

Antimycobacterials

Introduction

- Mycobacterial infections are among the most difficult of all bacterial infections to cure.
- Mycobacteria are slow growing organisms making them relatively resistant to antibiotics, the activity of which tends to depend on how rapidly the cell is dividing.
- The response of mycobacterial infections to chemotherapy is slow and treatment must be administered for months to years depending upon which drugs are used.

Drug used in Tuberculosis Chemotherapy for T.B

- Mycobacterium tuberculosis, one of a number of mycobacterium, can lead to serious infections of lungs, genitourinary tract, skeleton and meninges.

Drugs

(First Line)

- Ethambutal
- Isoniazid
- Pyrazinamide
- Rifampin

(Second Line)

- Streptomycin
- Aminoglycosides
- Aminosalicic acid
- Capreomycin
- Cycloserine
- Ethionamide
- Fluoroquinolone
- Macrolide

- Isoniazid and rifampin are two most active drugs. An isoniazid-rifampin combination administered for a month will cure 95-98% of cases of tuberculosis
- The addition of pyrazinamide to an isoniazid-rifampin combination for first 2 month allow total duration of therapy to reduced to 6 months without loss of efficacy.
- In practice therapy is initiated with a 4 drug regimen of isoniazid, rifampin, pyrazinamide and either ethambutal or streptomycin

- Most patients with tuberculosis can be treated entirely as outpatient, hospitalization require for serious patient
- One successful strategy for therapy also known as DOT (DIRECTLY OBSERVED THERAPY) in which patient take their medication while being supervised and observed.



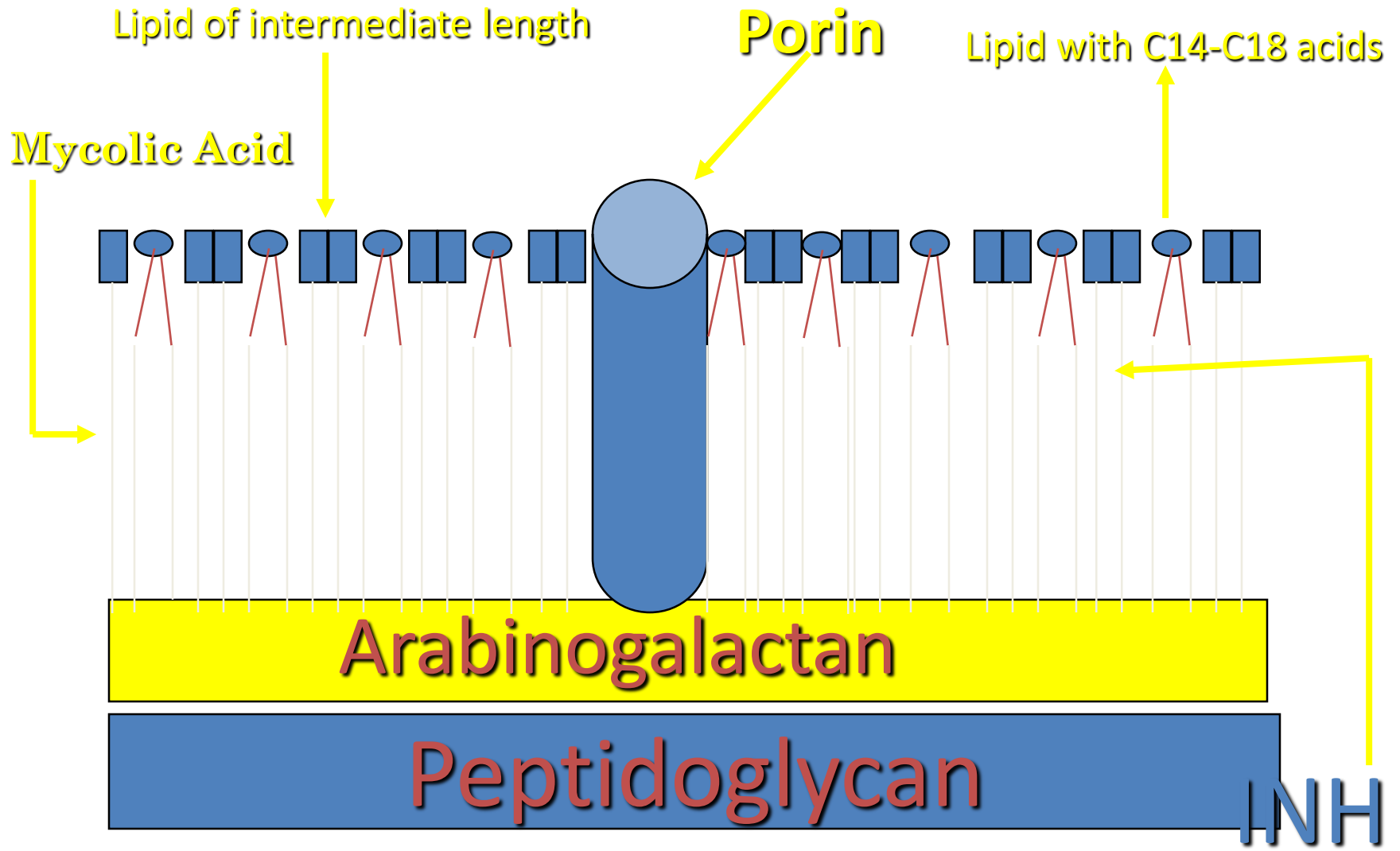
Isoniazid

- Most potent drug (pro-drug) but never given as a single agent in treatment of tuberculosis.
- After orally administered, well absorbed, widely distributed in body, including cerebrospinal fluid. INH can also penetrate into macrophages.
- Most INH is metabolized in the liver.

Mechanism of action

- probably related to *the inhibition of synthesis of mycolic acids*, which are important and characteristic components of mycobacterial cell wall. As a result of the activity, tubercle bacilli lose their features of acid-resistance, water-resistance and proliferating ability, leading to death.

Mycobacterial Cell Wall



Pharmacological Activity

- It is bactericidal for actively *growing tubercle bacilli*. But, for *resting tubercle bacilli*, it is *bacteriostatic*.
- Isoniazid is able to penetrate into phagocytic cells and thus is active against both extracellular and intracellular organisms.
- This drug is not effective against *atypical mycobacteria*.

Clinical uses

- Isoniazid is the most widely used agent in the treatment and prophylaxis of tuberculosis.
- Isoniazid is usually given by mouth but can be given parenterally in the same dosage.

Adverse effects

- **Allergic Reaction:** fever, skin rash
- **Hepatotoxicity :** Up to 20% of patients taking INH develop elevated serum amino transferase levels.
- “Severe hepatic injury occurs more frequently in patients over the age of 35, especially in those who drink alcohol daily.
- “Isoniazid is discontinued if symptoms of hepatitis develop or if the aminotransferase activity increases to more than three times normal.

Rifampin

- **Synthetic derivatives** of rifamycin B produced by *Sterptomyces mediterranei*
- oral administration, well absorbed, widely
- distributed in body, including sputum and tuberculous caverna; adequate CSF concentrations are achieved only in the presence of meningeal inflammation.
- most of the drug is excreted as a deacylated metabolite in feces and in the urine. half-life is about 4 hours.

Pharmacologic activity

- *broad-spectrum*
- It is active against G+ cocci (including drug resistant S.aureus), some bacteria, mycobacteria
- It is ***bactericidal*** for mycobacteria.
- It can kill organisms that are poorly accessible to many other drugs, such as intracellular organisms and those sequestered in abscesses and lung cavities.

Mechanism of rifampin

- RFP binds strongly to the β -subunit of *DNA-dependent RNA polymerase* and thereby inhibits RNA synthesis.
- Drug-resistance to RFP, due to *target mutations in RNA polymerase*, occurs readily.
- No cross-resistance to other classes of antimicrobial drugs.

Clinical uses

Mycobacterial infections

It often uses in combination with other agents (Tuberculosis, rifampin) in order to **prevent** emergence of drug-resistant mycobacteria.

Leprosy

Other infections

“ Rifampin can be used in a variety of gram-positive coccal infections, especially the serious cases that cannot be effectively treated with other drugs.

“ It is also used as prophylaxis for meningitis caused by highly penicillin-resistant strains of pneumococci.

Adverse effects

- *Urine, sweat, tears, and contact lenses* may take on an **orange color** because of rifampin administration, this effect is harmless.
- Light-chain proteinuria and impaired antibody response may occur.
- Rifampin induces hepatic microsomal enzymes and therefore, affects the half-life of a number of drugs.
- When taken erratically in large doses, a febrile “flu-like” syndrome can occur.

Ethambutol

- Inhibits many strains of M. tuberculosis, bacteriostatic
- *Inhibits arabinosyl transferases involved in cell wall biosynthesis*
- Well absorbed from the gut and widely distributed in all body tissues and fluids.
- As with all antituberculous drugs, resistance to ethambutol emerges rapidly when the drug is used alone.
- The most common serious adverse effect is dose-related optic neuritis, causing loss of visual acuity and red-green color-blindness, but are reversible

Pyrazinamide

- Pyrazinamide is a pyrazine analogue of nicotinamide. At neutral pH, it is inactive, but at pH 5.5 it inhibits tubercle bacilli and some other mycobacteria.
- Interferes with mycobacterial fatty acid synthesis
- Quickly absorbed after orally administered
Widely distributed in body tissues, including inflamed meninges.
- Excreted mainly by glomerular filtration

The second-line drugs

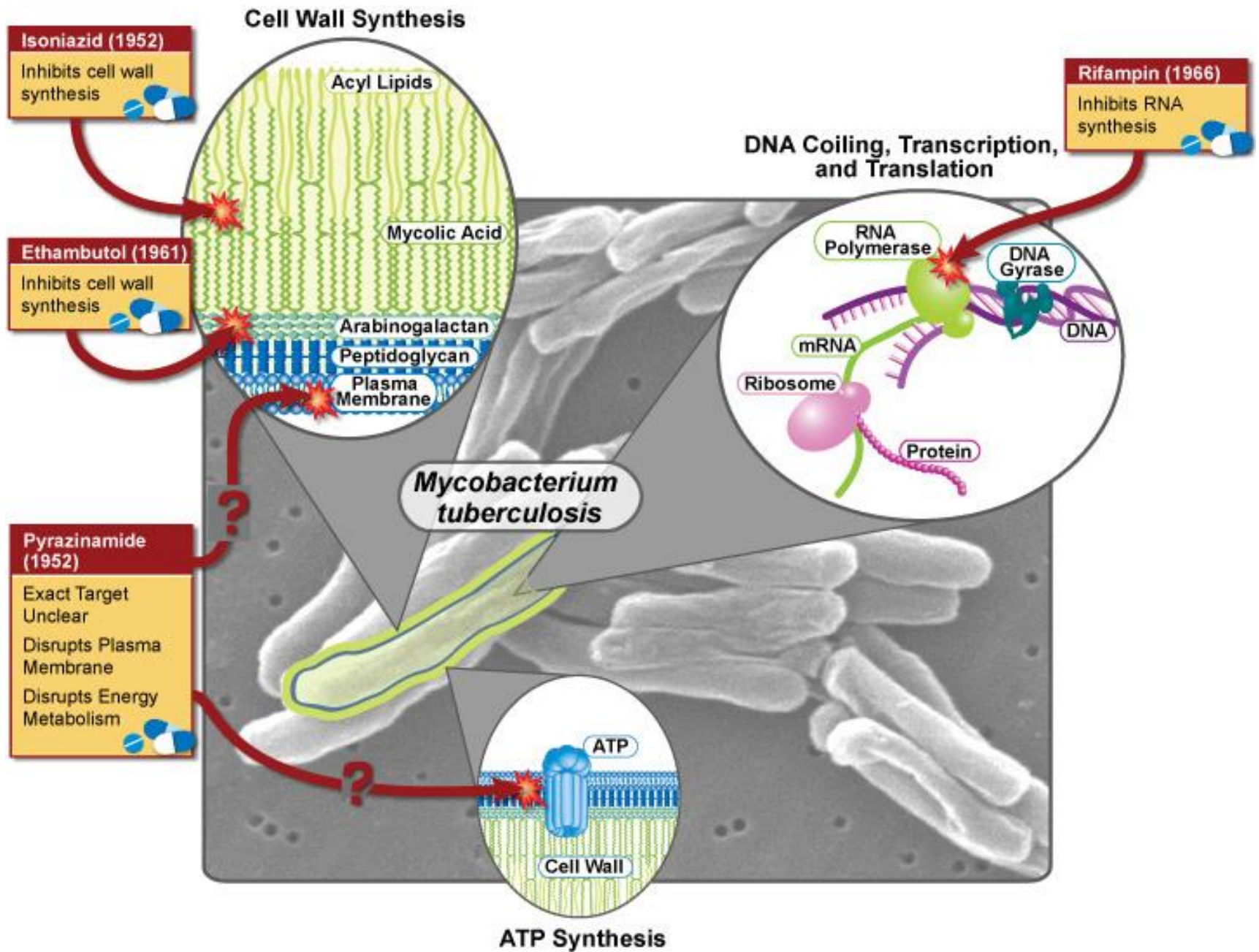
- The second-line drugs used for tuberculosis infections when first-line drugs have been discontinued owing to resistance or adverse effects.

Anti-TB therapy :

- For pulmonary TB – 6 months treatment
- For renal, bone and CNS infection – longer treatment

Summary

- Use combination of drugs for a long period
- Resistance is emerging
- First line drugs and second line drugs



Summary cont:

- Isoniazid – bactericidal to rapidly dividing bacteria
- Rifampicin - kill intracellular bacteria
- Ethambutol – bacteriostatic against multiplying bacteria
- Pyrazinamide - kill dormant mycobacteria