Al-Mustaqbal University

Pharmacology I

3rd stage

Antimycobacterial Drugs

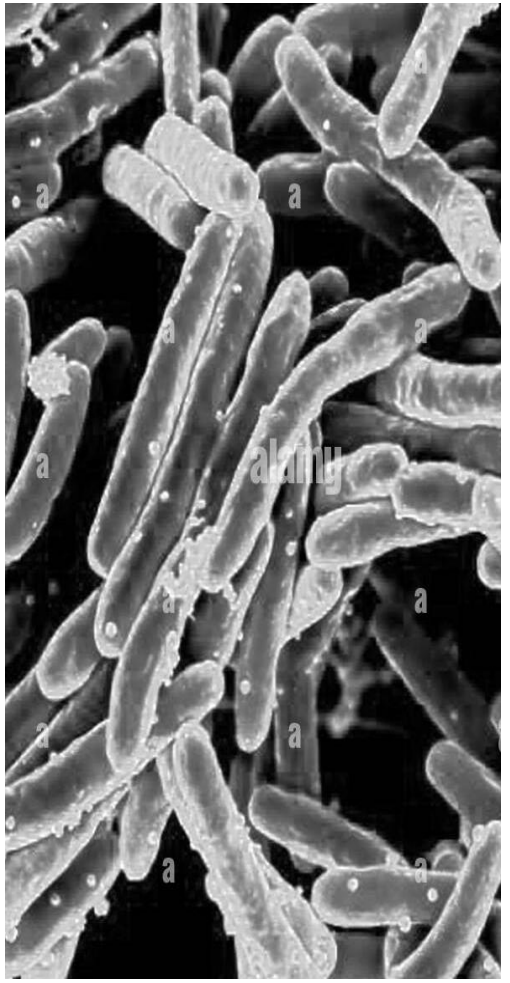
(166- 178)

Dr. Hasanain Owadh

Antimycobacterial Drugs

DRUGS USED TO TREAT TUBERCULOSIS
Ethambutol MYAMBUTOL
Isoniazid GENERIC ONLY
Pyrazinamide GENERIC ONLY
Rifabutin MYCOBUTIN
Rifampin RIFADIN
Rifapentine PRIFTIN
DRUGS USED TO TREAT TUBERCULOSIS (2ND LINE)
Aminoglycosides
Aminosalicylic acid PASER
Bedaquiline SIRTURO
Capreomycin CAPASTAT
Cycloserine SEROMYCIN
Ethionamide TRECATOR
Fluoroquinolones
Macrolides
DRUGS USED TO TREAT LEPROSY
Clofazimine LAMPRENE
Dapsone GENERIC ONLY
Rifampin (Rifampicin) RIFADIN

- Mycobacteria are rod-shaped aerobic bacilli that multiply slowly, every 18 to 24 hours in vitro. Their cell walls contain mycolic acids, which give the genus its name.



Mycobacterium tuberculosis can cause latent tuberculosis infection (LTBI) and the disease known as tuberculosis (TB).

CHEMOTHERAPY FOR TUBERCULOSIS

M. tuberculosis is slow growing and requires treatment for months to years. LTBI can be treated for 9 months with *isoniazid (INH)* monotherapy or with 12 once-weekly higher doses of *INH* and *rifapentine.* In contrast, active TB disease must be treated with several drugs.

Treatment for drug susceptible TB lasts for at least 6 months,
while treatment of multidrugresistant TB (MDR-TB) typically lasts for about
2 years.

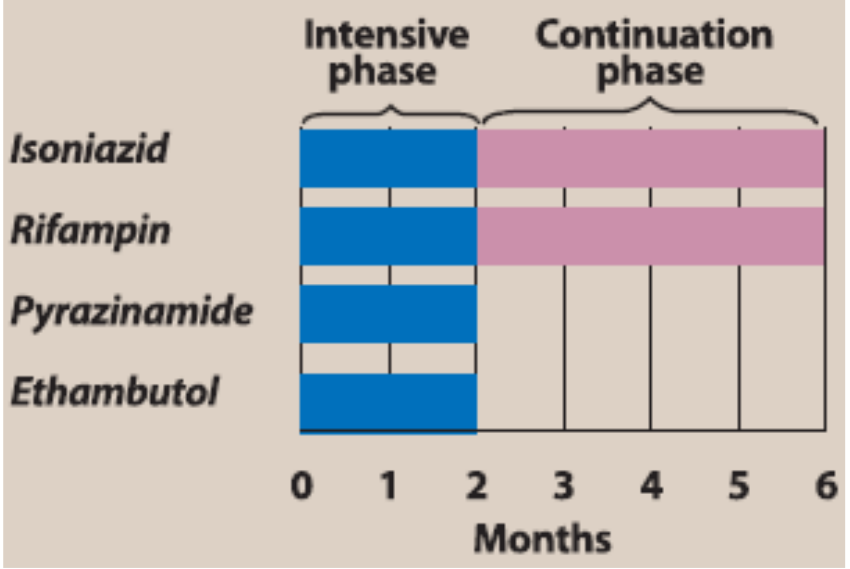
A. Strategies for addressing drug resistance

The resistance develops rapidly in TB patients given only *streptomycin.*
Multidrug therapy is employed to suppress these resistant organisms.

The first-line drugs:
isoniazid,
rifampin,
ethambutol,
and pyrazinamide
are preferred because of their high efficacy and acceptable incidence of toxicity. Rifabutin or rifapentine may replace rifampin under certain circumstances. Active disease requires treatment with three or more drugs.

Although clinical improvement can occur in the first several weeks of treatment, therapy is continued much longer to eradicate persistent organisms and to prevent relapse.

Standard short-course chemotherapy for tuberculosis includes
isoniazid, rifampin, ethambutol, and pyrazinamide for 2 months (the intensive phase),
followed by isoniazid and rifampin for 4 months (the continuation phase).



Once susceptibility data are available, the drug regimen can be individually tailored.

Second-line regimens for MDR-TB (TB resistant to at least isoniazid and rifampin).

normally include an aminoglycoside (streptomycin, kanamycin, or amikacin) or capreomycin (all injectable agents), a fluoroquinolone (typically, levofloxacin or moxifloxacin), any first-line drugs that remain active, and one or more of the following: cycloserine, ethionamide, or p-aminosalicylic acid.

For extensively drug-resistant TB (XDR-TB), other drugs such as clofazimine and linezolid may be employed empirically.

Patients take the medications under observation of a member of the health care team.

directly observed therapy (DOT) decreases drug resistance and improves cure rates.

Most public health departments offer DOT services.

I. Isoniazid (INH)

Isoniazid [eye-so-NYE-a-zid], along with rifampin, is one of the two most important TB drugs.

1. Mechanism of action: Isoniazid is a prodrug activated by a mycobacterial. Isoniazid inhibits synthesis of mycolic acid that leads to a disruption in the bacterial cell wall.

2. Antibacterial spectrum: Isoniazid is specific for treatment of M. tuberculosis, although M. kansasii may be susceptible at higher drug concentrations.
active against intracellular organisms.

3. Resistance: Resistance follows chromosomal mutations, including

1) mutation or deletion of enzyme require for prodrug activation,
2) varying mutations of the acyl carrier proteins, or
3) overexpression of the target enzyme InhA.

Crossresistance may occur between isoniazid and ethionamide.

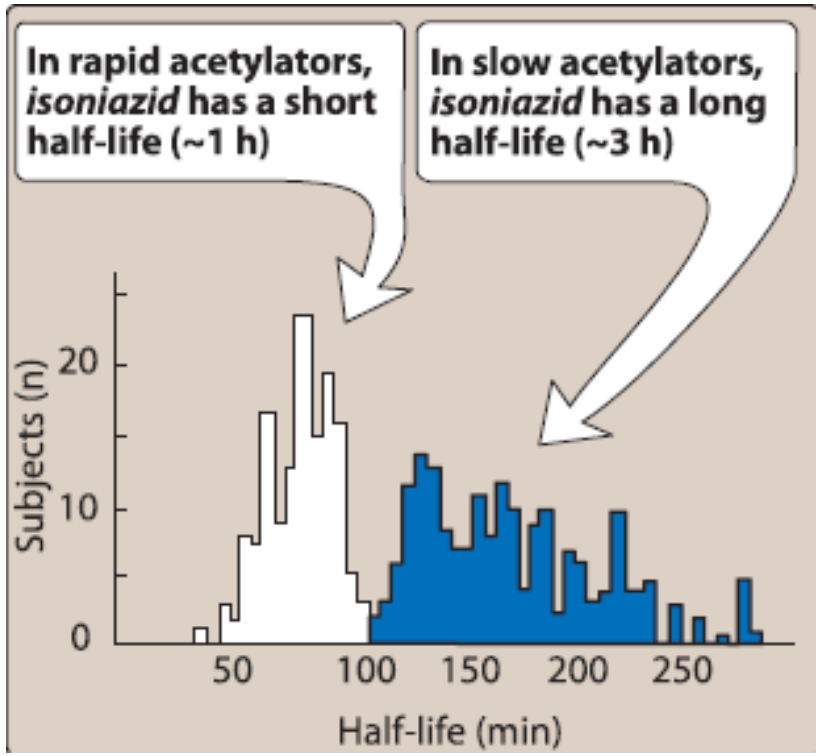
4. Pharmacokinetics:

Isoniazid is readily absorbed after oral administration.

GIT Absorption is impaired by high-fat meals.

The drug diffuses into (tuberculous lesions) and drug concentrations in the cerebrospinal fluid (CSF) are similar to those in the serum.

- Isoniazid metabolized by N-acetylation and hydrolysis (inactivation).
- Isoniazid acetylation is genetically regulated, with fast acetylators (patients) exhibiting a 90-minute serum half-life, as compared with 3 to 4 hours for slow acetylators.
- Excretion by glomerular filtration. Slow acetylators excrete more of the parent compound.



Adverse effects:

1- Hepatitis is the most serious adverse effect The incidence increases with age (greater than 35 years old), among patients who also take *rifampin,* or among those who drink alcohol daily.

2- Peripheral neuropathy, (paresthesia of the hands and feet) due to pyridoxine deficiency caused by *isoniazid.* This can be avoided by daily supplementation of pyridoxine (vitamin B6). Central nervous system

3- (CNS) adverse effects can occur, including convulsions in patients prone to seizures.

4- Hypersensitivity reactions with *isoniazid* include rashes and fever.

5- Drug interactions: Because isoniazid inhibits metabolism of phenytoin, isoniazid can potentiate the adverse effects of that drug (for example, nystagmus and ataxia).

C. Rifamycins: rifampin, rifabutin, and rifapentine

A group of structurally similar macrocyclic antibiotics, which are first line oral agents for tuberculosis.

Rifampin: has broader antimicrobial activity than isoniazid and can be used as part of treatment for several different bacterial infections. Because resistant susceptibility, it is never given as a single agent in the treatment of active tuberculosis.

Mechanism of action: Rifampin blocks RNA transcription by interacting with the β subunit of mycobacterial DNA dependent RNA polymerase.

Resistance is caused by mutations in the affinity of the bacterial DNA-dependent RNA polymerase gene for the drug.

Pharmacokinetics: Absorption is adequate after oral administration. Distribution of rifampin occurs to all body fluids and organs. Concentrations attained in the CSF are variable, often 10% to 20% of blood concentrations.

The drug is taken up by the liver and undergoes enterohepatic recycling.

Rifampin can induce hepatic cytochrome P450 enzymes and transporters, leading to numerous drug interactions. Also, it has autoinduction, leading to a shortened elimination half-life over the first 1 to 2 weeks of dosing.

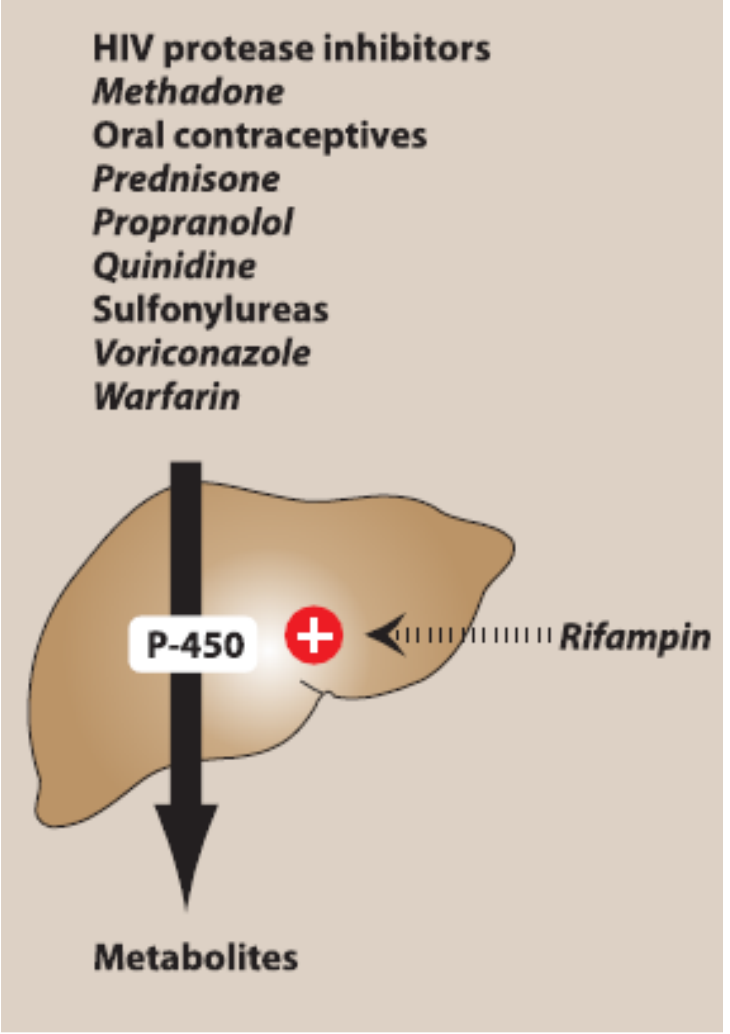
Elimination of rifampin and its metabolites is primarily through the bile and into the feces; a small percentage is cleared in the urine.

Urine, feces, and other secretions have an orange-red color, so patients should be forewarned. Tears may even stain soft contact lenses orange-red.

Antimicrobial spectrum: Rifampin is bactericidal for both intracellular and extracellular mycobacteria, including M. tuberculosis, and NTM, such as M. kansasii and Mycobacterium avium complex (MAC).
It is used prophylactically for individuals exposed to meningitis.
Rifampin also is highly active against M. leprae.

Adverse effects: The most common adverse reactions include nausea, vomiting, and rash.
Hepatitis and death due to liver failure are rare. However, the drug should be used judiciously in older patients, alcoholics, or those with chronic liver disease.
Intermittent and high dose can cause flu-like syndrome, with fever, chills, and myalgia, sometimes extending to acute renal failure, hemolytic anemia, and shock.

Drug interactions: Because rifampin induces a number of phase I cytochrome P450 enzymes and phase II enzymes, it can decrease the half-lives of coadministered drugs that are metabolized by these enzymes. This may necessitate higher dosages for coadministered drugs, a switch to drugs less affected by rifampin, or replacement of rifampin with rifabutin.



Rifabutin: [rif-a-BYOO-tin], a derivative of rifampin, is preferred for TB patients coinfected with the human immunodeficiency virus (HIV) who are receiving protease inhibitors or several of the nonnucleoside reverse transcriptase inhibitors..

Rifabutin is a less potent enzyme inducer, thus lessening drug interactions.

Rifabutin has adverse effects similar to those of rifampin but can also cause uveitis, skin hyperpigmentation, and neutropenia.

Rifapentine: Rifapentine [rih-fa-PEN-teen] has a longer half-life than that of rifampin. In combination with isoniazid, rifapentine may be used once weekly in patients with LTBI and in select HIV negative patients with minimal pulmonary TB.

Pyrazinamide is a synthetic, orally effective short course agent used in combination with isoniazid, rifampin, and ethambutol.

Mechanism of action. Pyrazinamide must be enzymatically hydrolyzed by pyrazinamidase to pyrazinoic acid, which is the active form of the drug. Some resistant strains lack the pyrazinamidase enzyme.

Pyrazinamide is active against tuberculosis bacilli in acidic lesions and in macrophages. The drug distributes throughout the body, penetrating the CSF.

Pyrazinamide may contribute to liver toxicity. Uric acid retention is common, but rarely precipitates a gouty attack.

This drug is usually discontinued after 2 months of a 6-month regimen.

Ethambutol [e-THAM-byoo-tole] is bacteriostatic and specific for mycobacteria.
Ethambutol inhibits arabinosyl transferase an enzyme important for the synthesis of the mycobacterial cell wall.
Ethambutol is used in combination with pyrazinamide, isoniazid, and rifampin pending culture and susceptibility data.
[Note: Ethambutol may be discontinued if the isolate is determined to be susceptible to isoniazid, rifampin, and pyrazinamide.]
Ethambutol distributes well throughout the body. Penetration into the CNS is variable, and it is questionably adequate for tuberculous meningitis.
Both the parent drug and its hepatic metabolites are primarily excreted in the urine.

The most important adverse effect is optic neuritis, which results in diminished visual acuity and loss of ability to discriminate between red and green. Visual acuity and color discrimination should be tested prior to initiating therapy and periodically thereafter. Uric acid excretion is decreased by ethambutol, and caution should be exercised in patients with gout.

DRUG	ADVERSE EFFECTS	COMMENTS
Ethambutol	Optic neuritis with blurred vision, red-green color blindness	Establish baseline visual acuity and color vision; test monthly.
Isoniazid	Hepatic enzyme elevation, hepatitis, peripheral neuropathy	Take baseline hepatic enzyme measurements; repeat if abnormal or patient is at risk or symptomatic. Clinically significant interaction with *phenytoin* and *carbamazepine*.
Pyrazinamide	Nausea, hepatitis, hyperuricemia, rash, joint ache, gout (rare)	Take baseline hepatic enzymes and uric acid measurements; repeat if abnormal or patient is at risk or symptomatic.
Rifampin	Hepatitis, GI upset, rash, flu-like syndrome, significant interaction with several drugs	Take baseline hepatic enzyme measurements and CBC; repeat if abnormal or patient is at risk or symptomatic. Warn patient that urine and tears may turn red-orange in color.

Q- Which of the following statement is incorrect about antimycobacterial drugs.
A- isoniazid, rifampin, ethambutol, and pyrazinamide are preferred because of their high efficacy and acceptable incidence of toxicity.
B- Peripheral neuropathy caused by isoniazid can be avoided by using B6 supplementation.
C- Rifampin has many drug interaction due to induction of phase I and II cytochrome P450 enzymes.
D- Pyrazinamide interacts with β subunit of mycobacterial DNA dependent RNA polymerase.
E- Infections due to streptomycin-resistant mycobacterium may be treated with kanamycin or amikacin.

Alternate second-line drugs

In general, these agents are less effective and more toxic than the first-line agents.

1. Streptomycin: Streptomycin, an aminoglycoside antibiotic, was one of the first effective agents for TB. (greater against extracellular organisms).

Infections due to streptomycin-resistant organisms may be treated with kanamycin or amikacin, to which these bacilli usually remain susceptible.

2. Para-aminosalicylic acid: Para-aminosalicylic acid (PAS) works via folic acid inhibition. While largely replaced by ethambutol for drug-susceptible TB, PAS remains an important component of many regimens for MDR-TB.

Capreomycin: This is a parenterally administered polypeptide that inhibits protein synthesis similar to aminoglycosides. Capreomycin is primarily reserved for the treatment of MDR-TB. Careful monitoring of renal function and hearing is necessary to minimize nephrotoxicity and ototoxicity, respectively.

Cycloserine: Cycloserine is an orally effective, tuberculostatic drug that disrupts o-alanine incorporation into the bacterial cell wall.

It distributes well throughout body fluids, including the CSF.
Cycloserine is primarily excreted unchanged in urine.
Accumulation occurs with renal insufficiency.
Adverse effects involve CNS disturbances (for example, lethargy, difficulty concentrating, anxiety, and suicidal tendency), and seizures may occur.

Ethionamide: Ethionamide is a structural analog of isoniazid that also disrupts mycolic acid synthesis.
The mechanism of action is not identical to isoniazid, but there is some overlap in the resistance patterns.
Ethionamide is widely distributed throughout the body, including the CSF.
Metabolism is extensive, most likely in the liver, to active and inactive metabolites.

Adverse effects that limit its use include nausea, vomiting, and hepatotoxicity.
Hypothyroidism, gynecomastia, alopecia, impotence, and CNS effects also have been reported.

6. Fluoroquinolones: The fluoroquinolones, specifically moxifloxacin and levofloxacin, have an important place in the treatment of multidrug-resistant tuberculosis. Some NTM also are susceptible.

Macrolides: The macrolides, azithromycin and clarithromycin are included in regimens for several NTM infections, including MAC. Azithromycin may be preferred for patients at greater risk for drug interactions, since clarithromycin is both a substrate and inhibitor of cytochrome P450 enzymes.

Bedaquiline: Bedaquiline, a diarylquinoline, is an ATP synthase inhibitor. It is approved for the treatment of MDR-TB. Bedaquiline is administered orally, and it is active against many types of mycobacteria.
Bedaquiline has a boxed warning for QT prolongation, and monitoring of the electrocardiogram is recommended.
Elevations in liver enzymes have also been reported and liver function should be monitored during therapy.

This agent is metabolized via CYP3A4, and administration with strong CYP3A4 inducers (for example, rifampin) should be avoided.

DRUG	ADVERSE EFFECTS	COMMENTS
Fluoroquinolones	GI intolerance, tendonitis, CNS toxicity including caffeine-like effects	Monitor LFTs, serum creatinine/BUN, QT interval prolongation. Avoid concomitant ingestion with antacids, multivitamins or drugs containing di- or trivalent cations.
Aminoglycosides, *Capreomycin*	Nephrotoxicity, ototoxicity	Not available orally. Monitor for vestibular, auditory and renal toxicity.
Macrolides	GI intolerance, tinnitus	Monitor LFTs, serum creatinine/BUN, QT interval prolongation. Monitor for drug interactions due to CYP inhibition (except *azithromycin*).
Ethionamide	GI intolerance, hepatotoxicity, hypothyroidism	Monitor LFTs, TSH. A majority of patients experience GI intolerance. Cross-resistance with *isoniazid* is possible.
Para-aminosalicylic acid (PAS)	GI intolerance, hepatotoxicity, hypothyroidism	Monitor LFTs, TSH. Patients with G6PD deficiency are at increased risk of hemolytic anemia.
Cycloserine	CNS toxicity	Close monitoring is needed for depression, anxiety, confusion, etc. Seizures may be exacerbated in patients with epilepsy. Monitor serum creatinine.

Q- Tuberculosis (TB) is a potentially serous infectious disease that mainly affects the lungs. Which of the following drugs isn't used in the treatment of tuberculosis?

A- Clofazimine. B- Pyrazinamide. C- Ethambutol. D- Isoniazid. E- Rifampin.

DRUGS FOR LEPROSY

Leprosy (or Hansen disease) can be treated effectively with dapsone and rifampin.

A. Dapsone

Dapsone [DAP-sone] is structurally related to the sulfonamides and similarly inhibits dihydropteroate synthase in the folate synthesis pathway.

It is bacteriostatic for M. leprae, and resistant strains may be encountered. Dapsone also is used in the treatment of pneumonia caused by Pneumocystis jirovecii in immunosuppressed patients.

The drug is well absorbed from GIT and is distributed throughout the body, with high concentrations in the skin.

The parent drug undergoes hepatic acetylation. Both parent drug and metabolites are eliminated in the urine. Adverse reactions include hemolysis (especially in patients with glucose-6-phosphate dehydrogenase deficiency), methemoglobinemia, and peripheral neuropathy.

Clofazimine [kloe-FAZ-i-meen] is a phenazine dye.

MOA. It binding to DNA and also may lead to generation of cytotoxic oxygen radicals that are toxic to the bacteria.
Clofazimine is bactericidal to M. leprae, and it has potentially useful activity against M. tuberculosis and NTM.
Use for shorter regimen (9 to 12 months) for MDR-TB.
Following oral absorption, clofazimine accumulates in tissues, allowing intermittent therapy but does not enter the CNS.
Patients typically develop a pink to brownish-black discoloration of the skin and should be informed of this in advance.
Eosinophilic and other forms of enteritis, sometimes requiring surgery, have been reported. Clofazimine has some anti-inflammatory and anti-immune activities. Thus, erythema nodosum leprosum may not develop in patients treated with this drug.

References

Lippincott Illustrated Reviews: Pharmacology. 7TH ed, Wolters Kluwer.

Thank you