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FROM SANATORIA TO SHORT COURSE REGIMENS: EVOLUTION OF TUBERCULOSIS(TB) TREATMENT ACROSS CENTURIES

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ABSTRACT

This review article examines the extensive historical progression of tuberculosis (TB) treatment, starting with the period of sanatoria and environmental therapy, characterised by rest, nutrition, and isolation as fundamental components of care, and advancing through the pivotal discoveries related to Mycobacterium tuberculosis, initial surgical collapse therapies, and the significant introduction of anti-tubercular antibiotics in the mid-20th century. This review elucidates the transition from extended institutional care to evidence-based multidrug chemotherapy and ultimately to contemporary short-course, rifampicin-centered regimens, demonstrating how scientific advancements, public health strategies, and global tuberculosis control initiatives have collectively influenced current management practices. The objective of this historical narrative is to elevate public understanding of tuberculosis's medical evolution, demonstrate how past lessons persistently influence contemporary strategies, and emphasise the necessity of ongoing innovation.

KEYWORDS: Sanatoria, Pivotal discoveries, Rifampicin, Short course, TB.

INTRODUCTION

Tuberculosis (TB) is a major life-threatening communicable disease caused by Mycobacterium tuberculosis, and despite its global impact, it remains a completely curable condition with timely diagnosis and appropriate therapy. For centuries, TB posed one of the greatest challenges to public health, leading to high morbidity and mortality across the world. The understanding of its etiology, mode of transmission, and disease mechanism has progressed significantly, shaping the way clinicians approach its management. TB develops through a complex pathophysiological process involving inhalation of airborne bacilli, immune activation, granuloma formation, and potential progression to active disease.

The evolution of TB treatment reflects one of the most remarkable journeys in medical history. From the early days of sanatorium-based management focused solely on rest, nutrition, and fresh air to the discovery of streptomycin, the first effective anti-tubercular drug, and later the development of multidrug regimens, TB care has continuously advanced. The introduction of short-course chemotherapy by the WHO, the emergence of drug-resistant strains, and the formulation of newer drugs and treatment strategies have further shaped the modern therapeutic landscape. This article aims to provide a comprehensive overview of tuberculosis by outlining its definition, etiology, and pathophysiology, while emphasizing the historical and scientific milestones that have transformed TB treatment over time. Through this review, readers can appreciate the significant advancements that have improved patient outcomes and guided current global TB control strategies.

DEFINITION[1,2]

TB is a bacterial (Mycobacterium Tuberculosis) disease that primarily affects the lungs and also affects other parts of the body including brain, spine, lymph nodes, pleura, bones and joints, genitourinary system, GI tract, skin etc...

→ Latent TB: Bacteria present on the body but doesn't cause any symptoms

→ Active TB: Bacteria actively multiplying in the body causing symptoms

ETIOLOGY[1,2]

→ Caused by Mycobacterium tuberculosis
→ Pulmonary TB spread from person to person if it is in the active state.

RISK FACTORS[1,2]

→ Close contact with person who has active pulmonary TB
→ Weak immune system
→ Smoking
→ Malnutrition
→ Living in poor socioeconomic conditions
→ Alcohol abuse
→ Genetic susceptibility etc…

SYMPTOMS[2,3]

→ Fever
→ Night sweats
→ Loss of appetite
→ Weight loss
→ Fatigue
→ Chills
→ Chest pain
→ Haemoptysis
→ Dyspnoea
→ Chest pain
→ Painless enlarged lymph nodes
→ Back pain etc...

TYPES OF TB[2,3]

1. Pulmonary TB
2. Extra pulmonary TB

- TB of lymph node
- Pleural TB
- Skeletal TB
- Meningitis
- Genito Urinary TB
- Gastro intestinal TB
- Miliary TB

Also, symptoms differ depending on the location of the TB infection.

PATHOGENESIS[3]

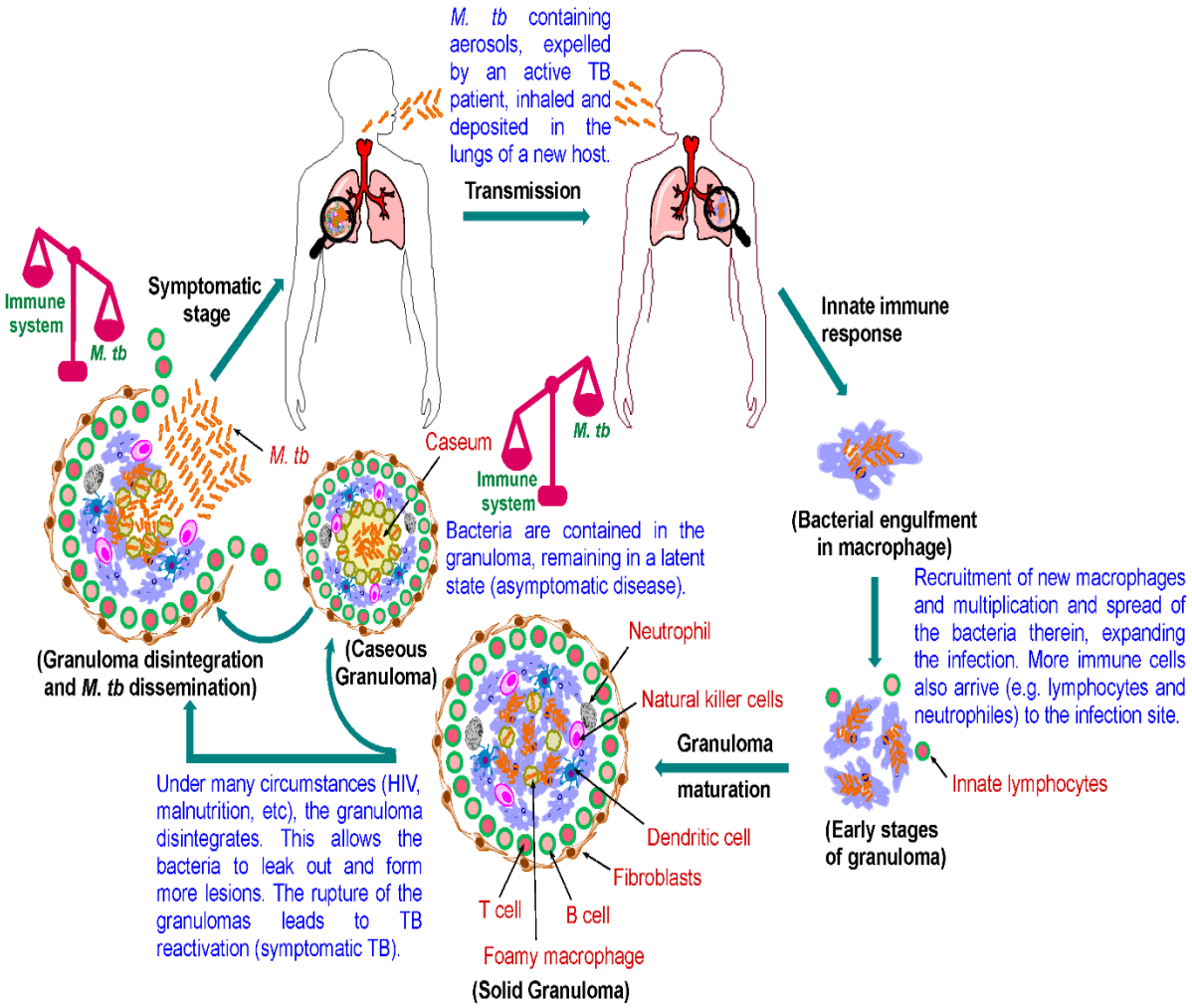

Figure 1: Pathophysiology of Pulmonary Tuberculosis.

TB pathogenesis

Inhalation of Mycobacterium tuberculosis
↓
Droplet nuclei reach alveoli
↓
Phagocytosis by alveolar macrophages
↓
Failure of intracellular killing
(Mycobacterium inhibits phagolysosome fusion)
↓
Intracellular multiplication of bacilli
↓
Spread to regional lymph nodes
↓
PRIMARY TB (Primary complex)
↓
Activation of cell-mediated immunity (2–8 weeks)
↓
CD4+ T cells → IFN-γ, TNF-α
↓
Macrophage activation
↓
Granuloma formation
(Epithelioid cells + Langhans giant cells)
↓
Caseous necrosis
↓
OUTCOMES
HEALING
↓
Fibrosis + Calcification
(Latent TB infection)

PROGRESSION
↓
PRIMARY PROGRESSIVE TB
(Common in children, HIV)
↓
Hematogenous spread
↓
→ Miliary TB
→ TB meningitis
→ TB osteomyelitis
→ Abdominal TB
→ Genitourinary TB

REACTIVATION (Years later)
↓
SECONDARY (POST-PRIMARY) TB
↓
Reactivation in oxygen-rich areas
(Upper lobes of lung)
↓
Extensive caseation
↓
Cavitation
↓
Highly infectious pulmonary TB
↓
→ Haemoptysis
→ Bronchogenic spread
→ Pleural TB

DISSEMINATION
↓
Hematogenous spread from lung focus
↓
EXTRAPULMONARY TB
→ Lymph node TB
→ CNS TB (meningitis, tuberculoma)
→ Skeletal TB (Pott's spine)
→ Abdominal TB
→ Pericardial TB
→ Genitourinary TB

TREATMENT JOURNEY

PRE BACTERIOLOGICAL ERA[4]

Long period (1880s) in the medical history before the discovery of causative organism for the TB. During that period the peoples believed that diseases are punishment from GOD/Results of Evil spirits. Prayers, rituals, sacrifices believed as the cure for this. TB was known by many names in this period such as phthisis(consumption) scrofula-cervical lymph node TB(King'sEvil), White plague due to pallor and wasting. TB described in VEDIC text as YAKSHMA. Isolation, nutritious diet, herbal remedies, are the major management for Tb during that time. According to the Miasma theory in 16th and 19th century the diseases are arised due to bad atmosphere/bad air so they bring some changes including exposure to fresh air in the seaside, rural country side, mountain region-fresh air strengthen the lungs, sunlight thought to have healing effects and rest. This is called sanatorium movement.

→ SIGNIFICANCE OF PRE BACTERIOLOGICAL TREATMENT

- Recognized importance of rest, nutrition, and environment
- Established early isolation practices
- Highlighted social determinants of disease
- Provided foundation for future scientific breakthroughs

→ LIMITATIONS OF PRE BACTERIOLOGICAL ERA

- No understanding of pathogens
- No understanding of mode of transmission
- No understanding of infection control
- Treatments are also embirical, symptomatic and often harmful.

BACTERIOLOGICAL ERA[4]

Period begins with the discovery of causative organism for TB.

In 1882- Robert koch discovered Mycobacterium tuberculosis as the causative organism for TB.And this Era extend up to 1943.

In 1890- Koch introduced Tuberculin for therapy but it didn't work

In 1905- Acceptance of Germ theory and Nobel prize
In 1907- Development of Mantoux skin test for diagnosis
In 1921- Usage of BCG vaccine
In 1930s- Microscopic establishments and culture methods for diagnosis
1943- Marked as the end of the bacteriological era. Streptomycin introduction.

→ SIGNIFICANCE OF BACTERIOLOGICAL ERA

- Discovery of causative organism for TB
- Establishment of laboratory diagnosis
- Introduction of BCG vaccination

→ LIMITATIONS OF BACTERIOLOGICAL ERA

- No effective management options
- Limited access to diagnostic facilities
- High morbidity and mortality
- Increased transmission risk

ENTRY OF STREPTOMYCIN[5,6,7,8]

Streptomycin was discovered in 1943 by selman waksman's team, the team include Albert schatz (who isolated streptomycin), H.Boyd Woodruff (who found actinomycin and streptothricin), and also the team include Elizabeth Horning, Ed Karow, and Christine Reilly.The discovery done in the basement laboratory at Rutgers University.

Streptomycin isolated from microroganism and it have the property of inhibiting the growth as well as destroying other microorganisms. And it is effective against Gram negative bacteria, acid fast bacteria as well as penicillin resistant gram positive organisms. Streptomyces griseus is the streptomycin producing strain. It was found to be soluble in water and insoluble in organic solvents.Studies proved that streptomycin is effective for so many infections including Salmonella schottmulleri, Shigella gallinarum, Brucella abortus, Pseudomonas aeruginosa, Klebsiella or Friedlander's bacillus, Diplococcus pneumoniae, and a number of organisms commonly found in urinary tract infections. Later streptomycin tested in guinea pigs with TB infection and it proved that streptomycin is effective against TB also.

→ LIMITATIONS

- Developed resistance(when used alone)
- It cause ototoxicity
- Streptomycin is Nephrotoxic
- Contraindicated in pregnancy bacause it cause fetal ototoxicity

→Dose : 15mg/kg, for elderly 10mg/kg
Maximum dose: 1gm/day

ENTRY OF PAS (PARA AMINO SALICYLIC ACID)[9]

The work for the discovery of para amino salicylic acid started from 1940 onwords by Bern Heim. He tested(added) sodium salicylate in a phosphate buffer solution containing suspension of tubercle bacilli having pH 6.7 and this test indicated the increased oxygen consumption by the tubrcle bacilli.He also confirmed the sodium benzoate is also have similar effect. Later the work of Bern Heim was extended by Lehman in 1946. He showed that only pathogenic specific strain of tubercle bacilli manifest an increased oxygen consumption in presence of salicylates and benzoate.

PAS was effective against streptomycin resistant strains of tubercle bacilli. It have strong bacteriostatic effect.It cause GI irritations and renal disturbances.And the PAS was introduced for use in 1946.

Dose : 150mg/kg/day

INTRODUCTION OF STREPTOMYCIN + PAS COMBINATION[11]

PAS in combination with streptomycin helps to reduce resistance of streptomycin. Several studies shows the combination of PAS and streptomycin is effective for some patients with mycobacterium tuberculosis infection and reports of reduced resistance.
It was flourished in late 1940's.

ENTRY OF ISONIAZID(INH)[10]

INH is the most important first line agent for the treatment of TB. INH was introduced for treatment in 1952. It was otherwise called as Isonicotinic acid hydrazide(INH). It have high selectivity and high potency against mycobacterium tuberculosis. Some drawbacks include hepatotoxicity, Peripheral neuropathy, neurotoxicity, hypersensitivity reactions etc. Research of INH done by Herbert Fox, William Barry, Frank Bernheim. Study conducted in US Research laboratories.
Dose : 300mg/day

COMBINATION OF INH+STREPTOMYCIN+PAS[11,12]

Emergence of this combination therapy is also in 1952. It was introduced into TB therapy especially pulmonary TB in between 1952-1953. Drug resistance reports are reduced but tixicity rates increased and the patients complaince are also reduced. Therapy given as intermittent streptomycin+daily PAS and daily INH.

INTRODUCTION OF ETHAMBUTOL(EMB)[13,14]

Ethambutol was discovered in 1961 and was introduced for TB treatment in 1966. It is a bacteriostatic agent. Ethambutol was included in the first line agent for the

treatment of TB. Ethambutol inhibits the transfer of glucose in to D-arabinose residue of arabinogalactan.It led to the building up of mycolic acid in to the cell wall resulting in inhibition of cell wall synthesis due to thickening of the cell wall. It cause optic neuritis, head ache, dizziness, pruritis and rarely cause peripheral neuropathy, confusions in elderly, hepatotoxicity. So dosage adjustment is reqiured for renally impaired patient.
Dose : 800-1200mg/day

EMERGENCE OF RIFAMPICIN(RIF)[15]
Rifampicin was introduced as an oral daily dose of 600mg (8-12mg/kg body weight). It was inroduced in to TB treatment in 1966. Developed in Lepetit research laboratories by group of scientists including Piero Sensi, Maria Teresa Timbal, Giancarlo Lancini. It is a first line anti TB drug and comes under the class of rifamycin antibiotic. Acts by inhibiting RNA synthesis. Initially it binds to beta subunit of DNA dependent RNA polymerase in Mycobacterium tuberculosis and it inhibit the initiation of RNA transcription and there by prevents the synthesis of m RNA, Potein and results in bacteriocidal effect.Common adverse events associated with rifampicin include orange-red discolouration of the body fluids, gastric discomforts, hepatotoxicity, nephritis, heematological side effects etc.
Dose: 600mg/day

INTRODUCTION OF PYRAZINAMIDE[16]
Pyrazinamide comes under nicotinamide analogue. It was synthesized in 1936. Higher dosages can cause hepatoxixcity. Emergence of this pyrazinamide in to TB treatment is in 1952. It was recommended as a first line choice for TB treatment and used along with INH, EMB, RIF. Pyrazinamide was discovered by Konrad Bloch and William H. Stein. Pyrazinamide is a prodrug. So, after administration it converted in to pyrazinamidase and then to pyrazinoic acid, thereby create an acidic environment results in bacterial cell membrane disruption. Along with hepatotoxicity it can also cause hyperuricemia and other adverse events including rashes, photosensitivity etc.
Dose: 20-25 mg/kg/day

STANDARD SHORT COURSE THERAPY[17]
6month standard TB therapy was developed in 1970s. Including intensive and continous phase. Intensive phase is of 2months and the continuous phase is of 4months. In the intensive phase there are 4 drugs are included such as Isoniazid(INH), Rifampicin(RIF), Ethambutol(EMB), Pyrazinamide and then in continuos phase Isoniazid and Rifampicin are included. Drug resistance in this regimen is also reported.

DOTS THERAPY(Directly Observed Treatment Short Course)[18]
DOTS therapy emerged in 1990s. Aim of DOTS is global control of TB. It was formally launched in 1995.Direct observation of the patient who taking anti TB drug to improve their adherence to drug by a health professional is the mechanism involved in the DOTS therapy. It have some limitations of patient's non complaince, lack of trained health professsionals, disruption of therapy due to recurrent adverse events etc.

DRUG RESISTANT TB GUIDELINES BY WHO[19,20,22,24,26]
Due to development of resistance against TB drug WHO published treatment guidelines for drug resistant TB from 1990 onwards. First official guideline was published in 2000 in the form of DOTS plus frame work and in which for multi drug resistant TB the duration of therapy was increased by 18-24 months or longer. So, according to this guideline the intensive phase comprised of 6-8 months with one injectable and 4 or more oral effective agents including fluoroquinolone, ethionamide, cycloserine, PAS, pyrazinamide/ethambutol. Injectables including Canamycin, Capreomycin, Amikacin. Continous phase comprised of 12-18months and in this phase injectables stopped and oral medication continued.

In 2006 guideline for the programmatic management of MDR TB developed. According to this guideline treatment only initiate after checking drug susceptability, history of treatment and local resistant pattern. Regimen is desingned with duration of 6-8months of intensive phase and 12-18 months of continuation phase. According to 2011 guideline, duration is 18-24 months with second line drugs and injectables. 2016 guideline bring major changes incudes shorter standardised regimen of 9-12 months. In 2018 longer regimen of 18-20 months with the introduction of Bedaquilin and linezolid along with injectables. According to 2019 guideline injectables removed and switched to long term oral drugs including bedaquiline. fluoroquinolones, linezolid, clofazamine, cycloserine for 18-20 months. 2022 initiated shorter oral regimen for 9-11 months.

CURRENT TREATMENT ALGORITHM FOR TUBERCULOSIS[32,33,34]
Diagnosis place a major role in TB control.So in current treatment algorithm TB is detected by using advanced techniques named NAAT/CB-NAAT.

First line therapy is standard 6month course in which 2months of Isoniazid, Rifampicin, Ethambutol and Pyrazinamide and 4 months with atleast Isoniazid and rifampicin. Given in fixed dose combination and weight based dosing. This regimen is in the case of drug susceptible TB.

Shorter regimen for Drug susceptible TB is Rifapentin and moxifloxacin for 4months. Treatment in case of drug resistant TB is on the basis of Drug susceptability tests. Therapy for multi drug resitant TB or rifampicin resitant TB is the short term regimen of BPALM/BPAL for 9months containing Bedaquiline, pretomanid, linezolid and moxifloxacin. If the short term is not much effective then increase the duration to 18 months.Nutritional

support and better adherence should be maintained pproperly.

THINGS EVERY TB PATIENTS MUST KNOW

→ Take anti TB drugs as prescribed by the doctor at the same time every day.
→ Should not stop the medicine even if feels better.
→ Report adverese drug reactions such as jaundice, severe nausea, vomiting, visual disturbances, skin rashes, hearing problems immediately to the health care providers.
→ Avoid alcohol consumption during TB treatment because it increase the risk of hepatotoxicity.
→ Maintain good nutrition, adequate rest and hydration to support recovery
→ Proper ventillation is adequate to prevent the transmission
→ Wear mask while going outside.
→ Regular follow up is also very necessary
→ Past medical and medication history should be informed to the doctor.

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