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Epidemiology, Clinical Features, Diagnosis and Treatment Failure of Tuberculosis: A Narrative Review

Sonia Islam Khan

Project Manager, KMSS, TB Control Programme, Dhaka, Bangladesh

Abstract

Tuberculosis (TB) remains one of the world's leading infectious causes of morbidity and mortality, despite decades of public health efforts and the availability of effective treatment. This narrative review explores the current understanding of the epidemiology, clinical features, diagnostic approaches, and challenges related to treatment failure in TB. Globally, an estimated 10 million new TB cases and 1.3 million TB-related deaths were reported in 2022, with the burden disproportionately affecting low- and middle-income countries. Risk factors such as HIV co-infection, malnutrition, poverty, and crowded living conditions contribute significantly to disease transmission and persistence. Clinically, TB primarily affects the lungs but can involve almost any organ, presenting with a wide spectrum of symptoms ranging from persistent cough, fever, night sweats, and weight loss to non-specific signs in extra-pulmonary cases. Early and accurate diagnosis is crucial for controlling the spread and improving patient outcomes. Conventional diagnostic methods such as sputum smear microscopy have limited sensitivity, while newer tools like GeneXpert MTB/RIF and culture methods have improved diagnostic accuracy but face challenges of cost and accessibility in resource-limited settings. Despite standardized treatment regimens, treatment failure remains a critical issue due to factors including non-adherence, drug resistance, inadequate healthcare infrastructure, and patient-related social determinants. Multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) have emerged as major threats to global TB control, requiring longer, more toxic, and costlier treatment courses with variable success rates. Addressing treatment failure demands a multifaceted approach, incorporating patient education, community-based support, strengthened healthcare systems, and robust public health policies. This review underscores the need for continuous innovation in diagnostics, treatment regimens, and patient-centered interventions to achieve global targets for TB elimination. *[Journal of National Institute of Neurosciences Bangladesh, July 2024;10(2):130-137]*

Keywords: Tuberculosis; epidemiology; clinical features; diagnosis; treatment failure

Introduction

The consequences of tuberculosis (TB) on society are immense. Worldwide, one person out of three is infected with Mycobacterium tuberculosis – two billion people in total. TB accounts for 2.5% of the global burden of disease and is the commonest cause of death in young women, killing more women than all causes of maternal mortality combined[1-2].

Global Epidemiology of Tuberculosis

TB currently holds the seventh place in the global ranking of causes of death[3]. Unless intensive efforts are made, it is likely to maintain that position through to 2020, despite a substantial projected decline in disease burden from other infectious diseases[4]. Effective drugs to treat and cure the disease have been available for more than 50 years, yet every 15 seconds, someone in the world dies from TB2. Even more alarming: a person is newly infected with M. tuberculosis every second of every day. Left untreated, a person with active TB will infect an average of 10 to 15 other people every year[5]. TB hinders socioeconomic development: 75.0% of people with TB are within the economically productive age group of 15 to 54 years. Ninety-five per cent of all cases and 99.0% of deaths occur in developing countries, with the greatest burden in sub-Saharan Africa and South East Asia. Household costs of TB are substantial[3].

In most countries, more cases of TB are reported among

Correspondence: Sonia Islam Khan, Project Manager, KMSS, TB Control Programme, Dhaka, Bangladesh; Email: soniaislam45@yahoo.com; Cell No.: +8801766046186;
ORCID: https://orcid.org/0009-0000-6549-6543

men than women[5]. This difference is partly due to the fact that women have less access to diagnostic facilities in some settings, but the broader pattern also reflects real epidemiological differences between men and women, both in exposure to infection and in susceptibility to disease. In regions where the transmission of *M. tuberculosis* has been stable or increasing for many years, the incidence rate is highest among young adults, and most cases are caused by recent infection or re-infection. As transmission falls, the caseload shifts to the older age groups, and a higher proportion of cases come from the reactivation of latent infection[6]. While the human immunodeficiency virus (HIV) infection has clearly had a profound effect on TB epidemiology, other potentially important risk factors have been somewhat neglected. In the coming years, more attention needs to be given to the interaction between chronic diseases and TB, including diabetes, under nutrition. Although the "direct costs" of diagnosis and treatment are significant for poor families, the greatest economic loss occurs as a result of "indirect" costs, such as loss of employment, travel to health facilities, sale of assets to pay for treatment related costs, and in particular, lost productivity from illness and premature death[7].

Transmission

The most common way of transmission of *M. tuberculosis* is the respiratory droplets. *M. bovis* infection arises from drinking non-sterilized milk from infected cows; otherwise, *M. tuberculosis* is spread by the inhalation of aerosolized droplet nuclei from other infected patients[8].

Pathogenesis

The smallest particles (1-5 μm) enter the periphery of the lung and are engulfed by macrophages. In response to antigen presentation, CD4+ T lymphocytes produce an array of cytokines, including interferon-gamma (IFN-γ), that drive the recruitment of monocytes and direct the formation of granulomas limiting the replication and spread of the organism[9]. Classical tuberculous granulomas display central caseous necrosis The formation of a mass of granulomas surrounding an area of caseation leads to the appearance of the primary lesion in the lung, referred to as the 'Ghon focus'. The combination of a primary lesion and regional lymph node involvement is termed the 'Ghon complex'. If the bacilli spread either by lymph or blood before immunity is established, secondary foci may be established in other organs including lymph nodes, serous membranes, meninges, bones, liver, kidneys and lungs. These foci resolve once an immune response is mounted and the organisms gradually lose viability. However, 'latent bacilli' may persist for many years. In most cases, infection of a healthy individual is subclinical and indicated only by the appearance of a cell-mediated, delayed-type hypersensitivity reaction to tuberculin demonstrated by tuberculin skin testing. However, if the organism cannot be contained, primary progressive disease ensues. The estimated lifetime risk of developing disease after primary infection is 10%, with roughly half of this risk occurring in the first 2 years after infection[10].

Factors related to Tuberculosis

Patient-Related[11]

- Age (children > young adults < elderly)
- First-generation immigrants from high-prevalence countries
- Close contacts of patients with smear-positive pulmonary tuberculosis
- Overcrowding: prisons, collective dormitories
- Chest radiographic evidence of self-healed tuberculosis
- Primary infection < 1 year previously

Associated Diseases[11]

- Immunosuppression-HIV, infliximab, high-dose corticosteroids, cytotoxic agents
- Malignancy (especially lymphoma and leukaemia)
- Type 1 diabetes mellitus
- Chronic renal failure
- Silicosis
- Gastrointestinal disease associated with malnutrition (gastrectomy, jejuno-ileal bypass, cancer of the pancreas, malabsorption)
- Deficiency of vitamin D or A: Factors Increasing the Risk of TB

Clinical Features

Clinical Presentations of Pulmonary TB are chronic cough, often with haemoptysis, pyrexia of unknown origin, unresolved pneumonia, exudative pleural effusion, asymptomatic (diagnosis on chest X-ray), weight loss, general debility and spontaneous pneumothorax[12].

Primary Pulmonary TB: Primary TB refers to the infection of a previously uninfected (tuberculin-negative) individual. A few patients develop a self-limiting febrile illness but clinical disease only occurs if there is a hypersensitivity reaction or progressive infection. Progressive primary disease may appear during the course of the initial illness or after a latent period of

weeks or months[13].

Post-Primary Pulmonary TB: Pulmonary TB is the most frequent form of post-primary disease. The onset is typically insidious and develops slowly over several weeks. Systemic symptoms include fever, night sweats, malaise, loss of appetite and weight, and are accompanied by progressive pulmonary symptoms. The earliest radiographical change is typically an ill-defined opacity situated in one of the upper lobes. Disease often involves two or more areas of lung and may be bilateral. As disease progresses, consolidation, collapse and cavitations develop to varying degrees. The presence of a military pattern or cavitations indicates active disease although there is a wide differential. In extensive disease, collapse may be marked and result in significant displacement of the trachea and mediastinum. Occasionally, a caseous lymph node may drain into an adjoining bronchus, resulting in tuberculous pneumonia[14].

Clinical Features of Primary Tuberculosis[15]

Infection (4-8 weeks)

- Influenza-like illness
- Skin test conversion
- Primary complex

Disease

- Lymphadenopathy (hilar-often unilateral, paratracheal or mediastinal)
  - o Collapse (especially right middle lobe
  - o Consolidation (especially right middle lobe)
  - o Obstructive emphysema
  - o Cavitation (rare)
- Pleural effusion
- Endobronchial
- Military
- Meningitis
- Peri-carditis

Hypersensitivity

- Erythema nodosum
- Phlyctenular conjunctivitis
- Dactylitis

Diagnosis of Tuberculosis

AFB Smear Staining: AFB smear microscopy plays an important role in the early diagnosis of mycobacterial infections because most mycobacteria grow slowly and culture results become available only after weeks of incubation. In addition, AFB smear microscopy is often the only available diagnostic method in developing countries. Smear staining is based on the high lipid content of the cell wall of mycobacteria which makes them resistant to decolorization by acid-alcohol after the primary staining[15]. To determine that a clinical specimen contains AFB, the specimen is spread onto a microscope slide, heat-fixed, stained with a primary staining, decolorized with acid-alcohol solution and counterstained with a contrasting dye in order to obtain better differentiation between the microorganism and the background. The slide is observed under the microscope for the detection of AFB. Severalmethods can be used for determining the acid-fast nature of an organism. Two methods, Ziehl-Neelsen and Kinyoun, utilize basic fuchsin in ethanol for primary staining[28]. In both cases, AFB appear red after decolorization with acid alcohol. Ziehl-Neelsen is a hot acid-fast stain because the slide has to be heated during incubation with fuchsin. In contrast, Kinyoun staining is a cold acid-fast staining procedure and therefore does not require heating. Kinyoun's cold carbolfuchsin method is inferior to the Ziehl-Neelsen staining[16].

Culture of Mycobacterium tuberculosis: Different culture media are in use for the isolation of mycobacteria. The most common are based on egg and also contain high concentrations of malachite green to overcome contamination with other bacteria. In general, after the centrifugation step, sediments are inoculated onto two Löwenstein-Jensen slants. In areas with a high incidence of bovine TB, a tube with Stone-brink medium should be added[17]. *M. bovis* and other species of the *Mycobacterium tuberculosis* complex (*Mycobacterium microti and Mycobacterium africanum*) are unable to use glycerol as a carbon source due to the lack of a functioning pyruvate kinase. Thus, these organisms will often fail to grow on Löwenstein-Jensen medium, which contains glycerol as the only available carbon source[29]. Stonebrink medium has the same composition as Löwenstein-Jensen, with the exception that glycerol is replaced by 0.5% sodium pyruvate. Many diagnostic laboratories that employ egg based medium for the isolation of mycobacteria, omit the use of Stonebrink medium[18]. This probably leads to an underestimation of the actual weight of *Mycobacterium bovis* of human TB agent, especially in developing countries. The Ogawa medium is another egg-based medium, which is comparable in its composition with Löwenstein-Jensen. It is more economic because it replaces asparagine by sodium glutamate, an amino acid more readily available and much cheaper. Modified Ogawa medium (pH 6.4) is the same egg-based Ogawa medium that has been acidified in such a way as to allow the direct inoculation

of specimens decontaminated by the Kudoh method[19]. This combination is very suitable for culturing sputum specimens in rural settings. Middlebrook 7H10 and 7H11 are agar-based media.

Follow-up of Patients on Anti-Tuberculosis Treatment and Defaulter Tracing

TB treatment is a long process and it is critical to maintain contact with patients throughout treatment to ensure successful outcomes[20]. However, sometimes circumstances interfere with maintaining contact, so that these patients stop their medication or take their drugs irregularly, often resulting in development of drug resistance by the TB bacteria in the patient's body.

Monitoring of TB Patients During Treatment: Monitoring is the regular observation and recording of activities and results taking place in a programme. Follow up the patients throughout the course of anti-TB treatment is necessary by checking the results of sputum examinations and hence monitor their clinical response to treatment. Like any medical activity, TB programmes need continuous monitoring. To achieve this, patients need to be followed very strictly and the outcome of treatment needs to be clearly defined. The role of health worker is very important in ensuring patients are taking their drugs properly. This is called adherence to treatment[21]. Part of the responsibility is to tell the patients very clearly not to interrupt their treatment and to look for side-effects of drugs and to seek help accordingly.

Refilling of Medication and Adherence to Treatment: It is important to monitor all individuals with TB during treatment, both adults and children by checking that they are taking their medication properly during the intensive phase of treatment, and that they are periodically collecting their drugs during the continuation phase; this is called refilling their drugs[22]. Monitoring with sputum examination is readily available only for patients with sputum smear-positive pulmonary tuberculosis and these are usually adults and older children. Routine monitoring of treatment response by chest X-ray is unnecessary and wasteful of resources because it is not readily available and also costly to the patient. But if patients with smear-negative TB and extra-pulmonary TB do not show clinical improvement, their symptoms do not improve and there is no weight gain, or if patients get worse during or after anti-TB drug treatment, it must be referred such patients to a hospital for further evaluation. For such patients, it is essential to monitor the clinical symptoms and keep monitoring their weight over time[17].

Monitoring of Patients with Sputum Smear-Positive Pulmonary TB

Sputum examination is required for diagnosis for all persons suspected of TB and is able to produce sputum; this test is also essential for follow-up of smear-positive TB individuals. The patient must be referred for testing at the times on this schedule[22].

Sputum smears at the end of the intensive phase: The majority of patients will have a negative sputum smear at the end of the intensive phase. If the sputum smear is still positive at this time, intensive phase treatment with the same four drugs 1 (RHZE) should be continued for four more weeks. When the sputum smear is checked again after this extra period, it is unlikely still to be positive. The continuation phase should be continued even if the sputum smear after the extra four weeks of intensive phase treatment is still positive[23].

Sputum smears in continuation phase: In eight-month treatments, a positive smear at five months or any time after five months means treatment failure. In six months, treatments, a positive sputum smear at five months or any time after five months means treatment failure. The patient treatment category changes to Category II and the re-treatment regimen begins[24].

Sputum smears on completion of treatment: If a

Table 1: Monitoring of Patients with Sputum Smear-Positive Pulmonary TB[22]

Time to refer patients	8-month treatment regimen	6-month treatment regimen
At time of diagnosis	All suspected TB persons	All persons suspected of having TB and producing sputum
At end of intensive phase (end of two months)	Smear-positive TB patient at diagnosis needs sputum examination at end of two months	Smear-positive TB patient at diagnosis needs sputum examination at end of two months
In continuation phase	Smear-positive TB patient at diagnosis needs sputum examination at month five	Smear-positive TB patient at diagnosis needs sputum examination at month five
At end of treatment	Smear-positive TB patient at diagnosis needs sputum examination at month eight	Smear-positive TB patient at diagnosis needs sputum examination at month six

patient has a negative sputum result at the end of treatment and one additional result at the end of two months, or at five months, that is also negative the patient is defined as cured[21].

Referral of People Suspected of Being Infected with TB and TB cases: Referring people suspected of having TB should be done specifically those with a cough for two or more weeks to a health institution for TB diagnosis[25-26]. Referrals can come about in other ways. Sometimes a doctor may diagnose TB and then refer the patient with the drugs to your health facility to continue their treatment under your supervision. Those patients need registration at the level and continued follow-up needs to be put into place. If a patient is very sick or has major treatment side-effects, it may be necessary to refer the patient to a doctor or to a hospital for care of the acute problem. However, sometimes such a patient then believes that, because of the treatment received at the hospital, there is no need to come for regular TB treatment and he/she may then discontinue treatment[17]. When a referral of this type comes, discuss the situation with the patient and their family and emphasize the need to return to health facility to continue treatment after discharge from the doctor or hospital.

Coordinating Transfers When a Patient is Moving: If a registered patient plans to move out of the area permanently, find out when and where the patient is moving and identify an appropriate treatment facility in the new area. In discussions with the patient in the period before the move, stress the need to continue treatment and the importance of reporting to the new health facility[21]. Make sure that the patient understands that to be cured, he/she must continue taking all of the required drugs for the entire time required. If necessary, provide self-administered doses for several days until the patient has reached their new home. If it is not received confirmation from the receiving health facility, contact the facility to ask whether the patient has reported for treatment. If not, tell the facility where to locate the patient. The District TB Coordinator will ask whether there is any new information about the patient. If the transfer is never confirmed i.e. the patient never reports to the new facility, the patient's treatment outcome will be recorded as a transfer out, transfer TB patient to other health facility[27]. If the transfer is confirmed, at the appropriate time, ask the new health facility where the patient was referred about his or her treatment outcome, so that you can record it on the patient's registration. It is important to contact with the District TB Coordinator; this is the person who controls and coordinates TB activity at district level. If the patient originates from the district, it is the district's responsibility to find the treatment outcome for the patient. So, it is the responsibility of the originating health facility to find out about the treatment outcome for a patient who transfers out. When a patient has been received from another health facility, make a note that this is a transferred-in patient to remind to report the treatment outcome to the originating health facility. When any patient completes treatment, check to see whether the patient has been transferred in. If so, contact the originating health facility and report the treatment outcome[17].

Arrangements for patients who travel: If a patient will be travelling or absent for longer than two weeks, identify a health facility in the area where the patient's treatment can be followed[23-25]. During their regular treatment visits, ask patients to inform if they have plans to travel, so that arrangements can be made to continue treatment without interruption. If a patient is to travel out of the area, or will be unable to have directly observed treatment for one or more days, provide instructions and drugs for a short period of self-administration; if necessary, you may provide drugs for up to two weeks. If the patient's drugs are not pre-packaged, prepare a separate packet of drugs for each day that the patient will be absent[19]. Give the patient careful instructions, in conversation with him/her and in writing, about how to take the drugs. Point out the number and colour of the drugs in each day's packet and tell the patient to take the drugs at the same time each day, take the pills with water and take all of the drugs for the day together.

Tracing Patients Who Missed Doses and Defaulters

Conducting Home Visits for Patients Who Miss a Dose: Give the patient the missed doses one day at a time an extra dose on any days do not give. If a patient misses a dose of anti-tuberculosis medication during intensive treatment for more than 24 hours, find the patient by making a home visit within the next couple of days. Use the address on the patient's TB registration to find the patient. When you go on the home visit, take the patient's drugs with you. If the patient is not at home, ask the family or neighbors where the patient is and see if you can find out why treatment was missed. If necessary, visit the contact person listed on the patient's TB registration. When the patient is found, talk to the patient and the family about the problem that caused the interruption in treatment[11].

Table 2: Some examples of possible causes and solutions for missed doses of anti-TB medication[27]

Examples of Possible Causes of Missed Doses	Possible Solutions
Coming to the health facility is inconvenient	Identify a convenient community TB treatment supporter
Patient dislikes coming to the health facility because of the long queue	Make arrangements so that TB patients do not have to wait in a queue. For example, let them enter through a back or side door
Supervisor at work kept the patient late	Offer to talk with the supervisor and explain the importance of the treatment, or Identify a community TB treatment supporter at work
Patient had troublesome side-effects	Give appropriate advice for side effects, or Refer the patient for further evaluation
Patient had difficulty swallowing because of pain (due to oral ulceration, common in AIDS patients)	Give appropriate advice and refer patient as necessary for further evaluation
Patient cannot leave small children at home and is tired of bringing them to the health facility	Suggest that a family member or neighbour watch the children Remind family members/neighbours that the patient must continue treatment to protect their health, and particularly the health of the children If possible, identify a community TB treatment supporter closer to the patient's home
The patient may simply need to be forced to comply and be reminded of the reasons not to interrupt treatment	Remind the patient of the need to take all of the recommended drugs together, for the recommended time, to be cured. Even after beginning to feel better, the patient must continue taking the drugs for the entire period of treatment Motivate the patient with statements such as the following: • TB can be cured if you keep coming for the medicine, and then you will not have to worry about it any more. • You only have 10 more doses to take every day. After that, you will come less often. • These are the safest, most effective drugs available to treat TB anywhere in the world. • Almost all patients who take their medicines as recommended are cured • If you keep taking your medicine, you will not spread TB to your family

Home visits for Patients Who Fail to Collect Drugs for Self-Administration: A patient on a self-administered continuation regimen may fail to collect the drug supply on the appointment day. If a patient does not come for the drugs within a week, visit the patient's home to find the patient, deliver the drugs and determine the problem. Try to solve any problems after discussion with the patient[28].

Tracing Patients who Interrupt Treatment

If you cannot locate a 'defaulter' patient who has interrupted treatment at the home address recorded on the TB unit register form, try to find the patient through the contact person listed on the card20. Information will be sought and leave messages with neighbors and relatives or at the patient's workplace and try to find out whether the patient is just temporarily missing or has permanently moved. If the patient has moved, try to find out the new location and notify the District TB Coordinator. In this way the patient may eventually be transferred to the care of another health facility. If a patient is found and resumes treatment within a month, the same treatment should be continued and should be prolonged to make-up for the missed doses. If treatment is interrupted for between one and two months, the patient will need a new sputum examination before the appropriate treatment can be determined. If treatment is interrupted for two months or more, the patient has defaulted. The treatment outcome 'default' should be entered on the TB unit register form. If the patient returns, he or she will need to be re-assessed to determine the appropriate treatment.

Conclusion

Tuberculosis continues to pose a significant global health threat, especially in resource-limited settings. Understanding its epidemiology, diverse clinical presentations, diagnostic challenges, and the factors contributing to treatment failure is vital for effective control and management. Addressing TB requires

timely diagnosis with accessible, sensitive tools, patient-centered care to improve adherence, and robust strategies to combat drug resistance. Strengthening health systems, community engagement, and sustained research are critical to overcoming persistent barriers. This narrative review highlights the urgent need for comprehensive, integrated efforts to reduce TB's burden and move closer to the ultimate goal of its global elimination.

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Data Availability
Any inquiries regarding supporting data availability of this study should be directed to the corresponding author and are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate
Not Applicable

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ORCID:
Sonia Islam Khan: https://orcid.org/0009-0000-6549-6543

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