



Anti Tuberculosis Therapy

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Tuberculosis (TB)

- Caused by mycobacterium tuberculosis
- The disease may have to be treated for 6 months to 2 years.
- Strains of M. Tuberculosis are resistant to a particular agent emerge during treatment with a single drug.

Anti Tuberculosis Therapy

- First-line agents (isoniazid, rifampin (or rifabutin or rifapentine), ethambutol, and pyrazinamide are the principal or a first-line drugs because of their efficacy and acceptable degree of toxicity.
- Second-line medications are either less effective, more toxic. They are useful in patients :
 - Who cannot tolerate the first-line drugs
 - Who are infected with myobacteria that are resistant to the first-line agents.

Drug Resistance

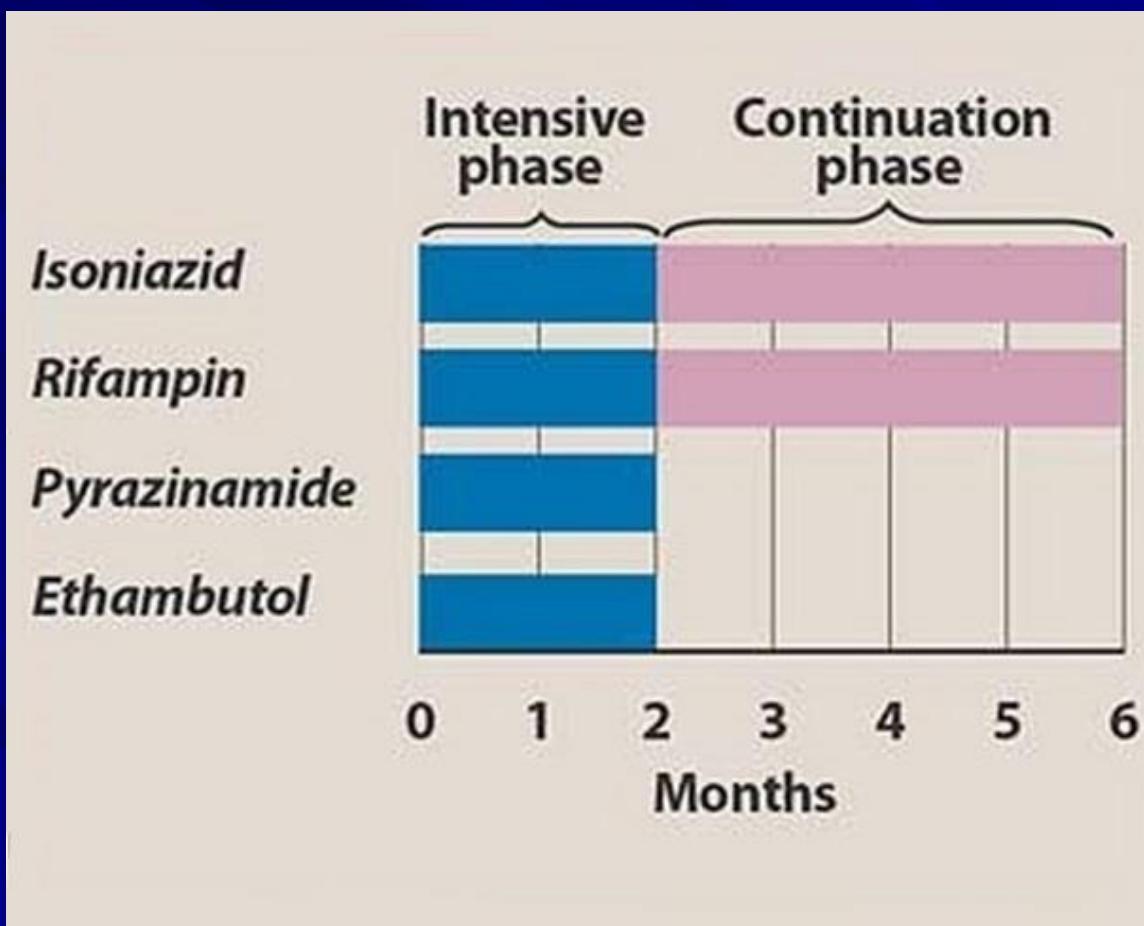
- Strains of M. Tuberculosis that are resistant to a particular agent during treatment with a single drug.
- Multidrug therapy is employed when treating tuberculosis to delay or prevent the resistant strains.
- A minimum of two drugs, preferably with both being bactericidal

Treatment regimens include

- The combination of drugs should prevent the emergence of resistant strains.
- The multidrug regimen is continued well beyond the disappearance of clinical disease to eradicate any persistent organisms.

For example: The initial short-course chemotherapy for tuberculosis includes isoniazid, rifampin, ethambutol and pyrazinamide for 2 months and then isoniazid and rifampin for the next 4 months (the continuation phase).

One of several recommended multidrug schedules for the treatment of tuberculosis



Isoniazid

- The most potent antitubercular drugs
- Isoniazid is bacteriostatic (for bacilli in the stationary phase), but it is bactericidal (for rapidly dividing organisms)
- It is never given as a single agent in the treatment of active tuberculosis
- It inhibits cell wall synthesis by covalently binding and inhibiting the enzymes, which are essential for the synthesis of mycolic acid that is found in mycobacterial cell walls.

Pharmacokinetics of Isoniazid

- Orally administered
- Absorption is impaired if isoniazid is taken with carbohydrates, or with aluminum-containing antacids.
- It undergoes N-acetylation and hydrolysis, resulting in inactive products (Chronic liver disease decreases metabolism).
- Excretion is through glomerular filtration, predominantly as metabolites

Note: Acetylation is genetically regulated.

- The fast acetylators
- Slow acetylators (excrete more of the parent compound). so, Severely depressed renal function results in accumulation of the drug, primarily in slow acetylators.

Adverse Effects of Isoniazid

1. Peripheral neuritis: due to pyridoxine deficiency.
This side effect can be corrected by supplementation of 25 to 50 mg per day of pyridoxine (vitamin B₆)
2. Hepatitis
3. Mental abnormalities, convulsions and optic neuritis.
4. Hypersensitivity reactions (rashes and fever).
5. Drug interactions: isoniazid inhibits metabolism of phenytoin

Rifamycins: (Rifampin, Rifabutin and Rifapentine)

- They are first-line drugs for tuberculosis
- Used in combination with at least one other antituberculosis drug

Rifampin

- Has a broader antimicrobial activity than Isoniazid
- It is bactericidal for M. tuberculosis
- Rifampin blocks transcription by interacting with the bacterial DNA-dependent RNA polymerase
- Resistance to Rifampin can be caused by:
 - Mutation in the affinity of the bacterial DNA-dependent RNA polymerase for the drug
 - Decreased permeability.

Pharmacokinetics of Rifampin

- Oral administration
- The drug is taken up by the liver and undergoes enterohepatic cycling
- It is inducer of cytochrome P450 enzymes.
- Cause orange-red color of the urine, feces, Tears and other secretions, stain soft contact lenses

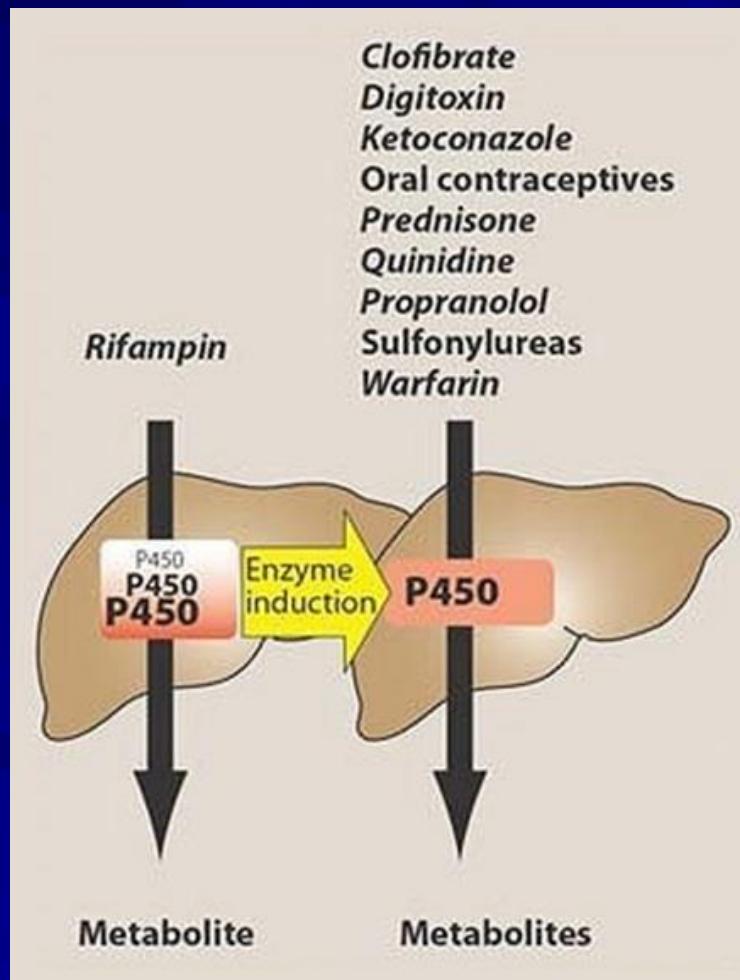
Adverse Effects of Rifampin

1. Nausea, vomiting, and rash
2. Hepatitis (specially in alcoholic, elderly or have chronic liver disease)
3. A flu-like syndrome (fever, chills and myalgias)
4. Acute renal failure
5. Hemolytic anemia
6. Shock.

Rifabutin

- Use in tuberculosis-infected with the human immunodeficiency virus (HIV) patients who are concomitantly treated with protease inhibitors or nonnucleoside reverse transcriptase inhibitors,
- It is a less potent inducer of cytochrome P450 enzymes.
- Rifabutin has adverse effects similar to those of Rifampin but can also cause uveitis, skin hyperpigmentation and neutropenia.

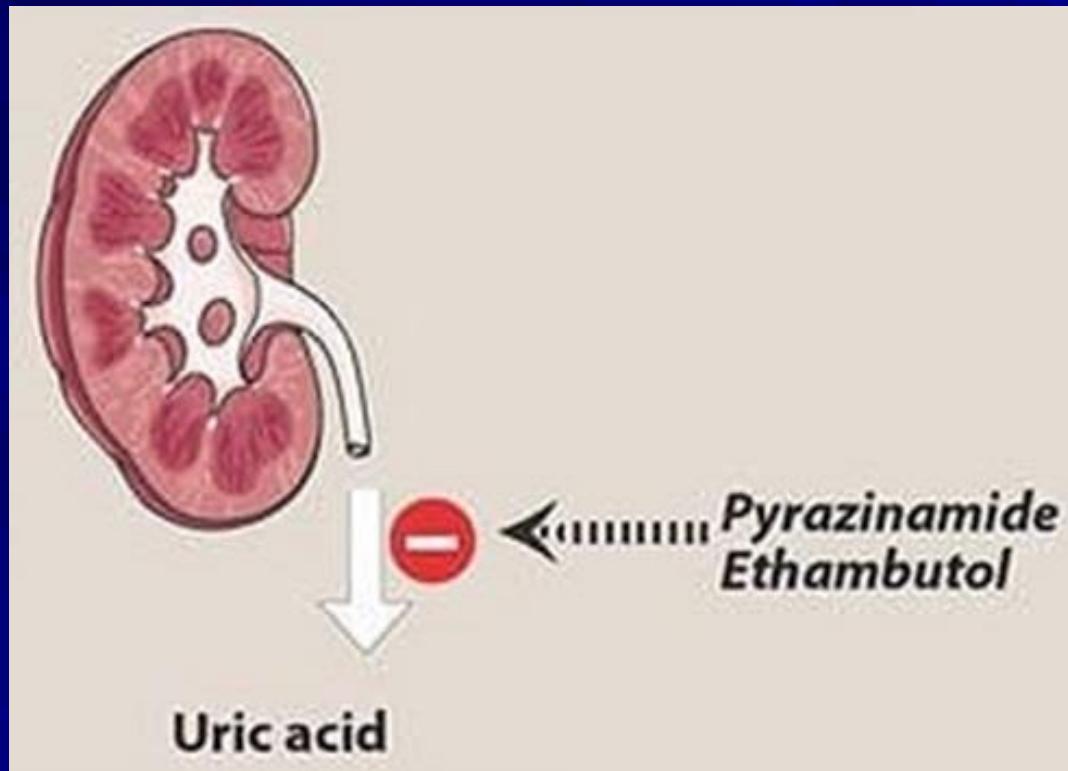
Rifampin induces cytochrome P450, which can decrease the half-lives of coadministered drugs that are metabolized by this system



Pyrazinamide

- It is bactericidal to actively dividing organisms
- Orally effective
- Used in combination with isoniazid, rifampin, and ethambutol.
- Pyrazinamide distributes throughout the body, penetrating the CSF.
- It undergoes extensive metabolism (may cause liver dysfunction).
- Urate retention can also occur and may precipitate a gouty attack .

Pyrazinamide and ethambutol may cause urate retention and gouty attacks



Ethambutol

- It is bacteriostatic
- Ethambutol inhibits the enzyme that is important for the synthesis of the mycobacterial cell wall.
- Ethambutol can be used in combination with pyrazinamide, isoniazid, and rifampin to treat tuberculosis.
- Oral administration
- It used for tuberculous meningitis (Penetrate into the central nervous system).
- The drug and its metabolites are excreted by kidney
- The most important adverse effect is optic neuritis
- Urate excretion is decreased by the drug

Some characteristics of first-line drugs used in treating tuberculosis.

CBC = complete blood count

DRUG	ADVERSE EFFECTS	COMMENTS
<i>Ethambutol</i>	Optic neuritis with blurred vision, red-green color blindness	Establish baseline visual acuity and color vision; test monthly.
<i>Isoniazid</i>	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 <i>phenytoin</i> and antifungal agents (azoles).
<i>Pyrazinamide</i>	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.
<i>Rifampin</i>	Hepatitis, GI upset, rash, flu-like syndrome, significant interaction with several drugs	Take baseline hepatic enzyme measurements and CBC count; repeat if abnormal or patient is at risk or symptomatic. Warn patient that urine and tears may turn red-orange in color.

Alternate second-line Drugs

(Streptomycin, para-aminosalicylic acid, ethionamide, cycloserine, capreomycin, fluoroquinolones and macrolides)

- They are particularly active against atypical strains of mycobacteria
- They are no more effective than the first-line agents
- They are often more serious toxicities

Streptomycin

- Its action is directed against extracellular organisms.
- Infections due to streptomycin-resistant organisms may be treated with kanamycin or amikacin, to which these bacilli remain sensitive.
- Capreomycin: it inhibits protein synthesis, it is administered parenterally.
- Capreomycin is primarily reserved for the treatment of multidrug-resistant tuberculosis.
- Careful monitoring of the patient is necessary to prevent its nephrotoxicity and ototoxicity

Cycloserine

- Orally effective agent
- Antagonize bacterial cell wall synthesis.
- The drugs and its metabolite are excreted in urine.

Adverse Effects of Cycloserine

1. CNS disturbances
2. Exacerbation of epileptic seizure .
3. Peripheral neuropathies, but respond to pyridoxine.

Ethionamide (a Structural Analog of Isoniazid)

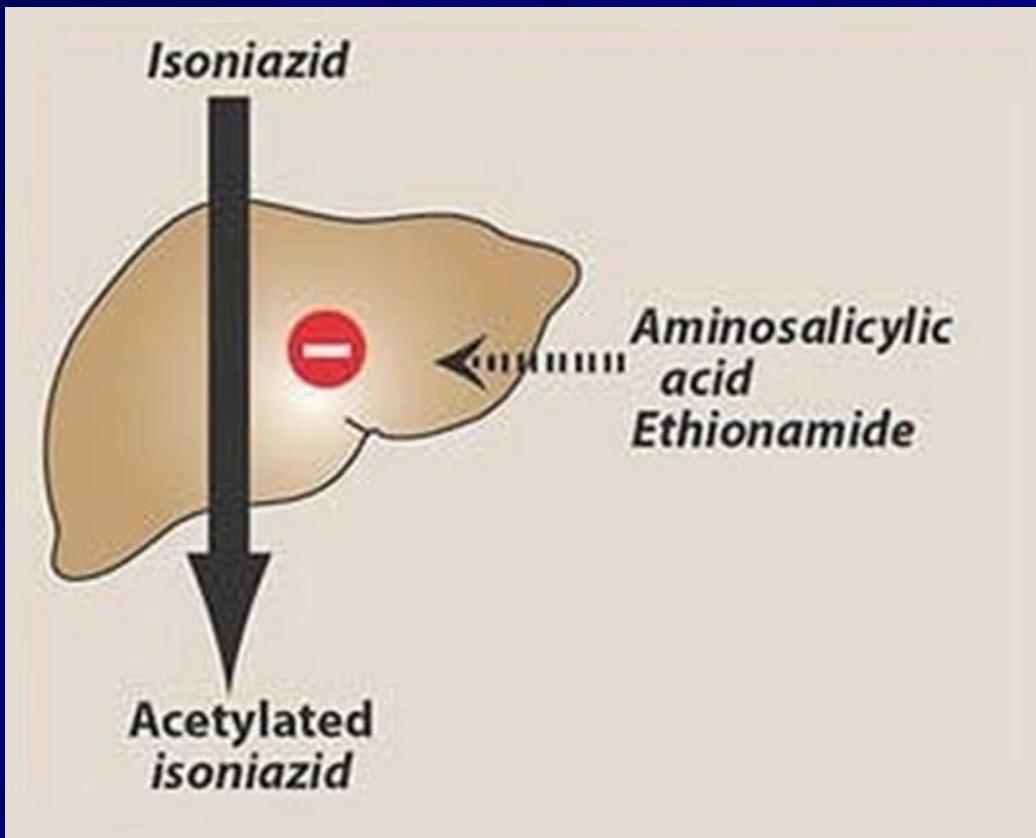
- It inhibit acetylation of isoniazid.
- Oral administration
- Widely distributed throughout the body, including the CSF.
- Metabolism is extensive,
- The main route of excretion is the urine .

Adverse Effects of Ethionamide

1. Gastric irritation
2. Hepatotoxicity
3. Peripheral neuropathies
4. Optic neuritis

Note: Supplementation with pyridoxine decrease severity of the neurologic side effects.

Aminosalicylic acid and ethionamide can inhibit the acetylation of isoniazid



Fluoroquinolones, Moxifloxacin and levofloxacin

have an important place in the treatment of multidrug-resistant tuberculosis.

Macrolides

- Azithromycin and Clarithromycin, are part of the regimen that includes ethambutol and rifabutin used for the treatment of infections by *M. avium-intracellulare* complex.

Note: Azithromycin is preferred for HIV-infected patients because it is least likely to interfere with the metabolism of antiretroviral drugs.