

## **The evolution of anti tuberculosis treatment in newly diagnosis pulmonary tuberculosis patients.**

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**ABSTRACT:** Tuberculosis (TB), which is one of the oldest diseases known to affect humans and is likely to have existed in prehomnids, is a major cause of death worldwide. This disease is caused by bacteria of the *Mycobacterium tuberculosis* complex and usually affects the lungs, although other organs are involved in up to one third of cases. If properly treated, TB caused by drug susceptible strains is curable in virtually all cases. If untreated, the disease may be fatal within 5 years in 50 -65% of cases. Transmission usually takes place through the airborne spread of droplet nuclei produced by patients with infectious pulmonary TB. With a population of about 1252 million, India is the largest country in the Region. It is ranked first among the high burden countries and contributed 24% of the estimated global incident TB cases and about 20% of global TB related deaths in 2013<sup>(1)</sup>. Since its inception in 1997, the RNTCP has initiated almost 20 million patients on treatment. Since 2005, the programme has consistently achieved and exceeded the global target of 85% treatment success rate among new smear positive cases, as well as among all new and relapse TB cases, with 88% for the cohort of patients registered in 2012, slightly below the newly set target of 90% success rate. In the 2012 cohort, the treatment success rate for retreatment cases (excluding relapse) and HIV positive TB cases (all forms) was 74% and 77% respectively; among retreatment cases the higher proportion of unsuccessful treatment was related to “lost to follow-up” (13%), and among HIV positive cases to deaths (13%)<sup>(2,3)</sup>.

**Keywords:** Tuberculosis, calcium, vitamin D, Protein, albumin,

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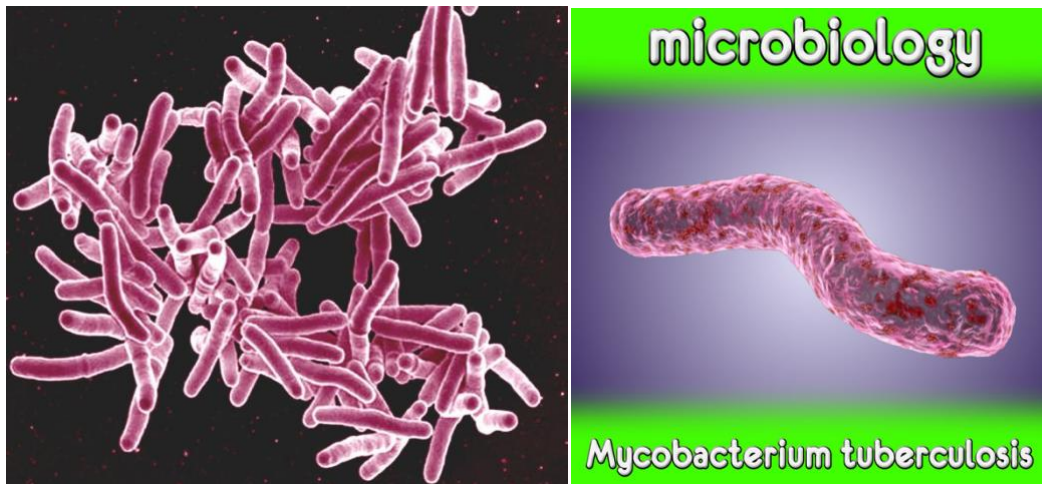
### **I. INTRODUCTION**

Tuberculosis (TB) is a major global health problem. It causes ill health among millions of people each year and ranks alongside the human immunodeficiency virus (HIV) as a leading cause of death worldwide<sup>(4)</sup>

In 2014, there were an estimated 9.6 million new TB cases: 5.4million among men, 3.2 million among women and 1.0 million among children. There were also 1.5 million TB deaths (1.1 million among HIV negative people and 0.4 million among HIV positive people), of which approximately 890000 were men, 480000 were women and 140000 were children. The number of TB deaths is unacceptably high: with a timely diagnosis and correct treatment, almost all people with TB can be cured. With a population of about 1252 million, India is the largest country in the Region. It is ranked first among the high burden countries and contributed 24% of the estimated global incident TB cases and about 20% of global TB related deaths in 2013.<sup>(1)</sup> Since its inception in 1997, the RNTCP has initiated almost 20 million patients on treatment. Since 2005, the programme has consistently achieved and exceeded the global target of 85% treatment success rate among new smear positive cases, as well as among all new and relapse TB cases, with 88% for the cohort of patients registered in 2012, slightly below the newly set target of 90% success rate. In the 2012 cohort, the treatment success rate for retreatment cases (excluding relapse) and HIV positive TB cases (all forms) was 74% and 77% respectively; among retreatment cases the higher proportion of unsuccessful treatment was related to “lost to follow up” (13%), and among HIV positive cases to deaths (13%).

### **II. ETIOLOGY**

Mycobacteria belong to the family Mycobacteriaceae and the order Actinomycetales. Of the pathogenic species belonging to the *M. tuberculosis* complex, the most common and important agent of human disease is *M. tuberculosis*. *M. tuberculosis* is a rod shaped, non spore forming, thin aerobic bacterium measuring 0.5µm by 3µm. Mycobacteria, including *M. tuberculosis*, are often neutral on Gram's staining. However, once stained, the bacilli cannot be decolorized by acid alcohol; this characteristic justifies their classification as acid fast bacilli.



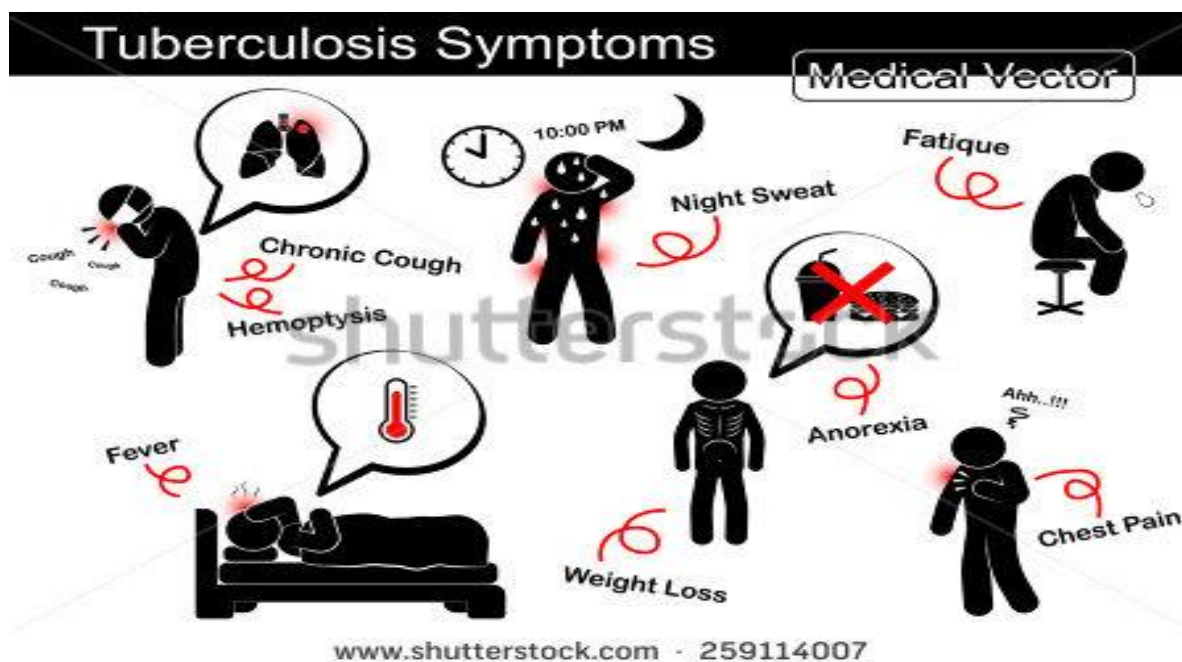
### **III. EXPOSURE TO INFECTION**

*M. tuberculosis* is most commonly transmitted from a person with infectious pulmonary TB to others by droplet nuclei, which are aerosolized by coughing, sneezing, or speaking. The tiny droplets dry rapidly; the smallest (<5–10  $\mu\text{m}$  in diameter) may remain suspended in the air for several hours and may reach the terminal air passages when inhaled. There may be as many as 3000 infectious nuclei per cough<sup>(5,6)</sup>. Other routes of transmission of tubercle bacilli (e.g., through the skin or the placenta) are uncommon and of no epidemiologic significance. The probability of contact with a person who has an infectious form of TB, the intimacy and duration of that contact, the degree of infectiousness of the case, and the shared environment in which the contact takes place are all important determinants of the likelihood of transmission. Several studies of close-contact situations have clearly demonstrated that TB patients whose sputum contains AFB visible by microscopy are the most likely to transmit the infection. The most infectious patients have cavitary pulmonary disease or, much less commonly, laryngeal TB and produce sputum containing as many as 105–107 AFB/mL. Patients with sputum smear–negative/culture-positive TB are less infectious, although they have been responsible for up to 20% of transmission in some studies in the United States, and those with culture-negative pulmonary TB and extra pulmonary TB are essentially non infectious. Because persons with both HIV infection and TB are less likely to have cavitations, they may be less infectious than persons without HIV co infection. Crowding in poorly ventilated rooms is one of the most important factors in the transmission of tubercle bacilli, since it increases the intensity of contact with case<sup>(5,6)</sup>

### **IV. INFECTION TO DISEASE**

Unlike the risk of acquiring infection with *M. tuberculosis*, the risk of developing disease after being infected depends largely on endogenous factors, such as the individual's innate immunologic and non immunologic defences and level of function of cell-mediated immunity (CMI). Clinical illness directly following infection is classified as primary TB and is common among children in the first few years of life and among immune compromised persons<sup>(7)</sup>. Overall, it is estimated that up to 10% of infected persons will eventually develop active TB in their lifetime, with half of them doing so during the first year after infection. The risk is much higher among HIV-infected persons. Re infection of a previously infected individual, which is common in areas with high rates of TB transmission, may also favour the development of disease<sup>(8, 9)</sup>.

## V. SYMPTOMS OF TUBERCULOSIS



## VI. DIAGNOSIS OF TUBERCULOSIS:

The diagnosis of tuberculosis is based on physical examination and laboratory. Physical examination finds weight loss, lymph node with swelling. The most commonly used diagnosis tool for TB is simple skin test. A small amount of substance called as PPD tuberculin is injected just below the skin, after 48-72hrs. Check the area for swelling at the injected site. A hard raised red bump means likely to have TB infection. The size of the bump determine the test result were significant<sup>(10)</sup>.

- A) **Blood test**- QuantiFERON-TB Gold in tube-test T-spot TB Test is the TB blood tests<sup>(11,12)</sup>.
- B) **Imaging Tests**- if a positive skin test, the chest x-ray OR CT scan also done.
- C) **Sputum tests**: if the x- ray shows signs of tuberculosis. The mucus that comes up after cough, that sample tested for TB bacteria.

## VII. SERUM CALCIUM

Calcium, an important constituent of bones and teeth, is the fifth most common metallic element in the body and highly essential for normal body development. It is found in three body compartments: the skeleton, soft tissues and extracellular fluid. While soft tissues and extracellular fluid contain about 1% of the body's calcium, the skeleton contains 99% of the body's calcium. Tuberculosis is one of the granulomatous diseases that change the status of plasma calcium concentration<sup>(13)</sup>. Serum Calcium abnormalities have been variably reported in studies carried out on the subject. In a Swedish study hypercalcaemia was found in 25% of 67 patients of Pulmonary TB<sup>(14)</sup>. In United States 16% to 28% patients of Pulmonary TB have been found to be suffering from hypercalcaemia<sup>(15)</sup> though lower incidence of hypercalcaemia has also been reported from US<sup>(16)</sup>. Hypercalcaemia was detected in 25% Greek patients<sup>(17)</sup>. And in 27.5% of the Malaysian patients<sup>(18)</sup> with pulmonary tuberculosis, with symptoms of hypercalcaemia present in only 5% and 12% of these patients, respectively. Hypercalcaemia and hyperphosphataemia in Pulmonary TB has also been reported from Germany<sup>(19)</sup>. Albumin Corrected Calcium (ACC) was also found significantly higher in Pulmonary TB patients from Hong Kong despite a lower calcium intake<sup>(20)</sup>. However, comparatively low percentage of hypercalcaemia was found in another study from Hong Kong's (6%)<sup>(21)</sup>. Pulmonary TB has also been found associated with hypocalcaemia in some studies. In a Japanese study 38% patient showed Ca level lower than reference range.<sup>(22)</sup> Serum Ca and Parathyroid hormone (PTH) levels were found significantly reduced in an Egyptian group of Pulmonary TB patients<sup>(23)</sup>. Similar results were also found in a Nigerian study<sup>(24)</sup>. In pulmonary tuberculosis, there is abnormal functioning of parathyroid gland to produce more PTH, leading to hypercalcaemia of free calcium. Very low albumin in the system may also results in hypocalcaemia of plasma-bound calcium<sup>(13)</sup>.

There is no study done in Indian population determining the levels of serum calcium in the patients of tuberculosis and also there is no Indian study determining the effect of anti tubercular treatment on the blood calcium levels.

### **VIII. SERUM VITAMIN D**

Vitamin D modulates monocyte-macrophage activity in the body and plays a role in human innate immunity to certain infectious agents. This role maybe important in the body's defense against tuberculosis, in which attack of macrophages is a key step in pathogenesis. Vitamin D acts by binding to nuclei receptors on target cells. Therefore both low levels often vitamin and abnormalities in receptor structure and function may result in impairments in host immunity to the tubercle bacillus. The contribution of vitamin D receptor abnormalities has been examined in a systematic review, which was inconclusive, but no similar review of low body vitamin D levels has been undertaken. This is in spite of a number of studies reaching varying conclusions about the risk of tuberculosis associated with vitamin D deficiency<sup>(25)</sup>. Low serum vitamin D levels are associated with higher risk of active tuberculosis. Although more prospectively designed studies are needed to firmly establish the direction of this association, it is more likely that low body vitamin D levels increase the risk of active tuberculosis. In view of this, the potential role of vitamin D supplementation in people with tuberculosis and hypovitaminosis D-associated conditions like chronic kidney disease should be evaluated<sup>(26)</sup>. Patients with tuberculosis can produce vitamin D and other vitamin D metabolites at sites of disease activity. The spontaneous production of vitamin D metabolites by granulomatous tissues could have both unfavourable and favourable clinical consequences. The production of Vitamin D or other vitamin D metabolites could have deleterious effects, mediated through an endocrine pathway. Hypercalcaemia with increased levels of plasma 1,25(OH)<sub>2</sub>D has been observed in some tuberculosis patients, including several anaphoric patients. It has also been suggested that the production of 1, 25 (OH) 2D<sub>3</sub>by granulomatous tissues could contribute to the cachexia and fever seen in patients with tuberculosis. On the other hand, several lines of evidence suggest that 1,25(OH)<sub>2</sub>D<sub>3</sub>, operating through anautocrine/paracrine pathway, may be beneficial. Indeed, it has been demonstrated that cells obtained from sites of granulomatous reactions both convert 25hydroxyvitamin D<sub>3</sub>(25(OH)D<sub>3</sub>) into 1,25(OH)<sub>2</sub>D<sub>3</sub>and express 1,25(OH)<sub>2</sub>D<sub>3</sub> receptors. Further more ,in vitro studies indicate that 1,25(OH)<sub>2</sub>D<sub>3</sub>may play an important role in the regulation of granulomatous reactions, and can improve the ability of alveolar macrophages to inhibit the growth of Mycobacteria<sup>(26)</sup>. A study confirmed the findings that serum calcium is raised in tuberculosis but the effect may be reduced by a low calcium intake and a low parathyroid hormone level. Although the calcium and vitamin D metabolism appeared to be altered in tuberculosis, no direct relationship between serum calcium and 1, 25(OH) 2D, was found<sup>(20)</sup>.

In another study, the effect of anti-tuberculosis chemotherapy on vitamin D and calcium metabolism shows that standard anti-tuberculosis chemotherapy may depress Vitamin D stores<sup>(27)</sup>. Considering this, monitoring of Vitamin D levels is under question.

### **IX. SERUM PHOSPHORUS**

Of the phosphorus contained in the body, 88% is present in bone as hydroxyapatite; the remaining 12% plays a role in intermediary carbohydrate metabolism and serves as a component of phospholipids (in which the small amount of extracellular organic phosphorus is exclusively found), nucleic acids, adenosine triphosphate (ATP), and other physiologically important substances.

In the blood, phosphorus is present either as inorganic phosphate or as organically bound phosphoric acid. Inorganic phosphate is the fraction measured in a routine biochemical assay, and the usual range in serum is approximately 2.5-4.5 mg/dl. Serum phosphate concentrations may be highly variable, depending on meals ingested and on fluctuations in the secretion of hormones such as parathyroid hormone (PTH). Before the advent of effective chemotherapy, numerous studies on the biochemistry of tuberculosis were carried out in the hope of finding some metabolic anomaly or defect whose rectification would lead to a cure. Thus calcium metabolism was investigated in the belief that calcification played an important role in the healing of lesions (Kaminsky and Davidson, 1931) but phosphorus has received relatively little attention<sup>(28)</sup>. Sweany, Weathers and that phosphorus levels varied considerably from patient to patient and they suggested that some of the phosphorus might be associated with lipoproteins liberated by the destruction of cell membranes<sup>(29)</sup>. Wells, DeWitt and Long (1923) referred to a few early reports of phosphorus retention and reduced excretion and also to a few reports of increased urinary levels of lipid-bound phosphorus in patients with tuberculosis. Sharma (1981) observed elevated phosphorus levels in Indian patients who were hypercalcaemic but not in those who were normal calcaemic .A study showed that phosphorus levels tend to be elevated in Indonesian patients with tuberculosis but whether this finding is common to patients throughout the world and whether it has a primary bearing on the immune pathology of the disease remains to be determined<sup>(29)</sup>.

### **X. TOTAL SERUM PROTEIN**

A total serum protein test measures the total amount of protein in the blood. It also measures the amounts of two major groups of proteins in the blood: albumin and globulin. Infection induces a reduction in serum albumin and total protein level in human beings as well as experimental animals. It has been known for some time, and is here confirmed, that there are alterations of serum proteins in the course of tuberculosis

infection. Such changes are not in themselves diagnostic of, or specific to, any particular disease, but probably reflect the clinical state of the patient.

In chronic infectious diseases like tuberculosis, the albumin content of serum proteins shows a decrease while the globulin content shows an increase leading to low albumin to globulin (A/G) and albumin to Alpha2 Globulin (A/ Alpha2) ratios. Studies showed that as the disease progressed, there was an increase in the alpha and gamma globulins with corresponding decrease in the albumin, and it was suggested that increase in gamma globulin was due to antibody formation. Baldwin and Hand in 1953 found patients with pulmonary Tuberculosis to have elevated Alpha globulins as well as gamma globulin, while the albumin fraction was reduced. The gamma globulin proved to decrease towards normal in the course of treatment.<sup>(22)</sup>

## **XI. PROTEINURIA**

Proteinuria—also called albuminuria or urine albumin—is a condition in which urine contains an abnormal amount of protein. Granulomas can hematogenously seed from the lungs to renal glomeruli. When these granulomas case ate and enter the medulla, this results in hematuria (but not proteinuria). Proteinuria is seen with amyloidosis secondary to TB. Chronic inflammation causes persistently high circulating levels of serum amyloid A protein (acute-phase reactant), which causes secondary amyloidosis. Therefore heavy proteinuria in the nephritic range (> 3.5 g of protein in 24 hrs) may be seen in someone with TB. Also, obstruction of lymphatic drainage by TB can cause chyluria<sup>(14)</sup>

## **XII. TREATMENT FOR TUBERCULOSIS:**

Medications are the cornerstone of tuberculosis treatment. But treating TB takes much longer than treating other types of bacterial infections. With tuberculosis, patients must take antibiotics for at least six to nine months. The exact drugs and length of treatment depend on your age, overall health, possible drug resistance, the form of TB (latent or active) and the infection's location in the body. Recent research suggests that a shorter term of treatment four months instead of nine with combined medication may be effective in keeping latent TB from becoming active TB. With the shorter course of treatment, people are more likely to take all their medication, and the risk of side effects is lessened. Studies are ongoing.

### **Most common TB drugs**

If Patient has latent tuberculosis, patient may need to take just one type of TB drug. Active tuberculosis, particularly if it's a drug-resistant strain, will require several drugs at once the most common medications used to treat tuberculosis include:

- Isoniazid
- Rifampin (Rifadin, Rimactane)
- Ethambutol (Myambutol)
- Pyrazinamide

If patients have drug-resistant TB, a combination of antibiotics called fluoroquinolones and injectable medications, such as amikacin, kanamycin or capreomycin, are generally used for 20 to 30 months. Some types of TB are developing resistance to these medications as well

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