

Review Article

Recent advances in the management of tuberculosis

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Abstract The importance of tuberculosis in Pakistan and other underdeveloped countries cannot be over emphasized. Despite inclusion of BCG vaccination in the EPI program and availability of the anti-tuberculosis medicines at affordable prices, tuberculosis is still the number one cause of prolonged morbidity. The emergence of *Human Immunodeficiency Virus* and multi-drug resistant tuberculosis has added another dimension to an already complicated situation of tuberculosis globally. In response, vigorous efforts have been made to stratify the patient population and streamline the treatment of various categories of tuberculosis patients.

Key words

Tuberculosis, *Mycobacterium tuberculosis*, sputum microscopy, Mantoux test, anti-tuberculosis drugs.

Introduction

Tuberculosis (TB) is as old as human race. The DNA of *Mycobacterium tuberculosis* has been detected in a Peruvian mummy and has recently been demonstrated in a skeleton from 300 BC. Tuberculosis had always been prevalent in third world countries like Pakistan, although it has shown a declining trend in the west from last century, but there has been resurgence since mid eighties due to the emergence of human immunodeficiency virus. There has been an increase in the number of outbreaks of

multi-drug resistance (MDR) tuberculosis in recent years.¹

Burden of the disease

One in every three individuals world-wide is considered to be infected with *M. tuberculosis*, and there is a 5% chance of an infected person to develop active disease in his life time.

Third world countries bear the major brunt of the disease which is almost 90% of global TB burden.² What makes the disease even more important is that about three-fourth of the cases occur in the most economically productive age group (15-54 years).³

Pakistan bears 44% of the TB burden in Eastern Mediterranean region marked by World Health Organization and is ranked 6th in the world as far as the disease burden is

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concerned. In Pakistan, 2-3 million people suffer from pulmonary tuberculosis and another 15% may have extrapulmonary tuberculosis. More than 300,000 new cases occur every year and one active case of tuberculosis if untreated can infect 10-15 people in one year.^{2,3}

As far as skin TB is concerned its incidence is much lower than the pulmonary or other extra-pulmonary TB. It is roughly estimated as 0.1%. The clinical picture is always confusing and it mimics cutaneous leishmaniasis and tertiary syphilis. Lupus vulgaris and scrofuloderma are the most common types of cutaneous TB encountered. The infection is acquired either by direct inoculation (TB chancre, warty TB, lupus vulgaris), contiguous spread from underlying lymph node, bone or joint (scrofuloderma), autoinoculation (orificial TB), hematogenous spread (lupus vulgaris, tuberculous gumma, miliary TB) or as a result of hypersensitivity reaction to *M. tuberculosis* (lichen scrofulosorum, tuberculides, erythema induratum).

Prevalence of the infection

Various national prevalence surveys in Pakistan showed infection rate of 54% of the total population.⁴ The prevalence of infection based on the tuberculin testing was found to be 70% in individuals above the age of 10 years in various states of India. In industrialized cities, 75% of the children showed a positive reaction by the age of 15. However, the percentage of positive reactors was found to be little more than 50% of the total population.⁵

Bacteriology

The disease is caused by *Mycobacterium tuberculosis* which is widely distributed in the environment. It is a thin rod-shaped or slightly curved organism which is longer and more curved in the cells of the tissues. It is not easily stained by Gram's method because the lipid rich cell wall prevents the entry of the stain. The organism is acid- and alcohol-fast (AAFB) probably because of formation of complexes between the dye and the mycolic acid in the cell wall. The bacillus stained with auramine O or auramine-rhodamine emits a bright yellow-orange colour when examined under ultraviolet light, thus allowing more rapid and accurate diagnosis.⁵

The organism is rapidly killed on exposure to sunlight and heat. However, it can withstand cold conditions and can survive for many months. *M. tuberculosis* exhibits very slow growth and the growth requires environment with high oxygen contents. This probably is the reason of the predominant involvement of the apical areas of the lungs.⁵

The risk of infection is directly related to the duration and intensity of exposure to the air contaminated with infected droplets from a smear positive patient. The infection also occurs by ingestion but the incidence of bovine infection is extremely low. Very rarely do tubercle bacilli gain entry by the way of injured skin of persons handling infective materials. This is occasionally seen happening accidentally to laboratory workers and pathologists.

Laboratory Diagnosis

Sputum microscopy

The most infectious patients of TB can be rapidly detected using sputum microscopy. The sputum should be collected in a clean container. Patient must first rinse the oral cavity with clean water and clean teeth without using toothpaste or disinfectant. The sputum should be obtained empty stomach and the patient encouraged to cough deeply to avoid saliva and nasopharyngeal secretions. Exposure of the specimen to direct sunlight may result in loss of acid fastness of the bacteria.³

Culture

Many mycobacterium culture media are available. Lowenstein-Jensen medium is the most commonly used one for culture. It takes about 4-6 weeks for the mycobacteria to form visible colonies in the above medium. Hence for rapid diagnosis transparent liquid medium (Middle Brook) or the radioactive (Bactec) or non-radioactive (MGIT media) can be used. The bacilli can be detected in 8-14 days by this method.⁵

Chest radiograph

Chest X-ray (postero-anterior view) picks up the lesions in active cases of TB in majority of the patients except in rare instance of endobronchial TB. Occasionally an apical lordotic view is required for lesions in apical or subapical areas obscured by rib cage. Crofton and Douglas consider that the following characters of a chest x-ray favour the diagnosis of TB:^{5,6,7}

a) Shadows in upper zone.

b) Patchy or nodular shadows especially in upper zone.

c) Unaltered abnormal shadow for weeks.

Computed tomography (CT)

CT scan can at times pick up the cases of endobronchial and miliary TB when chest X-ray may be normal. CT scan is very helpful in defining the presence and extent of mediastinal lymphadenopathy, and in recognizing the presence of minimally exudative lesions and small mediastinal lymphadenopathy.⁵

Erythrocyte sedimentation rate

Erythrocyte sedimentation rate (ESR) is raised in extensive disease. In the past ESR used to be taken as an index of the activity of the disease and has been given disproportionately undue significance in the diagnosis and monitoring of the disease activity by the general practitioners and physicians. Over the time its importance has decreased in assessing the activity of the disease.^{3,5} According to WHO, ESR has no diagnostic or prognostic value.

Serology

Various tests like enzyme-linked immunosorbent assay (ELISA) and modified soluble antigen fluorescent antibody tests have been used for serodiagnosis of TB, but due to the inadequacy of these tests to accurately differentiate between past infection and active disease, no serological test is recommended for routine clinical use.⁵

Polymerase chain reaction

The technique has been used for rapid detection of mycobacterium DNA in clinical

specimens. It has the potential to shorten the time required for the diagnosis from 2-3 weeks to 24 hrs. It is capable of detecting a single organism in biological specimen. This technique has not yet replaced conventional ways of diagnosis.⁶

Mantoux test

Mantoux is the most commonly used tuberculin test. It becomes positive within 6 weeks of primary infection and precedes the radiological changes. In most people this sensitivity persists throughout life. A weak positive reaction to tuberculin is noted following BCG vaccination. However, the reaction tends to wane with time. An infant who has received BCG and has not been infected with *M tuberculosis* will have a Mantoux reaction of less than 5 mm by 3-5 years after vaccination. The interpretation of Mantoux test is given in **Table 1**.

Tuberculin skin test does not differentiate between exposure and disease. It is much more useful in epidemiological work and cohort screening. A strongly positive test indicates infection but is unhelpful on its own in case of normal clinical examination and chest radiograph.^{5,6,7} Hence, it is rarely clinically helpful in making a diagnosis of clinical tuberculosis.

Histopathology

Early non-specific inflammation changes into a characteristic tubercle in 3-6 weeks of infection. Bacilli are very scanty, at this stage but the inoculation cultures may be positive. A fully formed tubercle is diagnostic of cutaneous tuberculosis. The histopathological examination of the specimen is useful for various types of extrapulmonary TB like skin, lymph nodes,

Table 1 Interpretation of skin reactions to 5-TU Mantoux test⁷

Induration > 5mm

1. HIV infected persons
2. Recent close contacts
3. Persons with chest radiographs consistent with old healed lesions

Induration > 10mm

1. Persons from high prevalence countries
2. Intravenous drug users
3. Socially deprived groups
4. Residents of long term care facilities
5. Persons with medical conditions predisposing to TB e.g. silicosis, gastric surgery, chronic renal failure, diabetes mellitus and immunosuppressive therapy.

Induration > 15mm

1. Considered positive in all people
-

bones, joints etc. A tubercle is composed of epithelioid cells and variable amount of Langhan's giant cells and a surrounding mononuclear cell infiltrate. There is caseation in the centre of the tubercle. Endovascular and perivascular changes become marked in the vicinity of the tubercle leading to fibrosis.

Evaluation of a patient of TB

Once the diagnosis of an active case of tuberculosis is made, the next immediate requirement is case definition. There are four determinants of case definition:³

1. Site of TB.
2. Bacteriology (sputum smear result).
3. Severity of TB.
4. History of previous treatment.

1. Site of tuberculosis

Pulmonary TB It refers to the disease involving only the lung parenchyma.³

Extrapulmonary TB It refers to the TB of organs other than lungs e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints, bones and meninges.

2. Bacteriology

Based on the results of sputum microscopy, patients are labelled as sputum smear positive or negative.

3. Severity of the disease

Severity of disease is determined by the bacillary load, extent of disease and anatomical site.

Following forms of extrapulmonary TB are classified as severe:

- Meningeal, pericardial, peritoneal, bilateral or extensive pleural effusion, spinal and genitourinary.

Less severe forms are:

- Lymph node, unilateral pleural effusion, bone excluding spine, peripheral joint and skin.

4. History of previous treatment

Following definitions are used:³

New A patient who has never taken the treatment of TB or those who have taken anti-TB drugs for less than one month.

Relapse A patient previously treated for TB who had been declared cured and is diagnosed again with active disease.

Treatment failure A patient who is started on a re-treatment regimen after having failed past treatment.

WHO based categorization of severity of TB

Based on the definitions and from the public health point of view, WHO has categorized the TB cases in 4 categories ranked from I (highest priority) to III (lowest priority).³ Category IV is reserved for multi-drug resistant TB.

Drugs and regimens

1. New cases

This group includes smear-positive pulmonary TB, smear-negative pulmonary TB and extra pulmonary TB³. The treatment is given in two phases:-

Initial intensive phase

2 RHZE i.e. rifampicin (R), INH (H), PZA (Z) and ethambutol (E) advised under strict supervision during first 2 months.

Continuation phase

4 RH i.e. rifampicin and INH for 4 months, or **6HE** i.e. INH and ethambutol for 6 months.

2. Re-treatment cases

It includes patients who have taken treatment in the past and declared as relapses, treatment failures or defaulters. The treatment regimen for this group of patients is very important, because most clinicians are unaware of it, and are treating the above patients on the same lines as of the 'new cases'. The recommendation for such patients is to treat them for 8 months. Use 5 drugs for initial 2 months, 4 drugs for next 1 month and 3 drugs for last 5 months according to the following protocol.^{3,4,6}

Table 2 Recommended treatment regimens for each diagnostic category³

<i>TB Diagnostic Category</i>	<i>TB Patients</i>	<i>TB Treatment Regimens</i>	
		<i>Initial Phase (Daily or 3 times Weekly)</i>	<i>Continuation phase (daily or 3 times weekly)</i>
I	New smear-positive patients; New smear-negative PTB with extensive parenchymal involvement; Severe concomitant HIV disease or severe forms of EPTB	2 HRZE	4 HR or 6 HE daily
II	Previously treated sputum smear-positive PTB: ▪ Relapse; ▪ Treatment after interruption ▪ Treatment failure.	2 HRZES/ 1 HRZE	5 HRE
III	Smear-negative pulmonary TB (other than in category I); Less severe forms of extra pulmonary TB	2 HRZE	4 HR or 6 HE daily
IV	Chronic and Multi drug resistance-TB cases (still sputum-positive after supervised re-treatment)	Specially designed, individualized regimens	standardized or suggested for this category

Initial phase

2 RHZE+S i.e. rifampicin, INH, PZA, ethambutol and streptomycin (S) for 2 months.

Follow-up phase

1 RHZE for one month.

Continuation phase

5 RHE i.e. rifampicin, INH and ethambutol for another 5 months.

Recommended treatment regimens for each diagnostic category is given in **Table 2**.

Treatment in special situations

Pregnancy and breast feeding

With the exception of streptomycin, most anti-tuberculosis drugs are safe in pregnancy. The former should not be used in pregnancy due to risk of ototoxicity to fetus.

All anti-tuberculosis drugs are safe in breast feeding mothers.^{3,6}

Drug-induced hepatitis

Hepatitis may be induced by INH, rifampicin and PZA. Among the three drugs, rifampicin is the least likely to cause hepatocellular damage while PZA is the most hepatotoxic. If diagnosis of drug-induced hepatitis has been made the antituberculous treatment should be stopped. The suggested regimen in such patients is 2 months initial phase of daily streptomycin, INH and ethambutol followed by 10 months continuation phase of INH and ethambutol **2SHE/10HE**³. After the hepatitis is resolved the patient should revert to the usual TB treatment. However, it is advisable to avoid PZA.

Acute viral hepatitis

Patients who are hepatitis B surface antigen-carriers can receive full course of chemotherapy but if there is established

chronic liver disease, PZA should not be used. INH + Rifampicin + one of the non-hepatotoxic drugs like streptomycin or ethambutol can be used for the duration of 8 months. Recommended regimens are therefore **2SRHE/6HR**, **9RE** or **2SHE/10HE**.³

Renal failure

INH, rifampicin and PZA can be safely given to the patients of renal failure. Ethambutol and streptomycin can be given in reduced doses if renal function can be closely monitored. The safest regimen for the patients of renal failure is **2RHZ/4RH**.^{6,7}

Follow up of the patients:

Sputum microscopy is the only investigation which helps in monitoring the response of the treatment. It is unnecessary, unreliable and wasteful to carry out repeated radiographs to monitor the patient. For patients with smear negative or extra pulmonary TB, clinical monitoring is the usual way of assessing the response to treatment.

In a smear positive patient, segregation on account of infectivity is required for only 2 months as these patients become non-infective with only two weeks of treatment.^{6,7} Sputum examination should be performed at the end of second month and in the last of 6 or 8 months regimen.^{3,7} At the end of second month, most patients will have a negative sputum smear and will then start the continuation phase. If the sputum smear is positive at the end of second month, initial phase is prolonged for another month. If the sputum smear is still positive after 5 months, this constitutes treatment

failure. Such a patient should be started on category-II or category-IV regimen with reserve drugs.

Fixed dose combination (FDC) therapy

It is recommended by WHO to use FDC tablets for the treatment of TB. The fixed dose combinations have several advantages over individual drugs;

1. Prescription errors are likely to be less frequent because dosage recommendations are straight forward and adjustment of dosage according to the patient's weight is easy.
2. Due to the small number of tablets to be ingested patient's compliance improves.

However, quality assurance is essential as the bioavailability of rifampicin is poor in some of the FDCs. Moreover a minority of patients do need separate drugs in some situations especially when they develop drug toxicity.^{3,5,6,7}

Directly observed therapy (DOT)

It means to directly observe the patients swallowing their tablets in a way that is both sensitive and supportive to the patient's needs. This is meant to ensure that a TB patient takes the right drugs in the right doses for the right duration. It is recommended in:

1. The initial phase of treatment in all smear positive cases
2. Continuation phase of Rifampicin based regimens

Management of multi-drug resistance tuberculosis (MDR-TB)

Multi-drug resistance tuberculosis (MDR-TB) is defined as active TB in which bacilli are resistant to both rifampicin and INH. MDR-TB is now being observed in new cases as well. It is most frequent in re-treatment cases, especially treatment failures. Full implementation of DOT is the best prevention against chronic disease and MDR positive bacteria.

Principles of treatment

- The treatment regimen should include at least 4-5 drugs which have never been used by the patient before, including an injectable antibiotic and a fluoro-quinolone in the initial phase and at least 3 of the most active and best tolerated drugs in the continuation phase.
- The drugs used for this purpose are amikacin (Am) [15mg/kg], capreomycin (Cm) [15mg/kg], ciprofloxacin (Cx) [10-20mg/kg], cycloserine (Cs) [10-20mg/kg], ethionamide (Et) [10-20mg/kg], kanamycin (Km) [15mg/kg], ofloxacin (O) [7.5-15mg/kg], p-aminosalicylic acid (PAS) [150 mg/kg], and prothionamide (Pt) [10-20mg/kg].
- An initial phase of 06 months should be followed by a continuation phase of 12-18 months and even up to 24 months.^{9,10}
- A single drug is never added to a failing regimen.

- Sometimes for localized disease (unilateral) surgery under drug cover is an option.
- All treatment both indoor and outdoor should be directly observed.
- Follow-up after completion of treatment should be indefinite.
- MDR-TB cases should be managed by specialized physician and hospital.

Treatment of chronic and MDR cases with reserve drugs is more expensive and more toxic than treatment with essential drugs. There are two methods to manage MDR cases:

- Standardized regimens.
- Individualized regimens.^{3,11}

Standardized regimens are applied in resource constrained situations where susceptibility testing is not available or is unreliable. It, however, can not be overemphasized that in situations where MDR cases are to be treated, culture and sensitivity testing should be done. But in real life situations, in the absence of such facilities in resource limited countries, standardized regimens have shown to be feasible and cost effective. However, there is no choice but to perform culture susceptibility tests in patients who fail the standardized regimen.¹²

Individualized regimens include drugs according to the susceptibility pattern and have probably higher cure rates. The approach is more costly when quality assured laboratory services and drugs are required along with trained staff.

Suggested treatment options for MDR-TB are given in **Table 3**.

Table 3 Suggested treatment regimens^{3,13}

<i>Susceptibility testing to essential drugs</i>	<i>Initial phase</i>		<i>Continuation phase</i>	
	<i>Drugs</i>	<i>Duration</i>	<i>Drugs</i>	<i>Duration</i>
<i>Not available*</i>	Km+Et+Q+Z+/-E	At least 6 months	Et+Q+Z+/-E	12-18 months
<i>Available^o</i>				
Resistance to H+R	S+Et+Q+Z+/-E	At least 6 months	Et+Q+Z+/-E	12-18 months
Resistance to all essential drugs	1 injectable +1 fluoro-quinolone + 2 of these 3 drugs: PAS, Et, Cs	At least 6 months	The same drugs except injectable	18 months
Susceptibility testing to reserve drugs available	Tailor regimen according to susceptibility pattern			

Q-Quinolones

*Use of standardized regimen is feasible in resource limited countries with high burden of TB.

^oIndividualized regimen is probably a better option in designated centres of excellence.¹⁴

Treatment of latent tuberculosis

There is a recent trend of treating the patients of latent TB infection. A patient with latent TB is the one who is infected with *M. tuberculosis* and likely to progress to active disease.¹

Current recommendations of American Thoracic Society for Mantoux test-positive individuals in the following situations,¹⁰ is treatment with rifampicin + INH for 3 months:

1. HIV infection.
2. Close contacts of smear positive TB patients. Recent tuberculin skin test converters.
3. Persons with healed fibrotic lesions on chest radiographs.
4. Intravenous drug abusers.
5. Persons with medical conditions predisposed to tuberculosis.

As far as the treatment of latent TB in high prevalence countries is concerned, trials involving large number of patients⁷ have shown that the individuals with such latent infections should not receive INH chemoprophylaxis, but should be advised to seek medical advice if they develop any symptoms suggestive of TB. The difficulty in such situations is that so many healthy individuals have to be treated to prevent so few cases for a disease which is eminently curable.¹⁴ Those infected with HIV and with positive tuberculin test qualify for treatment as there is 5-10% per annum chances of developing tuberculosis.⁷

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