Pharmacology I

Antimycobacterial Drugs

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Lecture No. : 10

مستقبل له تاريخ

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)

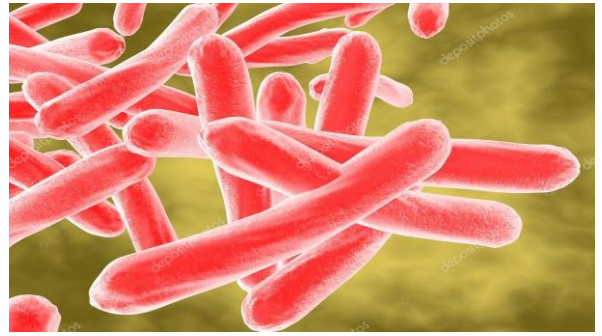
Aminoglycosides
Aminosalicylic acid PASER
Bedaquiline SIRTURO
Capreomycin CAPASTAT
Cycloserine SEROMYCIN
Ethionamide TRECATOR
Fluoroquinolones
Macrolides

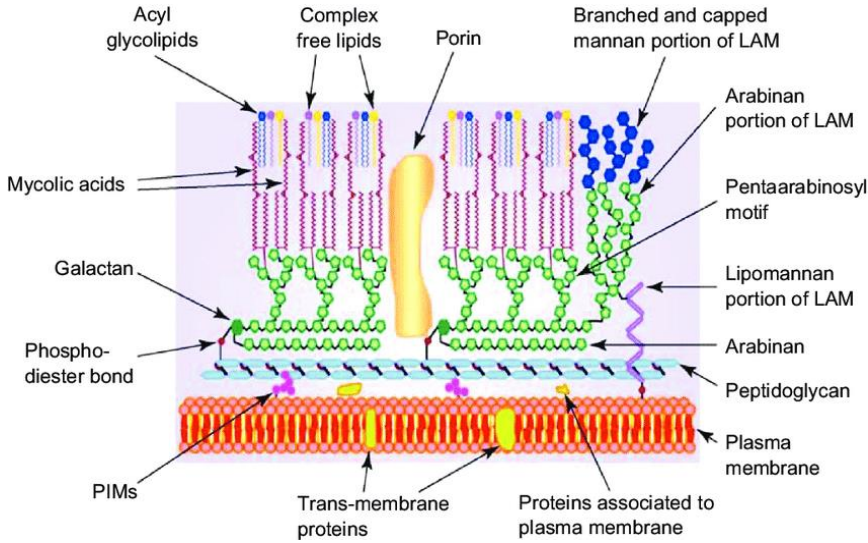
DRUGS USED TO TREAT LEPROSY

Clofazimine LAMPRENE
Dapsone GENERIC ONLY
Rifampin (*Rifampicin*) RIFADIN

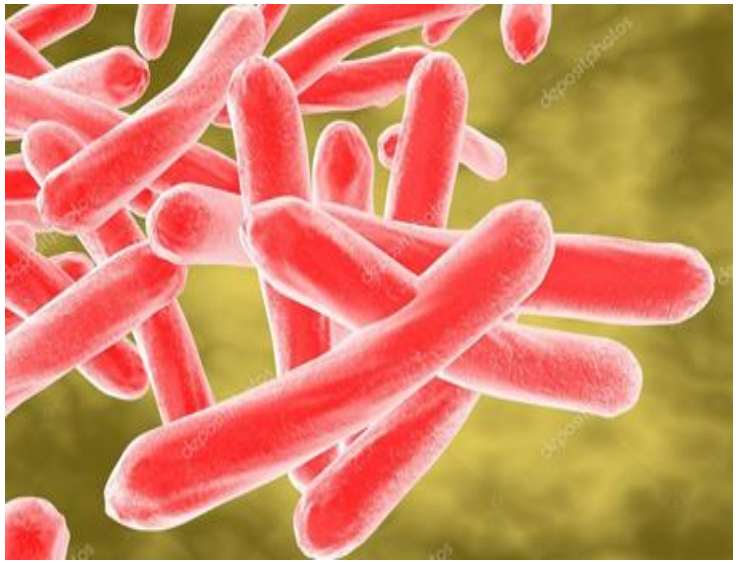
Mycobacteria

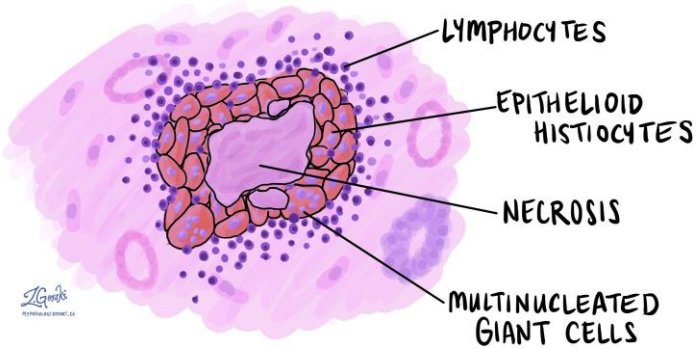
- **Mycobacteria** are **rod-shaped aerobic bacilli** that **multiply slowly**, every 18 to 24 hours *in vitro*.
- Their cell walls contain **mycolic acids**, which give the genus its **name**.
- **Mycolic acids** are **long-chain, β-hydroxylated fatty acids**.





- **Mycobacteria** produce **highly lipophilic cell walls** that stain **poorly** with Gram stain.
- Once stained, the bacilli are **not decolorized** easily by acidified organic solvents.
- Hence, the organisms are called "**acid-fast bacilli**."
- Mycobacterial infections classically result in the formation of **slow-growing, granulomatous lesions** that cause **tissue destruction** anywhere in the body.





granulomatous lesions

- **Mycobacterium** tuberculosis can cause
- 1- **Latent tuberculosis infection** (LTBI) and
- 2- The disease known as **Tuberculosis** (TB).
- [Note: In LTBI, the patient is infected with **M. tuberculosis** **without signs or symptoms** of active TB disease.]
- TB is the **leading infectious cause of death worldwide**, and a **quarter** of the world's population is infected with TB.

• **In 2023, TB caused 1.3 million deaths**

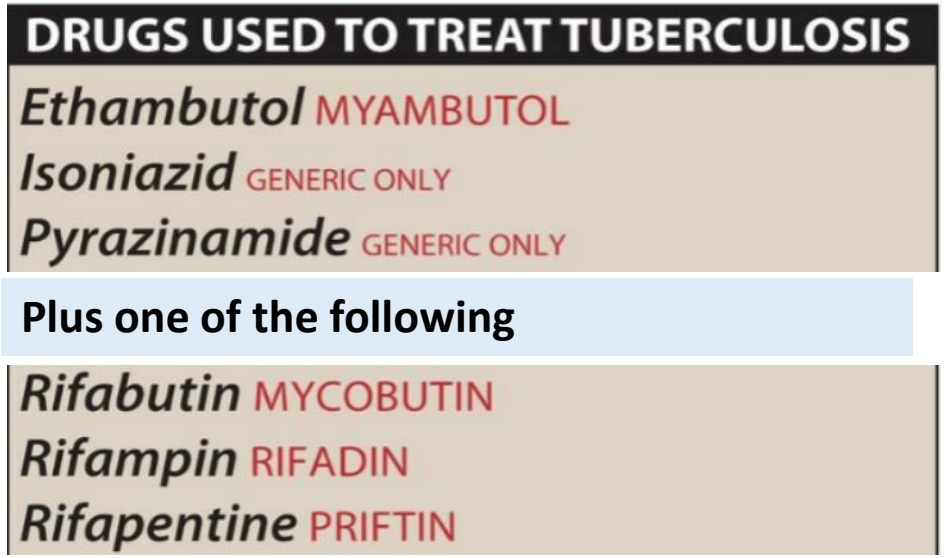
- Increasing in frequency are diseases caused by **nontuberculous mycobacteria (NTM). These species include :**

1. M. avium-intracellulare,
2. M. chelonae,
3. M. abscessus,
4. M. kansasii, and
5. M. fortuitum

- **Finally**, **M. leprae causes leprosy**.

TB treatment

- TB treatment generally includes **four first-line drugs** (Figure 32.1).



- **Second-line drugs** are typically

1. **Less effective,**
2. **More toxic, and**
3. **Less extensively studied.**

- They are used for patients who **cannot tolerate** first-line drugs or who are infected with **resistant TB**.
- No drugs are specifically developed for **NTM infections**.
- **Macrolides, rifamycins, and aminoglycosides** are frequently included, but NTM regimens vary widely by organism.

II. Chemotherapy for Tuberculosis

- **M. tuberculosis** is slow-growing and requires treatment for **months to years**.

- **LTBI** can be treated for **9 months with:**

1. **Isoniazid (INH) monotherapy**
2. **Or once-weekly** higher doses of **INH and Rifapentine**.

Dosage: Isoniazid 300 mg daily (adults) for monotherapy

II. Chemotherapy for Tuberculosis

- 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 **multidrug-resistant TB (MDR-TB) typically lasts for about 2 years**.

A. Strategies for addressing drug resistance

- Populations of M. tuberculosis contain small numbers of organisms that are **naturally resistant** to a particular drug.
- Under selective pressure from **inadequate treatment**, especially from **monotherapy**, these resistant organisms can **emerge** as the **dominant population.**
- Figure 32.2 shows that resistance develops rapidly in TB patients given **only streptomycin**.

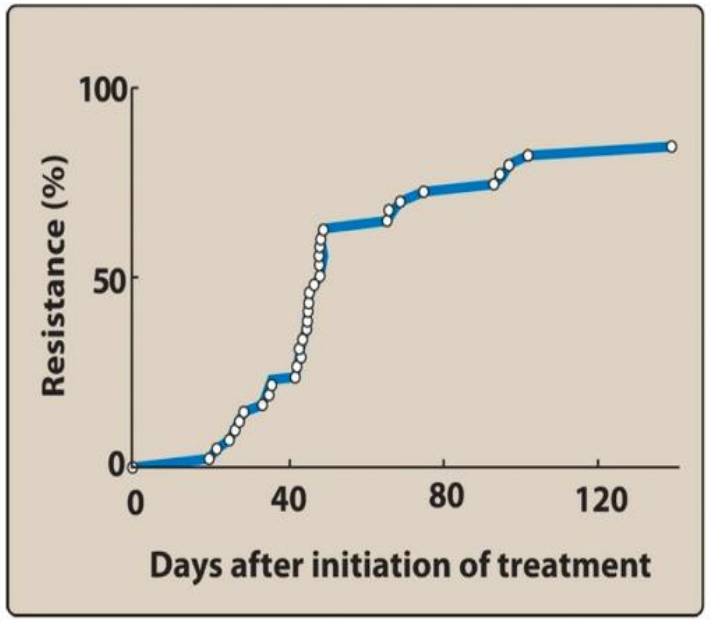


Figure 32.2 Cumulative percentage of strains of Mycobacterium tuberculosis showing resistance to *streptomycin*.

A. Strategies for addressing drug resistance

- **Multidrug therapy** is employed to suppress these resistant organisms.
- **The first-line drugs**

1. **Isoniazid,**
2. **Rifampin,**
3. **Ethambutol,** and
4. **Pyrazinamide**

- These are preferred because of **their high efficacy** and **acceptable incidence of toxicity**.
- Rifabutin or rifapentine may replace rifampin under certain circumstances.

A. Strategies for addressing drug resistance

- **Active disease** always requires treatment with **multidrug regimens**, and preferably three or more drugs with proven in vitro activity against the isolate.
- Although clinical improvement can occur in the **first several weeks** of treatment, therapy is continued much longer to:

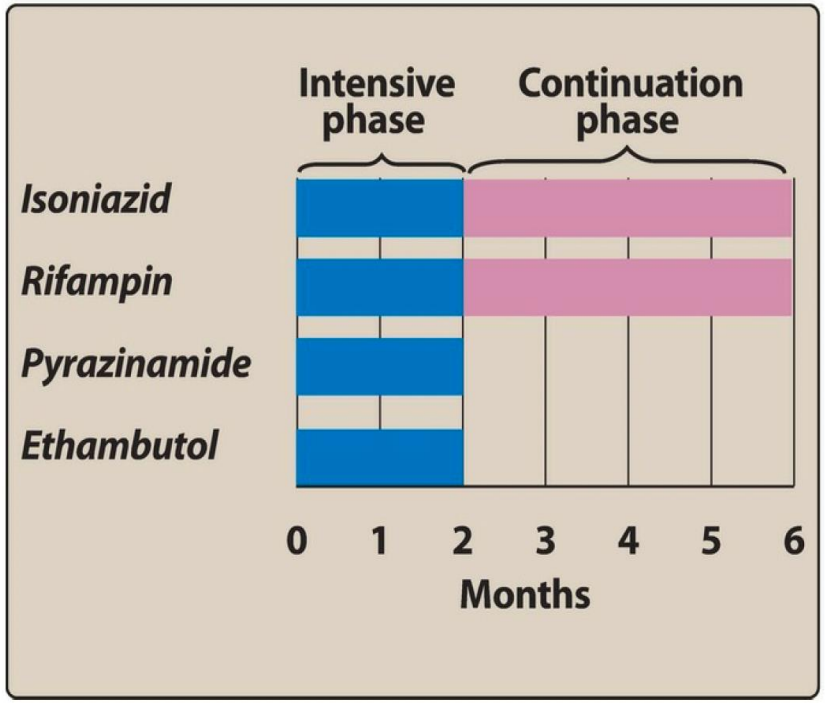
1. **Eradicate** persistent organisms and
2. To **Prevent** relapse.

A. Strategies for addressing drug resistance

- **Standard short-course chemotherapy for tuberculosis includes**

1. **Isoniazid,**
2. **Rifampin,**
3. **Ethambutol,**
4. **Pyrazinamide**

For 2 months (Intensive Phase)



- **Followed by :**

1. **Isoniazid and**
2. **Rifampin for**

4 months (continuation phase).

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

A. Strategies for addressing drug resistance

- **Second-line regimens** for **MDR-TB** (TB resistant to at least isoniazid and rifampin) normally include an:

1. **Aminoglycoside** (streptomycin, kanamycin, or amikacin) **or Capreomycin** (all injectable agents),
2. **A fluoroquinolone** (typically **Levo**floxacin or **Moxi**floxacin),
3. **Any first-line drugs that remain active**, And
4. 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**.

A. Strategies for addressing drug resistance

- Patient adherence can be **low** when multidrug regimens last for 6 months or longer.
- One **successful strategy** for achieving better treatment completion rates is **directly observed therapy** (**DOT**) : Patients take the medications under the observation of a member of the health care team.
- **DOT decreases drug resistance** and **improves cure rates**.
- **Most public health** departments offer **DOT services**.

B. Isoniazid

- **Isoniazid**, along with rifampin, is one of the two most important TB drugs.

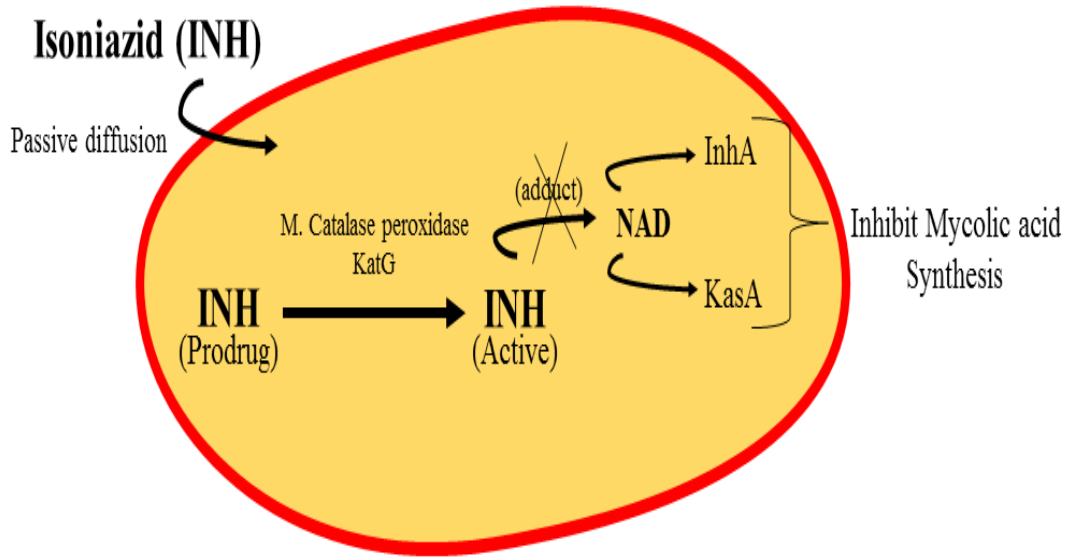
❑ Mechanism of action

- Isoniazid is a **prodrug** activated by a **mycobacterial catalase–peroxidase** (KatG).

- Isoniazid targets the enzymes

1. **Acyl carrier protein reductase** (InhA) and
2. **β-ketoacyl-ACP synthase (KasA),** which are essential for the **synthesis** of **mycolic acid**.

- **Inhibiting** mycolic acid leads to a disruption in the **bacterial cell wall.**



B. Isoniazid

- **Antibacterial spectrum**
- Isoniazid is specific for the treatment of **M. tuberculosis**, although **M. kansasii** may be susceptible at higher drug concentrations.
- **Most NTM are resistant to INH**.
- The drug is particularly effective **against:**

1. **Rapidly growing bacilli** and is also active against
2. **Intracellular organisms**.

B. Isoniazid

- **Resistance**

- Resistance follows chromosomal mutations, including

1) **Mutation or deletion of KatG** (producing mutants incapable of prodrug activation),

2) **Varying mutations of the acyl carrier proteins**, or

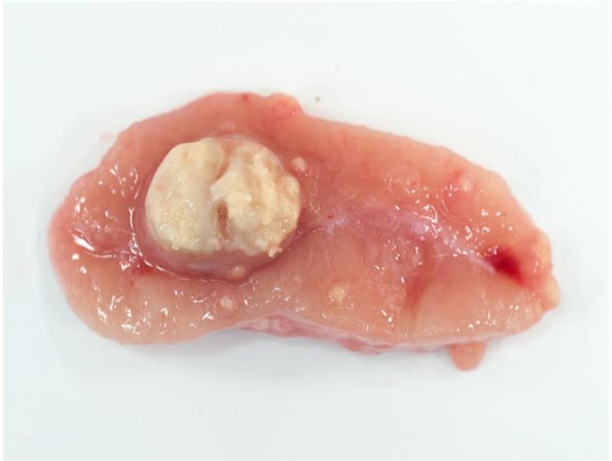
3) **Overexpression of the target enzyme InhA**.

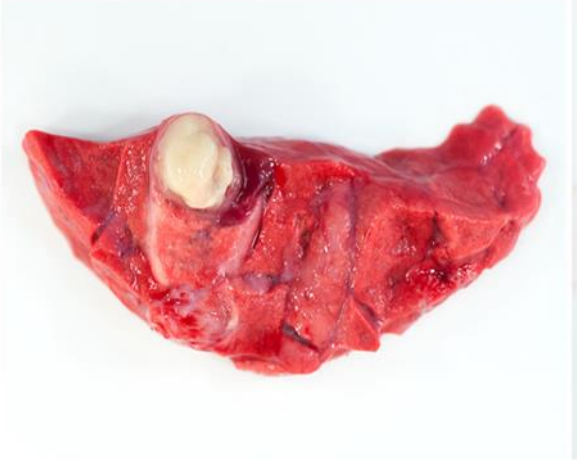
- **Cross-resistance** may occur between **Isoniazid** and **Ethionamide**.

B. Isoniazid

❑ Pharmacokinetics

- Isoniazid is **readily** absorbed after **oral administration**.
- Absorption is **impaired** if isoniazid is taken with **food**, particularly high-fat meals.
- The drug diffuses into all body fluids, cells, and caseous material (necrotic tissue resembling **cheese** that is produced in tuberculous lesions).



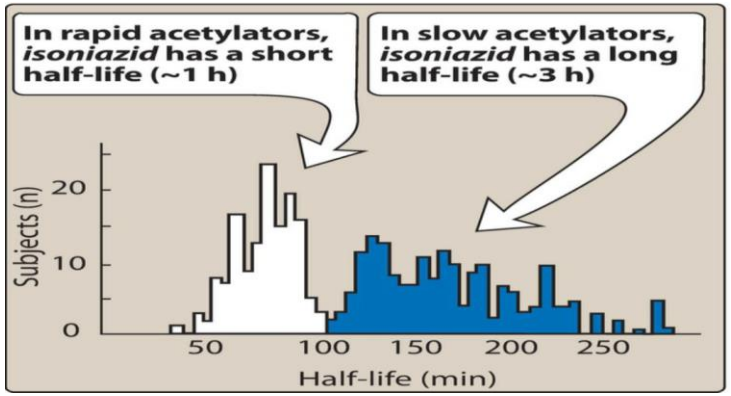


B. Isoniazid

❑ Pharmacokinetics

- Drug concentrations in the cerebrospinal fluid (CSF) are similar to those in the serum.
- Isoniazid undergoes **N-acetylation and hydrolysis**, resulting in inactive products.
- Isoniazid acetylation is genetically regulated, with

1. **Fast acetylators** exhibiting a **90-minute serum half-life**,
2. **Slow acetylators exhibit 3 to 4 hours serum half-life**.



B. Isoniazid

❑ Pharmacokinetics

- **Excretion** is through glomerular filtration and secretion, predominantly as metabolites.
- **Slow acetylators** excrete more of the parent compound.

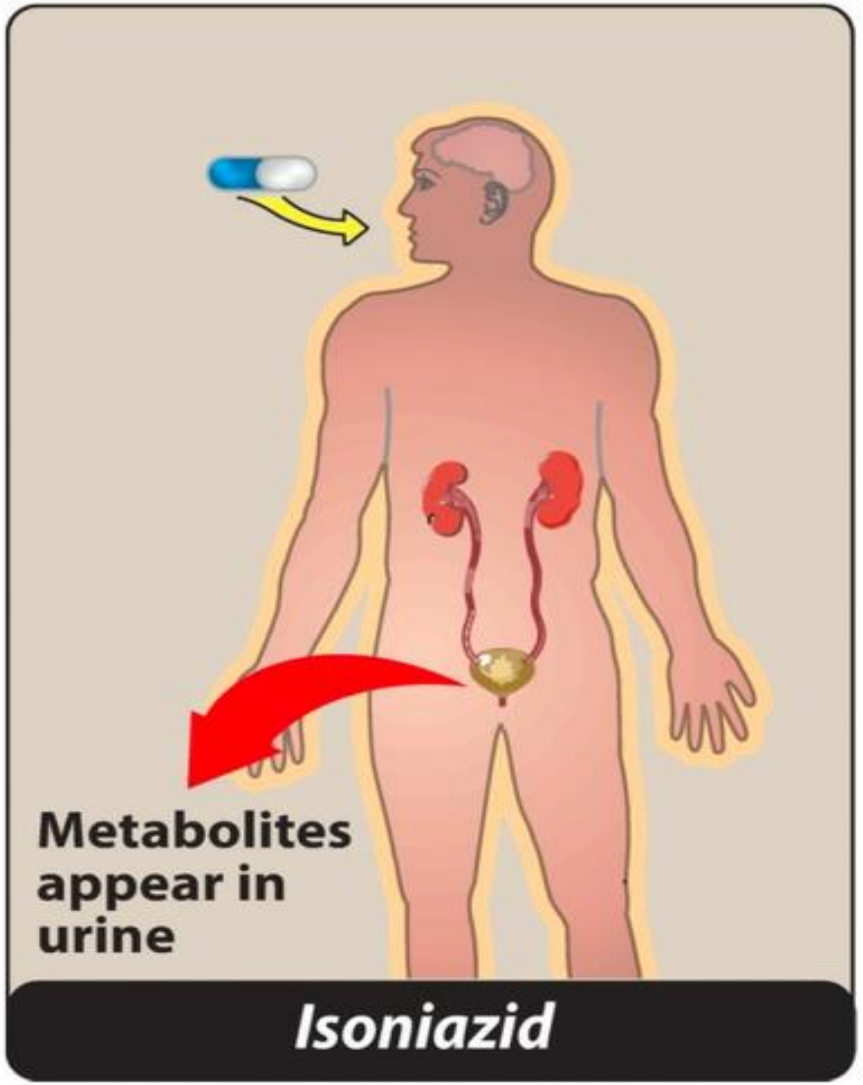


Figure 32.5 Administration and fate of *isoniazid*.

B. Isoniazid

- **Adverse effects**

1. **Hepatitis** is the most serious adverse effect associated with isoniazid.

- If hepatitis goes unrecognized, and if isoniazid is continued, **it can be fatal**. The incidence increases with

Ⓐ **Age** (greater than 35 years old),

Ⓑ Among patients who also take **rifampin**, or

Ⓒ Among those who **drink alcohol** daily.

Category	Adverse Effect
Hepatic	Hepatotoxicity Elevated liver enzymes
Neurological	Peripheral neuropathy CNS toxicity
Dermatologic	Rash Fever

B. Isoniazid

- **Adverse effects**

2. **Peripheral neuropathy**, manifesting as paraesthesia of the hands and feet, appears to be due to a **relative pyridoxine deficiency** caused by isoniazid.

- This can be avoided by daily **supplementation of pyridoxine** (vitamin B6)

3. **Central nervous system (CNS)** adverse effects can occur, including convulsions in patients prone to seizures.

B. Isoniazid

- **Adverse effects**

3. **Hypersensitivity reactions** with isoniazid include rashes and fever.

4. Because isoniazid **inhibits the metabolism** of carbamazepine and phenytoin, isoniazid can **potentiate** the adverse effects of these drugs (for example, nystagmus and ataxia).

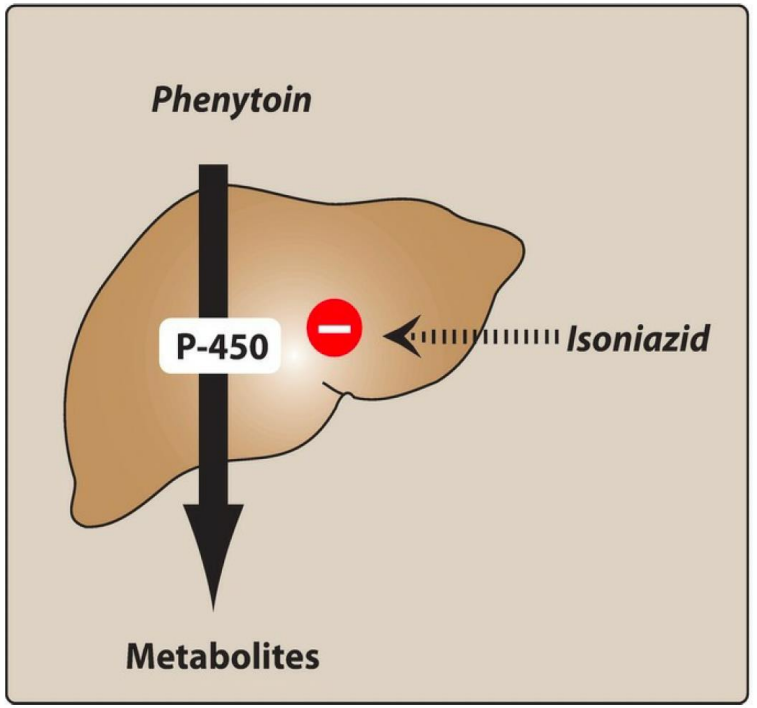
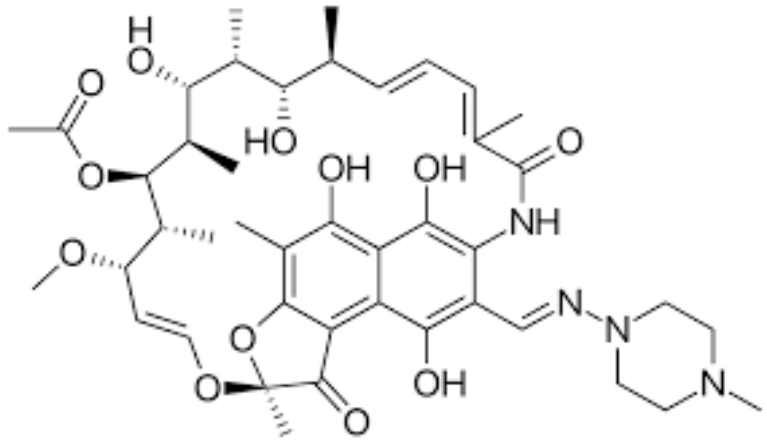


Figure 32.6 *Isoniazid* potentiates the adverse effects of *phenytoin*.

C. Rifamycins: rifampin, rifabutin, and rifapentine

- **Rifampin, rifabutin, and rifapentine** are all considered **rifamycins**,
- A group of structurally similar **macrocyclic antibiotics**, which are **first-line oral agents for tuberculosis**.



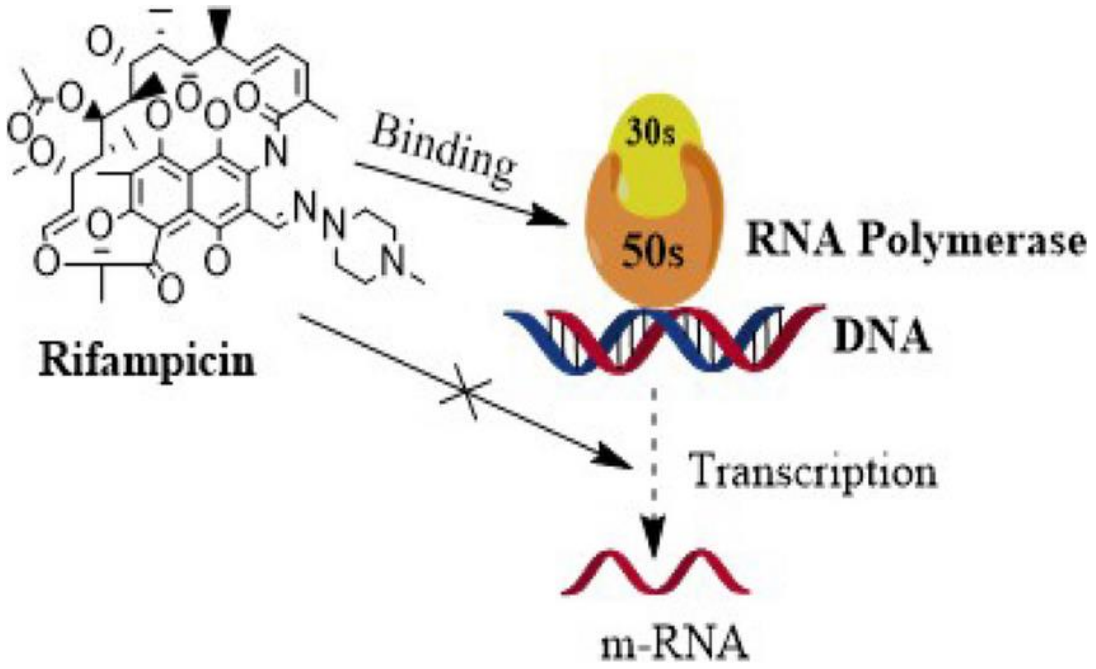
1. Rifampin

- **Rifampin** has **broader** antimicrobial activity than **isoniazid** and can be used as part of treatment for several different bacterial infections.
- Because resistant strains rapidly emerge during monotherapy, **it is never given as a single agent in the treatment of active tuberculosis**.

1. Rifampin

- **Mechanism of action**

- **Rifampin** blocks **RNA transcription** by interacting with the **β subunit of mycobacterial DNA-dependent RNA polymerase**.



1. Rifampin

- **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 effective against **many gram-positive** and **gram-negative organisms** and is **used prophylactically** for individuals exposed to **meningitis** caused by **meningococci** or **Haemophilus influenzae**.
- Rifampin also is highly active against **M. leprae**.

#	Indication
1	Tuberculosis (TB)
2	Latent TB Infection (LTBI)
3	Leprosy (Hansen's disease)
4	Meningococcal meningitis prophylaxis
5	Haemophilus influenzae prophylaxis

1. Rifampin

- **Resistance**

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

1. Rifampin

- **Pharmacokinetics**

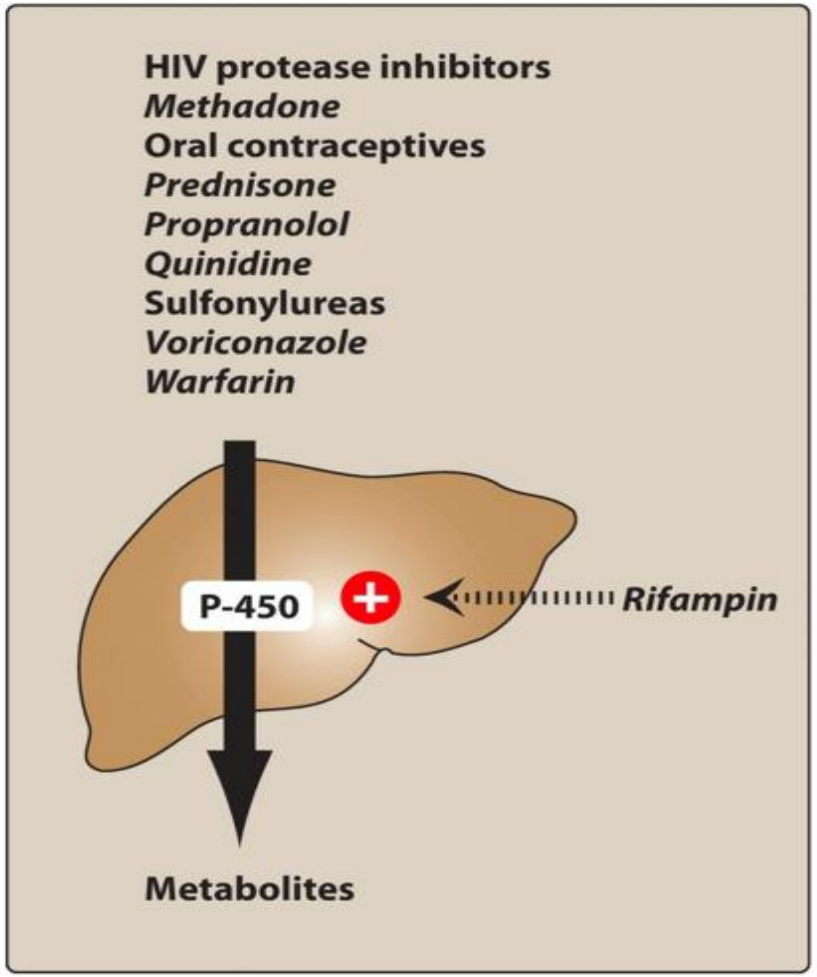
❑**Absorption** is **adequate** after oral administration.

❑**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.

1. Rifampin

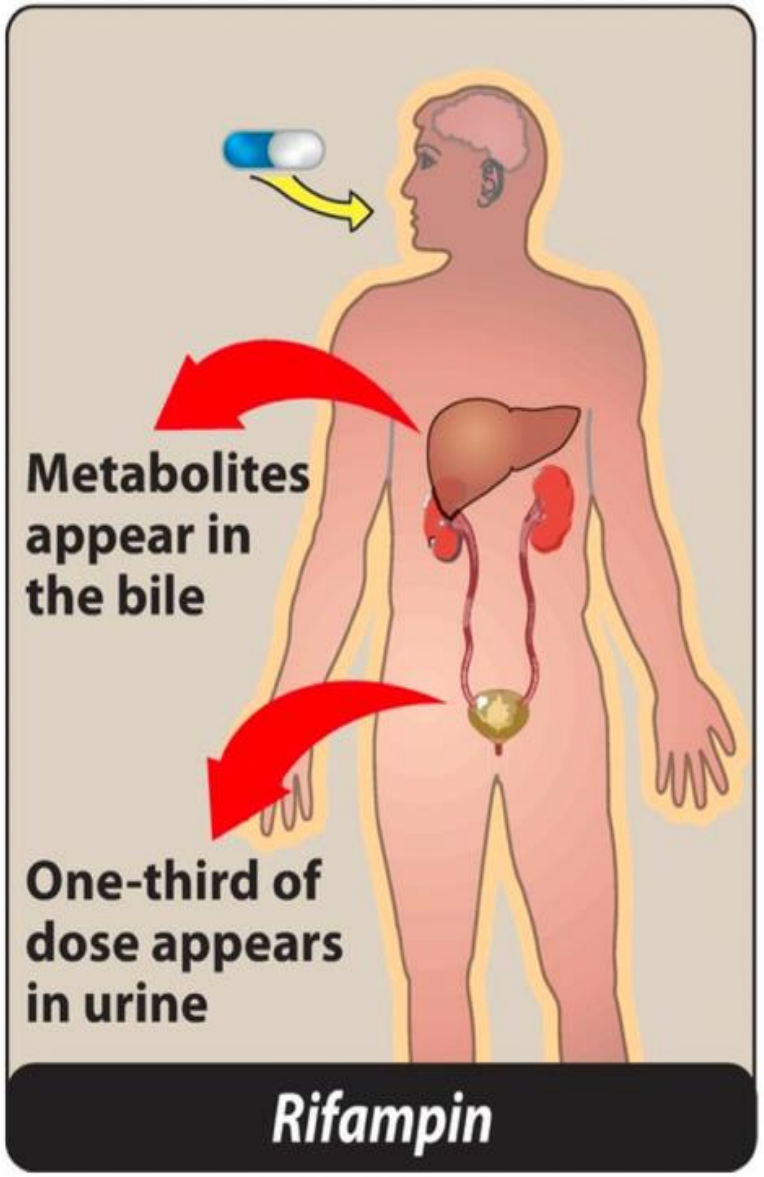
- **Pharmacokinetics**
- Rifampin can **induce** **hepatic cytochrome P450 enzymes** and transporters, leading to numerous drug interactions.
- Unrelated to its effects on **cytochrome P450 enzymes**, rifampin undergoes **Autoinduction**, leading to a shortened elimination half-life over the first 1 to 2 weeks of dosing.



Enzyme Inhibitors	Enzyme Inducers
Erythromycin, Clarithromycin	Rifampin
Ciprofloxacin, Levofloxacin	Phenytoin
Isoniazid	Carbamazepine
Metronidazole	Phenobarbital

1. Rifampin

- **Pharmacokinetics**
- **Elimination** of rifampin and its metabolites is primarily **through the bile** and **into the feces**; a small percentage is cleared **in the urine**.
- [Note: Urine, feces, and other secretions have an **orange-red color**, so patients should be forewarned. Tears may even stain soft contact lenses orange-red.]



1. Rifampin

❑Adverse effects

- Rifampin is generally well tolerated.

1. The most common adverse reactions include **nausea, vomiting, and rash**.
2. **Hepatitis** and **death** due to **liver failure** are rare. However, the drug should be used cautiously in **older patients**, **alcoholics**, or those with **chronic liver disease**.

1. Rifampin

❑Adverse effects

- There is a modest **increase** in the **incidence of hepatic dysfunction** when rifampin is coadministered with **isoniazid** and **pyrazinamide**.

1. When rifampin is dosed intermittently, especially with **higher doses**, a flu-like syndrome can occur, with fever, chills, and myalgia, sometimes extending to acute renal failure, hemolytic anemia, and shock.

1. Rifampin

❑ 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:
  1. Higher dosages for coadministered drugs,
  2. Or a **switch** to drugs less affected by rifampin,
  3. Or **replacement** of rifampin with rifabutin.

2. Rifabutin

- **Rifabutin**, a derivative of rifampin, is preferred for TB patients co-infected with the **human immunodeficiency virus (HIV)** who are receiving **protease inhibitors** or **several of the nonnucleoside reverse transcriptase inhibitors**.
- **Rifabutin** is a **less potent inducer** (approximately 40% less) of cytochrome P450 enzymes, thus lessening drug interactions.
- **Rifabutin** has adverse effects similar to those of **rifampin** but can also cause **uveitis**, **skin hyperpigmentation**, and **neutropenia**.

Uveitis inflammation of the uvea, which is the middle layer of the eye

3. Rifapentine

- **Rifapentine** 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**.

D. Pyrazinamide

- **Pyrazinamide** is a **synthetic**, **orally** effective short-course agent used in combination with isoniazid, rifampin, and ethambutol.
- The precise **mechanism of action is unclear**.
- **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**.

D. Pyrazinamide

- The drug is distributed throughout the body, **penetrating the CSF**.
- Pyrazinamide may contribute to **liver toxicity**.
- **Uric acid retention** is common but rarely **precipitates a gouty attack**.
- Most of the clinical benefit from pyrazinamide occurs early in treatment.
- Therefore, this drug is usually **discontinued after 2 months** of a 6-month regimen.

E. Ethambutol

- Ethambutol 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.]

E. Ethambutol

- 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**.

E. Ethambutol

- The most important **adverse effect** is

1. **Optic neuritis**, which results in diminished visual acuity and loss of ability to discriminate between **red** and **green**.

- The risk of **optic neuritis increases** with higher doses and in patients with renal impairment.

- **Visual acuity** and **color discrimination** should be tested prior to initiating therapy and periodically thereafter.

2. **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.

F. Alternate second-line drugs

- **Streptomycin**, **para-aminosalicylic** acid, **capreomycin**, **cycloserine**, **ethionamide**, **bedaquiline**, **fluoroquinolones**, and **macrolides** are **second-line TB drugs**.
- In general, these agents are **less effective** and **more toxic than the first-line agents.**

F. Alternate second-line drugs

1. Streptomycin

- Streptomycin, an **aminoglycoside** antibiotic, was one of the first effective agents for TB.
- Its action appears to be **greater against extracellular organisms**.
- Infections due to **streptomycin-resistant** organisms may be treated with **kanamycin** **or** **amikacin**, to which these bacilli **usually** remain **susceptible**.

F. Alternate second-line drugs

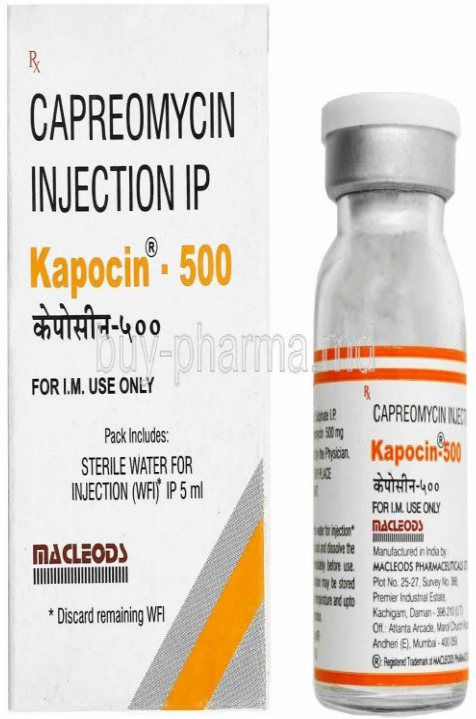
2. Para-aminosalicylic acid

- 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**.

F. Alternate second-line drugs

3. 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.



F. Alternate second-line drugs

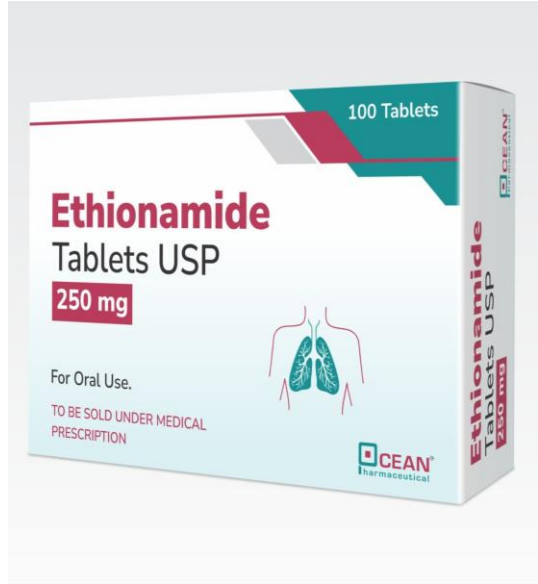
4. Cycloserine

- Cycloserine is an **orally** effective, **tuberculostatic** drug that **disrupts D-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 tendencies**), and seizures may occur.

F. Alternate second-line drugs

5. Ethionamide

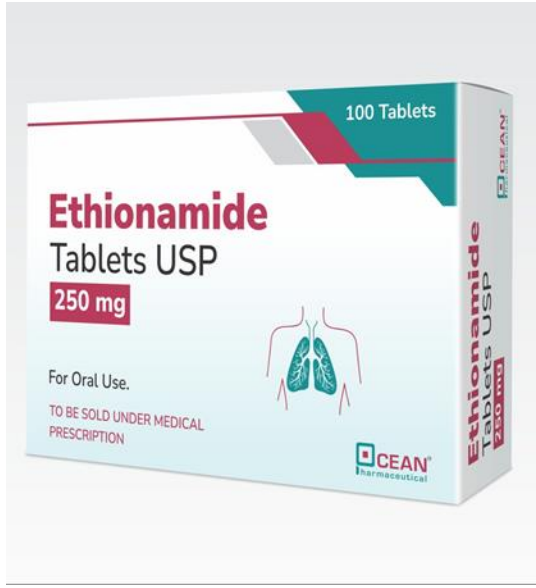
- **Ethionamide** is a structural analog of isoniazid that also disrupts **mycolic acid synthesis.**
- **The mechanism of action is** not identical to isoniazid, but there is some **overlap** in the resistance patterns.
- Ethionamide is widely **distributed** throughout the body, including the **CSF**.



F. Alternate second-line drugs

5. Ethionamide

- **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.



F. Alternate second-line drugs

6. Fluoroquinolones

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

F. Alternate second-line drugs

7. Macrolides

- The macrolides **azithromycin** and **clarithromycin** are included in regimens for several NTM infections, including Mycobacterium avium Complex (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.

F. Alternate second-line drugs

8. 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.

F. Alternate second-line drugs

8. Bedaquiline

- 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**.
- The figure below summarizes some of the characteristics of second-line drugs.

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.

Figure 32.10 Some characteristics of second-line drugs used in treating tuberculosis.
BUN = blood urea nitrogen; CNS = central nervous system; CYP = cytochrome; G6PD = glucose-6-phosphate dehydrogenase; GI = gastrointestinal; LFTs = liver function tests; TSH = thyroid-stimulating hormone.

III. Drugs for Leprosy

- **Leprosy** (or Hansen disease) is uncommon in the United States; however, worldwide, it is a much larger problem (Figure 32.11).
- Leprosy can be treated effectively with **dapsone and rifampin** (Figure 32.12).

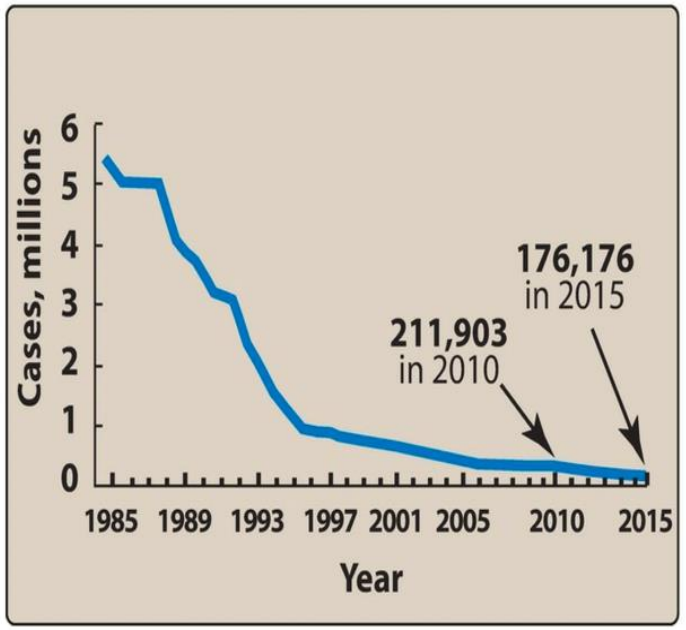


Figure 32.11 Reported prevalence of leprosy worldwide.

III. Drugs for Leprosy

A. Dapsone

- Dapsone 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.

III. Drugs for Leprosy

A. Dapsone

- The drug is **well absorbed** from the gastrointestinal tract 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**.

III. Drugs for Leprosy

B. Clofazimine

- Clofazimine is a phenazine dye.
- Its mechanism of action may involve **binding to DNA**, although alternative mechanisms have been proposed.
- Its **redox** properties may lead to the 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**.

Fig.32.12 Patient with leprosy

III. Drugs for Leprosy

B. Clofazimine

- The drug is recommended by the World Health Organization as part of a 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.

III. Drugs for Leprosy

B. Clofazimine

- 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 antiinflammatory and anti-immune activities. Thus, **erythema nodosum leprosum** may not develop in patients treated with this drug.