

## REVIEW ARTICLE

# Understanding Tuberculosis

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### What is Tuberculosis?

Tuberculosis, commonly known as TB, is an often severe and contagious airborne disease caused by a bacterial infection. TB typically affects the lungs but other organs of the body such as bones, spines, lymph glands, endometrium, brain meninges etc can be involved as well. In most cases, the bacteria attack the lungs. However, whatever the site of infection, the line of management is similar but the duration of treatment depends upon the site involved. Successful treatment usually combines with different antibiotics and chemotherapeutic agents that are given at least for 6 months, sometimes for as long as 12 months.

### History of TB

First evidence of tubercular decay has been found in the spines of Egyptian mummies thousands of years did and TB was common both in Greece and Imperial Rome. Since that time, scientific advances including the discovery of the TB bacteria, development of new anti-TB drug 'streptomycin' and 'Bacille Calmette- Guerin vaccine (BCG) caused TB to lessen its grip on mankind during some periods of history. However, TB never completely let go and today, it is one of the leading Infectious diseases killers around the world. This is further aggravated by emerging drug-resistant strains of the disease which is presenting a new public health threat and challenge for whole of the world.

### What causes TB?

TB is caused by an infectious agent known as Mycobacterium Tuberculosis (Mtb). This is a rod-

shaped, small, slow-growing bacterium that can live only in human and bovine species. It is not found in other animal species, insects, soil, or other non-living things. Mtb is an aerobic bacterium, meaning it needs oxygen to survive. For this reason, during active TB disease Mtb complexes are always found in the upper respiratory tract.

TB primarily is an air born contagious disease.<sup>1</sup> The bacteria (Mtb) are spread from person to person in tiny microscopic droplets when a TB patient coughs, sneezes, speaks, sings or laughs. Only people with active TB can spread the disease from person to person. Thus when a person breaths in Mtb-contaminated air, the inhaled TB bacteria reach the lungs. This causes an Mtb infection. However, not everyone infected with Mtb becomes sick. The bacteria can remain dormant (asleep) for years and do not cause any TB disease. This is called latent TB infection. Many people worldwide have latent or active tuberculosis and the number of active cases is expected to increase in the future.<sup>2</sup> It is to be noted here that if host's body defense mechanism is low (i.e. immuno-compromized) due to malnutrition, diabetes, HIV-AIDS, prolonged corticosteroids therapy etc. The bacteria may break out of hiding and cause active disease. However, for someone to develop active TB disease, the bacteria Mtb must enter into the body and produce infection. It is to be noted that 1 in 10 people infected with Mtb develops active TB at some points in their lives. The active bacteria multiply in the host and destroy the affected tissues and characteristically form 'Tubercle'. Hence, the disease is called 'Tuberculosis'.

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## Global Epidemiology of TB

Many people used to think that TB was a disease of the past. TB however, is still a leading killer of young adult world wide. The South East Asia region, with an estimated prevalence of 4.88 million (old and new cases) and an annual incidence of new cases of 1.3 million, carries one-third of the global burden of TB. About one-third of worlds' population (around 2 billion) are thought to be infected with TB bacteria. According to WHO, each year about 8 million people worldwide develop active TB and nearly 2 million die of the disease.<sup>2</sup>

## Bangladesh situation

With a population of 150 million, Bangladesh ranks sixth among countries with a high TB burden. The estimated prevalence and incidence rates of all forms of TB were 387 and 223 per 100,000 population respectively in 2007. TB control activities were expanded by increasing the number of peripheral laboratories, sputum collection or smearing centers and thus, access to TB diagnostic services have been increased. The case-detection rate has increased to 73 percent in 2007. The reported treatment success rate has increased to 92 percent for cohort patients registered in 2006. Furthermore, with the introduction of DOTS, the mortality has declined significantly than what it was in the past (78 vs. 50 per 100,000 population).<sup>2</sup>

## Gross clinical features

Early symptoms of active TB include cough with or without blood (haemoptysis), fever, weight loss, night sweats, and loss of appetite. Symptoms may be vague and go unnoticed by the affected person. For some, the disease either goes into remission (halts) or becomes chronic and more debilitating with cough, chest pain and bloody sputum.

## How can one know that some one has infected with Mtb?

To identify those who may have been exposed to Mtb, healthcare providers typically inject a substance called 'tuberculin' under the skin of the forearm. If a red wheal (welt) forms around the injection site within 72 hours, it can be

interpreted that the person may have been infected. This doesn't necessarily mean that he or she has active disease. Persons who show positive tuberculin test might have been previously exposed to Mtb or exposed to bacteria related to Mtb. If any person shows reaction to the skin test, then other conventional tests such as X-ray chest, blood for ESR, sputum examination for direct evidence of presence of Mtb germs in the sputum (smear) of cough, blood culture etc may show evidence of Mtb infection. Side by side of the conventional diagnosis, modern diagnosis include bronchial lavage (washing smear) examination, polymer chain reaction (PCR) etc. for confirmatory evidence of Mtb infection.

## Treatment of TB

**(a) Treatment in the past:** Attempts made in the past to cure TB were varied but found uniformly ineffective and looked gloomy. Roman physicians recommended bathing in human urine, eating wolfs liver, and drinking elephant blood for cure of the disease. Recommendations were also made to drink fresh milk-huan goat, or camel but proved scientifically invalid.

**(b) Present treatment (Land mark of treatment):** The major historical land mark of TB therapy began with the discovery of 'streptomycin' (SM) by an American scientist Selman Waksman derived from a soil fungus in 1944. On November, 20, 1944, a critically ill TB patient received streptomycin. Within days, he miraculously recovered from TB. Following the discovery of streptomycin, a host of other drugs followed the heels of streptomycin – rifampicin (RIF) and ethambutal (EMB) in 1950s.<sup>3</sup>

In fact, the major advance in anti-TB therapy at that time was the introduction of RIF. It was observed that when these drugs were used in combination, they assured cure of TB in more than 95 percent cases with-out emerging drug resistant bacteria. In 1970, it was first recognized that INH and RIF could reduce the duration of treatment from 18 to 9 months. This was further revolutionized in 1980s that addition of pyrazinamide (PZA) to INH, RIF and EMB, the duration of treatment was reduced further from 9 months to only 6 months.<sup>3</sup> This is due to the fact that PZA kills the intracellular Mtb, the so called 'persisters'. They constitute around 5 percent of

the Mtb population. Complete cure of TB cannot be achieved unless the 'persisters' are killed. It has been observed that among all anti-TB drugs, only PZA can kill the 'persisters' Mtb. Because the intracellular pH is acidic and to kill these 'persisters' Mtb, drug must work in acid environment. When PZA is given, it is converted in the body into pyrazinoic acid and thus, works in intracellular acid environment and kills the organisms. No other anti-TB drugs possess this property. As such, they are not completely effective to cure TB without the addition of PZA. Furthermore, if PZA is not included in treatment regimen, the regimen is said to inferior. Currently used pivotal anti-TB drugs are RIF, INH, EMB and PZA constitute the cornerstone therapy against TB. It is good news for us that TB which was previously called 'incurable disease' can now be called as completely curable (more than 95 percent). The current management of TB constitutes 'initial intensive' therapy with all these four drugs (i.e., RIF, INH, EMB and PZA) for 4 months followed by a maintenance therapy with RIF and INH for another 2 months. Thus, the total duration of anti-TB therapy now becomes only for six months.<sup>3</sup> The directly observed therapy (DOT) which has been introduced to keep strict adherence to the anti-TB therapy that ensures daily intake of the recommended doses of anti-TB drugs by the patients plays an important role to complete this duration and is the most effective means of combating non-adherence, intermittent (less than daily) regimens facilitate the therapy.<sup>4</sup>

**(c) Treatment of TB in future:** The Fluoroquinolones (FQNs), Linezolid and PNU 10048 both are derivatives of Oxazolidinediones appear to be

novel and most promising agents in the future for the management of multi-drug resistance TB (MDR-TB) including resistant to INH and RIF. Other novel drugs include Thiolactomycins, and Morphazinamide – an analogue of PZI, congeners of Metronidazole-Nitroimidazo-pyrans etc. are in the process of clinical development. Current evidence-based phase-II clinical data on a new regimen of anti-TB drugs using a fixed-dose combination of gatifloxacin (GTF), a new generation of FQNs with RIF and INH have been demonstrated more potent than the conventional INH-RIF regimen. Further, in this trial, the new regimen has also been found to reduce the present duration of six months treatment to only four months.<sup>5</sup> GTF was used in place of EMB. This new regimen is called GTF regimen which is likely to make further break-through in the treatment of TB. The days are not so far when this new regimen (i.e. GTF regimen) shall be made introduced in clinical practice.

## References

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