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An Overview on: Tuberculosis

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ABSTRACT:

Tuberculosis (TB) remains a significant global health challenge, with a complex interplay between the pathogen, Mycobacterium tuberculosis, and the host immune response. This comprehensive review explores the dynamic interactions between the bacterium and the host immune system, highlighting key mechanisms underlying TB pathogenesis. We discuss the initial encounter of M. tuberculosis with the host, the ensuing immune response, and the formation of granulomas, which serve as the hallmark of TB infection. Furthermore, we delve into the intricate balance between protective immunity and immunopathology, shedding light on factors influencing disease progression and outcome. Insights into the molecular and cellular mechanisms governing TB pathogenesis offer potential avenues for the development of novel therapeutics and vaccines to combat this formidable disease.

KEYWORDS:- Mycobacterium tuberculosis, Diagnosis, Tretment, Global Impact etc

INTRODUCTION:-

One of the biggest risks to public health is tuberculosis (TB), which ranks second globally in terms of infectious disease-related deaths only to HIV[1].More individuals die from tuberculosis than from any other infection. For a long time, it was believed that treating patients with symptomatic tuberculosis and diagnosing them appropriately would stop enough transmission to keep the disease under control[2.]The earliest known molecular evidence of tuberculosis (TB) appears in both 9000-year-old human bones that were found from a Neolithic community in the Eastern Mediterranean and a fossil of an extinct bison (Pleistocene bison), which was radiocarbon dated at 17,870±230 years[3].Despite the fact that Dr. Richard Morton had proven in 1689 that the pulmonary form was linked to "tubercles" because of the wide range of symptoms, tuberculosis (TB) was not recognized as a distinct illness until the 1820s, when J.

L. Schönlein finally dubbed it "tuberculosis" in 1839[4]. TB, which ranks second globally in terms of infectious disease-related deaths only to HIV. Wherever it occurs, tuberculosis (TB) is a disease associated with poverty that disproportionately affects the most vulnerable, impoverished, and marginalized population groups[1].In 2011, tuberculosis (TB) accounted for

1.7 million fatalities globally, making it the leading infectious illness cause of mortality behind HIV[5].The situation has gotten so bad that the World Health Organization designated tuberculosis a global emergency in 1993 due to the co-infection of HIV and TB as well as the rise of drug-resistant TB[6].As the most common cause of mortality from an infectious disease in 2015, tuberculosis was estimated to have caused 1.8 million deaths, including deaths linked to HIV.In order to accomplish the targets of the World Health Organization's End TB Strategy, the current worldwide rate of decline in tuberculosis incidence is 1.5%; however, it will need to grow to 4%–5% by 2020 and then to 10% per year by 2025 (Figure 1)[7.]Comparable pathologies found in fossilized bighorn sheep and musk ox point to the widespread occurrence of Mycobacterium tuberculosis complex species in bovids that crossed the Bering Strait and emerged in North America in the late Pleistocene. It implies that the white plague had a holarctic distribution and that bovids were most likely the disease's reservoir and vector of spread[8].

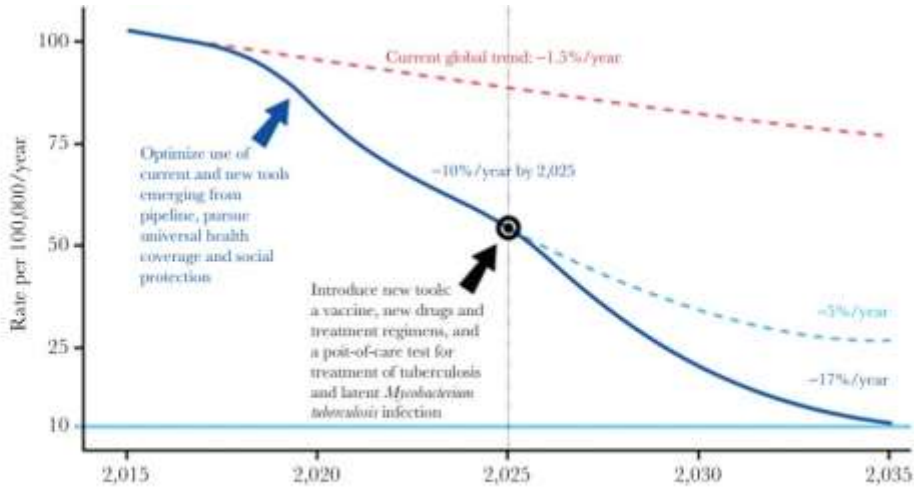


Figure 1. Projected acceleration in the decline of global tuberculosis incidence rates to target levels. From WHO END TB Strategy [3].

TAXONOMY AND DESCRIPTION OF THE GENUS:-

Mycobacterium tuberculosis belongs to

1. KINGDOM-Bacteria
2. PHYLUM-Actinomycetales
3. ORDER- Actinomycetales
4. CLASS- Actinomycetes
5. FAMILY- Mycobacteriaceae
6. GENUS- Mycobacterium
7. SPECIES-Mycobacterium tuberculosis

There are different strains and variants of M. tuberculosis, but they all belong to this taxonomic classification. Additionally, there are other mycobacteria species that can cause diseases similar to TB, such as Mycobacterium bovis and Mycobacterium leprae.

GLOBAL IMPACT:-

9.2 million new cases of tuberculosis (TB) were estimated by the World Health Organization (WHO) in 2006, of which 4.1 million were smear-positive cases; these numbers translate to incidence rates of 139/100,000 and 61/100,000, respectively[9].Globally, tuberculosis (TB) continues to pose a serious threat to public health. Globally, there were an estimated 9.0 million incident cases (the number of new cases that occur in a population in a year) and 11 million prevalent cases (the number of illnesses in a population at any given moment) in 2013[10].Since the early 2000s, the prevalence, incidence, and mortality rates of tuberculosis have been decreasing globally (Figure 2). Different forms of treatment have been investigated; results have varied. Control efforts going forward need to address the social and economic drivers of disease, be incorporated into development agendas and advocate for universal health coverage as a way to reduce obstacles to service accessibility[10]Between 1997 and 2001, the global TB incidence rate decreased gradually; however, in 2001, it increased as a result of an increase in HIV-positive patients' cases in Africa (Figure 1).From 2002 onwards, an average annual decline rate of 1.3% has been noted, with a peak of 2.2% between 2010 and 2011[1].

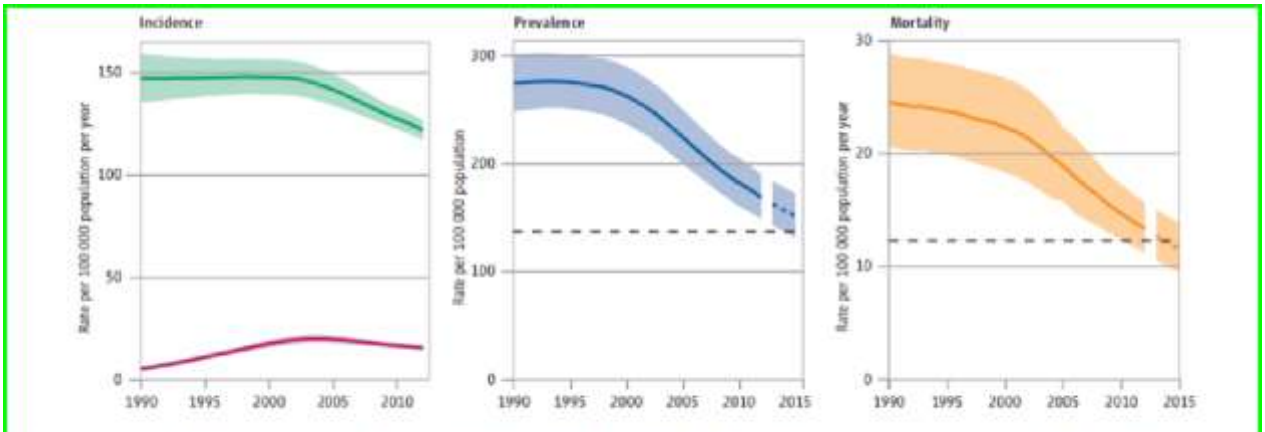


Figure 1. Global trends in estimated rates of TB incidence, prevalence and mortality 1990-2012 and forecast TB prevalence and mortality rates 2013-2015 [*World Health Organization (WHO), Global Tuberculosis Report 2013*].

Through more than 350 cases per 100,000 people, Sub-Saharan Africa is thought to have an incidence rate that is over twice as high as the SEAR.An estimated 1.3 million individuals died from tuberculosis in the same year (2008). While the African area had the highest mortality rate per capita, SEAR had the highest number of deaths[11].

EPIDEMIOLOGY:-

M. tuberculosis was first recognized in 1882 by Robert Koch. All who come into contact with tuberculosis patients get infected, but they stay healthy as long as they take care of themselves and maintain an environment that is not conducive to the spread of the disease, according to a 1909 report by William Osler [7].An estimated 10 million individuals globally were afflicted with active tuberculosis last year, with the bulk of these cases involving the lung. Global treatment success rates for patients receiving antimycobacterial medication average 85%, and the World Health Organization (WHO) estimates that between 2000 and 2018 alone, tuberculosis detection and treatment saved over 58 million lives[12].Almost one-third of the global population is infected with M. tuberculosis bacilli, which carries a 10% lifetime risk of tuberculosis illness.Rifampicin-resistant tuberculosis (RR-TB) has been reported in 558 000 new cases (range: 483 000e639 000), with over half of these cases occurring in three nations: China (13%), India (24%), and the Russian Federation (10%)[6] .Though it can also damage other sections of the body, its primary effect is on the lungs. When a person with tuberculosis coughs or sneezes and another person inhales the bacterium, the disease is transmitted through the air. TB can spread quickly through crowded living quarters, inadequate ventilation, starvation, and compromised immune systems. It is more common in places where access to sanitary facilities and healthcare is restricted.Latent disease occurs when the germs are present but do not produce symptoms; active disease is characterized by the presence of symptoms such as fever, coughing, exhaustion, and weight loss. Antibiotics are typically given in combination over the course of several months as treatment.

PATHOGENESIS:-

Mycobacterium tuberculosis, a small aerobic, non motile bacillus is the main causative organism of TB.M. tuberculosis and its very closely related seven mycobacterial species (M. bovis, M. africanum, M. microti, M. caprae, M. pinnipedii, M. canetti and and M. mungi) together form the classical M. tuberculosis complex.[5].Throughout their replication, the fleeing organisms injure the alveolar macrophage, which attracts additional neutrophils and other inflammatory cells. Furthermore, antigen-presenting dendritic cells have gone to lymph nodes over a period of 6–8 weeks in order to activate and draw T lymphocytes, which then migrate to the infection site to proliferate and form early granulomas.[12]Afterwards, the mycobacteria attach themselves to the alveolar macrophages' cell surface by type A scavenger, complement, or mannose receptors. Mycobacteria decrease the acidity of the phagosome after phagocytosis, and a component of the cell wall called lipoarabinomannan affects the Caþ/calmodulin pathway, which prevents the fusion of the phagosome with the lysosome. After the development of the phagosome is successfully stopped, the bacilli multiply and the macrophage finally bursts to release its bacilli, which are then picked up by macrophages and continue the infection cycle, further spreading the infection.[6]The overwhelming majority of tuberculosis infections are brought on by breathing in infectious particles that have been aerosolized through talking, sneezing, coughing, or handling diseased tissues[13].Individuals are more vulnerable to tuberculosis infections due to a multitude of risk factors. These include alcoholism, silicosis, HIV, diabetes mellitus, malnourishment, and cigarette smoke[14].

PREVENTION:-The possibility of developing active tuberculosis following infection can be lowered if the person has received BCG vaccination prior to exposure.The vaccination is normally given intradermally with a dosage of 2 × 106 bacilli for newborns and 4-5 × 106 for older children and adults[15].The sole serious contraindication of BCG vaccination is severe immunodeficiency, either inherited or acquired; the spread of BCG, which can be lethal, may occur in infants with these illnesses[16].A higher number of people die from tuberculosis than from any other infection. For a long time, it was believed that treating patients with symptomatic tuberculosis and diagnosing them with the illness would stop enough transmission to keep it under control. Nevertheless, a number of studies have demonstrated that while tuberculosis programs have reduced mortality at a reasonable cost, they have had no discernible impact on the incidence of the illness worldwide[2].There are multiple steps involved in preventing tuberculosis:1. accination: Vaccinate yourself against severe types of tuberculosis, particularly in children, by getting the BCG vaccination.2. Healthy lifestyle: To strengthen your immune system, eat a balanced diet, exercise frequently, and get enough sleep.

DIAGNOSIS:-Despite its limited sensitivity (especially in immunocompromised persons) and low specificity (especially in the presence of prior BCG vaccination and exposure to environmental mycobacteria), the tuberculin skin test remains the conventional method of diagnosing tuberculosis infection.It is not possible to evaluate the sensitivity and specificity of these tests because there is no gold standard for diagnosing tuberculosis infection. It is uncertain if their sensitivity is sufficient to rule out tuberculosis infection in the event of a negative test result[17] .

Diagnosis of tuberculosis in pregnancy:-

A history of contact with people who have a persistent cough or a recent visit to a region where tuberculosis is endemic should be gathered in order to diagnose this illness. It's also crucial to have a history of symptoms, which should be the same for non-pregnant women. However, as these symptoms might not be specific during pregnancy, caution must be taken[13].

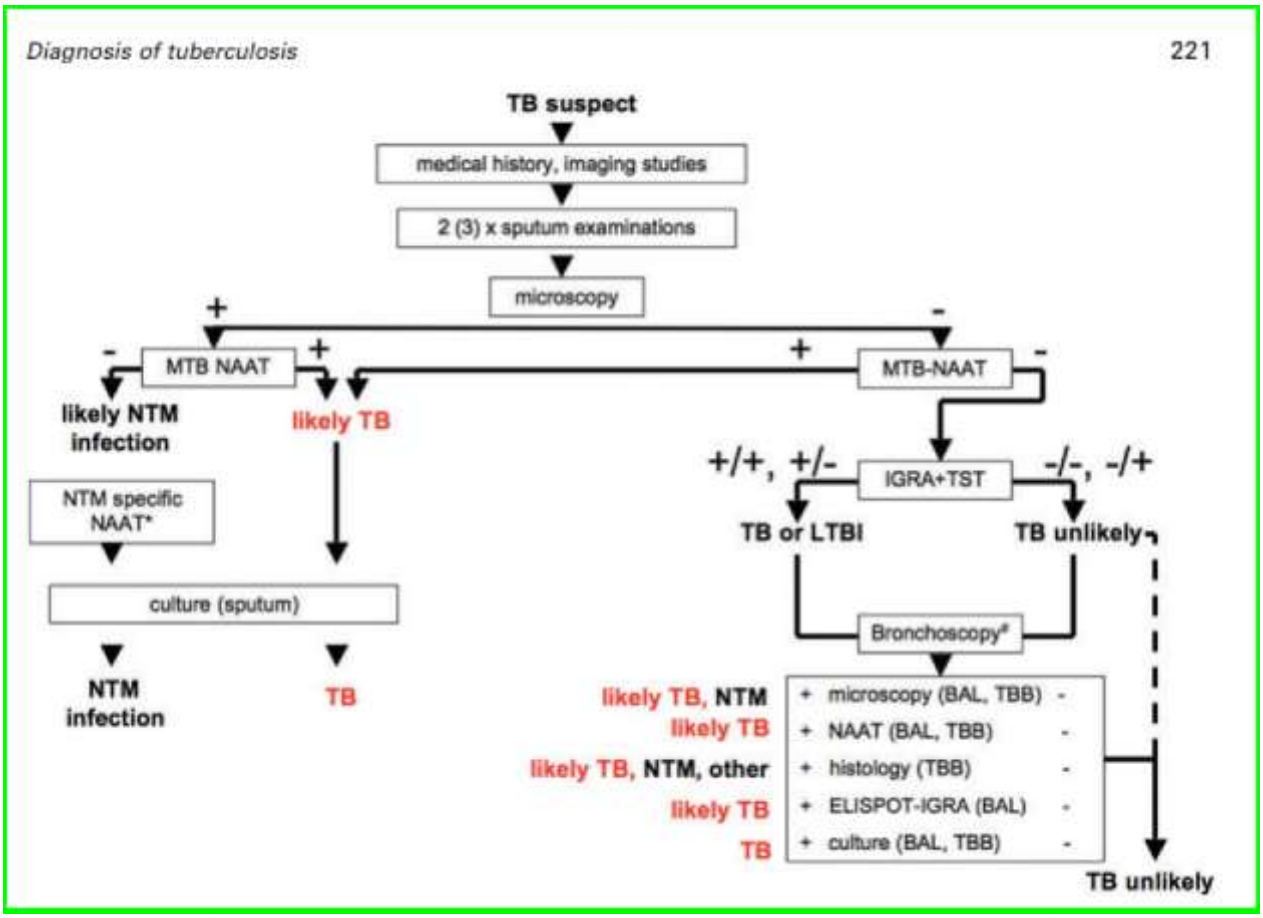


Figure 1 Flow diagram for the diagnosis of tuberculosis in clinical practice[18]

TREATMENT:-

1. TB diagnosis: The patient exhibits symptoms that correspond to tuberculosis.

- Sputum tests and/or chest X-rays verify TB infection.
- Drug susceptibility testing can be carried out to choose the right prescription.

2. therapy Initiation: - Start TB therapy as soon as possible after diagnosis to stop problems and spread.

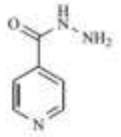
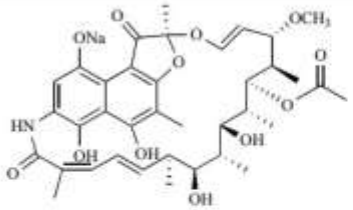
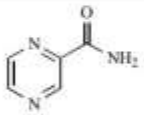
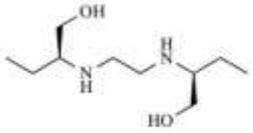
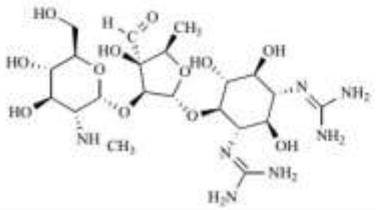
The First-Line Drugs for TB:**Table1**[5]

- Begin by mixing four antibiotics together:

- Rifampin (RIF) - Pyrazinamide (PZA) - Ethambutol (EMB) - Isoniazid (INH)

- Given under direct observation (DOTS) for a few months, either daily or occasionally.

4. Monitoring: - Consistently keeping an eye on side effects, sputum testing, and symptoms. Treatment should be modified as needed in accordance with patient response and drug sensitivity findings.

Drug	Chemical Class	Structure	Target
Isoniazid (INH)	Isonicotinic acid		Enoyl-ACP reductase, mycolic acid elongation
Rifampicin (RIF)	Rifamycin		DNA-primed RNA polymerase
Pyrazinamide (PZA)	Pyrazine		Fatty acid biosynthesis/membrane depolari- zation/ribosomal protein S1 (RpsA), protein translation and the ribosome-sparing process of translation
Ethambutol (EMB)	Ethylenediamine		Cell wall arabinan deposition
Streptomycin	Aminoglycosides		Protein synthesis inhibition

Around 1948 and 1986, a number of clinical trials carried out by the U.S. Public Health Services and the U.K. Medical Research Council shown that drug-susceptible tuberculosis may be cured with less than a 5 to 8% likelihood of relapse after completing a 6-month course of combination therapy.The last ten years have seen a significant change in tuberculosis diagnosis. Molecular DNA-based diagnostics are now widely accessible and allow for both quick diagnosis and an initial assessment of drug susceptibility, even if culture is still the gold standard for both diagnosis and drug susceptibility testing[1].Although the diagnosis and treatment of tuberculosis are the same in industrialized and underdeveloped nations in theory, there are notable practical disparities due to financial constraints.When tuberculosis strains are resistant to at least one antibiotic, it results in multidrug resistant tuberculosis.rifampicin—is important clinically because it substantially increases the risks of treatment failure, further acquired resistance, and death[16].

Treatment of tuberculosis in pregnancy:-A multidisciplinary team including the obstetrician, public health officials, neonatologists, counseling unit, and specialists in communicable diseases manages tuberculosis in pregnancy.The World Health Organization, the International Union Against Tuberculosis and Lung Disease, and the British Thoracic Society all believe that using these first-line antituberculous medications during pregnancy is safe for both the mother and the unborn child[13].

Antibiotics are usually administered in combination over a period of several months to treat tuberculosis. The most typical regimen consists of drugs like pyrazinamide, rifampin, ethambutol, and isoniazid. While the length of the treatment can vary, it usually lasts for at least six months to guarantee the germs are completely eradicated. Patients must follow their treatment plan exactly in order to avoid drug resistance and guarantee a full recovery.

Indications for Initiating Therapy

To initiate combination anti-TB chemotherapy (e.g., 4-drug therapy), consider epidemiological information, clinical, pathological, and radiographic findings, as well as microscopic examination of acid-fast bacilli (AFB)-stained sputum smears, other diagnostic specimens, and mycobacteria cultures.Empirical therapy should be initiated early for patients with potentially life-threatening illnesses including tuberculous meningitis, pericarditis, or miliary disease[19]

Tuberculin skin test The recommended tuberculin skin test in Spain uses PPD-RT23 with Tween

80 at a dosage of 2 TU per 0.1 mL[20]False-negative tuberculin test results occur in 20% of HIV-infected patients with CD4 cell counts above 500 × 109/L and 80% to 100% of those with CD4 cell levels below 200 × 109/L[21,22]

A positive tuberculin skin test (TST) indicates primary infection with M tuberculosis. Tuberculin reactivity in children typically appears within 3-6 weeks of infection, but can sometimes take up to 3 months.There are two main approaches for TST: the Mantoux test and the multi-puncture technique.The Mantoux test, which employs 5-10 tuberculin units of pure protein derivative, is widely used in many countries to identify M tuberculosis infection[23]]

latent tuberculosis treatment:-Latent tuberculosis (TB) is described as M. tuberculosis infection with a positive TST or IGRA test result.Throughout many years, high-income nations have prioritized treating latent tuberculosis infection (LTBI) as a critical component of TB control programs. This was first established as a way to limit disease progression in guinea pigs and people. Isoniazid (INH) has been shown to be useful not only for illness treatment but also prevention.Latent tuberculosis infection testing, using either the tuberculin skin test (TST) or an interferon-gamma release assay (IGRA), should be considered for persons who are at risk for Mycobacterium tuberculosis infection or progression to TB disease[24]

CONCLUSION

Tuberculosis (TB) remains a significant global health challenge, despite advances in diagnosis and treatment. In conclusion, several key points can be made about tuberculosis:

Global Burden: TB continues to be one of the leading causes of death worldwide, particularly in low- and middle-income countries. The disease disproportionately affects vulnerable populations such as those living with HIV/AIDS, malnourished individuals, and those with limited access to healthcare.

Challenges in Diagnosis: Diagnosing TB remains a challenge, especially in resource-limited settings where access to advanced diagnostic tools may be limited. Improving early detection methods and point-of-care testing is crucial for timely initiation of treatment and containment of the disease.

Treatment and Drug Resistance: While TB is curable with appropriate treatment, the emergence of drug-resistant strains, particularly multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB), poses a significant threat to global TB control efforts. Addressing drug resistance requires a multifaceted approach, including improved access to effective drugs, better treatment adherence, and infection control measures.

Vaccination: The Bacillus Calmette-Guérin (BCG) vaccine is currently the only vaccine available for TB prevention, but its efficacy varies and it does not provide lifelong immunity. Efforts to develop more effective vaccines against TB are ongoing and represent a critical area of research.

Social Determinants: Addressing TB requires a holistic approach that takes into account social determinants of health such as poverty, overcrowded living conditions, and lack of access to healthcare. Strengthening health systems and addressing underlying socioeconomic factors are essential for TB control and elimination.

Research and Innovation: Continued investment in research and innovation is crucial for advancing our understanding of TB epidemiology, improving diagnostic tools, developing new treatments, and ultimately working towards the goal of TB elimination.

In conclusion, while progress has been made in the fight against TB, concerted efforts are needed at both the global and local levels to address the remaining challenges and achieve the goal of ending the TB epidemic by 2030, as outlined in the Sustainable Development Goals.

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