wjpmr, 2020,6(10),163-179

SJIF Impact Factor: 5.922

WORLD JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.wjpmr.com

Review Article

ISSN 2455-3301

WJPMR

MYCOBACTERIUM TUBERCULOSIS: A REVIEW

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Article Received on 05/08/2020 **Article Revised on 26/08/2020** **Article Accepted on 16/09/2020**

ABSTRACT

This review on tuberculosis includes an introduction that describes how the lung is the portal of entry for the tuberculosis bacilli to enter the body and then spread to the rest of the body. The symptoms and signs of both primary and reactivation tuberculosis are described. Routine laboratory tests are rarely helpful for making the diagnosis of tuberculosis. The differences between the chest X ray in primary and reactivation tuberculosis is also described. The chest computed tomography appearance in primary and reactivation tuberculosis is also described. The criteria for the diagnosis of pulmonary tuberculosis are described, and the differential is discussed. The pulmonary findings of tuberculosis in HIV infection are described and differentiated from those in patients without HIV infection. The occurrence of tuberculosis in the elderly and in those patients on anti-tumor necrosis factor alpha inhibitors is described. Pleural tuberculosis and its diagnosis are described. Efforts to define the activity of tuberculosis and the need for respiratory isolation are discussed. The complications of pulmonary tuberculosis are also described.

KEYWORDS: Tuberculosis, *Mycobacterium tuberculosis*, HIV, Mycolic acid, DOTS, 1st Line Drug, 2nd Line Drug.

INTRODUCTION

Tuberculosis (TB) is an infectious disease usually caused by *Mycobacterium tuberculosis* (MTB) bacteria. Tuberculosis generally affects the lungs, but can also affect other parts of the body. Most infections show no symptoms, in which case it is known as latent tuberculosis.

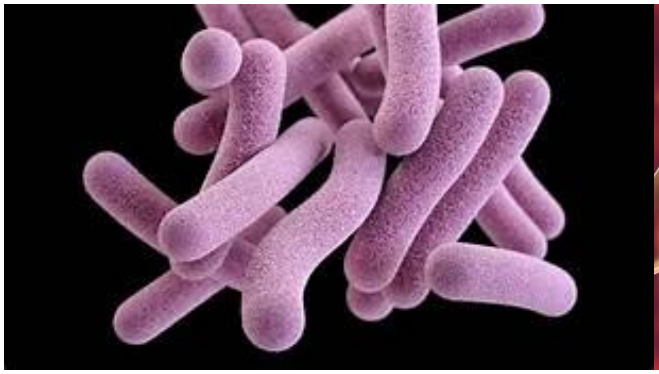


Figure-1 Tubercle bacilli

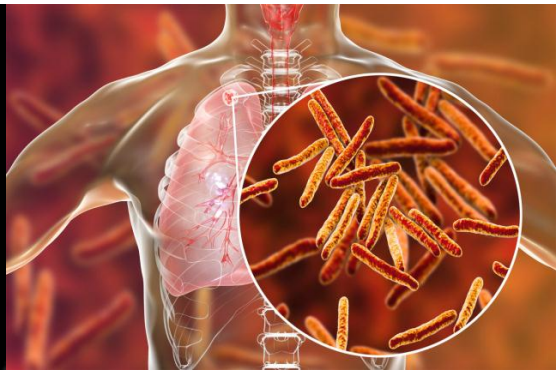


Figure-2

Tuberculosis (TB) is caused by bacteria (*Mycobacterium tuberculosis*) that most often affect the lungs. Tuberculosis is curable and preventable. TB is spread from person to person through the air. When people with lung TB cough, sneeze or spit, they propel the TB germs into the air. A person needs to inhale only a few of these germs to become infected. About one-quarter of the world's population has latent TB, which means people have been infected by TB bacteria but are not (yet) ill with the disease and cannot transmit the disease. People

infected with TB bacteria have a 5–15% lifetime risk of falling ill with TB. Persons with compromised immune systems, such as people living with HIV, malnutrition or diabetes, or people who use tobacco, have a higher risk of falling ill. When a person develops active TB disease, the symptoms (such as cough, fever, night sweats, or weight loss) may be mild for many months. This can lead to delays in seeking care, and results in transmission of the bacteria to others. People with active TB can infect 5–15 other people through close contact over the course of a year. Without proper treatment, 45% of HIV-negative people with TB on average and nearly all HIV-positive people with TB will die.[1]

Frequency: 25% of people (latent TB), Causes: *Mycobacterium tuberculosis*, Symptoms: Chronic cough, fever, cough, Specialty: Infectious disease, pulmonology

Can tuberculosis be cured?
In the 20th century, TB was a leading cause of death in the United States. Today, most cases are cured with antibiotics. But it takes a long time. You have to take medications for at least 6 to 9 months.

Tuberculosis Types: A TB infection doesn't always mean you'll get sick. There are two forms of the disease:

- **Latent TB:** You have the germs in your body, but your immune system keeps them from spreading. You don't have any symptoms, and you're not contagious. But the infection is still alive and can one day become active. If you're at high risk for re-activation -- for instance, if you have HIV, you had an infection in the past 2 years, your chest X-ray is unusual, or your immune system is weakened -- your doctor will give you medications to prevent active TB.
- **Active TB:** The germs multiply and make you sick. You can spread the disease to others. Ninety percent of active cases in adults come from a latent TB infection.

A latent or active TB infection can also be drug-resistant, meaning certain medications don't work against the bacteria.[2]

Who is most at risk?
Tuberculosis mostly affects adults in their most productive years. However, all age groups are at risk. Over 95% of cases and deaths are in developing countries. People who are infected with HIV are 19 times more likely to develop active TB. The risk of active TB is also greater in persons suffering from other conditions that impair the immune system. People with undernutrition are 3 times more at risk. There were globally 2.3 million new TB cases in 2018 that were attributable to under nutrition.

1.1 million children (0–14 years of age) fell ill with TB, and 230 000 children (including children with HIV associated TB) died from the disease in 2018.Alcohol use disorder and tobacco smoking increase the risk of TB disease by a factor of 3.3 and 1.6, respectively. In 2018, 0.83 million new TB cases worldwide were attributable to alcohol use disorder and 0.86 million were attributable to smoking.

Global impact of TB: TB occurs in every part of the world. In 2018, the largest number of new TB cases occurred in the South-East Asian region, with 44% of new cases, followed by the African region, with 24% of new cases and the Western Pacific with 18%.In 2018, 87% of new TB cases occurred in the 30 high TB burden countries. Eight countries accounted for two thirds of the new TB cases: India, China, Indonesia, Philippines, Pakistan, Nigeria, Bangladesh and South Africa.

Tuberculosis Transmission: When someone who has TB coughs, sneezes, talks, laughs, or sings, they release tiny droplets that contain the germs. If you breathe in these germs, you can get it. TB isn't easy to catch. You usually have to spend a long time around someone who has a lot of the bacteria in their lungs. You're most likely to catch it from co-workers, friends, and family members. Tuberculosis germs don't thrive on surfaces. You can't get it from shaking hands with someone who has it or by sharing their food or drink.

TB and HIV: People living with HIV are 19 (15-22) times more likely to develop active TB disease than people without HIV.HIV and TB form a lethal combination, each speeding the other's progress. In 2018 about 251 000 people died of HIV-associated TB. In 2018, there were an estimated 862 000 new cases of TB amongst people who were HIV-positive, 72% of whom were living in Africa. WHO recommends a 12-component approach of collaborative TB-HIV activities, including actions for prevention and treatment of infection and disease, to reduce deaths.[3]

Multidrug-resistant TB: Anti-TB medicines have been used for decades and strains that are resistant to one or more of the medicines have been documented in every country surveyed. Drug resistance emerges when anti-TB medicines are used inappropriately, through incorrect prescription by health care providers, poor quality drugs, and patients stopping treatment prematurely. Multidrug-resistant tuberculosis (MDR-TB) is a form of TB caused by bacteria that do not respond to isoniazid and rifampicin, the 2 most powerful first-line anti-TB drugs. MDR-TB is treatable and curable by using second-line drugs. However, second-line treatment options are limited and require extensive chemotherapy (up to 2 years of treatment) with medicines that are expensive and toxic. In some cases, more severe drug resistance can develop. Extensively drug-resistant TB (XDR-TB) is a more serious form of MDR-TB caused by bacteria that do not respond to the most effective second-line anti-TB drugs, often leaving patients without any further treatment options. In 2018, MDR-TB remains a public health crisis and a health security threat. WHO estimates

that there were 484 000 new cases with resistance to rifampicin – the most effective first-line drug – of which 78% had MDR-TB. The MDR-TB burden largely falls on 3 countries – India, China and the Russian Federation – which together account for half of the global cases. About 6.2% of MDR-TB cases had extensively drug-resistant TB (XDR-TB) in 2018. Worldwide, only 56% of MDR-TB patients are currently successfully treated. In 2016, WHO approved the use of a short, standardized regimen for MDR-TB patients who do not have strains that are resistant to second-line TB medicines. This regimen takes 9–12 months and is much less expensive than the conventional treatment for MDR-TB, which can take up to 2 years. Patients with XDR-TB or resistance to second-line anti-TB drugs cannot use this regimen, however, and need to be put on longer MDR-TB regimens to which 1 of the new drugs (bedquiline and delamanid) may be added.[4]

WHO also approved in 2016 a rapid diagnostic test to quickly identify these patients. Sixty-two countries have started using shorter MDR-TB regimens. By the end of 2018, 90 countries reported having introduced bedaquiline and 57 countries reported having introduced delamanid, in an effort to improve the effectiveness of MDR-TB treatment regimens.

Global commitments and the WHO response: On 26 September 2018, the United Nations (UN) held its first-ever high-level meeting on TB, elevating discussion about the status of the TB epidemic and how to end it to the level of heads of state and government. It followed the first global ministerial conference on TB hosted by WHO and the Russian government in November 2017. The outcome was a political declaration agreed by all UN Member States, in which existing commitments to the Sustainable Development Goals (SDGs) and WHO's End TB Strategy were reaffirmed, and new ones added.[5]

SDG Target 3.3 includes ending the TB epidemic by 2030. The End TB Strategy defines milestones (for 2020 and 2025) and targets (for 2030 and 2035) for reductions in TB cases and deaths. The targets for 2030 are a 90% reduction in the number of TB deaths and an 80% reduction in the TB incidence rate (new cases per 100 000 population per year) compared with levels in 2015. The milestones for 2020 are a 35% reduction in the number of TB deaths and a 20% reduction in the TB incidence rate. The strategy also includes a 2020 milestone that no TB patients and their households face catastrophic costs as a result of TB disease.

The political declaration of the UN high-level meeting included four new global targets:

- Treat 40 million people for TB disease in the 5-year period 2018–2022;
- Reach at least 30 million people with TB preventive treatment for a latent TB infection in the 5-year period 2018–2022;
- Mobilize at least US$ 13 billion annually for universal access to TB diagnosis, treatment and care by 2022;
- Mobilize at least US$ 2 billion annually for TB research.

The political declaration also requested the UN Secretary-General, with support from WHO, to provide a report in 2020 to the General Assembly on global and national progress, as the basis for a comprehensive review at a high-level meeting in 2023. The Director-General of WHO was requested to continue to develop a multisectoral accountability framework for TB (MAF-TB) and to ensure its timely implementation.[6]

WHO is working closely with countries, partners and civil society in scaling up the TB response. Six core functions are being pursued by WHO to contribute to achieving the targets of the UN high-level meeting political declaration, SDGs, End TB Strategy and WHO strategic priorities:

- Providing global leadership to end TB through strategy development, political and multisectoral engagement, strengthening review and accountability, advocacy, and partnerships, including with civil society;
- Shaping the TB research and innovation agenda and stimulating the generation, translation and dissemination of knowledge;
- Setting norms and standards on TB prevention and care and promoting and facilitating their implementation;
- Developing and promoting ethical and evidence-based policy options for TB prevention and care;
- Ensuring the provision of specialized technical support to Member States and partners jointly with WHO regional and country offices, catalyzing change, and building sustainable capacity;
- Monitoring and reporting on the status of the TB epidemic and progress in financing and implementation of the response at global, regional and country levels.[7]

Symptoms: Common symptoms of active lung TB are cough with sputum and blood at times, chest pains, weakness, weight loss, fever and night sweats. Many countries still rely on a long-used method called sputum smear microscopy to diagnose TB. Trained laboratory technicians look at sputum samples under a microscope to see if TB bacteria are present. Microscopy detects only half the number of TB cases and cannot detect drug-resistance.

The use of the rapid test Xpert MTB/RIF® has expanded substantially since 2010, when WHO first recommended its use. The test simultaneously detects TB and resistance to rifampicin, the most important TB medicine. Diagnosis can be made within 2 hours and the test is now recommended by WHO as the initial diagnostic test in all persons with signs and symptoms of TB.[8]

Signs of active TB disease include:

- A cough that lasts more than 3 weeks
- Chest pain
- Coughing up blood
- Feeling tired all the time
- Night sweats
- Chills
- Fever
- Loss of appetite
- Weight loss

If you have any of these symptoms, see your doctor to get tested. Get medical help right away if you have chest pain.[9]

Figure-3 Pathology of Tuberculosis Figure-4

Diagnostics: Diagnosing multidrug-resistant and extensively drug-resistant TB (see Multidrug-resistant TB section below) as well as HIV-associated TB can be complex and expensive. In 2016, 4 new diagnostic tests were recommended by WHO – a rapid molecular test to detect TB at peripheral health centres where Xpert MTB/RIF cannot be used, and 3 tests to detect resistance to first- and second-line TB medicines. There are two common tests for tuberculosis:

- Skin test. This is also known as the Mantoux tuberculin skin test. A technician injects a small amount of fluid into the skin of your lower arm. After 2 or 3 days, they'll check for swelling in your arm. If your results are positive, you probably have TB bacteria. But you could also get a false positive. If you've gotten a tuberculosis vaccine called bacillus Calmette-Guerin (BCG), the test could say that you have TB when you really don't. The results can also be false negative, saying that you don't have TB when you really do, if you have a very new infection. You might get this test more than once.[10]
- Blood test. These tests, also called interferon-gamma release assays (IGRAs), measure the response when TB proteins are mixed with a small amount of your blood.

Tuberculosis is particularly difficult to diagnose in children.

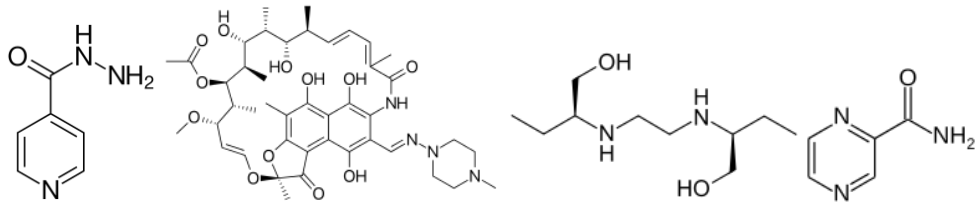


Figure-5: Antitubercular drugs [INH, Rifampicin, Ethambutol, Pyrazinamide].

Treatment: TB is a treatable and curable disease. Active, drug-susceptible TB disease is treated with a standard 6-month course of 4 antimicrobial drugs that are provided with information and support to the patient by a health worker or trained volunteer. Without such support, treatment adherence is more difficult.

Between 2000 and 2018, an estimated 58 million lives were saved through TB diagnosis and treatment.

Most common TB drugs: If you have latent tuberculosis, you may need to take only one or two types of TB drug. Active tuberculosis, particularly if it's a drug-resistant strain, will require several drugs at once. The most common medications used to treat tuberculosis include:

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

If you have drug-resistant TB, a combination of antibiotics called fluoroquinolones and injectable medications, such as amikacin or capreomycin (Capastat), are generally used for 20 to 30 months. Some types of TB are developing resistance to these medications as well.[11]

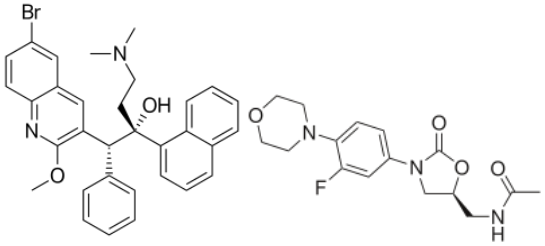


Figure-6: Bedaquiline and Linezolid [Newer Drugs].

Some drugs may be used as add-on therapy to the current drug-resistant combination treatment, including:

- Bedaquiline (Sirturo)
- Linezolid (Zyvox)

Medication side effects: Serious side effects of TB drugs aren't common but can be dangerous when they do occur. All tuberculosis medications can be highly toxic to your liver. When taking these medications, call your doctor immediately if you experience any of the following:

- Nausea or vomiting
- Loss of appetite
- A yellow color to your skin (jaundice)
- Dark urine
- A fever that lasts three or more days and has no obvious cause

Completing treatment is essential

After a few weeks, you won't be contagious and you may start to feel better. It might be tempting to stop taking your TB drugs. But it is crucial that you finish the full course of therapy and take the medications exactly as prescribed by your doctor. Stopping treatment too soon or skipping doses can allow the bacteria that are still alive to become resistant to those drugs, leading to TB that is much more dangerous and difficult to treat.[12]

Tuberculosis or TB is a common and often deadly infectious disease caused by mycobacteria, usually *Mycobacterium tuberculosis* in humans. Tuberculosis usually attacks the lungs but can also affect other parts of the body. It is spread through the air, when people who have the disease cough, sneeze, or spit.[13]

Tuberculosis has been present in human since antiquity. The earliest unambiguous detection of *Mycobacterium tuberculosis* is in the remains of bison dated 18,000 years before the present. Whether tuberculosis originated in cattle and then transferred to humans, or diverged from a common ancestor infecting a different species, is currently unclear.[14] However, it is clear that *M. tuberculosis* is not directly descended from *M. bovis*, which seems to have evolved relatively recently. Skeletal remains from a Neolithic Settlement in the Eastern Mediterranean show prehistoric humans (7000 BC) had TB, and tubercular decay has been found in the spines of mummies from 3000–2400 BC. Phthisis is a Greek term for tuberculosis; around 460 BC, Hippocrates identified phthisis as the most widespread disease of the times involving coughing up blood and fever, which was almost always fatal. In South America, the earliest evidence of tuberculosis is associated with the Paracas-Caverna culture (circa 750 BC to circa 100 AD).[15]

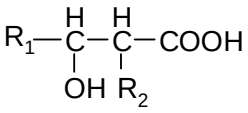
Folklore: Before the Industrial Revolution, tuberculosis may sometimes have been regarded as vampirism. When one member of a family died from it, the other members that were infected would lose their health slowly. People believed that this was caused by the original victim draining the life from the other family members. Furthermore, people who had TB exhibited symptoms similar to what people considered to be vampire traits. People with TB often have symptoms such as red, swollen eyes (which also creates a sensitivity to bright light), pale skin, extremely low body heat, a weak heart and coughing blood, suggesting the idea that the only way for the afflicted to replenish this loss of blood was by sucking blood. Another folk belief told that the affected individual was being forced, nightly, to attend fairy revels, so that the victim wasted away owing to lack of rest; this belief was most common when a strong connection was seen between the fairies and the dead. Similarly, but less commonly, it was attributed to the victims being "hagridden"—being transformed into horses by witches (hags) to travel to their nightly meetings, again resulting in a lack of rest.

Evolution: Tuberculosis has co-evolved with humans for many thousands of years, and perhaps for several million years. The oldest known human remains showing signs of tuberculosis infection are 9,000 years old. During this evolution, *M. tuberculosis* has lost numerous coding and non-coding regions in its genome, losses that can be used to distinguish between strains of the bacteria. The implication is that *M. tuberculosis* strains differ geographically, so their genetic differences can be used to track the origins and movement of each strain.[16]

Biology of Mycobacterium Tuberculosis: Mycobacteria are the transition from between bacteria and fungi which belongs to the order *Actinomycetales*, family *Mycobacteriaceae* and genus *Mycobacterium*. These are slow growing aerobes distinguished by acid-fast staining. They show fungus like growth on the surface of the liquid cultures. Because of their hydrophobic cell wall and aerobic metabolism, they are found at the interface of water and air.

Morphology: *Mycobacterium tuberculosis* is generally having slender rod like structure, which may vary from 2 to 6 microns in length and 0.2 to 0.5 microns in width. It may be straight, but more frequently appears slightly curved. All the members of the family *mycobacterium* after staining resist decolorization with mineral acid and therefore referred as acid fast. They are resistant to drying and disinfectants but sensitive to heat (pasteurization) and UV light.

Structure and chemical composition of cell wall: The structure of cell wall of *mycobacterium tuberculosis* is unique among prokaryotes and it is a major determinant of virulence for the bacterium. Along with peptidoglycan, the acid-fast cell wall of mycobacterium contains a large number of glycolipids such as mycolic acid, arabiogalactan-lipid complex, and lipoarabinomannen. A waxy lipid called mycolic acid makes up approximately 60% of the dry weight of the mycobacterial cell envelops and makes the cell wall relatively impermeable. The core of the cell wall contains peptidoglycan (murein) that gives the bacterium specific shape and prevents osmotic lyses, arabinogalactan (a polysaccharide) and esters of mycolic acid (α-branched-β-hydroxy fattyacids) having the following general structure.[17]



Where R_1 and R_2 are long chain hydrocarbons

Mycolic acids are strong hydrophobic molecules that form a lipid shell around the organism and affect permeability at the cell surface. Mycolic acid is thought to be a significant determinant of virulence in *mycobacterium tuberculosis*. Probably they prevent the attack of cationic proteins, lysozyme and oxygen radicals in the phagocytic granules. There also present a series of soluble lipid components, which seem to be located in the outer part of the cell wall. Which includes Wax-D, lipoarabinomannan and Cord factor (6,6'-dimycotyltrehalose). Cord factor is a glycolipid that causes cells to grow in parallel chains and form entwined bundles. It is toxic to mammalian cells and is also an inhibitor of polymorphonuclear cell migration. Cording is characteristic of virulent strains of *Mycobacterium tuberculosis*. The ability of mycobacterium to exhibit acid fast staining i.e. when stained, the cells cannot be decolorized easily despite treatment with dilute acids or alcohol is correlated with the presence of cell wall mycolic acids. The lipid fraction of mycobacterial cell wall consists of three major components like mycolic acid, Cord factor and Wax-D. The type of mycolic acid can be used to distinguish different mycobacteria. Mycolic acid with short chain fatty acids from a pseudo outer membrane and are responsible for the unusual staining characteristics. They can however be readily stained by Ziel-Neilson technique. The mycolic acid and other glycolipids also impede the entry of chemicals causing the organisms to grow slowly and be more resistant to chemical agents and lysosomal components of phagocytes. The wall helps the organism to survive within the macrophage by resisting oxidative damage.

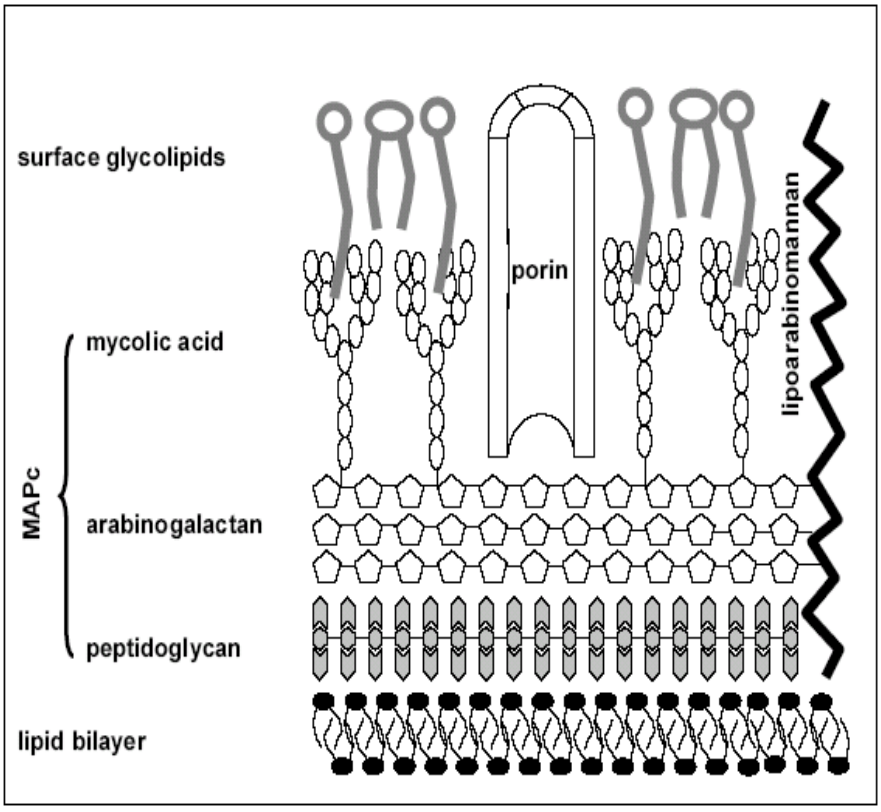


Figure-7: Schematic representation of the mycobacterial cell wall structure.

Here below the figure represents the model of peptidoglycan synthesis. Precursors are produced in the cytoplasm subsequently coupled to an undecaprenyl monophosphate, the carrier lipid, and modified. After translocation to the outer face, peptidoglycan is assembled and incorporated into the cell wall.[18]

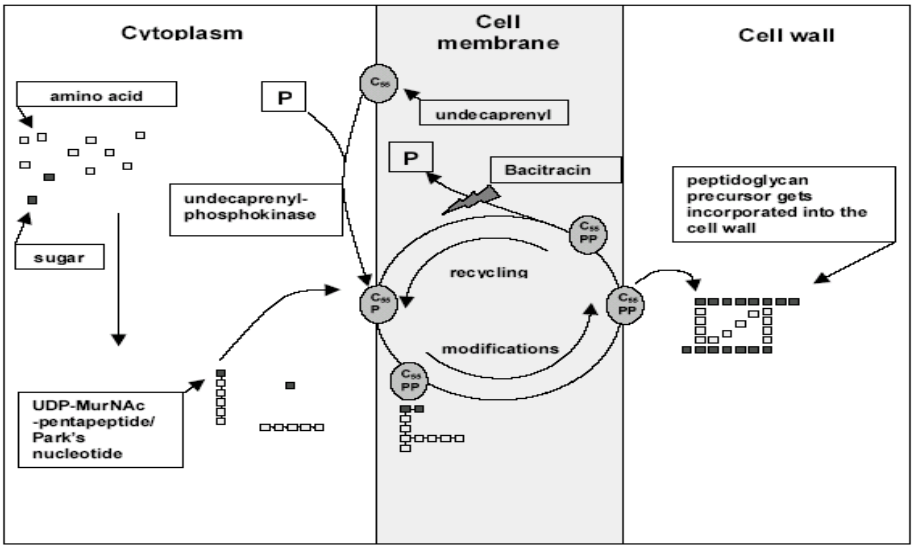


Figure-8: Peptidoglycan biosynthesis.

Genetic sequence: The complete genome sequence of the best characterized strain of *M.tuberculosis*, H37Rv has been recently determined. The genome contains 4411529 base pairs and an estimated 4000 gene (each gene approx 1000 base pairs). About 400 genes are the members of a newly discovered group, which are responsible for the changes in the bacterial cell wall. This is the organism's blueprint of life. Proteins provided by these genes can become new targets of a better control over the disease.

Two hypotheses have come out due to genome sequence

1) 10% of the genomics devoted to two very repetitive protein families of acidic, glycine-rich proteins. What is the biological function is still unknown. They may have immunological significance. Either it easily modifies the antigen it presents to the host or it interferes with the host ability to deal with antigens.

2) *M.tuberculosis* does not have an imperative need for oxygen to survive. Many enzymes have been identified and research is going on to identify the gene responsible for MDR strains.

***Mycobacterium avium-intercellular* complex:** Approximately half of all AIDS patients develop an infection caused by *M.avium* and *M.itracellular*. The organisms are difficult to distinguish and are considered as complex, thus the acronym MAC. The lungs are the organs more commonly involved in non-AIDS patient but the infection may involve bone marrow, lymphnodes, liver and blood in AIDS patients. *M.avium* complex organisms are niacin negative, do not reduce nitrate and produce only a small amount of catalase and there by differs from *M.tuberculosis*. They cause serious tuberculosis like infection that is most difficult to treat. Multiple drug regimen (typically 5 drugs)may be effective.[19]

Atypical Mycobacteria: Other mycobacteria species that resemble *M.tuberculosis* in some morphologic aspects and cultural requirements but show little or no pathogenic effect in humans. They were improperly defined in the past as "**Atypical Mycobacteria".** Raunyon classified them into four groups according to their growth rate and pigment production. This classification however is inadequate to define the different species in clear cut way.

Group-1: Photochromogens ---- Produce yellow pigment and grow in light.

Group-2: Scotochromogens ---- Pigments production and grow in light or dark.

Group-3: Non-chromogens ---- No pigment production

Group-4: Rapid growers ---- Grow fast in culture but less pathogenic

Nutrition and cultural characteristics: *M.tuberculosis*is a strict aerobe. Nutritionally it is one of the least fastidious pathogenic microorganisms. It grows readily on a chemically defined medium containing only aspargine, glycerol, potassium phosphate, potassium sulfate and magnesium sulfate. *M.tuberculosis* colonies are buff colored and waxy in appearance they are difficult to emulsify because of their hydrophobicity. The optimal temperature for the growth of mycobacterium is 37^0C. Growth is stimulated by atmosphere containing 5-10% CO_2 and pH at 6.4 to 7. It takes about 4 weeks for macroscopic growth.[20]

Pathophysiology and Etiology: Tuberculosis is transmitted by inhalation of droplet nuclei that is expelled by coughing, sneezing and other forceful respiratory activities. These droplets contain about 1-3 organism and remain suspended in air indefinitely, which when inhaled by a healthy person, reach the alveoli in the lungs. Once the bacteria are internalized by alveolar macrophages, they set up infection foci in the tissue of the alveolar wall. These foci expand through bacterial

growth and recruitment of macrophages and lymphocytes that build the granuloma (tubercle). The granuloma seems to support limited bacterial growth and prevents metastasis of the infection. The grnauloma also protects the bacterium from their immune response and is probably responsible for the persistent or latent nature of the infection. Clinical symptoms develop when this immune mediated constriction is abrogated through immune compromise. This is usually a consequence of old, malnutrition or a concurrent infection with Human Immunodeficiency Virus (HIV). But often occurs years after the primary infection. At this time, the granuloma casemates and spills its content into the lungs and is transmitted as an aerosol generated by coughing or sneezing.[21]

Type of Tuberculosis: Depending on the severity of infection, TB is classified as:
Primary infection: Occurs on first exposure to tubercle bacilli. Inhaled droplet nuclei are so small that they avoid the mucocilliary defences of the bronchi and lodge in the terminal of alveoli of the lungs. Infection begins with the multiplication of tubercle bacilli in the lungs, usually in the upper lobe, particularly towards the apex. Inflammation develops here and along the draining lymphatic to involve the hilar lymph nodes. This complex of peripheral lesion and hilar lymphadenopathy is known as the primary or Ghon focus. Bacilli may spread in the blood from the primary complex throughout the body. It is most commonly seen in young children and immunocompromised patients.

Secondary TB: It may result from reactivation of dormant lesion or quiescent lesion, or in some cases may follow reinfection of a person who is already hypersensitive (tuberculin positive) as a result of an earlier primary infection. Apart from the above types, TB is also classified on the basis of the site of infection as:

Pulmonary TB: It is the most common manifestation of TB, accounting for 85% of the disease in many cases. Pulmonary TB refers to the disease involving the lung parenchyma. In general, pulmonary TB is the only form considered infectious to others.

Extrapulmonary TB: It can occur alone or with pulmonary involvement. The most common sites of extrapulmonary disease are: lymph nodes, pleura, bones, are named depending on the site of infection as: tubercular meningitis, tuberculous pericarditis abdominal tuberculosis, genitourinary tuberculosis, tuberculosis of bones and joints, tuberculosis of spine, and tuberculous lymphadenitis.[22]

Stages of Mycobacterium growth: The progression of the disease can be divided into following five stages.

Stage 1: Pulmonary tuberculosis: Tuberculosis begins when droplet nuclei reaches the alveoli. When a person inhales air that contains droplets most of the lager droplets become lodged in the upper respiratory tract (the nose and throat), where the infection is unlikely to develop. However, the smaller droplet nuclei may reach the small air sacs of the lung where the infection begins. After the droplet nuclei are inhaled, the bacteria are non-specifically taken up by alveolar macrophages. So, the bacillary growth is not found in this stage. Still if the macrophages are not active, they are unable to destroy the intracellular organisms and the disease progresses further as in stage 2.

Stage 2: Symbiotic stage: Begins 7-21 days after initial infection. The bacilli grow logarithmically within the immature (none activated) macrophages of the developing lesion (called tubercle) until the macrophages burst. These macrophages enter the tubercle from the blood stream (in which they are called monocytes). This stage is termed symbiotic because localized bacilli multiply without apparent damage to the host.

Stage 3: Early stage of caseous necrosis: In this stage caseous necrosis occurs, the number of viable bacilli becomes stationary as their growth is inhibited by the immune response to tuberculin like antigens release from the bacilli. At this stage lymphocytes begin to infiltrate. The lymphocytes, specifically T-cells, recognize processed and presented M. tuberculosis antigen in context of Major Histocompatibility Complex (MHC) molecules. This results in T-cell activation and the liberation of cytokines including ɣ-interferon causes the activation of macrophages. These activated macrophages are now capable of destroying the bacilli. At this stage the individual becomes tuberculin positive. This positive tuberculin reaction is the result of the host developing a vigorous Cell Mediated Immune (CMI) response. A CMI response must be mounted to control an *M.tuberculosis* infection. An Antibody Mediated Immune (AMI) will not aid in the control of *M.tuberculosis* infection because *M.tuberculosis* is intracellular and if extra cellular, it is resistant to complement killing due to the high lipid concentration in its cell wall. Although a CMI response is necessary to control an *M.tuberculosis* infection, it is also responsible for much of the pathology associated with tuberculosis. Activated macrophages may release lytic enzymes and reactive intermediates that facilitate the development of immune pathology. Activated macrophages and T-cells also secrete cytokines that may also play a role in the development of immune pathology, including Interleukin-1 (IL-1), Tumor Necrosis Factor (TNF), and ɣ- interferon. In this stage tubercle formation begins. The center of the tubercle is characterized by "cassation necrosis" meaning semi-solid or cheesy consistency. Bacilli cannot persist within these tubercles for extended periods.

Stage 4: Interplay of cell-mediated immunity and tissue damaging delayed type hypersensitivity: Although many activated macrophages can be found surrounding the tubercles, many other macrophages present remain inactivated or poorly activated. Mycobacterium uses

these macrophages to replicate and hence the tubercle grows. The growing tubercle may invade a bronchus. If this happens, *M.tuberculosis* infection can spread to other parts of the lung. Similarly, the tubercle may invade an artery of other blood vessels. The hematogenous spread of *M.tuberculosis* may result in extra pulmonary tuberculosis otherwise known as milliary tuberculosis. The name "milliary" is derived from the fact that metastasizing tuberculosis are about the same size as millet seed. The secondary lesion caused by milliary TB can occur at almost any anatomical location, but usually involved the genitourinary system, bones, joints, lymph nodes, and peritoneum. These lesions are of two types.

1. Exudative lesion where bacteria replicate with virtually no resistance, which gives rise to the formation of a "soft tubercle".
2. Productive or granulomatous lesion where the host becomes hyper sensitive to tuberculo proteins, that gives rise to "hard tubercle".

Stage 5: The stage of liquefaction: Here the bacilli multiply extra cellularly for the first time frequently reaching tremendous numbers. Even well-developed CMI is often ineffective in controlling such a large number of bacilli. This high local concentration of tuberculin like products produced by these bacilli causes tissue damage. DTH response that evades the bronchial wall forming a cavity. The bacilli that enter the bronchial tree spread to other parts of the lugs and spread to the outside environment, most commonly during coughing. Arrest of the disease at this stage depends on antigenic load (of both bacilli and their products) which remains small enough for the host to cope it. In this stage the caseous centers of the tubercles liquefy. This liquid is very conducive to *M.tuberculosis* growth and hence the organism begins to rapidly multiply extracellularly. After some time, the large antigen load causes the walls of nearby bronchi to become necrotic and rupture. This results in cavity formation. Which allow the bacilli to spill into other airways and rapidly spread to other parts of the lung. Only a very small percent of *M.tuberculosis* infection result in disease, and even a smaller percentage of *M.tuberculosis* infection progress to an advanced stage. Usually the host will begin to control the infection at some point. When the primary lesion heals, it becomes fibrous and calcifies. When this happens, the lesion is referred to as the Ghon complex. Depending on the size and severity, the Ghon complex may never subside. Typically, the Ghon complex is readily visible upon chest X-ray. Small metastatic foci containing low numbers of bacilli may also calcify. However, in many cases these foci may contain viable organisms referred as "Simon foci". The Simon foci are also visible on chest X-ray and are often the sight of disease reactivation.

Symptoms of tuberculosis: Patient suffering from tuberculosis come up with symptoms like cough, chest pain, haemoptysis, syspnoea, weight loss, fever, loss of appetite and fatigue. The pathogenesis of tuberculosis can be considered as a series of battles between the host and tubercle bacilli. Each of these participants has its own weapons, which can be used against the other. In addition, both the host and the bacilli have sites of vulnerability where the adversity can get the upper hand.[23]

The weapons of the host

1. The activated macrophage**:** a phagocyte powerful enough to kill or inhibit the tubercle bacilli.
2. The ability to stop the intracellular growth of bacilli in non-activated macrophage by killing the macrophages.

Table 1: Uncommon finding of the Tuberculosis with characteristic patterns.

Uncommon findings of TB (Outside the lung)	Characteristic pattern
Skeletal TB	Thoracic and lumber vertebrae (pott's disease)followed by knee and hip
Genital TB	Dissemination of mycobacteria to the fallopian tube causing Granulomatous salpingitis.
Urinary tract TB	Progressive destruction of renal parenchyma, inflammation of uterial strictures.
Gastrointestinal TB	Circumferential ulceration of small intestine.
Adrenal TB	Bilateral and both adrenals are enlarged. Destruction of cortex leads to Addison's disease.
Scrofula	Tuberculous lymphadenitis of cervical nodes
Cardiac TB	Granulomatous pericarditis Constructive pericarditis due to calcification and fibrosis
CNS TB	Maningeal spread pattern and tuberculoma in base of brain leading to seizures.

The weapons of the bacilli

1. The ability to multiply logarithmically within non-activated macrophages (i.e. within the monocytes that had emigrated from the blood stream into the tissues at the sites of infection).
2. The ability to multiply extra cellularly often reaching tremendous numbers, in liquefied caseous material, including the lumens of cavities.

The vulnerabilities of the host

1. None activated macrophages which provide a favorable intracellular environment for the growth of the bacilli.
2. Liquefied caseous material the only thing in the host that supports the extra cellular growth of the bacilli.

The vulnerabilities of the bacilli

1. The inability to survive within a fully activated macrophage.
2. The inability to multiply in solid caseous tissue.

The progression of the disease depends on the strain of mycobacterium, prior exposure, vaccination, immune status and infectious dose. The factors responsible for TB infection includes close contact with large population, overcrowding of population, poor nutrition, i.v. drug use, alcoholism and the most important one is HIV infection. 10% of all HIV positive individuals harbor *M.tuberculosis*. Only 3-4% of infected individuals develop active disease upon initial infection and 5-10% within one year. These percent is much higher if the individual is HIV-positive.[24]

Multiple Drug Resistant Tuberculosis (MDR-TB): The growing incidence of bacterial resistance with marketed drugs is a serious problem. So, there is an urgent need to develop new classes of drugs to treat bacterial infections.[25-29] Patients with multiple drug resistant tuberculosis are resistant to at least isoniazid and rifampicin. This is a human generated problem and more fatal than tuberculosis itself. These are difficult to treat and remain infectious for longer period of time. MDR-TB can be treated with the combination of remaining 1st line and 2nd line drugs. The treatment duration takes up to two years. In general treatment of MDR-TB requires more complex intervention, longer hospitalization and extensive laboratory monitoring. Resistance has been noticed in almost all the available tubercular agents. It is likely that strains which are completely resistant to existing drugs will become increasingly common and therefore there is a critical need for new drugs that are active against alternative targets.[30]

The potential causes for the development of drug resistance are

- Use of unreliable combination with an appreciable failure rate.
- Misuse of specific drugs like rifampicin for other diseases
- Free availability of anti-TB drug over the counter
- Use of single drug instead of combination
- Failure of public health system
- Economic constrain
- Delay in diagnosis
- Ignorance

Diagnosis: Diagnosis of TB involves detection, isolation and identification of mycobacteria along with drug susceptibility testing of clinically relevant specimen isolates. There are substantial delays in laboratory confirmation of *M.tuberculosis* isolates by conventional methods the isolates can take up to six weeks for growth alone followed by up to three weeks for identification and additional three weeks for susceptibility determination. This can result in substantial treatment delays or unnecessary empiric TB therapy with its associated side effects. For that rapid diagnosis is highly desired. The methods available for the diagnosis of tuberculosis are:

Tuberculin Skin Test

Mantoux skin test: A standard dose of 5 Tuberculin units (0.1 ml) (The standard Mantoux test in the UK consists of an intradermal injection of 2TU of Statens Serum Institute (SSI) tuberculin RT23 in 0.1ml solution for injection.) is injected intradermally (between the layers of dermis) and read 48 to 72 hours later. A person who has been exposed to the bacteria is expected to mount an immune response in the skin containing the bacterial proteins. The reaction is read by measuring the diameter of induration (palpable raised hardened area) across the forearm (perpendicular to the long axis) in millimeters. If there is no induration, the result should be recorded as "0 mm". Erythema (redness) should not be measured. If a person has had a history of a positive tuberculin skin test, another skin test is not needed. but if negative another test may be needed.[31]

MICROSCOPY

Acid fast smear: It is the simplest and most rapid procedure currently available to detect acid fast bacilli in clinical specimen by Ziehl-Neelsin or Kinyoun carbol fuschi method (for acid fast staining) and has been in use for a long period. It is useful for rapid preliminary diagnosis of TB especially in the detection of active, infectious cases and to monitor the progress of treatment. At least three sputum samples must be collected on different days and examined to get proper results. But this method requires at least 10^4bacilli/ml of sputum. This limitation can be overcome by concentration of sputum sample by cyto centrifugation to enhance sensitivity to 100% or liquefaction of sputum with sodium hypochlorite followed by concentration of bacilli by overnight sedimentation to enhance sensitivity.

Fluorescence microscopy: It is an alternative method in which staining is done using a fluorescent dye like auramine-rhodamine stain. The mycobacteria fluoresce with a bright orange color and can be easily detected under low power microscope. This method has higher sensitivity. Fluorescence positive slides are confirmed by Zielhl Neelson method.[32]

Radiological methods & imaging techniques: Chest X-ray can be used to detect active TB. The abnormalities in chest X-ray are suggestive but never diagnostic of TB. It can be used to rule out the possibility of pulmonary TB in a person who has positive reaction to tuberculin skin

test but no symptoms of the disease. In pulmonary tuberculosis, chest radiograph abnormalities often occur in the apical and posterior signets of the upper lobe or in the superior signets of the lower lobe. However, the lesions may appear anywhere in the lungs and may differ in size, shape, density and cavitations especially in HIV infected and other immunosuppressed people. In HIV infected persons with pulmonary TB the chest X-ray may have an unusual appearance. CT scan is more sensitive than chest radiography for detection of cavities, it is also useful when findings on chest films are absent or inconsistent and for guiding diagnostic evaluations such as bronchoscope. Magnetic Resonance Imaging (MRI) is preferred for diagnosis of extra pulmonary disease such as skeletal and intracranial TB.[33]

Culture techniques: Mycobacterial culture can be performed on conventional egg based solid media (Lowenstein-Jensen medium) of agar based medium (Middle Brook 7H10 or 7H11). But mycobacteria growth may take up to 6 week therefore culturing may be done simultaneously in liquid media (Kirchner's or Middle Brook 7H9 broth) that take 2-3 weeks to show mycobacterial growth. Some new methods have also been developed for isolation of mycobacteria which are rapid than the conventional method. These include:

Micro colony detection on solid media: In this method, plates poured with thin layer of Middle Brook 7H11 agar medium and are incubated and examined microscopically on alternate day for first two days and less frequently thereafter. In less than 7 days, micro colonies of slow growing mycobacteria can be detected. This method is expensive and requires about half the time needed for conventional culture.[34]

Radiometric BACTEC 460 TB method: This method detects the presence of mycobacteria based on their metabolism rather than visible growth. It utilized C^{14} labelled palmitic acid in Middle Brook 7H12 broth medium. When the C^{14}labeled substance is metabolized, $C^{14}O_2$ is produced and is measured by BACTEC system instrument and reported in terms of growth index value. It is an automated system. The growth result can be obtained in about 10 days.[35]

Septi-check AFB method: This method consists of capped bottle containing 30ml of Middle Brook 7H9 broth under enhanced CO_2 (5-8%), a paddle with agar media enclosed in a plastic tube and enrichment broth containing glucose, glycerin, oleic acid, pyridoxal, catalase, albumin, polyoxyethylene-40, stearate, polymixin-B, azlocillin, nalidixic acid, trimethoprim and amphotericin-B. One side of the paddle is covered with non-selective Middle Brook 7H11 agar, and the other side is divided into two sections, one containing Middle Brook 7H11 agar with p-nitro-α-acetylamino-β-hydroxypropiophenone (NAP) for differentiation of *M.tuberculosis*from other mycobacteria and second contains chocolate agar for detection of contaminants. This method requires about three weeks of incubation.

MGIT 960 mycobacteria detection system: It is an automate system for growth and detection of mycobacteria with a capacity to incubate and continuously monitor 960 mycobacteria growth indicator tubes (MGIT) every 60 minutes for increase in fluorescence. Growth detection is based on metabolic utilization and subsequent intensification of an oxygen quenched florescent dye contained in a tube of modified MGIT.[36]

MB/Bac T system: It is a non-radiometric continuous monitoring system with a computerized database management. The system is based on colorimetric detection of CO_2. It is an alternative method for BACTEC 460 and growth can be detected in 13 to 14 days by this method.[37]

ESP culture system: This is fully automated continuous monitoring system based on the detection of pressure changes within the headspace above the broth culture medium in a sealed bottle. Either the gas production or gas consumption due to mycobacteria is measured by this method. The growth can be detected in 10-13 days and it is a reliable non radiometric method. But it should be used along with a solid medium as with other liquid cultures.

Molecular methods: Though this method is rapid, it has some disadvantages such as high cost, special equipment and high technical expertise required, therefore can't be used routinely.[38]

DNA probes: DNA probes are short segments of DNA that bind specifically to the unique sequence of DNA/RNA in the organism to be detected. These probes can be tailor made to be completely specific for one species that is the genetic probe's greatest advantage over the available tests. DNA probes depend on DNA hybridization and are limited by the stoichiometry of the reaction i.e. one target molecule binds one DNA probe molecule. So even the most efficient labelling techniques are only capable of detecting that number no molecules as the number of bacteria present.[39]

PCR-based Typing: The polymerase chain reaction (PCR) has emerged as a powerful tool in clinical medicine for exponential in vitro amplification of specific sequences of interest from minute quantities of DNA/RNA and was applied for rapid diagnosis of pathogens in clinical material. This technique is also termed as "**spoligotyping**" which is based on the presence or absence of specific spacer region of DNA. For diagnosis by PCR the most common target used is fragments of an insertion sequence known as IS 6110 which has been identified as specific to *M.tuberculosis* complex and is present up to 20 times in genome, thus offering multiple targets for amplification. A variety of PCR methods have been described in the search for a sensitive and reliable screening test for tuberculosis in clinical specimens. Species-specific and genus-specific

PCR methods are being used with various targets and modifications of PCR. Some of these methods include –

Transcription Mediated Amplification: It is also known as Direct Amplification Test (DAT). Here the identification of *M.tuberculosis*is done by direct amplification of rRNA (5,000-10,000 copies per cell) which is highly specific to the *M.tuberculosis*.[40]

Ligase Chain Reaction: It is a variant of PCR in which a pair of oligonucleotides is made to bind to one of the DNA target strands so that they are adjacent to each other. A second pair of oligonucletide is designed to hybridize to the same regions on the complementary DNA. The action of the DNA polymerase and ligase in the presence of nucleotides results in the gap between adjacent primers being filled with the appropriate nucleotides and ligation of the primers. It is used for respiratory samples and has high overall specificity ad sensitivity for smear positive and negative specimens. Other modification of PCR includes Strand Displacement Amplification (SDA), Nucleic Acid Based Amplification (NABA), branched DNA (b-DNA) and Line Probe Assay (LiPA).[41]

Polymerase Chain Reaction Restriction Analysis: It is an amplified DNA finger printing method for identification of microbes. The principle of the test is based on possession of a 65kDa heat shock protein by all mycobacteria. The gene encoding this protein (HSP65) contains regions that are unique to various species within the genus. The conserved nature enables the amplification of a portion of this gene using the PCR. The unique nature permits differentiation of mycobacterium to the species level by cleaving the amplified DNA into various fragments using restriction endonucleases. The restriction endonuclease is an enzyme that recognizes a specific nucleotide sequence within the DNA and cuts the DNA at or adjacent to that sequence. These fragments are separated using gel electrophoresis. The identification of the organism is obtained by comparing the resulting finger print with that of known mycobacterial reference strains. Related species show the same pattern.[42]

Luciferase Phase Assay: Using genetic engineering firefly luciferase gene is inserted into the genetic material of virus specific to the mycobacterium (mycobacteriophage). When this genetically modified virus infects *M.tuberculosis*, the viral DNA with luciferase gene is integrated into the bacterium's gene. *M.tuberculosis* can now produce luciferase. Luciferase acts with another substance, luciferin to change chemical energy in the cells into light energy. The genetically engineered virus and luciferin may be added to the specimen suspected of containing *M.tuberculosis*. The luciferin diffuses into the cells and if *M.tuberculosis*is present, they are infected and make luciferase. Light produced by reaction of luciferase and luciferin can be measured by a light sensitive instrument known as luminometer.[43]

Serological diagnosis of TB: Most of the serological tests have low turnaround time, high negative predictive value restricts its usefulness for screening tests only. The limitations of this method include low sensitivity I smear negative patients, HIV positive cases and in disease endemic countries with a high infection rate. The tests are also expensive, require trained personnel and often have difficulty in distinguishing between *M.tuberculosis* and non-tuberculous mycobacteria.

Capture ELISA: This test is based on the capture antibody derived from murine source (murine monoclonal antibody against lipoarabinomannan. The rabbit antiserum against *M.tuberculosis* is used as a source of detector of the antibody. This specific and sensitive assay for detection of lipoarabinomannan in sputum is potentially useful for diagnosis of TB.

TB STAT-PAK: Immunochromatographic test based on the detection of antibodies has been evolved with the capability to differentiate between active or dormant TB infection in whole blood, plasma or serum.[44]

Insta test TB:A rapid *in-vitro* assay for the detection of antibody in active TB disease using whole blood or serum. The test employs an antibody binding protein conjugated to a colloidal gold particle and a unique combination of TB antigens immobilized on the membrane.

TB MPB 64 patch test: MPB 64 is a specific mycobacterial antigen for *M.tuberculosis*complex. This patch test becomes positive in 3-4 days after patch application and lasts for a week. The test has a specificity of 100% and sensitivity of 98%.[45]

Current Therapy of Tuberculosis: The development of specific chemotherapeutic agents revolutionized the prognosis of TB infection, making TB truly curable and preventable. The aims of treatment of TB are to:

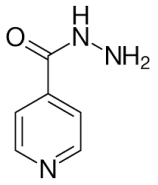
- Cure the patient suffering from TB
- Prevent death from active TB or its late effects
- Prevent relapse of TB
- Prevent transmission of TB to others

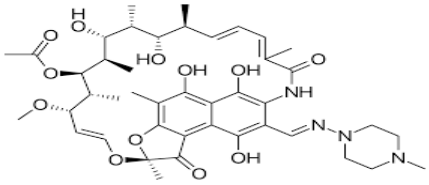
In the years since the advent of tuberculosis chemotherapy, controlled clinical trials have yielded three basic principles upon which recommendations for treatment are based: Regimens for treatment of the disease must contain multiple drugs to which the organisms are susceptible. The drugs must be taken regularly. Drug therapy must continue for a sufficient period of time. Chemotherapeutic agents for Tuberculosis may be divided into two main classes, the first line agents and second line agents as depicted in the table below.[46]

Table-2: (Classification of anti-TB agents).

First line agents	Second line agents
Isoniazide	Ethionamide
Rifampicin	p-Aminosalicylic acid
Pyrazinamide	Cycloserine
Ethambutol	Kanamycin
Streptomycin	Amikacin
	Sparfloxacin
	Ofloxacin
	Levofloxacin
	Clarithromycin
	Rifapentin

There are three main properties of anti-TB drugs


Isoniazid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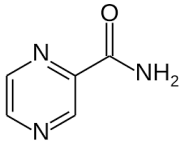
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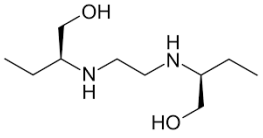
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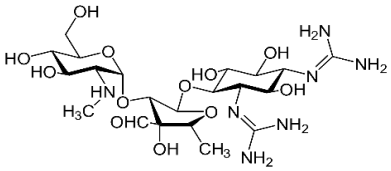
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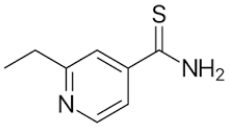
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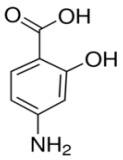
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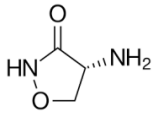
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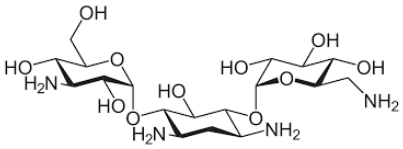
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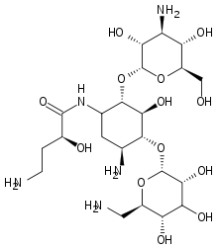
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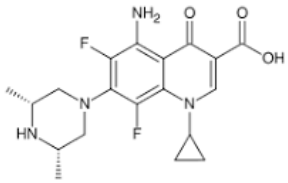
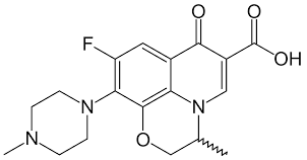

Sparfloxacin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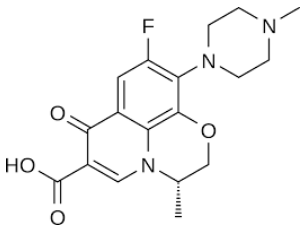
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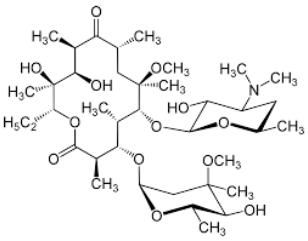
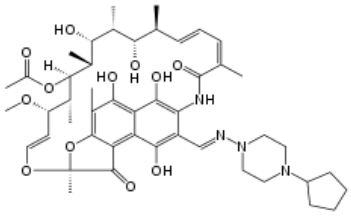

Clarithromycin


Rifapentin

Bactericidal activity: Anti-TB drugs possess these properties to different extents. Rifampicin and isoniazid are the most powerful bactericidal drugs, active against all populations of TB bacilli; isoniazid kills 90% of the total population of bacilli during the first few days of treatment and is most effective against the metabolically active continuously growing bacilli. Rifampicin can kill semi-dormant bacilli which isoniazid cannot. Pyrazinamide and streptomycin are also bactericidal against certain populations of TB bacilli. Pyrazinamide is active in an acid environment against TB bacilli inside macrophages. Streptomycin is active against rapidly multiplying extracellular TB bacilli. Ethambutol and thiocetazone are bacteriostatic drugs used in association with more powerful bactericidal drugs to prevent the emergence of resistant bacilli.[47]

Sterilizing ability: Rifampicin is the most effective sterilizing drug. Its effectiveness makes short course chemotherapy possible. Pyrazinamide is also a good

sterilizing drug since it kills the bacilli protected inside cells.

Ability to prevent resistance: Drug resistance occurs if inadequate anti-TB drugs combination is not used. Isoniazid and rifampicin are most effective in preventing resistance to other drugs. Streptomycin and ethambutol are slightly less effective. TB treatment regimens have an initial phase and a continuous phase. Initial phase is rapid killing of TB bacilli; infectious patients become non-infectious within about 2 weeks. The regimen in initial phase includes 4 drugs for the first 6-8 weeks. Symptoms improve, vast majority of patients with sputum positive become sputum negative within 2 months. Continuous phase requires fewer drugs for a period of 4-6 months in continuous phase; the drug eliminates the remaining bacilli. By killing the persistent bacilli, relapse can be prevented.[48]

Table 3: Standard daily treatment for tuberculosis.

TB treatment Category	TB Patients	Alternative TB treatment regimens	
		Initial phase	Continuation phase
01.	New sputumsmear-positive pulmonary tuberculosis; new smear-negative PTB with extensive parenchymal involvement; new cases of severe forms of extrapulmonary TB.	2EHRZ (SHRZ) 2EHRZ (SHRZ) 2EHRZ (SHRZ)	6 HE 4 HR 4 H_3 R_3
02.	Sputum smear-positive; relapse; treatment failure; treatment after interruption	2 SHRZE/1HRZE 2 SHRZE/1HRZE	5 H_3 R_3 E_3 5 HRE
03.	New smear-negative PTB (other than in category 1); new less severe forms of extrapulmonary TB.	2 HRZ 2 HRZ 2 HRZ	6 HE 4 HR 4 H_3 R_3
04.	Chronic case (still sputum-positive after supervised re-treatment)	Not Applicable (Refer to WHO guidelines for use of second-line drugs in specialized centre)	
Note: A 7 month continuation phase with daily isoniazid and rifampicin (7 HR) for category 1 patients has been recommended for: TB meningitis, military TB, spinal TB with neurological sings. E = ethambutol, H = isoniazid, R = rifampicin, Z= pyrazinamide			

Short-course chemotherapy regimens consisting of 4 drugs during this risk of selecting resistant bacilli. These regimens are practically as effective in patients with initially resistant organisms as in those with sensitive organisms. In patients with smear negative pulmonary or extra-pulmonary TB; there is little risk of selecting resistant bacilli since these patients harbour fewer bacilli in their lesions. Short course chemotherapy regimens with three drugs during the initial phase and two drugs in the continuation phase are of proven efficacy. Effective treatment with short-course multi-drug chemotherapy is the cornerstone of the modern approach to the control of the disease. To emphasize this principle, WHO and IUATLD recommend the use of FDC formulations of the essential antitubercular drugs as one further step to ensure adequate treatment. The other important steps during the treatment include:

- Monitoring of patients
- Recording the treatment response
- Monitoring for significant adverse effects of anti-TB drugs

If any adverse drug reactions occur, management of adverse drug reactions. The minimum inhibitory concentration (MIC), dose used and side effects of clinically important antitubercular agents are briefly summarized in table-4 below.[49]

Table 4: The minimum inhibitory concentration, dose and side effects of clinically important antitubercular agents.

No	Drug Used	MIC µg/ml	Dose (adult)	Side effects
01	Isoniazid	0.025 - 0.05	5mg/Kg (max 300 mg)	Peripheral neuritis, optic neuritis, fever, skin eruptions and hepatitis.
02	Rifampicin	0.005 - 0.2	600 mg o.d.	Toxicity to liver and kidney, allergy and sensitivity reactions, GI upset ad CNS disturbance.
03	Ethambutol	-	15mg/Kg o.d.	Visual acuity, optic neuritis at higher dose
04	Streptomycin	0.4 – 10	15mg/Kg b.d.	Vertigo, decreased hearing, blood dyscrasias, purities or acute anaphylaxis
05	Pyrazinamide	12.5	15/30 mg/Kg (3-4 equally spaced doses)	Liver injury, hyperuricemia, acute episodes of gout, arthalgia, anorexia, nausea, vomiting, dysuria, malaise and fever.
06	Ethionamide	0.6 – 2.5	250 mg b.d.	CNS effect, anorexia, hepatitis, hypersensitivity
07	p-aminosalicylic acid	1.0	10-12 g daily	GI irritation, hypersensitivity reaction,
08	Cycloserine	5-20	250-500 mg b.d.	CNS effects, vertigo, confusion

Except these important drugs there are several drugs which are conveniently used for various types of mycobacteria. They are tabulated here under.[50]

Vaccines: Many countries use Bacillus Calmette-Guérin (BCG) vaccine as part of their TB control programs, especially for infants. According to the W.H.O., this is the most often used vaccine worldwide, with 85% of infants in 172 countries immunized in 1993. This was the first vaccine for TB and developed at the Pasteur Institute in France between 1905 and 1921. However, mass vaccination with BCG did not start until after World War II.

Bacillus Calmette-Guérin (BCG): BCG is a vaccine against tuberculosis that is prepared from a strain of the attenuated (weakened) live bovine tuberculosis bacillus, *Mycobacterium bovis*, that has lost its virulence in humans by being specially cultured in an artificial medium for years.[51]

Uses

Leprosy: BCG has a small protective effect against leprosy of around 26%, although it is not used specifically for this purpose.

Buruli ulcer: It is possible that BCG may protect against or delay the onset of Buruli ulcer.

Cancer Immunotherapy: BCG is useful in the treatment of superficial forms of bladder cancer. BCG also finds use for immunotherapy of colorectal cancer and for the treatment of equine sarcoid in horses.

Diabetes, Type I: Clinical trials based on the work of Denise Faustman use BCG to induce production of TNF-α which can kill the T-cells responsible for Type 1 diabetes. Studies using mice have shown that a similar treatment results in a permanent cure for about a third of the test subjects.

Interstitial Cystitis (IC) / Painful Bladder Syndrome (PBS): BCG has been useful in treating some people with IC and/or PBS, which are chronic inflammatory bladder problems with unknown etiology. It is instilled directly into the bladder. It is not clear how it works, but the mechanism is likely immunotherapeutic, as the chronic inflammation could be the result of an autoimmune problem.

multiple sclerosis (MS): In humans, BCG has been shown to substantially reduce recurrence of symptoms in multiple sclerosis patients.[52]

Adverse Effects: BCG immunization causes pain and scarring at the site of injection. The main adverse effects are keloid—large, raised scars. If given subcutaneously, BCG causes a local skin infection that may spread to the regional lymph nodes causing a suppurative lymphadenitis. If BCG is accidentally given to an immunocompromised patient, it can cause life-threatening infection.[53]

Other Tuberculosis Vaccines: Several new vaccines to prevent TB infection are being developed. The first recombinant tuberculosis vaccine rBCG30, entered clinical trials in the United States in 2004, sponsored by the National Institute of Allergy and Infectious Diseases (NIAID). A very promising TB vaccine, MVA85A, is currently in phase II trials in South Africa by a group led by Oxford University, and is based on a genetically modified vaccinia virus. Many other strategies are also being used to develop novel vaccines, including both subunit vaccines (fusion molecules composed of two recombinant proteins delivered in an adjuvant) such as Hybrid-1, HyVac4 or M72, and recombinant adenoviruses such as Ad35.

DNA vaccine: The DNA which carried the information needed to make the bacterial heat shock protein, hsp65, was injected into mice. The mice were subsequently shown to have as much protection against tuberculosis as if they had received the live TB vaccine BCG. It is seen as a promising start to the development of a potential human DNA vaccine.[54]

Newer Approaches to Combat Tuberculosis

Directed Observed Treatment Short course (DOTS): "An effective tool for the management of Tuberculosis"

One of the major reasons of drug resistance in tuberculosis is non-compliance of therapy. This may be because of side effects of the anti-TB drugs, that are too severe and after about two months treatment the patient feels better and there by discontinue therapy.

To overcome this problem a new approach has been undertaken and that is **DOTS** therapy. **DOTS** has five key components like

- Government commitment to sustained TB control activities.
- Case detection by sputum smear microscopy among symptomatic patients self-reporting to health services.
- Standardized treatment regimen of six to eight months for at least allconfirmed sputum smear-positive cases, with directly-observed treatment for at least the initial two months.
- Regular and uninterrupted supply of all essential anti-TB drugs.
- A standardized recording and reporting system that allows assessment of treatment results for each patient and of the TB control program overall.

DOTS: is a long and intensive treatment, last for 6-8 months and require each patient to swallow the drug in front of the health worker every day for at least first two months. It is often expensive to implement as it requires effective health service, well trained staff and regular supply of quality drugs. To manage the problem of

MDR-TB effectively, WHO has formed a pilot project "**DOT-plus**", in the regions of high rate of MDR-TB also known as hot zones. The goal of DOTS-plus is to prevent further development and spread of MDR-TB.[55]

CONCLUSION

Tuberculosis is a bacterial deadly disease. It mainly affects lungs, but other organs can be infected as well. The most common symptom is cough. Tuberculosis could be latent or active. People with good immunity are able to fight the bacteria and keep it in the latent stage. If the immunity is weak, bacteria can become active and multiply. Individuals with Human Immunodeficiency Virus, chronic diseases like diabetes mellitus, kidney disease, and neoplasms are considered at high risk for developing a Tuberculosis disease. For this population it is recommended that they are treated in the latent stage. The treatment of the active diseasenormally lasts from six to nine months.

I **conclude** that **tuberculosis** infection and disease remain common in populations characterized by poor housing conditions, drug use, and HIV infection.[50]

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