PHYTOCHEMICAL AND PHARMACOLOGICAL INVESTIGATION OF ANTI-TUBERCULAR ACTIVITY OF CERTAIN INDIGENOUS PLANTS

CHAPTER-1

INTRODUCTION

TUBERCULOSIS:

Tuberculosis is an acute or chronic infectious disease caused by several species of Mycobacterium, collectively called as tubercle bacilli. Tuberculosis (abbreviated TB, which can also stand for tubercle bacillus) is a chronic granulomatous disease and a major health problem in developing countries.

In humans, Mycobacterium tuberculosis is the primary causative bacterium although other mycobacteria such as Mycobacterium bovis, Mycobacterium africanum, Mycobacterium canetti, and Mycobacterium microti are also infective.

Tuberculosis usually attacks the lungs but can also affect the central nervous system, lymphatic system, circulatory system, genitourinary system, gastrointestinal system, bones, joints, and even the skin\(^1\).

Tuberculosis is a major threat killing about 2 million people each year. WHO estimates that 1 billion people will be newly infected in the period 2000-2020, resulting in 35 million more deaths, nearly one billion more people will be newly infected, 200 million will get sick and 70 million will die from TB if control not strengthened and active TB left if untreated\(^2,3\).

HIV out-breaks; India can have an additional impact on the increase of TB in India. TB is now the world’s leading cause of death from a single agent. The problem in India is even greater as it estimated that India accounts for 1/4\(^\text{th}\) of global TB burden. India has an estimated 14 million TB cases to which about 2 million are added every year. More adults in India die from TB than from any other infectious disease, one every minute and more than 1,000 every day and 5 lakh people every year\(^4,5\).

1.1 HISTORY OF TUBERCULOSIS:

Consumption, phthisis, scrofula, Pott's disease and White Plague:

These all terms used to refer to tuberculosis throughout history. It is believed that at some point in its evolution, some species of the bacteria was able to invade animal hosts. This possibly took place with the first species Mycobacterium bovis which is considered by most to be the oldest of the species that make up the Mycobacterium tuberculosis complex. M. bovis eventually passed to humans at a time coinciding with the domestication of animals. Human bones from the Neolithic show a presence of the bacteria although the exact magnitude (incidence and prevalence) is not known before the nineteenth century. Over time, the various cultures of the world gave the illness different names: yaksma (India), phthisis (Greek), consumptione (Latin) and chaky oncay (Incan),
each of which make reference to the "drying" or "consuming" affect of the illness, cachexia. Its high mortality rate among middle-aged adults and the surge of romanticism which stressed feeling over reason caused many to refer to the disease as the "romantic disease."

**The East: Ancient India:**

The first reference to tuberculosis in Asian civilization is found in the Vedas. The oldest of them (Rigveda 1500 BCE) calls the disease *yaksma*. The Atharvaveda calls it another name *balasa*. It is in the Atharvaveda that the first description of scrofula is given. The Sushruta Sanhita, written around 600 BCE, recommends that the disease be treated with breast milk, various meats, alcohol and rest. The Yajurveda advises sufferers to move to higher altitudes. Hippocrates describes the characteristics of the disease: fever, colorless urine, cough resulting in a thick sputum, and loss of thirst and appetite. In 1895, Wilhelm Roentgen discovered the X-ray, which allowed physicians to diagnose and track the progression of the disease.

![Fig no.1: Photograph of Robert Koch](image)

In 1882, a Prussian physician, Robert Koch, utilized a new staining method and applied it to the sputum of tuberculosis patients, revealing for the first time the causal agent of the disease: *Mycobacterium tuberculosis*, or Koch's bacillus.

He made his result public at the Physiological Society of Berlin on 24th March 1882, in a famous lecture entitled *Über Tuberculose*, which was published three weeks later. Since 1982, 24th March has been known as World Tuberculosis Day. 

**1.2 TB INCIDENCE, PREVALENCE AND MORTALITY:**

- **Incidence:** Based on surveillance and survey data, WHO estimates that 9.27 million new cases of TB occurred in 2007 (139 per 100 000 population), compared with 9.24 million new cases (140 per 100 000 population) in 2006. Of
these 9.27 million new cases, an estimated 44% or 4.1 million (61 per 100,000 population) were new smear positive cases. India, China, Indonesia, Nigeria and South Africa rank first to fifth in terms of the total number of incident cases shown in Table no.1. Among the 15 countries with the highest estimated TB incidence rates, 13 are in Africa, a phenomenon linked to high rates of HIV co-infection.

Table no. 1: Estimated epidemiological burden of tuberculosis, 2007

<table>
<thead>
<tr>
<th>Country</th>
<th>Incidence (per 100,000)</th>
<th>Prevalence (per 100,000)</th>
<th>Mortality (per 100,000)</th>
<th>HIV-Positive (per 100,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>India</td>
<td>1199,016</td>
<td>1962</td>
<td>168</td>
<td>873</td>
</tr>
<tr>
<td>China</td>
<td>1,282,630</td>
<td>1,305</td>
<td>98</td>
<td>585</td>
</tr>
<tr>
<td>Indonesia</td>
<td>231,027</td>
<td>528</td>
<td>228</td>
<td>236</td>
</tr>
<tr>
<td>Nigeria</td>
<td>148,093</td>
<td>460</td>
<td>311</td>
<td>195</td>
</tr>
<tr>
<td>South Africa</td>
<td>48,377</td>
<td>461</td>
<td>948</td>
<td>174</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>158,665</td>
<td>353</td>
<td>223</td>
<td>159</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>83,090</td>
<td>314</td>
<td>378</td>
<td>135</td>
</tr>
<tr>
<td>Pakistan</td>
<td>163,902</td>
<td>297</td>
<td>181</td>
<td>133</td>
</tr>
<tr>
<td>Philippines</td>
<td>87,960</td>
<td>255</td>
<td>290</td>
<td>115</td>
</tr>
<tr>
<td>DR Congo</td>
<td>62,636</td>
<td>245</td>
<td>392</td>
<td>109</td>
</tr>
<tr>
<td>Russian Federation</td>
<td>142,499</td>
<td>157</td>
<td>110</td>
<td>68</td>
</tr>
<tr>
<td>Viet Nam</td>
<td>87,375</td>
<td>150</td>
<td>171</td>
<td>66</td>
</tr>
<tr>
<td>Kenya</td>
<td>37,338</td>
<td>132</td>
<td>353</td>
<td>53</td>
</tr>
<tr>
<td>Brazil</td>
<td>191,791</td>
<td>92</td>
<td>48</td>
<td>49</td>
</tr>
<tr>
<td>Tanzania</td>
<td>40,454</td>
<td>120</td>
<td>297</td>
<td>49</td>
</tr>
<tr>
<td>Uganda</td>
<td>30,884</td>
<td>102</td>
<td>330</td>
<td>42</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>13,349</td>
<td>104</td>
<td>782</td>
<td>40</td>
</tr>
<tr>
<td>Thailand</td>
<td>63,884</td>
<td>91</td>
<td>142</td>
<td>39</td>
</tr>
<tr>
<td>Mozambique</td>
<td>21,397</td>
<td>92</td>
<td>431</td>
<td>37</td>
</tr>
<tr>
<td>Myanmar</td>
<td>48,798</td>
<td>83</td>
<td>171</td>
<td>37</td>
</tr>
<tr>
<td>Cambodia</td>
<td>14,444</td>
<td>72</td>
<td>495</td>
<td>32</td>
</tr>
<tr>
<td>Afghanistan</td>
<td>27,145</td>
<td>46</td>
<td>168</td>
<td>21</td>
</tr>
</tbody>
</table>

High-burden countries: 4 201,761 2,743 177 7,245 77 11 301 269 1,058 25 339 8.1 14

- Incidence and prevalence estimates include TB in people with HIV.
- Prevalence of HIV in incident TB cases of all ages.
Incidence of TB among people infected with HIV:
Among the 9.27 millions incident cases of TB in 2007, an estimated 1.37 million (14.8%) were HIV-positive. This number although double the estimate of 0.7 million cases in 2006 that WHO published in 2008, does not mean that the number of HIV-positive cases of TB doubled between 2006 and 2007; rather, new data that became available during 2008 have been used to estimate both the number of HIV-positive TB cases in 2007 and to revise estimates of the number of such cases that occurred in previous years. The global number of incident HIV-positive TB cases is estimated to have peaked in 2005, at 1.39 million. In 2007, as in previous years, the African Region accounted for most (79%) HIV-positive TB cases, followed by the South-East Asia Region (mainly India) with 11% of total cases. South Africa accounted for 31% of cases in the African Region.

Estimated incidence of MDR-TB: In 2007, there were an estimated 9.27 million first episodes of TB and an additional 1.16 million subsequent episodes of TB. Among these, 10.4 million episodes of TB an estimated 4.9% or 511,000 were cases of MDR-TB. Of these, 289,000 were among new cases (3.1% of all new cases) and 2,21,000 were among cases that had been previously treated for TB.

Prevalence: There were an estimated 13.7 million prevalent cases in 2007 (206 per 100,000 population), a slight decrease from 13.9 million in 2006. Of these 13.7 million prevalent cases, an estimated 687,000 (5%) were HIV-positive.

Mortality: An estimated 1.32 million HIV-negative people (19.7 per 100,000 population) died from TB in 2007, and there were an additional 456,000 TB deaths among HIV-positive people. The global TB mortality rate (including TB deaths in HIV-positive people) is estimated to have increased during the 1990s; this trend was reversed around the year 2000, and mortality rates are now in decline shown in fig. no. 2.
Fig no. 2: Global rates of TB incidence, prevalence and mortality, including in people with HIV 1990-2007

- **Total case notifications**: A total of 37.3 million new and relapse cases, and 18.1 million new smear-positive cases, were notified by DOTS programmes in the 13 years between 1995 and 2007.

Fig no. 3: Contributions to the global increase in the no of new smear positive cases notified under DOTS made by highly burden countries, 2006-07
Re-treatment cases: A total of 564,131 patients were re-treated in DOTS programmes in 2006, an increase from 531,228 patients in 2005. The re-treatment success rate in 2006 was 70%. As expected from the results of treating new patients, re-treatment success rates were lowest in the European Region (42%) and highest in the Western Pacific Region (87%).

Summary

The latest estimates of the global burden of TB show that there were 9.27 million new cases of TB in 2007 (including 1.37 million cases among HIV-positive people), 1.32 million deaths from TB in HIV-negative people with an additional 0.46 million TB deaths in HIV-positive people, and 13.7 million prevalent cases (of which 687,000 were HIV-positive cases). There were 0.5 million cases of MDR - TB, of which 0.3 million were among people not previously treated for TB and 0.2 million were among previously treated TB cases. The estimates of cases and deaths in HIV-positive people in 2007 as well as in previous years are substantially higher than those published in previous years by WHO, and are based on new data that became available in 2008 and associated updates to analytical methods. The revised estimates suggest that TB cases and deaths from TB in HIV positive people peaked in 2005 at 1.39 million and 0.48 million respectively. Collectively, these statistics show that TB remains a major global health problem. The total number of global cases is still increasing in absolute terms as a result of population growth. Nonetheless, the number of incident cases per capital is falling globally, in five out of six WHO regions (the exception is Europe, where rates are approximately stable) and in seven out of nine epidemiological sub regions (the exceptions are Eastern Europe and African countries with a low prevalence of HIV in the general population)\(^7\).

In India: Though primary resistance is found to be low in developed countries, it is common in India and varies widely from area to area. Paramasivam\(^8\) reviewed some of the data on primary drug resistance. These are shown in table no.2

Table no. 2: Summary of studies primary drug resistance among *M. tuberculosis* isolates in India resistance to multiple drugs

<table>
<thead>
<tr>
<th>Location</th>
<th>Year</th>
<th>Isolates tested</th>
<th>Resistance to multiple drugs (%)</th>
<th>Total resistance %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>SH</td>
<td>HR</td>
</tr>
<tr>
<td>Gujarat</td>
<td>1983-86</td>
<td>570</td>
<td>3.3</td>
<td>0</td>
</tr>
<tr>
<td>North Arcot</td>
<td>1985-89</td>
<td>2779</td>
<td>7.0</td>
<td>0.7</td>
</tr>
</tbody>
</table>
Gohti reviewed the data reported from National tuberculosis Institute in 1995. There were 2040 culture positive patients, 1128 had previous treatment, 380 had no treatment and for 532 the history of treatment was not known. The proportion of patients with resistant strains in each of the above category was 81.3%, 26.3% and 50% respectively in the table no. 3(8).

**Table no. 3: Drug resistance in patients with varying history of prior treatment**

<table>
<thead>
<tr>
<th>Category of patients</th>
<th>Total cultures</th>
<th>Drug sensitive</th>
<th>Drug resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Number</td>
<td>%</td>
</tr>
<tr>
<td>Old treated</td>
<td>1128</td>
<td>210</td>
<td>18.7</td>
</tr>
<tr>
<td>New not treated</td>
<td>380</td>
<td>280</td>
<td>73.7</td>
</tr>
<tr>
<td>Treatment history not known</td>
<td>532</td>
<td>266</td>
<td>50</td>
</tr>
</tbody>
</table>

- **Impact on Women and Children:** TB is a leading cause of death among women of reproductive age and is estimated to cause more deaths among this group than all causes of maternal mortality. Women are less likely than men to be tested and treated for TB and are also less likely to develop an infection. Over 250,000 children die every year of TB. Children are particularly vulnerable to TB infection because of frequent household contact.

- **Regional Impact:** Low and lower middle-income countries account for more than 90% of TB cases and deaths. The regions most affected by TB include:

  1. **Southeast Asia:** With an estimated three million new cases of TB each year, this is the world's hardest-hit region.

  2. **Eastern Europe:** In Eastern Europe, TB deaths are increasing after almost 40 years of steady decline.

  3. **Sub-Saharan Africa:** More than 1.5 million TB cases occur in Sub-Saharan Africa each year. This number is rising rapidly, largely due to high prevalence of HIV.
Social, Economic and Development Impact: Poverty, a lack of basic health services, poor nutrition, and inadequate living conditions all contribute to the spread of TB. In turn, illness and death from TB reinforces and deepens poverty in many communities.

1.3 ETIOLOGY:

TB properly refers only to disease caused by *Mycobacterium tuberculosis*. Similar disease occasionally results from *M. bovis*, *M. africanum*, and *M. microti*. Family: Mycobactericeae and order: Actinomycetals.

*Mycobacterium tuberculosis*:
The primary cause of TB, *Mycobacterium tuberculosis*, is a small aerobic non-motile bacillus. *M. tuberculosis* is a straight or slightly curved rod, about 3 μm, occurring singly, in pairs or as small clumps. The size depends on conditions of growth, and long filamentous, club shaped and branching forms may be sometimes seen. *M. bovis* is usually straighter, shorter and stouter.

Since *M. tuberculosis* has a cell wall but lacks a phospholipid outer membrane, it is classified as a Gram-positive bacterium. *M. tuberculosis* either stains very weakly Gram-positive or does not retain dye due to the high lipid and mycolic acid content of its cell wall, strictly speaking this is not correct, as after staining with basic dyes they resist decolourisation by alcohol even without the mordanting effect of iodine.

When stained with carbolfuchsin by the Ziehl-Neelsen method or by fluorescent dyes (auramine O rhodamine), they resist decolourisation by 20 percent sulphuric acid and absolute alcohol for 10 minutes (acid and alcohol fast).

Acid fastness has been ascribed variously to the presence in the bacillus of an unsaponifiable wax (mycolic acid) or to a semi impermeable membrane around the cell. It is related to the integrity of the cell and appears to be a property of the lipid-rich waxy cell wall.

Staining may be uniform or granular. Beaded or barred forms are frequently seen in *M. tuberculosis*.

The bacilli grow slowly; it divides every 16 to 20 hours, the generation time in vitro being 14-15 hours. Colonies appear in about two weeks and may sometimes take up to eight weeks. Optimum temperature is 37°C and growth does not occur below 25°C or above 40°C. Optimum pH is 6.4- 7.0.
M. tuberculosis is an obligate aerobe, on primary isolation, becoming aerobic on subculture. M. tuberculosis grows luxuriantly in culture. The addition of 0.5% glycerol improves the growth of M. tuberculosis.

The solid medium most widely employed for routine culture is Lowen-stein-Jensen (LJ) medium. Liquid media are not generally employed for routine cultivation, but are used for sensitivity testing.

On solid media, M. tuberculosis forms dry, rough, raised, irregular colonies with a wrinkled surface. They are creamy white, becoming yellowish or buff coloured on further incubation. They are tenacious and not easily emulsified.

1.4 RESISTANCE:

Mycobacteria are not heat resistant, being killed at 60°C in 15-20 minutes. Cultures remain viable at room temperature for 6-8 months and may be stored for up to two years at -20°C. Cultures may be killed by exposure to direct sunlight for two hours. Bacilli in sputum may remain alive for 20-30 hours. Bacilli in droplet nuclei may retain viability for 8-10 days under suitable conditions.

Tubercle bacilli are relatively resistant to chemical disinfectants, surviving exposure to 5% phenol, 15% sulphuric acid, 3% nitric acid, 5% oxalic acid and 4% sodium hydroxide. They are sensitive to formaldehyde and gluteraldehyde. and destroyed by tincture of iodine in five minutes and by 80% ethanol in 2-10 minutes.

Ethanol is a suitable disinfectant for skin, gloves and clinical thermometers. M. tuberculosis can withstand weak disinfectants and survive in a dry state for weeks. In nature, the bacterium can grow only within the cells of a host organism, but M. tuberculosis can be cultured in vitro.

Using histological stains on expectorate samples from phlegm (also called sputum), scientists can identify M. tuberculosis under a regular microscope\(^{(11,12)}\).
1.5 MODE OF TRANSMISSION:

When people suffering from active pulmonary TB cough, sneeze, speak, or spit, they expel infectious aerosol droplets 0.5 to 5 µm in diameter. A single sneeze can release up to 40,000 droplets. Each one of these droplets may transmit the disease, since the infectious dose of tuberculosis is very low and inhaling less than ten bacteria may cause an infection. People with prolonged, frequent, or intense contact are at particularly high risk of becoming infected, with an estimated 22% infection rate. A person with active but untreated tuberculosis can infect 10–15 other people per year.

Human beings acquire infection with tubercle bacilli by one of the following routes:

1. Inhalation of organisms present in fresh cough droplets or in dried sputum from an open case of pulmonary tuberculosis.
2. Ingestion of the organisms leads to development to tonsillar or intestinal tuberculosis. This mode of infection of human tubercle bacilli is from self-swallowing of infected sputum of an open case of pulmonary tuberculosis, or ingestion of bovine tubercle bacilli from milk of diseased cows.
3. Inoculation of the organisms into the skin may rarely occur from infected postmortem tissue.
4. Transplacental route results in development of congenital tuberculosis in fetus from infected mother and is a rare mode of transmission.
1.6 EVOLUTION OF TUBERCLE:

The sequence of events which take place when tubercle bacilli are introduced into the tissue is illustrated in fig. no. 5.

1. When the tubercle bacilli are injected intravenously into the guinea pig, the bacilli are lodged in pulmonary capillaries where an *initial response of neutrophils* is evoked which are rapidly destroyed by the organisms.

2. After about 12 hours, there is *progressive infiltration by macrophages which* dominate the picture throughout the remaining life of the lesions. If the tubercle bacilli are, however, inhaled into the lung alveoli, macrophage predominate the picture from the beginning.

![Exogenous Infection](image1.png) ![Initial Acute Reaction](image2.png) ![Hard Tubercle](image3.png) ![Soft Tubercle](image4.png)

Fig no. 5: Evolution of tubercle

1.7 PATHOGENESIS OF TUBERCLE:

1. The macrophages start phagocytosing the tubercle bacilli. In 2-3 days, the macrophages undergo structural changes as a result of immune mechanisms the cytoplasm becomes pale and eosinophilic and their nuclei become elongated and
vesicular. These modified macrophages resemble epithelial cells and are called epithelioid cells.

2. The macrophages continue to enter the tissue either from circulating monocytes or from local proliferation and undergo changes to form more epithelioid cells. The epithelioid cells in time aggregate into tight clusters or granulomas.

3. Some of the macrophages form multinucleated giant cells either by fusion of adjacent cells or by internal nuclear division without cytoplasmic division. The giant cells may be Langerhans type having peripherally arranged nuclei in the form of horseshoe or ring, or clustered at the two poles of the giant cell; or they may be foreign body type having centrally placed nuclei.

4. Around the mass of epithelioid cells and giant cells is a zone of lymphocytes, plasma cells and fibroblasts. The lesion at this stage is called hard tubercle due to the absence of central necrosis.

5. Within 10-14 days, the centre of the cellular masses begins to undergo caseation necrosis, characterized by cheesy appearance and high lipid content. This stage is called soft tubercle which is the hallmark of tuberculous lesions. The development of caseation necrosis is related to tissue hypersensitivity tubercle bacilli and its products. Microscopically, caseation necrosis is structure-less, eosinophilic and granular material with nuclear debris.

6. The soft tubercle which is a fully developed granuloma with caseous centre does not favour rapid proliferation of tubercle bacilli. Acid fast bacilli are difficult to find in these lesions and may be demonstrated at the margins of recent necrotic foci and in the walls of the cavities.

The fate of a granuloma is variable:

- The caseous material may undergo liquefaction and extend into surrounding soft tissues, discharging the contents on the surface. This is called cold abscess although there are no pus cells in it.
- In tuberculosis of tissues like bones, joints, lymph nodes and epididymis, sinuses are formed and the sinus tracts are lined by tuberculous granulation tissue.
- The adjacent granulomas may coalesce together enlarging the lesion which is surrounded by progressive fibrosis.
- In the granuloma enclosed by fibrous tissue, calcium salts may get deposited in the caseous material (dystrophic calcification) and sometimes the lesion may even get ossified over the years.
1.8 SPREAD OF TUBERCULOSIS:
The disease spreads in the body by various routes:

1. **Local spread** - This takes place by macrophages carrying the bacilli into the surrounding tissues.

2. **Lymphatic spread** - Tuberculosis is primarily an infection of lymphoid tissues. The bacilli may pass into lymphoid follicles of pharynx, bronchi, intestines or regional lymph nodes resulting in regional tuberculosis lymphadenitis which is typical childhood infections. Primary complex is primary focus with lymphangitis and lymphadenitis.

3. **Haematogenous spread** - This occurs either as a result of tuberculous bacillaemia because of the drainage of lymphatics into the venous system or due to caseous material escaping through ulcerated wall of a vein. This produces millet seed sized lesions in different organs of the body like lungs, liver, kidneys, bones and other tissues and is known as miliary tuberculosis.

4. **By the natural passages** - Infection may spread from:
   - i. Lung lesions into pleura (tuberculous pleurisy);
   - ii. Trans bronchial spread into the adjacent lung segments;
   - iii. Tuberculous salpingitis into peritoneal cavity (tuberculous peritonitis);
   - iv. Infected sputum into larynx (tuberculous laryngitis);
   - v. Swallowing of infected sputum (ileocaecal tuberculosis);
   - vi. Renal lesions into ureter and down to trigone of bladder\(^{13}\).

1.9 PATHOGENESIS OF TUBERCULOSIS:

About 90% of those infected with *Mycobacterium tuberculosis* have asymptomatic, latent TB infection (sometimes called LTBI), with only a 10% lifetime chance that a latent infection will progress to TB disease. However, if untreated, the death rate for these active TB cases is more than 50%.

TB infection begins when the mycobacteria reach the pulmonary alveoli, where they invade and replicate within the endosomes of alveolar macrophages. The primary site of infection in the lungs is called the Ghon focus and is generally located in either the upper part of the lower lobe or the lower part of the upper lobe. Bacteria are picked up by dendrite cells which do not allow replication, although these cells can transport the bacilli to local (mediastinal) lymph nodes. Further spread is through the bloodstream to other tissues and organs where secondary TB lesions can develop in other parts of the lung.
(particularly the apex of the upper lobes), peripheral lymph nodes, kidneys, brain, and bone. All parts of the body can be affected by the disease, though it rarely affects the heart, skeletal muscles, pancreas and thyroid.

Tuberculosis is classified as one of the granulomatous inflammatory conditions. Macrophages, T lymphocytes, B lymphocytes and fibroblasts are among the cells that aggregate to form a granuloma, with lymphocytes surrounding the infected macrophages. The granuloma functions not only to prevent dissemination of the mycobacteria, but also provides a local environment for communication of cells of the immune system. Within the granuloma, T lymphocytes secrete cytokines such as interferon gamma, which activates macrophages to destroy the bacteria with which they are infected. Cytotoxic T cells can also directly kill infected cells by secreting perforin and granulysin.

Importantly, bacteria are not always eliminated within the granuloma, but can become dormant resulting in a latent infection. Another feature of the granulomas of human tuberculosis is the development of cell death also called necrosis, in the center of tubercles. To the naked eye this has the texture of soft white cheese and was termed caseous necrosis.

If TB bacteria gain entry to the bloodstream from an area of damaged tissue they spread through the body and set up many foci of infection, all appearing as tiny white tubercles in the tissues. This severe form of TB disease is most common in infants and elderly and is called miliary tuberculosis.

Tissue destruction and necrosis are balanced by healing and fibrosis. Affected tissue is replaced by scarring and cavities filled with cheese-like white necrotic material. During active disease some of these cavities are joined to the air passages bronchi and this material can be coughed up. It contains living bacteria and can therefore pass on infection. Treatment with appropriate antibiotics kills bacteria and allows healing to take place. Upon cure, affected areas are eventually replaced by scar tissue. If untreated, infection with Mycobacterium tuberculosis can become lobar pneumonia\(^{(14)}\).

**1.10 DIFFERENCE BETWEEN TB INFECTION AND TB DISEASE:**

In most people who become infected, the body's immune system is able to fight the TB bacteria and stop them from multiplying. The bacteria are not killed, but they become inactive and are stored harmlessly in the body, this is TB infection. People with TB infection have no symptoms and cannot spread the infection to others. However, the bacteria remain alive in the body and can become active again later.
If an infected person's immune system cannot stop the bacteria from multiplying, the bacteria eventually cause symptoms of active TB, or TB disease. To spread TB to others, a person must have TB disease.

Most people who have TB infection never develop TB disease, but some infected people are more likely to develop TB disease than others. They include babies and children, persons with weak immune systems, and persons with some other kinds of lung disease(15).

1.11 CLASSIFICATION SYSTEM FOR TUBERCULOSIS(16):

Table no. 4: Clinical classification system for tuberculosis based on pathogenesis of disease

<table>
<thead>
<tr>
<th>Class</th>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No TB exposure Not infected</td>
<td>No history of exposure Negative reaction to tuberculin skin test</td>
</tr>
<tr>
<td>1</td>
<td>TB exposure No evidence of infection</td>
<td>History of exposure Negative reaction to tuberculin skin test</td>
</tr>
<tr>
<td>2</td>
<td>TB infection No disease</td>
<td>Positive reaction to tuberculin skin test Negative bacteriologic studies (if done) No clinical, bacteriologic, or radiographic evidence of TB</td>
</tr>
<tr>
<td>3</td>
<td>TB, clinically active</td>
<td>M. Tuberculosis cultured (if done) Clinical, bacteriologic, or radiographic evidence of current disease</td>
</tr>
<tr>
<td>4</td>
<td>TB Not clinically active</td>
<td>History of episode(s) of TB or Abnormal but stable radiographic findings Positive reaction to the tuberculin skin test Negative bacteriologic studies (if done) and No clinical or radiographic evidence of current disease</td>
</tr>
<tr>
<td>5</td>
<td>TB suspect</td>
<td>Diagnosis pending TB disease should be ruled in or out within 3 months</td>
</tr>
</tbody>
</table>

1.12 PATTERNS OF INFECTION:

There are two major patterns of disease with TB:

- **Primary tuberculosis**: seen as an initial infection, usually in children. The initial focus of infection is a small subpleural granuloma accompanied by granulomatous hilar lymph node infection. Together, these make up the Ghon complex. In nearly all cases, these granulomas resolve and there is no further spread of the infection.
Secondary tuberculosis: seen mostly in adults as a reactivation of previous infection (or reinfection), particularly when health status declines. The granulomatous inflammation is much more florid and widespread. Typically, the upper lung lobes are most affected and cavitation can occur. When resistance to infection is particularly poor, a "miliary" pattern of spread can occur in which there are a myriad of small millet seed (1-3 mm) sized granulomas, either in lung or in other organs. Dissemination of tuberculosis outside of lungs can lead to the appearance of a number of uncommon findings with characteristic patterns.

1.13 TYPES OF TUBERCULOSIS:

- **Skeletal tuberculosis:** Tuberculous osteomyelitis involves mainly the thoracic and lumbar vertebrae (known as Pott's disease) followed by knee and hip. There is extensive necrosis and bony destruction with compressed fractures (with kyphosis) and extension to soft tissues, including psoas "cold" abscess.

- **Genital tract tuberculosis:** Tuberculous salpingitis and endometritis result from dissemination of tuberculosis to the fallopian tube that leads to granulomatous salpingitis, which can drain into the endometrial cavity and cause a granulomatous endometritis with irregular menstrual bleeding and infertility. In the male, tuberculosis involves prostate and epididymis most often with non-tender induration and infertility.

- **Urinary tract tuberculosis:** A "sterile pyuria" with WBC's present in urine but a negative routine bacterial culture may suggest the diagnosis of renal tuberculosis. Progressive destruction of renal parenchyma occurs if not treated. Drainage to the ureters can lead to inflammation with urethral stricture.

- **CNS tuberculosis:** A meningeal pattern of spread can occur and the cerebrospinal fluid typically shows a high protein, low glucose, and lymphocytosis. The base of the brain is often involved, so that various cranial nerve signs may be present. Rarely, a solitary granuloma, or "tuberculoma", may form and manifest with seizures.

- **Gastrointestinal tuberculosis:** This is uncommon today because routine pasteurization of milk has eliminated *Mycobacterium bovis* infections. However, *M. tuberculosis* organisms coughed up in sputum may be swallowed into the GI tract. The classic lesions are circumferential ulcerations with stricture of the small
intestine. There is a predilection for ileocaecal involvement because of the abundant lymphoid tissue and slower rate of passage of luminal contents.

- **Adrenal tuberculosis:** Spread of tuberculosis to adrenals is usually bilateral, so that both adrenals are markedly enlarged. Destruction of cortex leads to Addison's disease.

- **Scrofula:** Tuberculous lymphadenitis of the cervical nodes may produce a mass of firm, matted nodes just under the mandible. There can be chronic draining fistulous tracts to overlying skin. This complication may appear in children.

- **Cardiac tuberculosis:** The pericardium is the usual site for tuberculous infection of heart. The result is a granulomatous pericarditis that can be hemorrhagic. If extensive and chronic, there can be fibrosis with calcification, leading to a constrictive pericarditis\(^\text{(17)}\).

![Tuberculosis Affects Many Parts of the Body](image)

**Fig no. 6:** Illustrating the many parts of the body affecting tuberculosis.

### 1.14 SIGNS AND SYMPTOMS:

When the disease becomes active 75% of the cases are pulmonary TB, which is TB in the lungs. Symptoms include chest pain, coughing of blood, a productive, prolonged cough for more than three weeks. Systemic symptoms include fever, chills, night sweats, appetite loss, weight loss, pallor and often a tendency to fatigue very easily. In the other 25% of active cases, the infection moves from the lungs, causing other kinds of TB, collectively denoted extrapulmonary tuberculosis.
This occurs more commonly in immunosuppressed persons and young children. Extrapulmonary infection sites include the pleura in tuberculosis pleurisy, the central nervous system in meningitis, the lymphatic system in scrofula of the neck, the genitourinary system in urogenital tuberculosis, and bones and joints in Pott's disease of the spine. An especially serious form is disseminated TB, more commonly known as miliary tuberculosis. Extrapulmonary TB may co-exist with pulmonary TB as well\(^{(19)}\).

**Complications of pulmonary tuberculosis:**

- Haemoptysis pleural effusion
- Pericardial effusion
- Bronchopleural fistula
- Spontaneous pneumothorax
- Endobronchial or tracheal tuberculosis
- Tuberculous laryngitis
- Tuberculous enteritis\(^{(19)}\)

**Hypersensitivity and immunity in tuberculosis:**

Hypersensitivity or allergy and immunity or resistance plays a major role in the development of lesions in tuberculosis. Tubercle bacilli as such do not produce any toxins. Tissue changes seen in tuberculosis are a result of host response to the organism which is in the form of development of hypersensitivity and immunity. Both these host responses develop as a consequence of several lipids present in the microorganism which include the following:

1. *Mycosides* such as *'Cord factor'* which are essential for growth and virulence of the organism in animals.
2. *Glycolipids* present in the mycobacterial cell wall like *Wax-D* which acts as an adjuvant acting along with tuberculoprotein.

It has been known since the time of Robert Koch that the tissue reaction to tubercle bacilli is different in healthy animal not previously infected (primary infection) from an animal who is previously infected (secondary infection).

1. **In the primary infection**, intradermal injection of tubercle bacilli into the skin of a healthy guinea pig evokes no visible reaction for 10-14 days. After this period, a nodule develops at the inoculation site which subsequently ulcerates and heals poorly as the guinea pig, unlike human beings, does not possess any natural resistance. The regional lymph nodes also develop tubercles. This process is a
manifestation of delayed type of hypersensitivity and is comparable to primary tuberculosis in children although healing invariably occurs in children.

2. In the secondary infection, the sequence of changes is different. The tubercle bacilli are injected into the skin of the guinea pig that has been infected with tuberculosis 4-6 weeks earlier. In 1-2 days, the site of inoculation is indurate and dark, attaining a diameter of about 1 cm. The skin lesion ulcerates which heals quickly and the regional lymph nodes are not affected. This is called Koch's phenomenon and is indicative of hypersensitivity and immunity in the host. Similar type of changes can be produced if injection of live tubercle bacilli is replaced with old tuberculin (OT).

Hypersensitivity and immunity are closely related and are initiated through T lymphocytes sensitized against specific antigens in tuberculin. As a result of this sensitization, lymphokines are released from T cells which induce increased microbicidal activity of the macrophages\textsuperscript{(15)}.

\section*{1.15 RISK FACTORS FOR CAUSING TUBERCULOSIS:}
The following people are at higher risk for active TB:

- Elderly people and infants.
- Persons with \textit{silicosis} have an approximately 30-fold greater risk for developing TB. Silica particles irritate the respiratory system, causing immunogenic responses such as phagocytosis which consequently results in high lymphatic vessel deposits. It is this interference and blockage of macrophage function which increases the risk of tuberculosis.
- Persons with chronic renal failure who are on hemodialysis also have an increased risk 10-25 times greater than the general population.
- Persons with diabetes mellitus have a risk for developing active TB and this risk is likely greater in persons with insulin-dependent or poorly controlled diabetes.
- Other clinical conditions that have been associated with active TB include gastrectomy with attendant weight loss and malabsorption, jejunoileal bypass, renal and cardiac transplantation, carcinoma of the head or neck and other neoplasms (e.g. lung cancer, lymphoma, and leukemia).
- Low body weight is associated with risk of tuberculosis as well. A body mass index (BMI) below 18.5 increases the risk by 2-3 times and an increase in body
weight lowers the risk and they have a poorer response to treatment, possibly due to poorer drug absorption.

- IV drug abuse; recent TB infection or a history of inadequately treated TB; chest X-ray suggestive of previous TB, showing fibrotic lesions and nodules.
- Prolonged corticosteroid therapy and other immunosuppressive therapy; Immunocompromised patients (30-40% of AIDS patients in the world also have TB)
- Hematologic and reticuloendothelial diseases, such as leukemia and Hodgkin's disease; end-stage kidney disease, intestinal bypass, chronic malabsorption syndromes, vitamin D deficiency.
- Some drugs, including rheumatoid arthritis drugs that work by blocking tumor necrosis factor-alpha (an inflammation-causing cytokine), raise the risk of activating a latent infection due to the importance of this cytokine in the immune defense against TB\(^{(15,19)}\).

### 1.16 DIAGNOSIS OF TB:

Tuberculosis is diagnosed definitively by identifying the causative organism (\textit{M. tuberculosis}) in a clinical sample (for example, sputum or pus). When this is not possible, a probable diagnosis may be made using imaging (X-rays or scans) and/or a tuberculin skin test (Mantoux test).

A complete medical evaluation for TB must include a medical history, a physical examination, a chest X-ray, microbiological smears and cultures. It may also include a tuberculin skin test, a serological test. Tuberculin tests have the disadvantage of producing false negatives, especially when the patient is co-morbid with sarcoidosis, Hodgkins lymphoma, malnutrition or most notably active tuberculosis disease. Polymerase chain reaction assays for the detection of bacterial DNA. The development of a rapid and inexpensive diagnostic test would be particularly valuable in the developing world\(^{(19)}\).

**Tests may include**\(^{(19)}\)

- Biopsy of the affected tissue (rare)
- Bronchoscopy
- Chest CT scan
- Chest x-ray
- Interferon-gamma blood test such as the QFT-Gold test to test for TB infection
- Sputum examination and cultures
- Thoracentesis
- Tuberculin skin test

**Chest radiology:**

A standard posterior-anterior radiograph of the chest is usually enough for evidence of tuberculosis but in some cases lateral view or apicogram or tomogram may be required. The CT scan is used to diagnose mediastinal or hilar lymphadenopathy, cavities and intra lesion calcifications. It is very useful due to its speed, simplicity and ease of use when equipment is available. It is true that X-Ray has a high sensitivity, and it can detect TB in patients who do not excrete any bacilli. X-Ray for Pulmonary TB diagnosis has been reserved for the second line, after AFB-smears have been found consistently negative. Its value will be greater for diagnosis of Pulmonary TB in children and for some types of extra pulmonary TB\(^{(19,20)}\).

**Mantoux Tuberculin Skin-Test Screening:**

The preferred method of screening for TB infection is the Mantoux tuberculin skin test using 0.1 ml of 5 tuberculin units (TU) of PPD. Multiple puncture tests should not be used to determine if a person is infected. Persons who have a documented history of a positive skin-test result, a documented history of TB disease or a reported history of a severe necrotic reaction to tuberculin should be exempt from routine tuberculin skin-test screening. The Mantoux skin test is not a recommended method of screening for active TB disease; an average of 10% – 25% of patients with active TB disease have a negative reaction to the tuberculin skin test. The reaction to the Mantoux skin test should be interpreted by an experienced worker 48–72 hours after the injection by measuring the area of indurations (i.e. the palpable swelling) at the injection site. The maximum diameter of the indurations measured by palpation and not redness is recorded and interpreted as follows:

1)  15 mm or ulceration - strongly positive
2)  > 10 mm - positive
3)  5 to 9 mm - indeterminate
4)  < 5 mm - negative

However, if indurations of more than 5 mm are considered a positive result in persons in the following groups:

- Close contacts of a person who has infectious TB.
- Persons whose chest radiographs are suggestive of previous TB disease;
Persons known to have HIV infection; and
- Persons who are at risk for HIV infection, including injecting-drug users whose HIV status are unknown.

Persons who have a positive skin-test result and no symptoms suggestive of TB should be screened with a chest radiograph within 72 hours after the skin test is interpreted. Persons who have symptoms suggestive of TB disease should be evaluated immediately\(^{(21,22,23)}\).

### 1.17 PREVENTION:

TB is a preventable disease, even in those who have been exposed to an infected person. Skin testing (PPD) for TB is used in high risk populations or in people who may have been exposed to TB, such as health care workers. A positive skin test indicates TB exposure and an inactive infection. Some countries with a high incidence of TB give people a BCG vaccination to prevent TB\(^{(16)}\).

**Immunisation against tuberculosis: Vaccine**

The first genuine success in immunizing against tuberculosis was developed from attenuated bovine-strain tuberculosis by Albert Calmette and Camille Guerin in 1906. It was called "BCG" (Bacille Calmette-Guerin). The BCG vaccine was first used on humans in 1921 in France\(^{(3,11)}\). According to the WHO, this is the most often used vaccine worldwide, with 85% of infants in 172 countries immunized in 1993. BCG is given to all children under age three\(^{(6,24)}\).

**Resistance:** Resistance to each of the four anti-TB drugs routinely tested is defined according to the results of bacteriological testing. (MDR) is defined as resistance to both isoniazide and rifampicin, with or without resistance to other agents.

**Acquired resistance to anti-tuberculosis drugs:**

Patients diagnosed with TB who start anti-TB treatment and acquire resistance to one or more of the drugs used during the treatment are said to have developed “acquired drug resistance”\(^{(25)}\).

**Reasons for failure of drug treatment**\(^{(26)}\):

- Prescription of inadequate therapy.
- Drug default: Failure of patient to take drugs.
- Primary drug resistance
- Secondary drug resistance
- Dormant bacilli- persisters not affected by drugs.
- Improper drug combination
1.18 TREATMENT OF TUBERCULOSIS:

The therapy of tuberculosis has undergone remarkable change. The conventional 12-18 month treatment has been largely replaced by more effective and less toxic 6 month treatment which also yields higher completion rates. This has been possible due to better understanding of the biology of tubercular infection and the differential properties of the anti-tubercular drugs.

Biology of tubercular infection *M. tuberculosis* is an aerobic organism. In unfavourable conditions it grows only intermittently or remains dormant for prolonged periods. Several subpopulations of bacilli, each with a distinctive metabolic state, could exist in an infected patient, e.g.:

- **Rapidly growing with high bacillary load** as in the wall of a cavitary lesion where oxygen tension is high and pH is neutral. These bacilli are highly susceptible to H and to a lesser extent to R, E and S.
- **Slow growing** located intracellularly (in macrophages) and at inflamed sites where pH is low. They are particularly vulnerable to Z, while H, R and E are less active and S is inactive.
- **Spurters** within caseous material where oxygen tension is low but pH is neutral the bacilli grow intermittently with occasional spurts of active metabolism. R is most active on this subpopulation.
- **Dormant** some bacilli remain totally inactive for prolonged periods. No antitubercular drug is significantly active against them.
- **However there is continuous shifting of bacilli between these subpopulations**.[27]

1.18.1 The goals of treatment of tuberculosis are:

- Rapid identification of a new TB case.
- Initiation of specific anti-tuberculosis treatment.
- Prompt resolution of the signs and symptoms of disease.
- Achievement of a noninfectious state in the patient, thus ending isolation.
- Adherence to the treatment regimen by the patient.
- Cure of the patient as quickly as possible.
- Kill dividing bacilli by drugs with early bactericidal action
- Kill persisting bacilli for cure and prevent relapse.
- Prevent emergence of resistance.
Secondary goals:
1) Identification of the index case that infected the patient.
2) Identification of all persons infected by both the index case and the new case of TB and completion of appropriate treatments.

Thus, successful treatment of tuberculosis has benefits both for the individual patient and the community in which the patient resides. For this reason the prescribing physician has responsibility not only for prescribing an appropriate regimen but also for successful completion of therapy\(^{(26,27)}\).

1.18.2 Treatment: classification of antitubercular drugs

- **First line drugs**: These drugs have high antitubercular efficacy as well as low toxicity and are used routinely. Isoniazide (H), Rifampin (R), Pyrazinamide (Z), Ethambutol (E) Streptomycin (S)

- **Second line drugs**: These drugs have either low antitubercular efficacy or high toxicity or both and are used in special circumstances only. Thiacetazone (Tzn), Paraaminosalicylic acid (PAS) Ethionamide (Etrn), Cycloserine (Cys), Kanamycin (Kmc), Amikacin (Am), Capreomycin (Cpr)\(^{(25)}\).

- **Newer drugs**\(^{(13)}\)
  1. Ciprofloxacin, Ofloxacin, Clarithromycin, Azithromycin, Rifabutin
### Table no. 5: Treatment of Tuberculosis: Information on drugs\(^{(26)}\)

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Drug (year of discovery)</th>
<th>MIC (µg/ml)</th>
<th>Effect on bacterial cell</th>
<th>Mechanisms of action</th>
<th>Targets</th>
<th>Genes involved in resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1)</td>
<td>Isoniazide (1952)</td>
<td>0.01 - 0.20</td>
<td>Bactericidal</td>
<td>Inhibition of cell wall mycolic acid and other multiple effects on DNA, lipids, carbohydrates and NAD metabolism</td>
<td>Primarily acyl carrier protein reductase (inha)</td>
<td>Katg(^b); inha; ndh</td>
</tr>
<tr>
<td>2)</td>
<td>Rifampin (1966)</td>
<td>0.05 - 0.50</td>
<td>Bactericidal</td>
<td>Inhibition of RNA synthesis</td>
<td>RNA polymerase β subunit</td>
<td>Rpoβ</td>
</tr>
<tr>
<td>3)</td>
<td>Pyrazinamide (1952)</td>
<td>20 - 100ph 5.5 or 6.0</td>
<td>Bactericidal</td>
<td>Disruption of membrane transport and energy depletion</td>
<td>Membrane energy metabolism</td>
<td>Pnca(^b)</td>
</tr>
<tr>
<td>4)</td>
<td>Ethambutol (1961)</td>
<td>1 - 5</td>
<td>Bactericidal/Bacteriostatic</td>
<td>Inhibition of cell wall anabinogalactan synthesis</td>
<td>Arabinosyl transferase</td>
<td>Embcab</td>
</tr>
<tr>
<td>5)</td>
<td>Streptomycin (1944)</td>
<td>2 - 8</td>
<td>Bacteriostatic</td>
<td>Inhibition of protein synthesis</td>
<td>Ribosomal S12 protein and 16S rRNA</td>
<td>Rpsl; rrs (operon)</td>
</tr>
<tr>
<td>6)</td>
<td>Kanamycin (1957)</td>
<td>1 - 8</td>
<td>Bactericidal</td>
<td>Inhibition of protein synthesis</td>
<td>Ribosomal S12 protein and 16S rRNA</td>
<td>Rpsl; rrs (operon)</td>
</tr>
<tr>
<td>7)</td>
<td>Quinolones (1963)</td>
<td>0.2 - 4</td>
<td>Bactericidal</td>
<td>Inhibition of DNA replication and transcription</td>
<td>DNA gyrase</td>
<td>GyrA; gyrB</td>
</tr>
<tr>
<td>8)</td>
<td>Ethionamide (1956)</td>
<td>0.6 - 2.5</td>
<td>Bacteriostatic</td>
<td>Inhibition of mycolic acid synthesis</td>
<td>Acyl carrier protein reductase (inha)</td>
<td>Inha; etaA/ethA(^b)</td>
</tr>
<tr>
<td>9)</td>
<td>PAS (1946)</td>
<td>1 - 8</td>
<td>Bacteriostatic</td>
<td>Inhibition of folic acid and iron metabolism</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>10)</td>
<td>Cycloserine (1952)</td>
<td>5 - 20</td>
<td>Bacteriostatic</td>
<td>Inhibition of peptidoglycan synthesis</td>
<td>D-alanine racemase</td>
<td>Alra; Ddl(^b)</td>
</tr>
</tbody>
</table>
Table no. 6: Recommended doses of anti-TB drugs

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Daily dose (mg/kg)</th>
<th>3 × per week dose (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazide (H)</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Rifampicin (R)</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Pyrazinamide (Z)</td>
<td>25</td>
<td>35</td>
</tr>
<tr>
<td>Ethambutol (E)</td>
<td>15</td>
<td>30</td>
</tr>
<tr>
<td>Streptomycin (S)</td>
<td>15</td>
<td>15</td>
</tr>
</tbody>
</table>

The relative activity of the first line drugs in achieving these goals differs, e.g. H and R are the most potent bactericidal drugs active against all populations of TB bacilli, while Z acts best on intracellular bacilli and those at inflamed sites has very good sterilizing activity. On the other hand S is active only against rapidly multiplying extracellular bacilli. E is bacteriostatic mainly serves to prevent resistance and may hasten sputum conversion. Drug combinations are selected to maximize the above actions together with considerations of cost, convenience and feasibility. The general principles are:

- Use of any single drug in tuberculosis results in the emergence of resistant organisms and relapse in almost 3/4 patients. A combination of two or more drugs must be used.
- INH and R are the most efficacious drugs; their combination is definitely synergistic duration of therapy is shortened from 12 months to 9 months. Addition of Z for the initial 2 months further reduces duration of treatment to 6 months.
- A single daily dose of all first line anti-tubercular drugs is preferred. The directly observed treatment short course (DOTS) was recommended by WHO in 1995.
- Response is fast in the first few weeks as the fast dividing bacilli are eliminated rapidly. Symptomatic relief is evident within 2-4 weeks\(^{(30)}\).
Table no.7: First line anti-TB drugs$^{(29,31)}$

<table>
<thead>
<tr>
<th>Drug</th>
<th>Side effects</th>
<th>Potential interactions</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethambutol</td>
<td>Rash, joint pain, gut upset, fever, headache, dizziness, eyesight problems</td>
<td>Antacids</td>
<td>--</td>
</tr>
<tr>
<td>Isoniazide</td>
<td>Gut upset, loss of appetite, fever, rash, liver problems, peripheral neuropathy</td>
<td>Phenytoin, antacids, alcohol, steroids</td>
<td>Take on an empty stomach. Take pyridoxine (Vit. B6) to prevent peripheral neuropathy. Monitor liver function.</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Gut upset, fever, rash, joint pain, hepatitis, gout, light sensitivity</td>
<td>Protease inhibitors, azole antifungal drugs, oral contraceptives, methadone, dapsone</td>
<td>Monitor liver function.</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Gut upset, rash, fever, orange urine/tears/saliva, light sensitivity, liver problems, acute renal failure</td>
<td>----</td>
<td>Take on an empty stomach.</td>
</tr>
</tbody>
</table>

Table no. 8: Second line anti-TB drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Side effects</th>
<th>Potential interactions</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>Inner ear damage, kidney problems, joint pain</td>
<td>Some antibiotics, diuretics</td>
<td>Must be injected. Contraindicated for pregnant women.</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>Inner ear damage, kidney problems</td>
<td>Some antibiotics</td>
<td>Must be injected. Contraindicated for pregnant women.</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Nausea, diarrhea, stomach cramps, headache, rash, seizures, allergic reaction</td>
<td>Antacids, caffeine</td>
<td>----</td>
</tr>
<tr>
<td>Clofazimine</td>
<td>Gut upset with severe cramps, rash, eye irritation, coloring of</td>
<td>----</td>
<td>Take with food.</td>
</tr>
</tbody>
</table>
## Introduction

<table>
<thead>
<tr>
<th>Drug</th>
<th>Side Effects</th>
<th>Interactions</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycloserine</td>
<td>Dizziness, headache, mood changes, seizures, neuropathy</td>
<td>Alcohol, ethionamide, isoniazide</td>
<td>----</td>
</tr>
<tr>
<td>Ethionamide</td>
<td>Gut upset, rash, loss of appetite, liver problems</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>Inner ear damage, kidney problems</td>
<td>----</td>
<td>Contraindicated for pregnant women.</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>Gut upset, sleep problems, headaches</td>
<td>Antacids, insulin</td>
<td>----</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>Gut upset, rash, dizziness, sleep problems, anxiety, headache, seizures, allergic reaction, thrush</td>
<td>Antacids</td>
<td>----</td>
</tr>
<tr>
<td>Para-aminosalicylic acid</td>
<td>Gut upset, liver problems</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>Gut upset, rash, eye inflammation, blood cell changes, joint pain, orange urine/tears/saliva, liver function changes, fever</td>
<td>Protease inhibitors, fluconazole, oral contraceptives, steroids, methadone</td>
<td>Avoid wearing soft contact lenses as they can become discolored.</td>
</tr>
<tr>
<td>Rifapentine</td>
<td>Gut upset, rash, hepatitis, orange urine/tears/saliva, light sensitivity, acute renal failure, fever</td>
<td>Alcohol, protease inhibitors, oral contraceptives</td>
<td>Long-acting form of rifampin taken once or twice a week.</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>Nausea, rash, inner ear damage, kidney problems</td>
<td>Some antibiotics</td>
<td>Monitor hearing.</td>
</tr>
</tbody>
</table>

### 1.19: National Tuberculosis Control Programme (NTCP) Guidelines:

Patients of TB are categorized according to:

- **Site of disease (pulmonary or extrapulmonary) and its severity**: The bacillary load and acute threat to life or permanent handicap are taken into consideration.
- **Sputum smear positivity / negativity**: positive cases are infectious and have higher mortality.
- **History of previous treatment**: risk of drug resistance is more in irregularly treated patients.
All regimens consist of an initial intensive phase lasting 2-3 months aimed to rapidly kill the TB bacilli, bring about sputum conversion and afford symptomatic relief. This is followed by a continuation phase lasting 4-6 months during which the remaining bacilli are eliminated so that relapse does not occur. Patients who have been previously or have defaulted and relapsed are treated with a longer intensive initial (5 drugs for 2 months and 4 drugs for 1 month) followed by the continuation phase.

**Category I:** This includes new (untreated) smear positive pulmonary TB with extensive parenchymal damage and new severe forms of extrapulmonary TB.

**Initial Phase:** Four drugs HRZ+ E or S are given daily for 2 months. The NTCP recommends that if the patient is sputum positive after 2 months, the initial (intensive) phase be extended by 1 month and then the continuation phase is started at 3 months regardless of the sputum status.

**Continuation Phase:** Two drugs HR for 4 months or HE for 6 months are given. With HR administration, thrice weekly regimen is permissible. For TB meningitis, miliary and spinal TB this phase with HR is extended to 6-7 months.

**Category II:** This includes smear positive treatment failures; relapse; and interrupted treatment cases. These cases may have resistant bacilli with an increased risk of developing MDR-TB.

**Initial Phase:** All five (HRZES) drugs are given for 2 months followed by 4 drugs (HRZE) for another 1 month. Continuation phase is started if the sputum is negative, but 4 drugs (HRZE) treatment is continued for another 1 month if sputum is positive at 3 months.

**Continuation Phase:** Three drugs (HRE) are given for 5 months either daily or thrice weekly.

**Category III:** This includes new cases of smear negative pulmonary TB with limited parenchymal disease, or less severe forms of extrapulmonary TB. i.e. Lymph node, bone (excluding Spine), unilateral pleural effusion, peripheral joints or skin TB.

**Initial Phase:** Three drugs (HRZ) are given for 2 months are sufficient as the bacillary load is smaller.

**Continuation Phase:** Same as category I i.e. 4 months daily or thrice weekly HR or 6 months daily HE therapy.

**Category IV:** This includes chronic cases, which have remained or become smear positive after completion of fully supervised Category II (re-treatment) regimen. These are generally MDR cases. MDR-TB is defined as resistance to both H and R, and any
number of other anti-TB drugs. MDR-TB follows a rapid course and the prognosis is bad. Treatment is difficult as second-line drugs are less efficacious, more toxic and expensive. Effective treatment needs strict compliance on the part of the patient.

Therapy of MDR-TB cases depends on the drugs used in the earlier regimen and presence of associated disease like diabetes mellitus, leukemia or AIDS. Preferably the sensitivity of the TB bacilli should be known. First-line drugs are prescribed with / without 1 to 3 second-line drugs as under:

For H resistance cases – RZE is given for 12 months.
For H + R resistant cases – ZE + S/Ethionamide + Ciprofloxacin/ Ofloxacin can be used.

The actual regimen and its duration have to be individualized for each patient depending on the clinical features and response to therapy.

Table no. 9: The category-wise treatment regimens for tuberculosis

<table>
<thead>
<tr>
<th>Category</th>
<th>Initial Phase (Daily)</th>
<th>Continuation Phase (Daily/3X per week)</th>
<th>Total Duration (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>2 HRZE(S)</td>
<td>4 HR/4H$_3$R$_3$</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6HE</td>
<td>8</td>
</tr>
<tr>
<td>II</td>
<td>2 HRZE + 1HRZE</td>
<td>5 HRE</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 H$_3$R$_3$E$_3$</td>
<td>8</td>
</tr>
<tr>
<td>III</td>
<td>2 HRZ</td>
<td>4 HR/4 H$_3$R$_3$</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 HE</td>
<td>8</td>
</tr>
<tr>
<td>IV</td>
<td>Chronic TB Cases</td>
<td>Regimen in text</td>
<td></td>
</tr>
</tbody>
</table>

Notes:
2. The numeral prefixed to a phase is its duration in months.
3. The numeral in subscript (H$_3$, R$_3$, E$_3$) is the number of doses of that drug per week. Absence of a subscript numeral indicates that the drug is given daily$^{(31)}$.

1.20 CHEMOPROPHYLAXIS:

This is indicated only in:

a) Contacts of open cases, which show recent Mantoux conversion.
b) Children with positive Mantoux and a TB patient in the family.
c) Neonate of tubercular mother.
d) Patients of leukemia, diabetes, silicosis or are on corticosteroid therapy who show a positive Mantoux.

e) Patients with old inactive disease who are assessed to have received inadequate therapy.
The drug generally used for prophylaxis has been H 300 mg (10 mg/kg in children) daily for 6-12 months. Now because of high incidence of H resistance, a combination of H (5 mg/kg) and R (10 mg/kg) given for 6 months is preferred. In some countries combination of HRZ given for 2-3 months has been successfully tested\textsuperscript{(25)}.

1.21 DOTS - DIRECTLY OBSERVED TREATMENT SHORT COURSES:

It produces cure rates of up to 95% even in poorest countries. DOTS prevent new infection and the development of MDR-TB. Their effective procedure is to health community workers and trained volunteers. They observed and recorded patient swallowing the correct dosage of anti-TB medicines for 6-8 months\textsuperscript{(30,32)}.

DOTS is a systematic strategy which has five components-

- **Political and administrative commitment.** TB is the leading infectious cause of death among adults. TB kills more men than women, yet more women die of TB than all causes associated with childbirth combined. Since TB can be cured and the epidemic reversed, it warrants the topmost priority which it has been accorded by the Government of India. This priority must be continued and expanded at the state, district and local levels.

- **Good quality diagnosis.** Good quality microscopy allows health workers to see the tubercle bacilli and is essential to identify the infectious patients who need treatment the most.

- **Good quality drugs.** An uninterrupted supply of good quality anti-TB drugs must be available. In the RNTCP, a box of medications for the entire treatment is earmarked for every patient registered; ensuring the availability of the full course of treatment the moment the patient is initiated on treatment. Hence in DOTS, the treatment can never interrupt for lack of medicine.

- **Supervised treatment.** To ensure the right treatment, given in the right way. The RNTCP uses the best anti-TB medications available. But unless treatment is made convenient for patients, it will fail. This is why the heart of the DOTS programme is "directly observed treatment" in which a health worker or another trained person who is not a family member watches as the patient swallows the anti-TB medicines in their presence.

- **Systematic monitoring and accountability.** The programme is accountable for the outcome of every patient treated. This is done using standard recording and reporting system, and the technique of ‘cohort analysis’. The cure rate and other
key indicators are monitored at every level of the health system and if any area is not meeting expectations, supervision is intensified. The RNTCP shifts the responsibility for cure from the patient to the health system.

The new Stop TB Strategy published by WHO in 2006 has DOTS in the core with additional components to address TB/HIV and MDR-TB, health system strengthening, involvement of all care providers, engaging people with TB and affected communities, and enabling/promoting research. RNTCP is already implementing/ plans to implement the activities recommended under the new stop TB strategy\(^{(35)}\).

### 1.22 SURGICAL MANAGEMENT:

- The first successful treatments for tuberculosis were all surgical. They were based on the observation that healed tuberculous cavities were all closed. Surgical management was therefore directed at closing open cavities in order to encourage healing.

- In modern times, the surgical treatment of tuberculosis is confined to the management of multi-drug resistant TB. A patient with MDR-TB who remains culture positive after many months of treatment may be referred for Lobectomy or Pneumonectomy with the aim of cutting out the infected tissue. The optimal timing for surgery has not been defined and surgery still confers significant morbidity. Some complications of treated tuberculosis like recurrent hemoptysis, destroyed or bronchiectatic lungs and emphysema (a collection of pus in the pleural cavity) are also amenable to surgical therapy.

- In extrapulmonary TB, surgery is often needed to make a diagnosis (rather than to a cure) surgical excision of lymph nodes, drainage of abscesses, tissue biopsy, etc are all examples of this \(^{(36)}\).
REFERENCES:
   Tuberculosis: Estimated incidence prevalence and mortality by country. JAMA. 
5. Govt. of India, Ministry of health and family welfare, Times of India. 24th March, 
   1999.
   August 2010.
8. Paramasivan CN, An over view of drug resistant tuberculosis in India. Indian J 
11. R. Ananthanarayan, Panikar, CK, Mycobacterium-I tuberculosis Textbook of 
    Medical publishers (P) Ltd. 5th ed: 2005; 156-163.
    Robbins – Pathologic Basis of disease W.B. Saunders company Elsevier. 8th ed. 
    2007; 516-522.
17. www.icm.tn.gov.in accessed on Dec 2009
    32: 5-10.


35. TBC India Directorate General of Health services Ministry of Health and family Welfare.dot.htm.