TUBERCULOSIS UPDATE  
(Including MDR TB) 

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(Including MDR TB)

INDEX

<table>
<thead>
<tr>
<th>Topic</th>
<th>Page No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>1</td>
</tr>
<tr>
<td>Estimated Burdens of Tuberculosis in India</td>
<td>1</td>
</tr>
<tr>
<td>Etiopathogenesis</td>
<td>2</td>
</tr>
<tr>
<td>Immunology of Tuberculosis</td>
<td>6</td>
</tr>
<tr>
<td>Pathology</td>
<td>8</td>
</tr>
<tr>
<td>Complications and Sequelae</td>
<td>9</td>
</tr>
<tr>
<td>Clinical Presentation</td>
<td>9</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>11</td>
</tr>
<tr>
<td>Treatment</td>
<td>20</td>
</tr>
<tr>
<td>Tuberculosis and Special Conditions</td>
<td>23</td>
</tr>
<tr>
<td>MDR-TB</td>
<td>25</td>
</tr>
<tr>
<td>Surgery in the treatment of TB and MDR-TB</td>
<td>30</td>
</tr>
<tr>
<td>Various Vaccine Strategies</td>
<td>31</td>
</tr>
<tr>
<td>References</td>
<td>33</td>
</tr>
</tbody>
</table>
INTRODUCTION:

Tuberculosis (TB) is a disease which is as old as mankind and is still persisting. In developing countries like India & Africa, it is the most common cause of loss of productive human life thus leading to further economic loss of a nation as a whole.

The history of tuberculosis met a turning point, when Robert Koch presented about it on 24th March 1882. We now celebrate it as the World Tuberculosis Day. Alas, people are still dying of TB on World TB Day. In 1884, he published a paper “Die etiologic der tuberculose” and was awarded The Nobel Prize in 1905 for his contribution in Tuberculosis. The discovery of X-rays was done by Wilhelm Conard Roentgen in 1885, which later on has been used to study TB by Francis Williams, L.Bouchard, and John Macintyre etc. X-rays have now become an integral part of TB diagnosis. Over the years, a lot many changes have occurred in terms of manifestations, diagnosis and treatment. We shall discuss a few of these changes in this article.

Tuberculosis has been haunting our society years together. It is one such infection which does not confine itself to economical backgrounds. Once thought to be a disease of the poor, it now affects both the rich and the poor.

With the new emerging TB diseases like XDR/XXDR, it has now evolved as a life threatening condition in spite of the advanced medical facility of modern era.

ESTIMATED BURDEN OF TUBERCULOSIS IN INDIA*

As per letter dated 7/5/12 TB is now a notifiable disease in India

India’s Population in 2012 was: - 1,237 million.

<table>
<thead>
<tr>
<th>Estimates of TB burden 2012</th>
<th>No. in Thousands</th>
<th>Rate (per Lakh)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality (excludes HIV+TB)</td>
<td>270 (170-390)</td>
<td>22 (14-32)</td>
</tr>
<tr>
<td>Mortality (HIV+ TB only)</td>
<td>42 (37-46)</td>
<td>3.4 (3.0-3.9)</td>
</tr>
<tr>
<td>Prevalence (includes HIV+TB)</td>
<td>2800(1900-3900)</td>
<td>230 (155-319)</td>
</tr>
<tr>
<td>Incidence (includes HIV+TB)</td>
<td>2 200(2000-2400)</td>
<td>176 (159-193)</td>
</tr>
<tr>
<td>Incidence (HIV+TB only)</td>
<td>130(120-140)</td>
<td>10 (9.4-12)</td>
</tr>
<tr>
<td>Case detection, all forms (%)</td>
<td>59(54-66)</td>
<td></td>
</tr>
</tbody>
</table>
TB case notifications 2012

<table>
<thead>
<tr>
<th></th>
<th>(%)</th>
<th>RETREATMENT CASES (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEW CASES</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smear-positive</td>
<td>53</td>
<td>Relapse</td>
</tr>
<tr>
<td>Smear-negative</td>
<td>27</td>
<td>Treatment after failure</td>
</tr>
<tr>
<td>Smear-unknown/not done</td>
<td>20</td>
<td>Treatment after default</td>
</tr>
<tr>
<td>Extrapulmonary</td>
<td>&lt;1</td>
<td>Other</td>
</tr>
<tr>
<td>Total new</td>
<td>1 183 373</td>
<td>Total retreatment</td>
</tr>
<tr>
<td>Other (history unknown)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total new and relapse</td>
<td>1 289 836</td>
<td>Total cases notified</td>
</tr>
</tbody>
</table>

TB / HIV 2012

<table>
<thead>
<tr>
<th></th>
<th>NUMBER (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TB patients with known HIV status</td>
<td>821 807 (56)</td>
</tr>
<tr>
<td>HIV-positive TB patients</td>
<td>44 063 (5)</td>
</tr>
<tr>
<td>HIV-positive TB patients on Cotrimoxazole Preventive Tx (CPT)</td>
<td>40 537 (92)</td>
</tr>
<tr>
<td>HIV-positive TB patients on antiretroviral therapy (ART)</td>
<td>25 790 (59)</td>
</tr>
<tr>
<td>HIV-positive people screened for TB</td>
<td>13 24 836</td>
</tr>
</tbody>
</table>

Estimates of MDR-TB burden 2012

<table>
<thead>
<tr>
<th></th>
<th>NEW</th>
<th>RETREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of TB cases with MDR-TB</td>
<td>2.2 (1.9–2.6)</td>
<td>15 (11–19)</td>
</tr>
<tr>
<td>MDR-TB cases among notified</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary TB cases</td>
<td>21 000</td>
<td>43 000</td>
</tr>
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ETIOPATHOGENEIS:

Tuberculosis can affect any part of the human body. It is caused by Mycobacterium tuberculosis (MTB) which is an acid fast bacillus. There are other forms of Mycobacteria which are known as NTM (Non Tuberculous Mycobacteria) or MOTT (Mycobacteria other than Mycobacterium Tuberculosis) which can cause various pulmonary and extra pulmonary manifestations. These are however predominantly seen in immuno-compromised patients who develop Johne`s disease, chronic ulcerative and nodular lesions, swimming pool granuloma, Buruli`s ulcer etc.

The pathogenesis of TB is based on the decline in the immune status of the patient. Whether the person infected with TB bacilli will develop disease or not, depends on a number of factors. These include, Resistance (immunity) of a person, Age of a person, Factors responsible for disease manifestation include, resistance (immunity) of a person, age of a person & infectivity dose i.e. bacilli load and mycobacterium virulence.
and Infectivity dose i.e. bacilli load and mycobacterium virulence.

Immuno-compromised patients like those harboring Diabetes Mellitus, HIV, Leukemia and long term corticosteroid users etc are more likely to get diseased as compared to normal healthy individuals. Lung is the most common site affected by MTB.

The pathogenesis of Tuberculosis involves various stages which are as described below:

**Primary tuberculosis:**

In the days when understanding the pathogenesis of TB was a difficult task, Primary Tuberculosis was described in children on the basis of Parrots Law by Marie-Jules Parrot which is as follows: “Pulmonary TB does not exist in the child without involvement of the tracheobronchial gland.” This simply implies that the lymphatics carry the infection to the draining lymph nodes. Primary TB is usually seen as an initial infection in children. This focus of primary TB & the infected draining lymph nodes are known as Primary Complex of Ranke. In the lungs it is called as the Ghon’s complex (small subpleural granuloma – Ghon’s Focus, with the draining lymphatics & tracheobronchial lymph node). Most commonly involved are the ipsilateral hilar & less commonly the paratracheal nodes. The parenchymal lesion is usually located in the middle or lower region of the upper lobe or the upper region of the lower lobe.

The Ghon’s Focus is usually single, 2 millimeters or more in size & located within 1 centimeter of the pleura.

Other Foci of Tuberculosis include:\n
<table>
<thead>
<tr>
<th>Name</th>
<th>Site affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rich’s Focus</td>
<td>Subependymal region of Brain</td>
</tr>
<tr>
<td>Simon’s Focus</td>
<td>Lung Apices</td>
</tr>
<tr>
<td>Simmond’s Focus</td>
<td>Liver</td>
</tr>
<tr>
<td>Weigert’s Focus</td>
<td>Intima of Blood Vessels</td>
</tr>
<tr>
<td>Assman’s Focus</td>
<td>Lung apices</td>
</tr>
<tr>
<td>Huebschmann’s Focus</td>
<td>Nodules in both apices of lung in children</td>
</tr>
</tbody>
</table>

*Table 1. Foci of TB*

In nearly all cases, these primary lesions resolve and there is no further spread of the infection. Among primary infection about 95 % heal spontaneously which depends upon the immunity of individuals. Healing may occur with fibrosis and calcification (microscopic – 2 months, radiological - > 1 year)
Changes in the Primary Complex:

Understanding the pathogenesis of TB requires an in depth knowledge of the changes occurring in the primary complex. Healing occurs as a rule. The caseous focus gets replaced by reticulin & collagen fibres & later hyalinization & calcification occurs which may show on radiographs as scars or calcification. Early generalization occurs by a lymphohematogenous spread within hours or days from the focus of infection leading to dissemination of the bacillus to almost any organ of the body. In some patients, this may lead to Miliary TB. Hydrolytic enzymes released by the macrophages cause liquefaction of the solid caseous focus. This results in extensive parenchymal destruction & cavitation. Communication with a bronchus can lead to endobronchial spread which may lead to acute bronchopneumonia which can also be fatal. Complications include empyema and pneumothorax. This is Progressive Primary TB which directly follows the primary lesion. It includes TB bronchopneumonia and cavitation. It occurs mostly in infancy, at puberty and in the elderly. Lobar & Segmental Lesions occur due to endobronchial obstruction due to extrinsic luminal compression by enlarged lymph nodes or intrinsic lesions such as necrosis or cold abscess formation. Most commonly affected is the anterior segment of upper lobe & right middle lobe. Such lesions may lead to bronchostenosis & bronchiectasis later on in life.

Epituberculosis is a non tuberculous consolidation in a TB lung. It occurs due to two possible etiologies: resolving TB pneumonia or atelactasis produced by obstruction of a bronchus by a TB lymph node or by a primary pulmonary lesion. It is seen mainly in children than in adults. It is seen on a chest radiograph as a dense homogenous shadow extending from the hilum to the pleura. These lesions rarely grow AFB.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Duration</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3-8 weeks</td>
<td>The primary complex develops. Conversion to tuberculin positively occurs</td>
</tr>
<tr>
<td>2</td>
<td>~ 3 months</td>
<td>Life-threatening forms of disease due to hematogenous dissemination occur, i.e. tuberculosis meningitis and Miliary tuberculosis</td>
</tr>
<tr>
<td>3</td>
<td>3-4 months</td>
<td>Tuberculosis pleurisy may be the result of either hematogenous spread or direct spread from an enlarging primary focus</td>
</tr>
<tr>
<td>4</td>
<td>Up to 3 yrs.</td>
<td>This stage lasts until the primary complex resolves. More slowly developing extra pulmonary lesions, particularly in the bones and joints, may appear.</td>
</tr>
<tr>
<td>5</td>
<td>Up to 12 yrs.</td>
<td>Genitourinary tuberculosis may occur as a late manifestation of primary tuberculosis</td>
</tr>
</tbody>
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*Adapted from Wallgren and Ustvedt*
Post Primary Pulmonary Tuberculosis:
This represents the resurgence of dormant bacilli which occurs several years after the primary infection. It is seen predominantly in the apical or sub-apical region which is thought to be the “Vulnerable Region”. It is because of the higher oxygen tension which has a detrimental effect on the macrophages leading to intracellular growth & hence better survival of the bacillus. Reactivation occurs when health status declines.

Lesions in Post Primary Pulmonary Tuberculosis have a wide range of presentation. These include lobular pneumonia, nodules, cavity & bronchopneumonia. Bronchial lesions could manifest as bronchial inflammation, endobronchial tuberculosis or bronchiectasis. Miliary TB is another important manifestation seen in this group of patients. Pleural lesions are also seen.

In India, TB is the most common cause of caseous necrosis.

Other causes of caseous necrosis include: Other than Tuberculosis there are few other conditions which cause Caseation necrosis. These include Histoplasmosis, Cryptococcosis, Coccidioidomycosis and Syphilis.

Healing of Cavity: Cavity healing occurs in 1 of the following manners: Open negative syndrome, Collapse of cavity & Tuberculoma formation.

Congenital Tuberculosis:
It occurs due to either aspiration of amniotic fluid or hematogenous spread via the umbilical vein. It is characterized by a non-immune non-reactive response. In hematogenous spread the primary complex is in the liver & the accompanying portal lymph nodes. In spread due to aspiration, there is involvement of the lungs, hilar and mediastinal lymph nodes without any hepatic lesion. Liver lesions indicate congenital TB, whereas absence of liver lesions indicates perinatal TB, which occurs due to swallowing of infected material before or at birth.

Other Sites of Primary Complex:
Apart from the lung, there are many other sites which form a focus of primary complex of Tuberculosis. Site of BCG vaccination is one such commonly seen non pulmonary site of primary complex. Less commonly the Tonsils & Adenoids show primary complex formation. Uncommonly the Ileum may show such a primary complex formation.

Rarely, the Esophagus, Stomach, Duodenum, Colon, Pharynx, Uvula, Buccal mucosa, Tongue, Larynx, Parotid gland, Nose, Skin, Liver, Penile skin, Vulva, Conjunctiva, Retina, Lacrimal gland, Middle ear & Injection sites may show primary complexes.
IMMUNOLOGY OF TUBERCULOSIS

Inhalation → Macrophages
\[ \text{1st PHASE} \]
- Ingest the organism → Destroyed
- Fail to destroy the pathogen → Disruption of macrophages → Fresh infection of bystander macrophages
- Recruitment of PMN's followed by monocytes & other inflammatory cells

PHASES OF TB INFECTION

Post Primary Tuberculosis
- Endogenous reactivation in c/o loss of immunity
- Containment of infection

Dissemination
- 4th PHASE
- Defective
- Granuloma formation

Ingest the bacilli
- 3rd PHASE
- Incomplete removal
- Log growth of pathogens

Initial Encounter f/b Innate Immunity

Inhalation → Alveolar macrophages
- Endocytosis → ineffective

Opsonised bacilli
- Uptake by CR1, CR3, CR4
- Uptake by Mannose Receptors

Non opsonised bacilli
- Miscellaneous
- Collectins
- Surfactant A
- Fibronectins

Scavenger Receptor Type A
- Translocate NF-κB from cytosol to nucleus
- Stimulate production of cytokines for innate & acquired immunity
- TNF alpha, IL-1B, IL-6, IL-12, IL-15, IL-18

Protection against dissemination & re-activation

DC – APC
- With ESAT-6 Ag 85 in Lymph Nodes
- Stimulate proliferation of CD4 T-cells

Fig. 1. Phases of TB

Fig. 2. Immunological Response in TB
Various cytokines as seen in the above flowchart are involved in the pathogenesis of TB. Some help in curbing the spread of infection; whereas some are responsible for severe forms of disease. TNF – alpha and IL-1B are predominantly involved in Macrophage Activation, Immune Regulation and Granuloma formation. IL-6 may antagonize either TNF – alpha or IFN – gamma. IL-12 is the most potent Th1 driving regulatory cytokine. IL-18 is important for IFN – gamma axis of T-cell response. Its levels are in parallel to those of IFN – gamma.

IFN – gamma which is produced by the T lymphocytes is the terminal effector cytokine conferring protection.

**Fig. 3. T-cell mediated response in TB**

**Fig. 4. Process of Granuloma formation**
PATHOLOGY:

The histopathological hallmark of Tuberculosis is Granuloma, which is a Latin term from grain/granulum. Granuloma is a focal collection of inflammatory cells in which mononuclear cells predominate. Macrophages predominate in the centre attempting to phagocytose the Mycobacteria. Activated macrophages form epithelioid cells, characterized by a pale, eosinophilic cytoplasm. This is now known as an epithelioid cell granuloma. Caseation necrosis is seen in the centre of the granuloma. There are 2 types of Granuloma namely soft and hard.

**Soft granuloma:** These are poorly circumscribed granulomas, characterised by loose collections of neutrophils, lymphocytes, macrophages & epithelioid histiocytes with minimal fibroblastic proliferation. These lesions are more likely to contain AFB.

**Hard granuloma:** These are well circumscribed granulomas with epithelioid histiocytes & lymphocytes with numerous Langhans giant cells. More marked fibroblastic proliferation and few AFB is the characteristic.

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**Fig. 5.** Th1 vs Th2 responses in TB

IL-10, IL – 4 & TGF – B promote Th2 immunity & Inhibit Th1 response & are responsible for severe forms of TB

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**Fig. 6.** Microscopic picture of Tuberculous Granuloma and Caseous Necrosis
COMPLICATIONS AND SEQUELAE:

Complications seen in Tuberculosis patients include Hemoptysis, Pneumothorax, Empyema, Bronchopleural Fistula, Disseminated infection including laryngitis, meningitis, genitourinary TB, intestinal TB, arthritis, spinal involvement, MDR-TB, Ocular toxicity, Addison’s Disease and Amyloidosis.

After TB is completely treated patients can develop Sequelae like Hemoptysis, Post-tuberculous bronchitis and bronchiectasis, fungal ball formation (Aspergilloma) in a healed cavity, Spontaneous pneumothorax, tension cyst, Scar carcinoma, Obstructive airway disease and Secondary pyogenic infections. Systemic sequelae include Secondary Amyloidosis, Chronic respiratory failure and Cor Pulmonale.

CAUSES OF HEMOPTYSIS IN PULMONARY TUBERCULOSIS:

Hemoptysis is a very common cause of concern in patients with Tuberculosis. It varies in quantity from streaky hemoptysis to massive life threatening blood loss. It can occur due to bleeding from cavity wall, rupture of Rasmussen’s aneurysm, direct erosion of capillaries or arteries by granulomatous inflammation, Tuberculous endobronchitis, Post tuberculous bronchiectasis, Aspergilloma, Broncholith, Cavernolith, Scar carcinoma, Bronchopulmonary communications.

CLINICAL PRESENTATION:

The signs and symptoms of tuberculosis are very varied. However, one should always bear in mind that rare presentation of common diseases like tuberculosis is much more common than common presentations of rare diseases.

The most important aspect regarding the presentation of TB is that it is a slow growing disease and rarely acute. As we know TB can involve any part of the human body but pulmonary Koch’s (around 50% of all TB) is the most common among all. Among extra pulmonary tuberculosis lymph node TB is the most common and among them cervical LN is the commonest.

The rounded frequency order is as follows:

1. Lymph node- 35% of extrapulmonary
2. Pleural -20% of extrapulmonary
3. Genitourinary-10-15% of extrapulmonary
4. Skeletal (bone) - 10% of extrapulmonary
5. CNS (Meningitis/ Tuberculoma) - 5% of extrapulmonary
6. Pericardial – rare
7. Miliary and disseminated-rare
8. Ophthalmological involvement is the rarest form of TB but seen often-chorioretinitis, uveitis, panophthalmitis, and painful hypersensitivity-related phlyctenular conjunctivitis.

Tuberculosis most commonly presents with low grade fever, predominantly evening rise of temperature with weight loss & loss of appetite.

Apart from this the presentation depends upon the system involved as depicted below

- **Pulmonary** - hemoptysis /cough / sputum
- **Lymph node** –fever/lymphadenopathy/cold abscess, cough and fever (mediastinal LN)
- **Pleura**- Cough (non-productive) / pleuritic chest pain
- **Genitourinary**- Dysuria, frequency, nocturia, tenderness/swelling of the testis or epididymis. Presence of Sterile pyuria should always lead to search for Tuberculosis.
- **Skeletal TB** (Pott’s spine) - fever & backache is commonly seen. Paresis or plegia depending upon the duration of development is a cause of concern. Joint pain/swelling/cold abscess formation is also commonly seen.
- **CNS TB**- Fever, malaise, anorexia, irritability and later on as the disease progresses neurological symptoms like progressive headache, lethargy, personality changes, memory disturbance, impaired cognition, confusion, and then stupor-coma with or without neurological deficit. Features of meningism /meningitis like neck rigidity and seizures/ unconsciousness/coma in case of Tuberculoma.
- **Abdominal**- Peritonitis, followed by ileo-caecal, ano-rectal and mesenteric lymph node infection. In peritoneal TB, fever, ascites, pain, anorexia/weight loss are common
- **Pericardial**- Fever, dyspnoea, tachycardia, neck vein distension, edema, hepatomegaly, paradoxical pulse, pericardial rub.

Disseminated and Miliary Koch’s- This is the haematogenous spread and amongst one of the serious manifestations of tuberculosis. Patients are usually cachectic and present with fever, weight loss and multi organ symptoms. Bone marrow involvement is now a days frequently seen.
DIAGNOSIS:
The diagnostic approach involves a combination of clinical, radiological and microbiological analysis.

1. Clinical
2. Microbiological
3. Radiological
4. Mantoux test
5. Interferon Gamma Release Assay

1. Clinical:
History of low grade evening rise of temperature with loss of weight & appetite is a common mode of presentation. Additional symptoms depend on the site of involvement as already discussed.

2. Microbiological:
Microbiological tests have always been the mainstay in the diagnosis of Tuberculosis. Many modifications and additions have taken place in this area. However, many aspects are still unclear thus creating confusion amongst the clinicians. It is of utmost importance to understand the newer assays in order to ask for them at the right time and reducing the financial burden of the patients. In this section we will discuss about both the older and the newer diagnostics developed for TB.

Direct methods:
- Direct Microscopy (ZN, Kinyoun and Flurochrome).
- Culture (Traditional, Rapid methods).
- Detection of DNA or RNA of Mycobacterial origin (PCR, LAMP, TAA / NAA, LCR, Fast Plaque).

Direct microscopy:
Most important in diagnosis of Tuberculosis is Ziehl-Neelsen staining of specimens. It is one of the easiest & quickest diagnostic tests. It also has the advantage of reproducibility, good specificity and a low cost and that it can be done in any laboratory where microscopy facilities are available. However, it has a limited sensitivity (20-80%). Centrifugation & Flurochrome staining (Auramine O) with UV microscopy markedly increase the sensitivity & a large number can be examined in a much shorter time. ZN staining requires at least $10^6$ bacilli/ml to be detected by microscopy. Conventional fluorescent microscopy is around 10% more sensitive than ZN staining but requires technical expertise. By using LED microscopy one can have the same results like Fluorescent microscopy with lesser costs. By concentrating the sputum by centrifugation technique, the sensitivity of the smear
microscopy can be increased to almost 100%.

- TB bacilli appear as straight/curved rods (1-4µ x 0.2-0.8µ) singly, in pairs or in clumps.
- The yield of microscopic examination correlates well with the extent of disease, the presence of cavitation, and the quality of specimen.
- It is a good marker for infectiousness & the response to the treatment.

Fig. 7. Mycobacterium tuberculosis after ZN staining

**Traditional Culture:**

Culture methods have been the gold standard for the diagnosis of Mycobacterium Tuberculosis. For the traditional LJ medium culture (Egg, Malachite Green, Mineral salts and Glycerol) only 10 to 100 viable organisms per ml of sputum are required for sputum to grow on culture. It is required for precise identification of causative organisms and also for conducting the drug susceptibility tests.

Solid and liquid media are available for the culture methods. Solid media include LJ medium, Loeffler serum slope, Pawlowsky's medium and Tarshis medium. The liquid media include Dubos medium, Middlebrook’s medium, Sula’s medium and Sauton’s medium. The biggest disadvantage is that the growth is slow and takes 6-8 weeks. Thereafter the same length of time is required for sensitivity testing.

**Rapid culture method:**

In view of the prolonged duration of diagnosis by the use of traditional culture media, efforts have been put in to develop means of rapid and timely diagnosis if M.TB. Following are few of the rapid diagnostic culture methods:

**BACTEC culture:** In this method Middlebrook 7H12 broth containing carbon-14 labeled palmitic acid is used and processed specimen is added along with a mixture of antibiotics to the broth. Growth is indicated by liberation of $^{14}\text{CO}_2$ as metabolized by Mycobacteria and detected by BACTEC 460 instrument which is reported in terms of growth index (GI) value. It takes approximately 8 days for a smear positive sample to turn positive. It is more sensitive than traditional method and can also be used for drug susceptibility testing. The drawbacks are high cost and disposal of radioactive waste.
• Septi Check AFB Method: This method combines broth & solid media into a single device i.e. biphasic culture approach. It contains modified Middlebrook 7H9 broth in CO₂ enriched culture bottle & a peddle with agar media. It requires 3 weeks of incubation and its advantage is that it simultaneously detects MTB and NTM.

• Mycobacteria Growth Indicator Tube (MGIT): It consists of round bottom tubes containing modified Middlebrook 7H9 broth which has an oxygen sensitive fluorescent sensor at the bottom. When Mycobacteria grow, they deplete the dissolved oxygen in the broth and allow the indicator to fluoresce brightly in a 365nm UV light. The positive signals are obtained in 10-12 days. MGIT can also be used as a rapid method for the detection of drug resistant strains of MTB directly from acid-fast smear positive samples as well as from indirect drug susceptibility studies. Advantages over BACTEC are that it is cheaper and there is no problem of radioactive waste disposal.

Detection of DNA or RNA of Mycobacterial origin

Genotypic Methods:
• PCR
• LAMP
• TMA / NAA
• Ligase chain reaction

Polymerase Chain Reaction (PCR):

PCR plays an important role in the diagnosis of pulmonary & extra pulmonary TB. In pulmonary TB almost all smear positive and culture positive cases are detected. It also helps in rapid diagnosis of smear negative cases. It is able to diagnose 50-60% of smear negative cases. Stress should be laid on the fact that it should not be used to replace sputum microscopy.

In the PCR technique, millions of identical copies of a specific DNA sequence, which may be a gene, or a part of a gene, or simply a stretch of nucleotides with a known DNA sequence are made. The specimen is then heated to denature double stranded DNA. Specific synthetic oligonucleotide primers bind to the unique DNA sequences of interest and a heat stable DNA polymerase extends the primer to create a complete and complimentary strand of DNA. This process is repeated sequentially 25-40 times, thereby creating millions of copies of target sequence. The amplified sequence can then be detected by agarose gel electrophoresis.

• 65 KD antigen (HSPs):
  This is a heat shock protein used earlier. It is identical in all species of Mycobacteria. Hence it is unable to distinguish NTM from MTB.

• IS6110:
  This sequence has been found in the MTB complex organisms (MTB, M.africanum, M.microti, and M.bovis). IS6110 sequence generally occurs only once in M.bovis but is found as often as 20 times in certain strains of MTB, thus offering
multiple targets for amplification. It helps distinguish MTB from NTM in smear positive cases as IS6110 sequence is not found in NTM.

The Sensitivity and Specificity for PCR is 83.5% and 99% respectively. However its role is limited in extra pulmonary cases. Currently, it is a valuable adjunct in the diagnosis of TBM, pleurisy and pericardial TB.

This test has a couple of disadvantages which are requirement of a very high degree of quality control, Inter laboratory variation, sustained period of positivity after initiating therapy as compared to culture, high false positive results in patients previously treated with ATT & a high cost.

**Nucleic Acid Amplification Technique (NAAT):**

Transcription Mediated Amplification (TMA) and Nucleic Acid Amplification (NAA)- These techniques use chemical rather than biological amplification to produce nucleic acid. Test results are available within few hours. However, currently it is being used only for respiratory specimens. LPA (Line Probe Assay) and GeneXpert are one of them.

1) **XPERT MTB/RIF (GENEXPERT):** This is also one of the newer upcoming investigative modality for diagnosis of TB. It is cartridge based nucleic acid amplification assay (Xpert MTB/RIF). It is fully automated and has an integrated sample preparation It detects M. TB as well as Rifampicin (rpoB gene) resistance conferring mutations. It is done directly from sputum & provides results within two hours. There is no cross reactivity with NTM species. It has a sensitivity of 99% in Sputum positive cases. In Sputum negative, culture positive cases it is 72.5% (with 1 sample), 85.1% (with 2 samples) and 90.2% (with 3 samples). In Smear negative, culture negative cases sensitivity is 60%. It has a specificity of 99%. The sensitivity of Xpert MTB/RIF was 93.9% in HIV infected PTB patients. Sensitivity in detecting extra pulmonary samples is 81% (smear positive) with a specificity of 99.6%. Sensitivity in detecting Rifampicin resistance is 99.1% and Specificity is 100%. The rate of indeterminate Xpert MTB/RIF results was 3.7%, lower than the rate of culture contamination.

2) **Line Probe Assay (LPA):** This is one of the newer diagnostic modality which is basically Nucleic Acid Amplification Test and is becoming more common. It is also called Hain Test. It helps detect resistance to First- and Second-Line Anti-TB Drugs from decontaminated Smear-Positive Pulmonary Specimens and Culture Samples. LPA is of two types:

**Genotype MTBDRplus-**

The Genotype MTBDRplus is based on the DNA•STRIP technology and permits the simultaneous molecular genetics identification of The M. tuberculosis complex and Its resistance to Rifampicin by the detection of the most common mutations in the
rpoB gene. Its resistance to isoniazid by the detection of the most common mutations in the katG gene and inhA gene.

**Genotype MTBDRsl** - Genotype MTBDRsl is used for detection of resistance to fluoroquinolones like Ofloxacin and Moxifloxacin by the detection of the most common mutations in the gyrA gene, resistance to the injectable antibiotics (viomycin, Kanamycin, Amikacin and Capreomycin) and resistance to Ethambutol.

**Sensitivity Of The Current Diagnostics**:  
- Liquid culture: 10–100 cfu.mL$^{-1}$  
- Solid culture: 100–1000 cfu.mL$^{-1}$  
- Automated NAAT: 100–150 cfu.mL$^{-1}$  
- LAMP-TB: 100–1000 cfu.mL$^{-1}$  
- Line probe assay: 1000–10000 cfu.mL$^{-1}$  
- Fluorescent/LED microscopy: 5000–10000 cfu.mL$^{-1}$  
- Immunochromatography for speciation: 1000000 cfu.mL$^{-1}$

The above implies that liquid cultures performed by automated systems are the most sensitive tool available today, automated nucleic acid amplification techniques (NAAT) shows a sensitivity comparable to solid cultures.

The GOI has banned all the sero-diagnostical methods as per letter dated 19-07-2011 after the WHO recommendation: “Commercial serological tests provide inconsistent and imprecise findings resulting in highly variable values for sensitivity and specificity. There is no evidence that existing commercial serological assays improve patient-important outcomes, and high proportions of false-positive and false-negative results adversely impact patient safety. Overall data quality was graded as very low and it is strongly recommended that these tests not be used for the diagnosis of pulmonary and extra-pulmonary TB”.

3. **Radiological**:  
Radiological features of TB are usually very typical. These depend a lot on the immune status of a patient. In Immunocompetent patients commonly seen radiological manifestations include, pleural effusion, thick wall cavity, parenchymal consolidation & infiltrates mostly having an upper lobe predominance. Miliary shadows & Lymphadenopathy are also frequently seen. In immunocompromised individuals in the early stages of immunosuppression radiological features are
similar to those of immunocompetent patients. In advanced stages, lower zones are predominantly involved and show diffuse infiltrates, multiple pulmonary nodules with mass lesions.

CT, MRI & PET scan have all been used in the rapid diagnosis of Tuberculosis. However, emphasis should be laid on the fact that these diagnostic modalities do not replace the traditional culture and staining methods of diagnosis. Also point to be stressed is that these imaging modalities should be conducted only when doubtful lesions are found on a CXR.
4. **Tuberculin Skin Test (TST):**

Also known as the Mantoux Test, it is the standard test for the immuno-diagnosis of tuberculosis, though IGRA (Interferon Gamma release Assay), has replaced TST in many aspects. TST is still much more widely used as a screening test in India. Currently PPD-S-RT23-Tween80 is being used for TST. In India, it is maintained at BCG Vaccine Laboratory, Guindy, Chennai from where it is reconstituted & supplied as ready to use preparation in isotonic buffer solution.

The TST gives information about the infectivity of a person and not about the disease state.

In India TST is being used for:

- Epidemiological Surveys – Predicting prevalence or assess annual risk of infection
- BCG vaccination effect-TST become positive after three months of vaccination
- Children- If a child less than six year is TST positive then he/she should be considered for chemoprophylaxis against TB even if not diseased i.e. not any active disease.
- Diagnosis- Induration more than 20 mm x 20 mm in immune competent patients strongly suggests the presence of disease.

### Interpretation of Tuberculin Test

<table>
<thead>
<tr>
<th>Size of induration 15 mm and above</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Signifies infection with tubercle bacilli, irrespective of BCG vaccination status</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Size of induration 10 to 14 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Could be attributable to one or more of the following:</td>
</tr>
<tr>
<td>• Cross sensitivity induced by environmental mycobacteria</td>
</tr>
<tr>
<td>• BCG induced sensitivity</td>
</tr>
<tr>
<td>• Infection with Mycobacterium Tuberculosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Size of induration 5 to 9 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Majority of such reactions are attributable to cross sensitivity induced by environmental mycobacteria and/or BCG vaccination</td>
</tr>
<tr>
<td>• Could be attributable to infection with tubercle bacilli in the presence of immunosuppressive conditions</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Size of induration less than 5 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Indicates absence of any type of mycobacterial infection except in individuals with severe degree of immunosuppression</td>
</tr>
</tbody>
</table>

**Table 4.** Interpretation of Tuberculin Test based on induration size.
TST is widely used for screening of Latent MTB infection in areas where TB is not an endemic infection. Emphasis should be laid on the fact that TST does not aid in differentiating active disease from latent infection.

**Tuberculin Reaction Size & Latent MTB Infection**

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Tuberculin Reaction Size (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV infected persons or persons receiving immune suppressive therapy</td>
<td>&gt;= 5</td>
</tr>
<tr>
<td>Close contacts of Tuberculosis patients</td>
<td>&gt;= 5</td>
</tr>
<tr>
<td>Persons with fibrotic lesions on chest radiography</td>
<td>&gt;= 5</td>
</tr>
<tr>
<td>Recently infected persons (&lt;2 years)</td>
<td>&gt;=10</td>
</tr>
<tr>
<td>Persons with high risk medical conditions</td>
<td>&gt;=10</td>
</tr>
<tr>
<td>Low risk persons</td>
<td>&gt;=15</td>
</tr>
</tbody>
</table>

*Table 5. Tuberculin Reaction Size and Latent MTB infections*

**5. Interferon Gamma Release Assay (IGRA):**

INF- gamma is a cytokine and a marker of Th-1 type cellular response. In this test we in vitro measure INF-gamma which is released by sensitized T-lymphocytes after stimulation with MTB antigens. These antigens include ESAT-6 (Early Secreted Antigenic Target), CFP-10 (Culture Filtrate Protein) & TB7.7 (Rv2654).

The ESAT-6 and CFP-10 are encoded by genes located within the region of difference 1 [RD-1] segment of the MTB genome and are more specific than PPD as are not shared with any of the BCG vaccine strain or certain species of NTM. As there is no cross reactivity with BCG vaccination this newer modality has more specificity even in BCG vaccinated patients and hence is important. The IGRA has also importance in diagnosing Latent TB.

**CDC recommends use of IGRA in the following situations:**

**Situations in which an IGRA Is Preferred but aTST is Acceptable:**

- Groups that historically have low rates of returning to have TSTs read. For example, homeless persons and drug-users.
- Persons who have received BCG (as a vaccine or for cancer therapy). Use of IGRAs in this population is expected to increase diagnostic specificity and improve acceptance of treatment for LTBI.

**Situations in which aTST is Preferred but an IGRA is Acceptable**

- Children aged <5 years.
Situations in which Either a TST or an IGRA may be used Without Preference

- Recent contacts of persons know or suspected to have active tuberculosis with special considerations for follow-up testing.
- Periodic screening of persons who might have occupational exposure to M. tuberculosis (e.g., surveillance programs for health-care workers) with special considerations regarding conversions and reversions.

Situations in Which Testing with Both an IGRA and a TST May Be Considered

Although routine testing with both a TST and an IGRA is not generally recommended, results from both tests might be useful when the initial test (TST or IGRA) is negative in the following situations:

1) When the risk for infection, the risk for progression, and the risk for a poor outcome are increased (e.g., when persons with HIV infection or children aged <5 years are at increased risk for M. tuberculosis infection) or

2) When clinical suspicion exists for active tuberculosis (such as in persons with symptoms, signs, and/or radiographic evidence suggestive of active tuberculosis) and confirmation of M. tuberculosis infection is desired.

In such patients with an initial test that is negative, taking a positive result from a second test as evidence of infection increases detection sensitivity. However, multiple negative results from any combination of these tests cannot exclude M. tuberculosis infection.

- Using both a TST and an IGRA also might be useful when the initial test is positive in the following situations:
  1) when additional evidence of infection is required to encourage compliance (e.g., in foreign-born health-care workers who believe their positive TST result is attributable to BCG) or
  2) in healthy persons who have a low risk for both infection and progression. In the first situation, a positive IGRA might prompt greater acceptance of treatment for LTBI as compared with a positive TST alone. In the latter situation, requiring a positive result from the second test as evidence of infection increases the likelihood that the test result reflects infection. For the second situation, an alternative is to assume, without additional testing, that the initial result is a false positive or that the risk for disease does not warrant additional evaluation or treatment, regardless of test results. Steps should be taken to minimize unnecessary and misleading testing of persons at low risk.

- Repeating an IGRA or performing a TST might be useful when the initial IGRA result is indeterminate, borderline, or invalid and a reason for testing persists.
TREATMENT:

Correct & timely medical intervention can dramatically reduce the mortality and morbidity of tuberculosis. The purpose of timely treatment of tuberculosis is:

- Early sputum conversion
- Breaking the chain of transmission
- Ensuring high cure rates
- Preventing emergence of drug resistance
- Minimizing relapses

Treatment of Tuberculosis is becoming more and more crucial in view of rise in the resistant forms of Tuberculosis. Timely and correct treatment of sensitive strains can prevent the emergence of the drug resistant strains. Hence physicians should keep a low degree of threshold in suspecting Tuberculosis. Introduction of DOTS by RNTCP was a huge step towards better and assured treatment of the disease. DOTS ensured that the drugs are taken by the individual thus preventing defaulters.

The concept of short course chemotherapy has revolutionised the treatment of TB. It consists of:

a) Intensive phase of 2-3 months
b) Continuation phase of 4-5 months

DOTS has recently accepted the WHO classification of treatment groups which is as follows:

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Type of patient</th>
<th>Intensive phase</th>
<th>Continuation phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>New (Cat 1)</td>
<td>New Sputum smear-positive</td>
<td>2H3R3Z3E3</td>
<td>4H3R3</td>
</tr>
<tr>
<td></td>
<td>New Sputum smear-negative</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>New Extra-pulmonary</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>New Others</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previously treated (Cat 2)</td>
<td>Smear-positive relapse</td>
<td>2H3R3Z3E3S3/1H3R3Z3E3</td>
<td>5H3R3E3</td>
</tr>
<tr>
<td></td>
<td>Smear-positive failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Smear-positive treatment after default</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Others</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 6. Revised National Tuberculosis Control Programme

WHO in 2010 recommended the following for the treatment of sensitive cases of TB:

1. Wherever feasible, the optimal dosing frequency for new patients with pulmonary TB is daily throughout the course of therapy
2. New patients with pulmonary TB may receive a daily intensive phase followed by a three times weekly continuation phase, provided that each dose is directly observed.

3. Three times weekly dosing throughout the therapy may be used as another alternative, provided that every dose is directly observed and the patient is not living with HIV or living in a HIV prevalent setting.

4. New patients with TB should not receive twice weekly dosing for the full course of treatment unless this is done in the context of formal research.

We currently treat all our patients on a daily dosing regimen for both the Intensive Phase & the Continuation Phase.

Treatment of sensitive strains of Mycobacterium tuberculosis is not as complex and challenging as that of the resistant strains, provided the correct drugs are introduced in the correct dosage for the correct duration and patients are regularly monitored for side effects, progress of the disease and compliance. Imparting education to the patient regarding his disease and the possibility of complete cure is of vital importance. Patients and relatives should be educated about the methods to prevent spread of infection to close contacts. Screening of close contacts is also essential. Screening of all cases to rule out presence of associated HIV infection and Diabetes Mellitus has become important.

Rifampicin, Isoniazid, Ethambutol and Pyrazinamide are the drugs used for the treatment of sensitive strains of Mycobacterium Tuberculosis.

Rifampicin is the most active mycobacterial agent available for the treatment of TB. It is bactericidal and a good sterilizing agent and allows shortening of the duration of treatment of TB. It has both intracellular and extracellular actions and inhibits mycobacterial DNA-dependent RNA polymerase thus blocking RNA synthesis. It is to be administered in a dose of 10mg/kg in adults in daily/twice weekly/thrice weekly regimens. In children it is administered as 10-20mg/kg. Rifampicin is distributed well throughout the body tissues and has got a good CNS penetration. It causes reddish orange discoloration of body fluids which is seen in almost all patients on Rifampicin. Most commonly seen adverse effects with Rifampicin include gastrointestinal symptoms, pruritis and rash. Others frequently seen are hepatotoxicity and pancytopenia. Side effects seen particularly with the intermittent regimen are flu like syndrome, respiratory syndrome and abdominal syndrome. Rarely acute renal failure and hepatic failure can occur which are absolute contraindications of restarting Rifampicin in the regimen.

Isoniazid is the hydrazide of isonicotinic acid and is a bactericidal drug which is of
utmost importance in the treatment regimen of Tuberculosis. Like Rifampicin, Isoniazid also acts on both intracellular and extracellular organisms. Advantage of Isoniazid is that it acts on slowly growing organisms also. It acts by inhibiting fatty acid synthase and thus inhibiting mycolic acid synthesis which are required for mycobacterial cell wall. It is given at a dose of 5mg/kg in adults and 10-20mg/kg in children. It can also be given at 15mg/kg twice weekly in adults. It is well distributed in the body fluids and also in the CSF. Acetylator (Fast and Slow) status of an individual is said to have an impact on the development of its toxicity; slow acetylators are more prone to develop side effects. Important side effects are hepatotoxicity and peripheral neuropathy. Other side effects are acne, rash, asymptomatic liver enzyme elevation, optic atrophy, fever, anemia, seizures and psychiatric manifestations. In view of risk of development of peripheral neuropathy, patients prone to develop the same, such as those with pre-existing DM, HIV, malnutrition etc, should receive a daily prophylactic dose of 10mg/day of Pyridoxine.

Ethambutol is a bacteriostatic drug which acts by inhibiting arabinosyltransferase which is involved in cell wall synthesis. It is to be given in a dose of 15mg/kg/day and 50mg/kg twice weekly in adults. For a good CSF penetration it should be given at 25mg/kg. its most dangerous side effect is the development of optic neuritis which can be fully reversed within several months to up to 1 year if stopped early. It is more likely to occur in children and those with renal impairment. All patients should have a visual acuity and colour vision test done prior to starting on Ethambutol and should be intermittently monitored for development of symptoms of optic neuritis.

Pyrazinamide is bactericidal and is given at a dose of 15-30mg/kg/day for the first 2 months of Intensive Phase. It first gets converted to pyrazinoic acid which probably acts on fatty acid synthase 1. It is more active against the slowly replicating mycobacteria and is active in acidic environments such as within granulomas. Commonly seen side effects are hepatotoxicity and hyperuricemia.

Streptomycin which was discovered in 1943 was a landmark in the history of Tuberculosis. It was the first anti mycobacterial agent which was used in the treatment of Tuberculosis. It can be administered both by the intra muscular and the intra venous routes. In our country streptomycin is very frequently misused in the treatment of both drug sensitive and resistant cases of Tuberculosis. It acts by binding to 30S mycobacterial ribosome and thereby inhibiting protein synthesis. It should be administered at a dose of 15mk/kg/day in adults and 20-40mg/kg/day in children. It causes frequent side effects like ototoxicity, nephrotoxicity and neurotoxicity. It has a poor CSF penetration.

Rifabutin which is a semisynthetic derivative of rifamycin S is recommended in place of Rifampicin in patients with HIV-TB co infection who are being treated with Protease Inhibitors. This is because Rifabutin is not as strong an enzyme inducer as Rifampicin. Its mechanism of action is similar to that of Rifampicin and is well tolerated. Side effect profile is also similar to Rifampicin. It is recommended to a dose of 300 mg/day.
TUBERCULOSIS AND SPECIAL CONDITIONS:

Tuberculosis & Diabetes Mellitus:
TB and Diabetes Mellitus have a strong association. Early diagnosis and timely intervention helps to prevent the emergence of drug resistant strains of mycobacteria. Tuberculosis is found to be more common in patients with poorly controlled diabetes mellitus. In view of immunosuppressed status diabetic individuals may present with cough as the predominant symptom without a history of fever. They also have lesions more in the lower zones than the upper zones. The possible etiology of increased prevalence of TB amongst Diabetics is as follows:
• Presence of DRB(1)*09 & absence of DQB(1)*05
• Neutrophilic dysfunction
• Impaired cytokine production
• Reduced production of IFN – alpha & IL – 1B

Diabetic patients are more prone to the development of peripheral neuropathy hence should receive prophylactic pyridoxine supplementation. Insulin requirements may increase in patients on Rifampicin.

Tuberculosis & Liver Disorders:
Hepatitis is a common side effect seen in patients on TB regimens. It is seen to occur more in patients with pre existing liver diseases, elderly individuals, alcoholics, malnourished patients and those with a past history of hepatitis. Asymptomatic elevation of liver enzymes more than 5 times the upper normal limit and symptomatic elevation more than 3 times the upper normal limit warrant cessation of therapy. Complete disappearance of symptoms or drop in levels to less than 3 times the upper limit suggest that drugs can be reintroduced. Reintroduction can be done in various ways. Either all the drugs can be introduced at the same time in full doses or they can be introduced in a sequential manner. In sequential introduction, drugs are to be introduced one by one with the most hepatotoxic agent being introduced last or never at all in increasing doses. This can be done as follows; Isoniazid introduce at 50mg followed by 150 mg and then 300mg gradually over 9 days. Similarly followed by Rifampicin, Ethambutol and Pyrazinamide at a dose dependent on the body weight. In the event of development of symptoms, the last drug to be added should be withdrawn as it is the most likely drug causing hepatitis.

As per WHO 2010, patients with the following conditions can receive the usual TB regimens. However chronic liver disease should be ruled out first:
Hepatitis virus carriage
Past history of acute hepatitis
Current excessive alcohol consumption

Regular monitoring is very essential in these patients in view of higher risk of hepatotoxicity.

Patients who have unstable or advanced liver disease should have their liver function tests done before putting them on anti tuberculous therapy. Raised serum Alanine Aminotransferase level more than 3 times above the normal limit needs extra vigilance. One of the following regimens should then be considered.

Possible regimens include:

• Two hepatotoxic drugs (rather than the three in the standard regimen):— 9 months of Isoniazid and Rifampicin plus Ethambutol (until or unless isoniazid susceptibility is documented);— 2 months of Isoniazid, Rifampicin, Streptomycin and Ethambutol, followed by 6 months of Isoniazid and Rifampicin;— 6–9 months of Rifampicin, Pyrazinamide and Ethambutol.
• One hepatotoxic drug:— 2 months of Isoniazid, Ethambutol and Streptomycin followed by 10 months of Isoniazid and Ethambutol.
• No hepatotoxic drugs:— 18–24 months of Streptomycin, Ethambutol and a Fluoroquinolone.

Tuberculosis & Renal Failure:

As per WHO, all patients with renal failure or severe renal insufficiency should receive 2 months of Isoniazid, Rifampicin, Pyrazinamide and Ethambutol, followed by 4 months of Isoniazid and Rifampicin. Isoniazid and Rifampicin elimination occurs by biliary route. Hence dose adjustment is not needed. However, Ethambutol & Pyrazinamide have a significant renal excretion. Hence these should be administered thrice a week at doses of Pyrazinamide (25 mg/kg), and Ethambutol (15 mg/kg).

Streptomycin if needed can be given at a dose of 15mg/kg, two to three times a week to a maximum of 1 gram per dose.
Tuberculosis & Pregnancy:

Early diagnosis & timely treatment of Tuberculosis is very essential during pregnancy. Majority of the reactivation cases occur in the post partum period. Mantoux testing and microbiological examination play a crucial role in the diagnosis. Apart from Streptomycin, all the first line drugs are safe during pregnancy. Breast feeding is not a contraindication for anti Tuberculous therapy. After ruling out active TB in an exposed baby, the baby should receive 6 months of Isoniazid prophylaxis & then should be vaccinated with BCG. Particularly in the Indian scenario, all pregnant women should receive pyridoxine supplementation.

MDR – TB:

Multi drug resistant TB is a microbiological diagnosis when the TB bacilli show resistance to Isoniazid and Rifampicin. The resistance of the bacilli is mainly of two types. One is primary resistance where the bacilli affecting the patient is per se resistant to the said drug and the other is the acquired phenomenon which is called secondary resistance and this is either because of mismanagement or poor compliance leading to resistance. Secondary resistance is much more common than primary resistance. It develops over time. “Fall and Rise Phenomenon”, means the patient initially responds to the treatment and there is a fall in the bacterial load and the patient turns sputum negative. However, over a period of time as the resistant bacilli start growing and there is an increase in the bacterial load, sputum turns positive.

Criteria A (Currently used):

Failures of New TB CasesFailures and Non-Converters of Smear positive Re-Treatment TB Cases

All Pulmonary TB cases in contact with confirmed MDR TB cases.
Criteria B
All smear positive Re-Treatment Pulmonary TB cases at diagnosis
Any new or RT case found Smear positive at any follow up

Criteria C
All smear negative Re-treatment PTB cases at diagnosis & HIV - TB cases

XDR-TB  XDR-TB: Multi-drug resistant TB (MDR-TB) plus resistance to any Fluoroquinolone and at least 1 of the 3 injectable second line drugs (Capreomycin, Kanamycin, Amikacin).

Total Drug Resistance: Resistance to all conventionally tested drugs. This terminology has grey areas as not all drugs that are used routinely in the treatment of MDR-TB are tested in the panel. For example, cycloserine, terizidone, clofazamine, linezolid, carbapenems, clarithromycin or amoxicillin-clavulanic acid.

For treatment of MDR –TB we have to be very judicious regarding the selection of drugs and there are three lines of therapy

1) Individualised regimen based on the DST
2) Empirical treatment – ATT 2nd line is started empirically on the basis of trend and epidemiological survey and common resistance pattern found in the area
3) Standard regimen- as per RNTCP dots plus guideline the standard regimen is started on CAT- IV 6(9) Km Ofx (Lvx) Eto Cs Z E / 18 Ofx (Lvx)Eto Cs E

<table>
<thead>
<tr>
<th>Group</th>
<th>Anti-tuberculous agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Second line parenteral agents</td>
<td>Kanamycin, Amikacin, Capreomycin</td>
</tr>
<tr>
<td>Fluoroquinolone</td>
<td>Levofoxacin, Moxifloxacin, Gatifloxacin, Ofloxacin</td>
</tr>
<tr>
<td>Oral bacteriostatic second line anti-tuberculous agents</td>
<td>Ethionamide, Prothionamide, Cycloserine, Terizidone, Para-amino salicylic acid</td>
</tr>
<tr>
<td>Group 5 drugs</td>
<td>Clofazamine, Linezolid, Amoxicillin/clavulanate, Thioacetazone, Clarithromycin, Imipenem - Cilastatin, High dose INH</td>
</tr>
</tbody>
</table>

Table 7. Drugs used for MDR TB
WHO recommendations for MDR–TB:

- Rapid drug susceptibility testing (DST) of Isoniazid and Rifampicin or of Rifampicin alone is recommended over conventional testing or no testing at the time of diagnosis of TB, subject to available resources
- The use of sputum smear microscopy and culture rather than sputum smear microscopy alone is recommended for the monitoring of patients with MDRTB during treatment
- In the treatment of patients with MDR-TB, a Fluoroquinolone should be used
- In the treatment of patients with MDR-TB, a later-generation Fluoroquinolone rather than an earlier-generation Fluoroquinolone should be used
- In the treatment of patients with MDR-TB, Ethionamide (or Prothionamide) should be used
- In the treatment of patients with MDR-TB, four second-line antituberculosis drugs likely to be effective (including a parenteral agent), as well as Pyrazinamide, should be included in the intensive phase
- In the treatment of patients with MDR-TB, regimens should include at least Pyrazinamide, a Fluoroquinolone, a parenteral agent, Ethionamide (or Prothionamide), and either Cycloserine or PAS (pamino salicylic acid) if Cycloserine cannot be used
- In the treatment of patients with MDR-TB, an intensive phase of at least 8 months’ duration is recommended
- In the treatment of patients with MDR-TB, a total treatment duration of at least 20 months is recommended in patients without any previous MDR-TB treatment
- Antiretroviral therapy is recommended for all patients with HIV and drug-resistant TB requiring second-line anti-tuberculosis drugs, irrespective of CD4 cell-count, as early as possible (within the first 8 weeks) following initiation of anti-tuberculosis treatment
- Patients with MDR-TB should be treated using mainly ambulatory care rather than models of care based principally on hospitalization.

General Principles for designing MDR-TB treatment regimens:

1. Use at least 4 drugs certain to be effective The more of the following factors are present, the more likely it is that the drug will be effective:
• Resistance to these drugs is known from surveys to be rare in similar patients.
• DST results show susceptibility to drugs for which there is good laboratory reliability: injectable agents and Fluoroquinolone. The drug is not commonly used in the area.
• (For decisions about an individual patient – no prior history of treatment failure with the drug; no known close contacts with resistance to the drug.)

2. Do not use drugs for which there is the possibility of cross-resistance

Many antituberculosis agents exhibit cross-resistance both within and across drug classes.

3. Eliminate drugs that are not safe

• Quality of the drug is unknown. (For decisions about an individual patient – known severe allergy or unmanageable intolerance; high risk of severe adverse drug effects such as renal failure, deafness, hepatitis, depression and/or psychosis.)

4. Include drugs from Groups 1–5 in a hierarchical order based on potency

• Use any of the first-line oral agents (Group 1) that are likely to be effective.
• Use an effective amino glycoside or polypeptide by injection (Group 2).
• Use a Fluoroquinolone (Group 3).
• Use the remaining Group 4 drugs to complete a regimen of at least four effective drugs.
• For regimens with fewer than four effective drugs, consider adding two Group 5 drugs. The total number of drugs will depend on the degree of uncertainty, and regimens often contain five to seven.

I generally follow the following principles while starting my patients on second line therapy.

• Use at least 4 drugs certain to be effective.
• Ethambutol and PZA are not considered as the main drugs but are included in the Intensive Phase as per RNTCP.
• While selecting an amino glycoside, the order would be as follows: Kanamycin followed by Capreomycin followed by Amikacin.
• Avoid using Ethionamide and PAS together in view of higher incidence of adverse reactions. Resistance to Ethionamide seems to be higher than that of PAS.
• When drugs from group 5 are added, each drug is considered as ½ a drug.
New Drugs in Pipeline:

Delamanid:
Delamanid (OPC-67683), is a nitro-dihydro-imidazooxazole derivative, that acts by inhibiting mycolic acid synthesis and has shown potent in vitro and in vivo activity against drug-resistant strains of Mycobacterium tuberculosis. Dose recommended is 100-200 mg twice daily orally for 2 months with a back up drug regimen.

Bedaquiline:
Bedaquiline or TMC-207 has created a sensation in the world of MDR TB. It has given a new hope for patients & physicians who are dealing with TB which is resistant to almost all drugs or those who are not responding to the available regimens. It has been the first new class of drugs to be approved for treatment of TB in the last 4 decades. FDA has approved the use of Bedaquiline on December 28, 2012 for pulmonary MDR TB. CDC has now come up with specific recommendations as follows:

For adults > 18 years with laboratory confirmed pulmonary MDR TB, Bedaquiline should be administered by direct observation & used with clinical expert consultation as part of a combination treatment regimen containing atleast 4 drugs.

When treatment options are limited, use of Bedaquiline can be considered for individual persons with extrapulmonary TB, children, pregnant women, or persons with HIV or other comorbid conditions on a case-by-case basis. However, further research is needed before it can be routinely recommended in these populations.

Dose: 400mg once daily orally for 2 weeks, followed by 200mg 3 times a week orally for 22 weeks, taken with food.

Because of the extremely long terminal half life of Bedaquiline, acquired resistance might occur when Bedaquiline is the sole effective anti-TB drug in circulation. Hence it should be discontinued 4-5 months before scheduled termination of other drugs in the regimen.

Adverse effects are reported to be minimal, with nausea and slight prolongation of the QTc interval.

<table>
<thead>
<tr>
<th>DIAGNOSIS</th>
<th>DOTS</th>
<th>DOTS +</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPUTUM MICROSCOPY</td>
<td></td>
<td>CULTURE (SOLID)</td>
</tr>
<tr>
<td>D.O.T.</td>
<td>3 / WEEK</td>
<td>DAILY (EXC. SUNDAYS)</td>
</tr>
<tr>
<td>DRUGS GIVEN</td>
<td>4 (5)</td>
<td>6 (+1)</td>
</tr>
<tr>
<td>DURATION OF I.P.</td>
<td>2 – 4 months</td>
<td>6 – 9 months</td>
</tr>
<tr>
<td>DURATION OF C.P.</td>
<td>4 – 5 months</td>
<td>15 – 21 months</td>
</tr>
<tr>
<td>MICROBIOLOGICAL EXAMINATION</td>
<td>BASELINE, End of I.P., End of Rx</td>
<td>BASELINE, EVERY MONTH in I.P., EVERY 3 months in C.P.</td>
</tr>
</tbody>
</table>

Table 8. DOTS and DOTS + Programme
Prevention of MDR-TB spread:

Preventing the spread of MDR-TB has been a matter of growing concern in view of the rapid spread of the infection and its increasing number of cases. Its spread can be curbed by following simple rules at the outset. These include:

1. Early diagnosis and correct treatment of drug resistance cases.
2. Correct doses of correctly chosen drugs.
3. Regular therapy which also should include persistent motivation to the patients to consume the drugs; thus preventing default
4. Patient education about the disease
5. Avoiding addition of a single drug like quinolones and streptomycin in a new case whenever the 1st line treatment fails
6. Avoid use of quinolones for treatment of LRTi in a community setting like India

Social aspects:

Physicians play a crucial role in the management of Tuberculosis.

This includes:

1. Ensuring adherence to TB drugs in order to prevent Defaulters
2. Prevention of spread in the community
3. Notification to the concerned authorities
4. Awareness amongst the people that TB is a preventable and treatable disease
5. Providing fitness to employees after sputum conversion

SURGERY IN THE TREATMENT OF TB & MDR-TB:

Surgery is primarily indicated in MDR-TB patients or due to complications of TB like bronchiectasis causing recurrent or massive hemoptysis, cavity with fungal ball formation, etc. Pulmonary TB due to sensitive organisms per se usually does not require surgical intervention if adequately treated. Patients with MDR-TB meeting the following conditions can be subjected to a surgical intervention.

1) A fairly localized lesion
2) An adequate respiratory reserve

Surgery should be ideally performed when a patient has been adequately treated, has minimal disease and is sputum negative. If sputum positive it should be thought during Intensive Phase. Emphasis should be laid on the point that surgery does not reduce the total duration of medical therapy.
### VARIOUS VACCINE STRATEGIES:

#### BCG

<table>
<thead>
<tr>
<th>Trial and age-group in parenthesis</th>
<th>Period</th>
<th>Duration of Observation (Years)</th>
<th>% of protection</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>N. American Indian (1-18)</td>
<td>1935-38</td>
<td>9-11</td>
<td>80</td>
<td>Aronson</td>
</tr>
<tr>
<td>Chicago (infants)</td>
<td>1937-48</td>
<td>12-23</td>
<td>75</td>
<td>Rosenthal</td>
</tr>
<tr>
<td>Georgia (6-17)</td>
<td>1947</td>
<td>20</td>
<td>Nil</td>
<td>Comstock</td>
</tr>
<tr>
<td>Puerto Rico (below 20)</td>
<td>1949-51</td>
<td>5.5-7.5</td>
<td>31</td>
<td>Palmer</td>
</tr>
<tr>
<td>UK (14-15)</td>
<td>1950-52</td>
<td>15</td>
<td>78</td>
<td>MRC</td>
</tr>
<tr>
<td>Madanapalle (all ages)</td>
<td>1950-55</td>
<td>9-14</td>
<td>30</td>
<td>F.Moller</td>
</tr>
<tr>
<td>Chingelput (all ages)</td>
<td>1968-71</td>
<td>7.5</td>
<td>Nil</td>
<td>ICMR</td>
</tr>
</tbody>
</table>

*Table 9.* Protection Observed in Various Controlled Trials of BCG Vaccination
<table>
<thead>
<tr>
<th>Type of TB Vaccine</th>
<th>Vaccine Components</th>
<th>Vaccine Description</th>
<th>Clinical Trial Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fusion protein in adjuvant for pre-exposure vaccination as booster on top of BCG</td>
<td>Hybrid 1and IC31</td>
<td>Fusion protein consisting of Ag85B and ESAT-6 administered in adjuvant IC31</td>
<td>Phase Ila</td>
</tr>
<tr>
<td>Hybrid 56 and IC31</td>
<td>Fusion protein consisting of Ag85B, ESAT-6 and Rv2660c administered in adjuvant IC31</td>
<td>Phase I ongoing</td>
<td></td>
</tr>
<tr>
<td>Hybrid 1and CAF01</td>
<td>Fusion protein consisting of Ag85B and ESAT-6 administered in adjuvant CAF01</td>
<td>Phase I ongoing</td>
<td></td>
</tr>
<tr>
<td>M72 and AS01 or AS02</td>
<td>Fusion protein consisting of Rv1196 and Rv0125 administered in adjuvant AS01 or AS02</td>
<td>Phase Ila ongoing</td>
<td></td>
</tr>
<tr>
<td>Aeras-404 (HyVac4 and IC31)</td>
<td>Fusion protein consisting of Ag85B and TB10.4 administered in adjuvant IC31</td>
<td>Phase I</td>
<td></td>
</tr>
<tr>
<td>Viral vector for pre-exposure vaccination as booster on top of BCG</td>
<td>Oxford MVA85A/ Aeras-485</td>
<td>MVA expressing Ag85A</td>
<td>Phase IIb ongoing</td>
</tr>
<tr>
<td>Crucell Ad35/ Aeras-402</td>
<td>Replication-deficient Ad35 expressing Ag85A, Ag85B and TB10.4</td>
<td>Phase IIb ongoing</td>
<td></td>
</tr>
<tr>
<td>AdAg85A</td>
<td>Replication-deficient Ad5 expressing Ag85A</td>
<td>Phase I</td>
<td></td>
</tr>
<tr>
<td>rBCG for pre-exposure vaccination as priming vaccine, replacing BCG</td>
<td>VPM1002</td>
<td>rBCG expressing listeriolsyn and urease deletion</td>
<td>Phase Ila ongoing</td>
</tr>
<tr>
<td>rBCG30</td>
<td>rBCG expressing Ag85B</td>
<td>Phase I completed/ on hold</td>
<td></td>
</tr>
<tr>
<td>Aeras-422</td>
<td>rBCG expressing perfringolysin, Ag85A, Ag85B and Rv3407</td>
<td>Phase I terminated due to side-effects</td>
<td></td>
</tr>
<tr>
<td>Whole bacterial vaccines for therapeutic vaccination</td>
<td>RUT</td>
<td>Detoxified M. tuberculosis in Liposomes</td>
<td>Phase IIa ongoing</td>
</tr>
<tr>
<td>M. vaccae</td>
<td>Inactivated M. vaccae</td>
<td>Phase III completed</td>
<td></td>
</tr>
</tbody>
</table>

Table 10. The most advanced TB Vaccine Candidates in clinical trials
**REFERENCES:**

Please visit the site for more details of TB programmes in India and RNTCP http://www.tbcindia.nic.in/

1) Revised National Tuberculosis Control Program guidelines - TB India 2011
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3) Fishman’s Pulmonary Diseases & Disorders 4th edition
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7) Thorax 1992;47:690-694: Comparison of Polymerase Chain Reaction Amplification of two Mycobacterial DNA sequences, IS6110 and the 65kDa antigen gene, in the diagnosis of Tuberculosis
10) Updated Guidelines for Using Interferon Gamma Release Assays to Detect Mycobacterium tuberculosis Infection --- United States, 2010 Centres for Disease Control and Prevention
11) Immunology of Tuberculosis; V. K. Dhignra; Tuberculosis Treatment and Prevention; chapter 5 pg 11-12

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<table>
<thead>
<tr>
<th>Type of vaccine</th>
<th>Vaccine</th>
<th>Vaccine description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purified vaccine</td>
<td>HBHA</td>
<td>Methylated purified protein from M. bovis BCG</td>
</tr>
<tr>
<td>DNA vectored</td>
<td>Hq85A</td>
<td>DNA vaccine encoding Ag85A</td>
</tr>
<tr>
<td></td>
<td>Hsp DNA vaccine</td>
<td>Codon-optimised M. leprae Hsp</td>
</tr>
<tr>
<td>DNA vectored</td>
<td>Hq85A</td>
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</tr>
<tr>
<td></td>
<td>Hsp DNA vaccine</td>
<td>Codon-optimised M. leprae Hsp</td>
</tr>
<tr>
<td>Attenuated M Tuberculosis</td>
<td>MTBVAC</td>
<td>M. tuberculosis attenuated by stable deletion of M. tuberculosis phoP and fadD26 genes M. tuberculosis auxotrophic for lysine and pantothenate and attenuated by inactivation of the secA2 gene</td>
</tr>
</tbody>
</table>

Table 11. The most advanced tuberculosis vaccine candidates in pre-clinical development & production"