



A SHORT REVIEW ON FIRST LINE DRUGS IN TUBERCULOSIS TREATMENT

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INTRODUCTION

Tuberculosis

Tuberculosis (TB) is a potentially fatal contagious disease that can affect almost any part of the body but is mainly an infection of the lungs. It is caused by a bacterial microorganism, the tubercle bacillus or *Mycobacterium tuberculosis*^[1].

Classification

Organs involved: pulmonary or extra-pulmonary.

Sputum result: smear-positive or smear-negative.

History of TB treatment: new or previously treated or relapsed^[2].

Treatment

For initial empiric treatment of TB, patients start 4-drugs regimen: isoniazid, rifampin, pyrazinamide, and either ethambutol or streptomycin. Once the TB isolate is known to be fully susceptible, ethambutol (or streptomycin, if it is used as a fourth drug) can be discontinued. After 2 months of therapy (for a fully susceptible isolate), pyrazinamide can be stopped. Isoniazid plus rifampin are continued as daily or intermittent therapy for 4 more months. If isolated isoniazid resistance is

documented, discontinue isoniazid and continue treatment with rifampin, pyrazinamide, and ethambutol for the entire 6 months. Therapy must be extended if the patient has cavitory disease and remains culture-positive after 2 months of treatment.

Directly observed therapy (DOT) is recommended for all patients. With DOT, patients on the above regimens can be switched to 2- to 3-times per week dosing after an initial 2 weeks of daily dosing. Patients on twice-weekly dosing must not miss any doses. Prescribe daily therapy for patients on self-administered medication ^[4].

All regimens have an initial intensive phase lasting for 2 to 3 months aimed to rapidly kill the TB bacilli bring about sputum conversion and afford symptomatic relief. This is followed by continuation phase lasting for 4 to 6 months during which remaining bacilli are eliminated so that relapse does not occur ^[3].

ISONIAZID

Classification

Isoniazid belongs to the class of hydrazides. Used in the treatment of tuberculosis.

Mechanism of action

Isoniazid is a prodrug and must be activated by a bacterial catalase-peroxidase enzyme that is in *M. tuberculosis* and is called KatG. KatG couples the isonicotinic acyl with NADH to form isonicotinic acyl-NADH complex. This complex binds tightly to the enoyl-acyl carrier protein reductase known as InhA, thereby blocking the natural enoyl-AcpM substrate and the action of fatty acid synthase. This process inhibits the synthesis of mycolic acid, required for the mycobacterial cell wall ^[5].

Indication

Tuberculosis, meningitis, Atypical mycobacteria, Pericarditis, Enterocolitis, Pott's disease (spinal tuberculosis) ^[6].

Side effects and adverse reactions

Adverse reactions include rash, abnormal liver function tests, hepatitis, sideroblastic anemia, high anion gap metabolic acidosis, peripheral neuropathy, mild central nervous system (CNS) effects, Headache, poor concentration, weight gain, poor memory, insomnia and depression have all been associated with isoniazid use ^[7].

Dose

The standard dose of isoniazid in adults is 5 mg/kg/day (max 300 mg daily). In 2010, WHO increased the recommended dose of isoniazid to 10 mg/kg body weight^[8].

Special consideration

Patients who are at risk of neuropathy or pyridoxine deficiency, including those who are diabetic, alcoholic, malnourished, uraemic, or pregnant, should receive pyridoxine usually in a dose of 10 mg daily. If isoniazid develops symptoms of hepatitis such as malaise, fatigue, anorexia, and nausea, it should be discontinued. Liver function should be checked before treatment with isoniazid and special care should be taken in alcoholic patients or those with pre-existing liver disease ^[8].

ETHAMBUTAL**Classification**

Ethambutol is a bacteriostatic antimycobacterial drug prescribed to treat tuberculosis.

Mechanism of action

Ethambutol is bacteriostatic against actively growing TB bacilli. It works by obstructing the formation of cell wall. Mycolic acids attach to the 5'-hydroxyl groups of D-arabinose residues of arabinogalactan and form mycolyl-arabinogalactan-peptidoglycan complex in the cell wall. It disrupts arabinogalactan synthesis by inhibiting the enzyme arabinosyl transferase. Disruption of the arabinogalactan synthesis inhibits the formation of this complex and leads to increased permeability of the cell wall ^[9].

Indication

Ethambutol eliminates certain bacteria that cause tuberculosis (TB). It is used with other medicines to treat tuberculosis and to prevent you from giving the infection to others.

This medication is sometimes prescribed for other uses; ask your doctor or pharmacist for more information ^[10].

Side effects

Loss of appetite, stomach upset, vomiting, numbness and tingling in the hands or feet, optic neuritis, blurring of vision ^[11].

Dose

400 mg ^[12]

Special consideration**Pregnancy**

There are no adequate and well-controlled studies in pregnant women. There are reports of ophthalmic abnormalities occurring in infants born to women on antituberculous therapy that included MYAMBUTOL.

Pediatric use

MYAMBUTOL (ethambutol hydrochloride) is not recommended for use in pediatric patients under thirteen years of age since safe conditions for use have not been established ^[13].

PYRAZINAMIDE**Classification**

The pyrazine analogue of nicotinamide, is an antituberculous first-line agent.

Mechanism of action

Pyrazinamide is a prodrug that stops the growth of *Mycobacterium tuberculosis*.

Pyrazinamide diffuses into *M. tuberculosis*, where the enzyme pyrazinamidase converts pyrazinamide to the active form pyrazinoic acid. Under acidic conditions, the pyrazinoic acid that slowly leaks out converts to the protonated conjugate acid, which is thought to diffuse easily back into the bacilli and accumulate. The net effect is that more pyrazinoic acid accumulates inside the bacillus at acidic pH than at neutral pH.

Pyrazinoic acid was thought to inhibit the enzyme fatty acid synthase (FAS) I, which is required by the bacterium to synthesize fatty acids. It was also suggested that the accumulation of pyrazinoic acid disrupts membrane potential and interferes with energy production, necessary for survival of *M. tuberculosis* at an acidic site of infection ^[14].

Indication

Initial phase of the short-course (2 months) treatment of susceptible pulmonary tuberculosis. Pyrazinamide is used with other medications to treat tuberculosis (TB). It is an antibiotic and works by stopping the growth of bacteria.

Side and adverse effects

Joint pain, hepatotoxicity

Dose

20–25 mg/kg daily or 50–70 mg/kg three times a week ^[15].

Special consideration

In patients with diabetes mellitus, pyrazinamide therapy may hinder stabilization of serum glucose levels.

Monitor liver function, especially enzyme and bilirubin levels, and renal function, especially serum uric acid levels, before therapy and thereafter at 2- to 4-week intervals ^[16].

RIFAMPICIN

Classification

Rifampicin is a bactericidal antibiotic drug of the rifamycin group.

Mechanism of action

Rifampicin inhibits bacterial DNA-dependent RNA synthesis by inhibiting bacterial DNA-dependent RNA polymerase ^[17].

Indication

Rifampin is used with other medications to treat tuberculosis (TB; a serious infection that affects the lungs and sometimes other parts of the body). Rifampin is also used to treat some people who have *Neisseria meningitidis* (a type of bacteria that can cause a serious infection called meningitis) infections in their noses or throats ^[18].

Side and adverse effects

- Hepatotoxic - hepatitis, liver failure in severe cases
- Respiratory - breathlessness
- Cutaneous - flushing, pruritus, rash, redness and watering of eyes
- Abdominal - nausea, vomiting, abdominal cramps with or without diarrhea.

Dose

10 mg/kg (not to exceed 600 mg) orally or IV once a day ^[19].

Special consideration

Use cautiously with pregnancy (teratogenic effects have been reported in preclinical studies; safest antituberculous regimen for use in pregnancy is considered to be rifampin, isoniazid, and ethambutol) [18].

STREPTOMYCIN**Classification**

Streptomycin is an antibiotic (antimycobacterial) drug, the first of a class of drugs called aminoglycosides to be discovered, and it was the first antibiotic remedy for tuberculosis. It is derived from the actinobacterium *Streptomyces griseus*. Streptomycin is a bactericidal antibiotic.

Mechanism of action

Streptomycin is a protein synthesis inhibitor. It binds to the small S16 rRNA of the 30S subunit of the bacterial ribosome, interfering with the binding of formyl-methionyl-tRNA to the 30S subunit. This leads to codon misreading, eventual inhibition of protein synthesis and ultimately death of microbial cells [20].

Indication

Mycobacterium tuberculosis infections, Non-tuberculosis infections - H. influenza, respiratory, endocardial and meningeal infections, urinary tract infections, Plague.

Side and adverse effects

Vestibular ototoxicity (nausea, vomiting, and vertigo), paresthesia of face, rash, fever; urticaria, angioneurotic edema and eosinophilia.

Dose

1 gram/vial [12]

Special consideration

In older adults, they may have decreased kidney function. Therefore, older adults may be more sensitive to the kidney and hearing side effects.

Streptomycin is not recommended to use during pregnancy.

This medication passes into breast milk ^[21].

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