuberculocidal at acid pH.
- Pyrazinamide is interfere with cellular metabolism, specially in synthesis of mycolic acid, same mechanism as INH.
- It is effective against the intracellular organisms in macrophages because, after phagocytosis, the organisms are contained in phagolysosomes where the pH is low. Resistance develops rather readily, but cross-resistance with isoniazid does not occur. The drug is well absorbed after oral administration and is widely distributed, penetrating well into the meninges. It is excreted through the kidney, mainly by glomerular filtration.
- Unwanted effects include gout, which is associated with high concentrations of plasma urates(pain in joints). Gastrointestinal upsets, malaise and fever have also been reported. Serious hepatic damage due to high doses (hepatotoxicity), hyperuricemia.

5. Streptomycin

- First clinically used antitubercular drug,and tubercularcidal but less effective than INH or rifampin.
- It affect on tubercular site but not cross CSF and poor action in acidic medium.
- Mechanism of action similar as aminoglycoside ,act as tuberculocidal aminoglycoside.
- Not Effective orally and injected IM route.
- Cause nephrotoxicity, ototoxicity, NM receptor blockage.

SECOND LINE ANTI TB DRUG:

1. Kanamycin, amikacin:

- These aminoglycoside antibiotics are very similar to streptomycin in antitubercular activity.
- pharmacoknetic properties and types of adverse effects. Many resistant and MDR strains of M.tuberculosis remain sensitive to them. One of these is mostly included in the regimen for MDR-TB during the intensive phase. The RNTCP standardized regimen for MDR-TB includes Km (probably because it is less expensive than Am), but in many countries Am is preferred, because it is considered less toxic. Cross resistance between Km and Am is very common. Both Km and Am produce less vestibular toxicity than hearing loss, but are equally nephrotoxic. Patients should be instructed to report vertigo and tinnitus.Audiometry and monitoring of renal function is recommended. Dose: 0.75-1.0 g/day (10-15 mg/kg/day) i.m.

2. Capreomycin

- Capreomycin is a cyclic peptide antibiotic given by intramuscular injection, but with similar mycobactericidal activity.
- Unwanted effects include kidney damage and injury to the auditory nerve(ototoxicity), with consequent deafness and ataxia.
- The drug should not be given at the same time as streptomycin or other drugs that may cause deafness, nephrotoxicity.
- Cm often causes eosinophilia, rashes, fever and injection site pain. It has to be injected i.m. and is used only as alternative to aminoglycoside antibiotics.

3. Fluroquinolones:

Fluoroquinolones (FQs) like ofloxacin (Ofx), levofloxacin (Lfx), ciprofloxacin (Cfx) and moxifloxacin (Mfx) are relatively new potent oral bactericidal drugs for TB, that have gained prominence as well tolerated second line anti-TB drugs. Fluoroquinolones are broad-spectrum antibiotics that inhibit DNA supercoiling and disrupt DNA replication by trapping gyrase in Mycobacterium tuberculosis (and topoisomerase IV in other bacteria) on DNA as ternary complexes that block the movement of replication forks.

4. Ethionamid: The mechanism of action is also similar to INH: it is converted by mycobacteria into an active intermediate which interferes with mycolic acid synthesis and prevent synthesis of protein and DNA reduce RNA Synthesis. It is completely metabolized in liver and has a short 1 of 2-3 hours.

adverse effects are anorexia, nausea, vomiting, salivation, metallic taste, epigastric discomfort, sulfurous belching and hepatitis. It also causes aches and pains, peripheral neuritis, behavioural changes, rashes, impotence, menstrual disturbances and goiter on prolonged use. Ethionamide is used only for drug-resistant TB.

5. Prothionamide:

6. Cycloserine: Cycloserine is a broad-spectrum antibiotic that inhibits the growth of many bacteria, including coliforms and mycobacteria. It is water soluble and destroyed at acid pH. It acts by competitively inhibit in bacterial cell wall synthesis. It does this by preventing the formation of D-alanine and the D-Ala-D-Ala dipeptide that is added to the initial tripeptide side-chain on N-acetylmuramic acid, i.e. it prevents completion of the major building block of peptidoglycan .It is absorbed orally and distributed throughout the tissues and body fluids, including CSF. Most of the drug is eliminated in active for min the urine, but approximately 35% is metabolized.

- Cycloserine has unwanted effects mainly on the central nervous system. A wide variety of disturbances may occur, ranging from headache and irritability to depression, convulsions and psychotic states. Its use is limited to tuberculosis that is resistant to other drugs.

7.Terizidone:

- It contains 2 molecules of cycloserine and has antibacterial properties as well as mechanism of action similar to it, but is believed to be less neurotoxic; reported incidence of adverse effects is lower. It is used as a substitute of Cs, especially in genitourinary TB, because it attains higher and longer lasting concentration in urine.

8. Para amino salicylic acid:

- Introduced in 1946, PAS is related to sulfonamides and acts probably by the same mechanism, i.e. inhibition of folate synthase. It is not active against other bacteria, and this selectivity may be due to difference in the affinity for folate synthase of M.tuberculosis compared to that of other bacteria. However, other mechanisms of action are also possible.
- Patient acceptability of PAS is poor because of frequent anorexia, nausea and epigastric pain. Other adverse effects are rashes, fever, malaise, hypokalaemia, goiter, liver dysfunction and rarely blood dyscrasias.

9. **Refabutin:** Rifabutin acts via the inhibition of DNA-dependent RNA polymerase in gram-positive and some gram-negative bacteria, leading to a suppression of RNA synthesis and cell death.

The primary indication of rifabutin is for prophylaxis and treatment of MAC infection in HIV-AIDS patients For prophylaxis of MAC, rifabutin alone 300 mg/day is For alternative to azithromycin/clarithromycin, while for treatment of MAC infection, it is combined with 2-3 other anti-MAC drugs.

Adverse effect: Gastrointestinal intolerance, rashes, granulocytopenia, myalgia and uveitis have been reported with rifabutin.

10. Refapentin: Rifapentine It is a rifampin congener, very similar to it in mechanism of action as well as in activity against M tuberculosis and MAC. Cross resistance between the two is complete. Toxicity as well as drug interaction profile is also similar. Rifapentine is as potent an enzyme inducer as rifampicin.

11. Bedaqulline: NEWER DRUG

- Bedaquiline (BDQ) Introduced recently, this diarylquinoline anti-TB drug acts by a novel mechanism. Bedaquiline (BDQ) inhibits mycobacterial ATP synthase, thereby limiting energy production within mycobacterial cell. The human ATP synthase is 20,000 fold less sensitive to BDQ than is the mycobacterial enzyme.
- Bedaquiline is well absorbed orally; fatty meal improves absorption. It is highly plasma protein bound and extensively distributed in tissues. Metabolism occurs in liver, mainly by CYP3A4, and the principal des-methyl metabolite is 20% as active as BDQ, Clinically significant drug interactions occur with CYP3A4 inducers and inhibitors. The terminal t½ of BDQ is very long (-160 days), probably due to redistribution from tissues. It is excreted mainly in faeces.
- Adverse effects of BDQ are nausea, headache, arthralgia and prolongation of QTc interval. Caution is required in using BDQ in patients taking other QTc prolonging drugs. BDQ has the potential to cause hepatotoxicity

REFERENCE:

1. Sousa, Filipa & Nascimento, Cecilia & Ferreira, Domingos & Reis, Salette & Costa, Paulo. (2023). Reviving the interest in the versatile drug nystatin: A multitude of strategies to increase its potential as an effective and safe antifungal agent. Advanced Drug Delivery Reviews. 199. 114969. 10.1016/j.addr.2023.114969.
2. Rang and Dales book page no. 649-654.
3. https://www.slideshare.net/nasertadvi/antifungal-drugs-14709424
4. Dr. K.D.Tripati book page no.815-830