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A REVIEW: MANAGEMENT THERAPY OF TUBERCULOSIS

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ABSTRACT

Tuberculosis poses a serious threat to public health throughout the world but disproportionately afflicts low-income nations. Tuberculosis generally affects the lungs, but can also affect other parts of the body. Most patients with TB can recover if given appropriate medication for a sufficient length of time. The two antibiotics most commonly used are isoniazide and rifampicin and treatment can be prolonged, taking several months. Treatment requires the use of multiple antibiotics over a long period of time. Antibiotic resistance is a growing problem with increasing rates of multiple drug resistance-tuberculosis. The recommended treatment of new-onset pulmonary tuberculosis (2010) is six months of a combination of antibiotics containing rifampicin, isoniazide, pyrazinamide and ethambutol for the first two months and only rifampicin and isoniazide for the last four months.

INTRODUCTION

Tuberculosis is a bacterial infection that can spread through the lymph nodes and bloodstream to any organ in your body. It is most often found in the lungs. Most people who are exposed to TB never develop symptoms because the bacteria can live in an inactive form in the body. But if the immune system weakens, such as in people with HIV or elderly adults, TB bacteria can become active. In their active state, TB bacteria cause death of tissue in the organs they infect. Active TB disease can be fatal if left untreated. Because the bacteria that cause tuberculosis are transmitted through the air, the disease can be contagious. Infection is most likely to occur if you are exposed to someone with TB on a day-to-day basis, such as by living or working in close quarters with someone who has the active disease. Even then, because the bacteria generally stay latent (inactive) after they invade the body, only a small number of people infected with TB will ever have the active disease. [(1)]One-third of the world's population is thought to be infected with TB. In 2014, there were 9.6 million cases of active TB which resulted in 1.5 million deaths. More than 95% of deaths occurred in developing countries. The number of new cases each year has decreased since 2000.[(2)] About 80% of people in many Asian and African countries test positive while 5–10% of people in the United States population tests positive by the tuberculin test. Tuberculosis is more common in developing countries; about 80% of the population in many Asian and African countries test positive in tuberculin tests, while only 5–10% of the US population test positive.[(3)] Hopes of totally controlling the disease have been dramatically dampened because of a number of factors, including the difficulty of developing an effective vaccine, the expensive and time-consuming diagnostic process, the necessity of many months of treatment and the emergence of drug-resistant cases in the 1980s.[(4)]

Types of TB:

Tuberculosis mainly classified in two types

A) Pulmonary TB B) Extra pulmonary TB

A) Pulmonary TB: Pulmonary TB disease is caused by bacteria that attack on lungs. It is potentially deadly disease, but it is curable if you get medical help. [(5)] Pulmonary Tb again classified into 3 types are primary pulmonary TB, reactivation TB, endobronchial TB.

a) Primary pulmonary TB: Symptoms occurring around the time of inoculation are referred to as **primary pulmonary TB.** Symptoms are generally mild and include low-grade fever. [(6, 7)]

Two-thirds of persons with primary pulmonary TB remain asymptomatic. Physical examination findings are generally unremarkable and the most common radiographic finding is hilar adenopathy. [8]

b) Reactivation TB: Approximately 90% of TB cases among adults can be attributed to reactivation TB. Symptoms present insidiously, most commonly with fever, cough, weight loss, fatigue, and night sweats. Less common symptoms include chest pain, dyspnea, and hemoptysis. Physical examination findings are nonspecific and may include rales or signs of pleural effusion (eg, dullness to percussion). Chest radiography demonstrates infiltrates in the apical-posterior segment of the upper lobes, and up to 20% of these infiltrates are associated with cavities characterized by air-fluid levels. Although not specific for TB, apical computed tomographic findings may show a "tree in bud" morphology manifested by centrilobular lesions, nodules, and branching linear densities.[9,10]Among the roughly 15% of patients who present without upper lung field infiltrates, a variety of radiographic findings have been described, including lower lung infiltrates (especially superior segments), nodules, effusions, and hilar adenopathy. Finally, up to 5% of patients with active pulmonary disease may have normal findings on chest radiography. [11, 12]

c) Endobronchial TB: Endobronchial TB develops as the direct extension of TB from a pulmonary parenchymal source or sputum inoculation into the bronchial tree. [13]Symptoms may include barking cough with sputum production, and examination may reveal rhonchi and wheezing [14, 15]; the wheezing may lead to misdiagnosis of asthma. [16] Diagnosis and response to therapy may be assessed through bronchoscopy. [17]

B) Extrapulmonary TB: This infection of any organ in the body other than lungs by *Mycobacterium tuberculosis* is called as Extraplumonary TB. The most common sites of extraplumonary TB are lymph nodes, pleura, abdomen, bone & joint, spinal cord & brain & its covering.[18] Extrapulmonary TB again classified into 7 types are tuberculous lymphadenitis, pleural TB, central nervous system TB, tuberculous Peritonitis, tuberculous Pericarditis, skeletal TB, miliary TB.

a) **Tuberculous Lymphadenitis:** Up to 40% of extrapulmonary TB cases are attributable to tuberculous lymphadenitis. [19]It presents most commonly in the cervical lymph nodes, followed by the mediastinal and axillary nodes.[20,21]A typical presenting symptom is long-term, unilateral,

nontender lymphadenopathy; systemic symptoms are often absent. [22]If tuberculous lymphadenitis is clinically suspected, fine-needle aspiration should be pursued, followed by lymph node biopsy if the aspiration is nondiagnostic. [23, 24]

b) Pleural TB: Accounting for roughly 4% of all TB cases, pleural TB is the second leading cause of extrapulmonary TB. [25] In addition to constitutional symptoms, patients may present with nonproductive cough and pleuritic chest pain. [26] Chest radiography typically shows a unilateral effusion, and pleural fluid analysis shows lymphocyte-predominant exudative features with low glucose levels and low pH. [27]

c) Central nervous system TB: A devastating manifestation of the disease, central nervous system TB occurs in approximately 1% of all TB cases. [28] Tuberculous meningitis is clinically heralded by a 2 to 3 weeks prodrome of malaise, headache, personality changes and low-grade fever. This prodrome is followed first by a meningitic phase that mimics bacterial meningitis (fever, nuchal rigidity, altered mental status) and then by a paralytic phase characterized by rapid progression to stupor, coma, seizures, paralysis, and death.[29-31] A less common manifestation of the disease is central nervous system tuberculoma, which is characterized by single or multiple conglomerate caseous foci within the brain that cause focal neurologic symptoms and signs of elevated intracranial pressure.

d) **Tuberculous Peritonitis:** The most common manifestation of TB in the gastrointestinal tract is tuberculous peritonitis. [32, 33] Cirrhosis and portal hypertension are associated with an increased proclivity for tuberculous peritonitis. [34, 35] Patients present with insidious onset of ascites (73%), abdominal pain (65%), weight loss (61%), and low-grade fever (59%). [36]Clinically, tuberculous peritonitis may be mistaken for ovarian carcinoma or peritoneal carcinomatosis. [37, 38] Unexplained lymphocytic ascites should prompt definitive diagnostic testing for peritoneal TB. Culture of tubercles obtained through peritoneal biopsy remains the criterion standard for diagnosis.

e) Tuberculous Pericarditis: Pericarditis caused by tuberculosis is difficult to diagnose, because definitive diagnosis requires culturing *Mycobacterium tuberculosis* from aspirated pericardial fluid or pericardial biopsy, which requires high technical skill and is often not diagnostic. The Tygerberg scoring system helps the clinician to decide whether pericarditis is due to tuberculosis or whether it is due to another cause: night sweats (1 point), weight loss (1 point), fever (2 point),

serum globulin > 40g/l (3 points), blood total leucocyte count <10 x 10^9/l (3 points); a total score of 6 or more is highly suggestive of tuberculous pericarditis.[39] Pericardial fluid with an interferon-γ level greater than 50pg/ml is highly specific for tuberculous pericarditis. There are no randomized trials which evaluate the length of anti-tuberculosis treatment required for tuberculous pericarditis. [40] X-ray chest, EKG and 2D-echo confirm the pericardial effusion. [41]

f) Skeletal TB: Skeletal TB occurs in 1% to 5% of patients with TB [42] and presents most commonly in the thoracolumbar spine. Patients present with localized pain over the afflicted site; systemic symptoms are often absent. [43] Diagnosis is confirmed through culture of specimens obtained through needle aspiration or biopsy. [44]

g) Miliary TB: The lymphatic and hematogenous spread of TB is referred to as miliary TB. [45] Patient presentation is variable, and systemic symptoms (fever, weight loss, night sweats) are common. [46] When miliary TB occurs in the context of primary infection, patients may present with septic shock and acute respiratory distress syndrome.[47-49] Testing for miliary tuberculosis is conducted in a similar manner as for other forms of tuberculosis, although a number of tests must be conducted on a patient to confirm diagnosis.[50] A variety of neurological complications have been noted in miliary tuberculosis patients—tuberculous meningitis and cerebral tuberculomas being the most frequent. However, a majority of patients improve following antituberculous treatment. Rarely lymphangitic spread of lung cancer could mimic miliary pattern of tuberculosis on regular chest X-ray. [51]

Table 1 shows classification of Anti-TB drugs:

Pathogen	**First line Drug**	**Second line drug**
Mycobacterium-tuberculosis	Isoniazide	Streptomycin
	Rifampicin	Capreomycin
	Pyrazinamide	Moxifloxacin
	Ethambutol	Ethionamide
		Para amino salicylic acid
		Cycloserine
		Bendaquiline

Table 2 shows clinical data of anti-TB drug

Sr.No.	**Drug**	**Clinical Information**	
1.	Isoniazide	i) Administration and dosage	It normally taken orally but may be administered intramuscularly or intravenously to critically ill patients. Adults: 5 mg/kg (4–6 mg/kg) daily, maximum 300 mg 10 mg/kg (8–12 mg/kg) three times weekly, maximum 900 mg .[52]
		ii) Contraindications	•Known hypersensitivity.Active,unstable hepatic disease (with jaundice).

		iii) Precautions	Clinical monitoring should be performed during treatment of patients with pre-existing liver disease. Patients at risk of peripheral neuropathy, as a result of malnutrition, chronic alcohol dependence, HIV infection, pregnancy, breastfeeding, renal failure or diabetes, should additionally receive pyridoxine, 10 mg daily. Where the standard of health in the community is low, pyridoxine should be offered routinely. For established peripheral neuropathy, pyridoxine should be given at a larger dose of 50–75 mg daily.[53]
		iv) Use in pregnancy	Isoniazide is not known to be harmful in pregnancy. [54] Pyridoxine supplementation is recommended for all pregnant (or breastfeeding) women taking isoniazide.
		v) Adverse effects	Isoniazide is generally well tolerated at recommended doses. Systemic or cutaneous hypersensitivity reactions, sleepiness, Symptomatic hepatitis, etc.
		vi) Drug interactions	Isoniazide inhibits the metabolism of certain drugs, which can increase their plasma concentration to the point of toxicity. Rifampicin, however, has the opposite effect for many of these drugs. For example, the available data indicate that administering both rifampicin and isoniazide causes a reduction in plasma levels of phenytoin and diazepam. [52] Isoniazide may increase the toxicity.
		vii) Over dosage	Nausea, vomiting, dizziness, blurred vision and slurring of speech occur within 30 minutes to 3 hours of over dosage. Massive poisoning results in coma preceded by respiratory depression and stupor. Severe intractable seizures may occur. Emesis and gastric lavage, activated charcoal, antiepileptic and IV sodium bicarbonate can be of value if instituted within a few hours of ingestion.
		viii) Storage	Tablets should be kept in well-closed containers, protected from light. Solution for injection should be stored in ampoules, protected from light.
2.	Rifampicin	i) Administration and dosage	Rifampicin should preferably be given at least 30 minutes before meals, since absorption is reduced when it is taken with food. However, this may not be clinically significant, and food can reduce intolerance to drugs. Rifampicin should always be given in combination with other effective antimycobacterial agents. It is also available for intravenous administration in critically ill patients.[52] Adults: 10 mg/kg (8–12 mg/kg) daily or 3 times weekly, maximum 600 mg.
		ii) Contraindications	• Known hypersensitivity to rifamycins. • Active, unstable hepatic disease.
		iii) Precautions	Serious immunological reactions resulting in renal impairment, haemolysis is on record in patients who resume taking rifampicin after a prolonged lapse of treatment. In this rare situation, rifampicin should be immediately and permanently withdrawn. Clinical monitoring should be performed during treatment of all patients with pre-existing liver disease, who are at increased risk of further liver damage. Patients should be warned that treatment may cause reddish coloration of all body secretions (urine, tears, saliva, sweat, semen and sputum), and that contact lenses and clothing may be irreversibly stained.
		iv) Use in pregnancy	Vitamin K should be administered at birth to the infant of a mother taking rifampicin because of the risk of postnatal haemorrhage.
		v) Adverse effects	Rifampicin is well tolerated by most patients at currently recommended doses but may cause gastrointestinal reactions and pruritus with or without rash. [52] Other adverse effects (fever, influenza-like syndrome and thrombocytopenia) are more likely to occur with intermittent administration. Exfoliative dermatitis is more frequent in HIV-positive

			TB patients. Temporary oliguria, dyspnoea and haemolytic anaemia.
		vi) Drug interactions	Rifampicin induces hepatic enzymes, and may increase the dosage requirements of drugs metabolized in the liver [(52)], including: anti-infectives, hormonal therapy, anticonvulsant, etc. Since rifampicin reduces the effectiveness of oral contraceptives. Current antiretroviral drugs interact with rifampicin. This may result in ineffectiveness of antiretroviral drugs, ineffective treatment of TB or an increased risk of drug toxicity.
		vii) Over dosage	Gastric lavage may be of value if undertaken within a few hours of ingestion. Very large doses of rifampicin may depress central nervous function. There is no specific antidote and treatment is supportive.
		viii) Storage	Capsules and tablets should be kept in tightly closed containers, protected from light.
3.	Pyrazinamide	i) Administration and dosage	Pyrazinamide is administered orally. Adults (usually for the first 2 or 3 months of TB treatment): 25 mg/kg (20–30 mg/kg) daily 35 mg/kg (30–40 mg/kg) 3 times weekly.
		ii) Contraindications	• Known hypersensitivity. • Active, unstable hepatic disease (with jaundice) • Porphyria.
		iii) Precautions	Patients with diabetes should be carefully monitored since blood glucose concentrations may become labile. Gout may be exacerbated. Clinical monitoring (and liver function tests, if possible) should be performed during treatment of patients with pre-existing liver disease. In patients with renal failure, pyrazinamide should be administered three times per week, rather than daily.
		iv) Use in pregnancy	The 6-month regimen based upon isoniazide, rifampicin and pyrazinamide should be used whenever possible. Although detailed teratogenicity data are not available, pyrazinamide can probably be used safely during pregnancy.[(52)]
		v) Adverse effects	Pyrazinamide may cause gastrointestinal intolerance. Hypersensitivity reactions are rare, but some patients complain of slight flushing of the skin. Moderate rises in serum transaminase concentrations are common during the early phases of treatment. Severe hepatotoxicity is rare.
		vi) Over dosage	Little has been recorded on the management of pyrazinamide overdose. Acute liver damage and hyperuricaemia have been reported. Treatment is essentially symptomatic. Emesis and gastric lavage may be of value if undertaken within a few hours of ingestion. There is no specific antidote and treatment is supportive.
		vii) Storage	Tablets should be stored in tightly closed containers, protected from light.
4.	Ethambutol	i) Administration and dosage	Ethambutol is administered orally. Adults: 15 mg/kg (15–20 mg/kg) daily 30 mg/kg (25–35 mg/kg) 3 times weekly. Dosage must always be carefully calculated on a weight basis to avoid toxicity, and the dose or the dosing interval should be adjusted in patients with impaired renal function. If creatinine clearance is less than 30 ml/minute, ethambutol should be administered 3 times per week.[(52)]
		ii) Contraindications	• Known hypersensitivity. • Pre-existing optic neuritis from any cause.
		iii) Precautions	Patients should be advised to discontinue treatment immediately and to report to a clinician if their sight or perception of colour deteriorates.

			Ocular examination is recommended before and during treatment. [54] Whenever possible, renal function should be assessed before treatment. Plasma ethambutol concentration should be monitored if creatinine clearance is less than 30 ml/min.
		iv) Use in pregnancy	Ethambutol is not known to be harmful in pregnancy.[54]
		v) Adverse effects	Dose-dependent optic neuritis can result in impairment of visual acuity and colour vision in one or both eyes. Early changes are usually reversible, but blindness can occur if treatment is not discontinued promptly. Ocular toxicity is rare when ethambutol is used for 2–3 months at recommended doses. Signs of peripheral neuritis occasionally develop in the legs.
		vi) Over dosage	Emesis and gastric lavage may be of value if undertaken within a few hours of ingestion. Subsequently, dialysis may be of value. There is no specific antidote and treatment is supportive.
		vii) Storage	Tablets should be stored in tightly closed containers.
5.	Streptomycin	i) Administration and dosage	Streptomycin must be administered by deep intramuscular injection. Syringes and needles should be adequately sterilized to exclude any risk of transmitting viral pathogens. It is also available for intravenous administration.[52] Adults: 15 mg/kg (12–18 mg/kg) daily, or 2 or 3 times weekly; maximum daily dose is 1000 mg. Patients aged over 60 years may not be able to tolerate more than 500–750 mg daily, so some guidelines recommend reducing the dose to 10 mg/kg per day for patients in this age group. [52] Patients weighing less than 50 kg may not tolerate dose
		ii) Contraindications	• Auditory nerve impairment, Pregnancy.
		iii) Precautions	Hypersensitivity reactions are rare. If they do occur (usually during the first weeks of treatment), streptomycin should be withdrawn immediately. Once fever and skin rash have resolved, desensitization may be attempted. Both the elderly and patients with renal impairment are vulnerable to dose-related toxic effects resulting from accumulation. Streptomycin should be used with caution in patients with renal insufficiency, because of the increased risk of nephrotoxicity and ototoxicity. The dose should be maintained at 12– 15 mg/kg but at a reduced frequency of 2–3 times per week.[52]
		iv) Use in pregnancy	Streptomycin should not be used in pregnancy: it crosses the placenta and can cause auditory nerve impairment and nephrotoxicity in the fetus.
		v) Adverse effects	Streptomycin injections are painful. Rash, or sterile abscesses can form at injection sites. Numbness and tingling around the mouth occur immediately after injection. Impairment of vestibular function is uncommon with currently recommended doses. Hearing loss is less common than vertigo. Manifestations of damage to the 8th cranial (auditory) nerve include ringing in the ears, ataxia, vertigo and deafness; damage usually occurs in the first 2 months of treatment and is reversible if the dosage is reduced or the drug is stopped [53], etc.
		vi) Drug interactions	Other ototoxicity or nephrotoxicity drugs should not be administered to patients receiving streptomycin. These include other amino glycoside antibiotics, amphotericin B, cefalosporins, etacrynic acid, cyclosporin, cisplatin, furosemide and vancomycin. Streptomycin may potentiate the effect of neuromuscular blocking agents administered during anaesthesia.
		vii) Over dosage	Haemodialysis can be beneficial. There is no specific antidote and treatment is supportive.
		viii) Storage	Solutions retain their potency for 48 hours after reconstitution at room temperature and for up to 14 days when refrigerated. Powder for injection should be stored in closed containers, protected from light.

The Panel noted the difficulties of implementing the 2010 recommended dosages using either currently available fixed-dose combinations (FDCs). The principal difficulty is that the recommended dosage for isoniazide in 2010 (10 mg/kg) was the same as the lower limit of the range (10-15 mg/kg). Using an FDC of three essential drugs (rifampicin, isoniazide and pyrazinamide), for many children it would be impossible to provide an isoniazide dosage in the 10-15 mg/kg range without using a pyrazinamide dosage that exceeded the recommended range (thereby increasing the risk of hepatotoxicity) or without requiring additional tablets of isoniazide alone. It was recognized and supported by evidence. [55, 57] Minimal isoniazide dosage of 7 mg/kg will provide adequate levels in almost all children. Even children who are younger than 2 years and/or are isoniazide fast acetylators [56] will respond well to this dosage. The Panel therefore recommended extending the isoniazide dosing range from 10-15 mg/kg to 7-15 mg/kg, with the mid-range of 10 mg/kg.

Corticosteroids:

Corticosteroids may be used for the management of some complicated forms of TB, e.g., tuberculous meningitis, complications of airway obstruction by TB lymph glands, and pericardial TB. Corticosteroids have been shown to improve survival and reduce morbidity in advanced tuberculous meningitis and are thus recommended in all cases of tuberculous meningitis. [58] Prednisone is used most frequently, in a dosage of 2 mg/kg daily, increased to 4 mg/kg daily in the case of the most seriously ill children, with a maximum dosage of 60 mg/day for 4 weeks. The dose should then be gradually reduced over 1–2 weeks before stopping.

Multiple-drug therapy to treat TB means taking several different antibiotics at the same time. This is the first choice of treatment for TB that is growing in your body. Most of these medicines are given as pills. The American Thoracic Society, Centers for Disease Control and Prevention, and the Infectious Diseases Society of America recommend using one of several combinations of the first-choice medicines to start treatment. [59] The standard treatment is to take isoniazide, rifampicin, ethambutol and pyrazinamide for 2 months. Treatment is then continued for at least 4 months with fewer medicines. Also, there are special treatment recommendations for people with HIV and TB, people with drug-resistant TB, children with active TB and pregnant women with active TB. Combining antibiotics into a single pill makes it less likely that you will miss taking any doses. Failure to take a medicine could prolong your treatment and increase your chance of developing drug-resistant TB. Streptomycin usually is given only to people who cannot take

ethambutol. Some antibiotics (such as isoniazide or rifampicin) may be taken alone to prevent a latent TB infection from turning into active TB disease, which can spread to other people. [60] Or two or more antibiotics may be taken together to help prevent latent TB from becoming active TB.[61] You typically would take the single antibiotic for a longer time (6 to 9 months) than the combination of antibiotics (3 months). A health professional may have to watch you take all doses of your medicines. This is called directly observed therapy (DOT), and it helps make sure that people take their medicines exactly as they are supposed to. As a result, cure rates for TB have significantly improved. [59]

CONCLUSION

Tuberculosis remains a devasting disease throughout the world. The purpose of elimination of TB is achieved by all responsible parties come together for work. They support the discovery of new drugs and the development of novel regimens for tuberculosis. Various treatments are available to treat TB. Progress is evident, but the path towards tuberculosis elimination remains long, arduous, and challenging. With a joint effort, we have reasons to be optimistic that the challenges of tuberculosis drug research and development.

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