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CURRENT SCENARIO ON TUBERCULOSIS: A REVIEW

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ABSTRACT
Tuberculosis is an ancient disease of mankind suffering badly from very ancient years. Even though having sophisticated equipment and method of diagnosis and treatment, still remains like a life threatening disease in the world in firstly and second only to HIV. According to world health organisation, tuberculosis is a pandemic disease and in this mainly prospecting the reasons for disease causing the present situation. To eradicate the disease completely in future years, various health programmes were raised to get awareness of the disease and to prevent and to treat the people gets effected. Different types of diagnosing techniques were illustrated for TB, Management aspects, pathogenesis of the disease, and current situation of TB in the world, several programmes and challenges were discussed. By having complete and clean knowledge of the contagious diseases like tuberculosis and also encouragement is the most importantly needed for developing new and highly efficacious drugs with less toxicity against the disease and resistant drug development is necessary.

KEYWORDS: Tuberculosis, Pathogenesis, Diagnosis, TB Interferon gamma release assays, Management, Global and Indian scenario, Nikshay.

INTRODUCTION
Tuberculosis is a contagious disease and it is caused by mycobacterium tuberculosis. It mainly affects the lungs but may affect other parts of the body. Condition in which a person affected by tuberculosis but the absence of symptoms is latent tuberculosis. Up to 1820s TB was not considered as a distinct disease.[1] In 1882, mycobacterium tuberculosis, was discovered by Robert Koch, and for this discovery he was awarded the Nobel Prize in physiology or medicine in 1905.[2] TB is caused by a group of bacterial species known as mycobacterium tuberculosis complex.[3]

Mycobacterium complex
M. Tuberculosis, M. Bovis, M. Bovis Bacillus calmette Guerin, M. Africanum, M. Microti, M. Canetti, M. Pinnipedii. M. Tuberculosis causes TB in humans.[4] M. Bovis causes bovine TB in cattle, humans, sheep, goats, pigs, and other domestic & wild animals.[5] Vaccinated children live with disseminated BCG infection by M.Bovis.[6] Animals like apes are infected by M. Africanum.[7] M. Microti cause TB in voles and other small rodents. [8] Humans get affected by TB by the bacteria called M. Canetti. [9] Fish eating sea animals get affected by TB by the bacteria called M.Pinnipedii.[10]

Morphology of bacteria
M. tuberculosis is a straight or curved rod shaped bacteria of about 3×0.3µm in size. These are non-motile and non-capsulated. This is due to the presence of fatty acid, so called acid fast bacilli, and their cell wall is called mycolic acid.[11] Growth Characteristics are bacteria are obligate aerobes. The generation time in vitro is about 14-15 hours, colonies appear in 2weeks, and Optimum temperature is about 37oC. PH is 6.4-7.0.[12]

TYPES OF TB AND ITS SYMPTOMS
General symptoms of TB are Fatigue, fever, night sweats, and loss of weight, chest pain, and hoarseness of the voice. Cough which is non-productive, but it is purulent sputum, the sputum is triggered by inflammation and tissue necrosis. Sometimes the patient may cough up blood in sputum. Which indicates cavitation of the lungs. HIV positive patients are more susceptible to other pulmonary TB. It effects on lymph nodes, bones, joints, meninges, spine etc. And the symptoms are dependent upon the type of TB and the part which it is affected.[13] Tuberculosis may be termed as two types. They are active TB and latent TB. Where active TB is lung disease and latent TB is in other organs which are called extra pulmonary.

Active TB Disease
Active TB is in which the bacteria rapidly divide and invade different parts of the body. And the symptoms include severe cough, chills night sweats, phlegm, chest pain, etc.

Miliary TB
The presence of bacteria in the blood stream causes Miliary TB. And it spreads rapidly.

Latent TB Infection
It is not by causative. It may activate the disease and it finally increased by HIV and the immune system gets weakened by medications.

Lymph node TB
The inflammation and enlargement of the lymph node are lymphadenitis, occurs mostly in children. Symptoms are enlarging lymph nodes in the neck area and are painless.

Skeletal TB
Skeletal TB is termed as the place which it is affected by TB in bone or joint. Due to this bone may also get weakened and may fracture.

Spondylitis or POH disease is termed as TB in spinal, due to this there will be severe back pain.

TB Meningitis
TB meningitis is infection in tissues which cover brain and spinal cord meninges.

Common symptoms are fever, pains, aches, vomiting, neck stiffness, and seizures. **Gastrointestinal TB, Abdominal TB or TB of the Kidneys.**

Severe pain in the abdomen is the indication of abdominal TB. TB in the kidneys can cause blood in urine. Gastrointestinal TB - Diarrhoea, bleeding from anus rectum.[14]

Transmission
The disease is transmitted through infected air, which carries the contaminated droplets expelled by the patient while coughing sneezing and talking. [15] They expel the droplets of about 0.5 to 5.0mm in diameter. A single droplet consists of 40,000 droplets. [16] TB is transmitted through the fomites used by patient. It also transmitted through ingestion of bacteria. It may be through flies. In some cases, congenital TB is transmitted from mother to foetus.[17]

Risk Factors
At first people do not affect by active TB. It is developed into active TB from latent TB due to diabetes mellitus, low body weight, Hodgkin's disease, head or neck cancer, leukaemia, HIV, in which causes AIDS and weakens the immune system, silicosis, medical treatments followed by corticosteroids which are used for autoimmune, vasculitis disease, which decreases immune system.[18]

Incubation Period of Bacterium
The time period between initial infection and disease onset is called incubation period. The incubation period of TB is 10 to 20 years.[19]

PATHOGENESIS
TB is air borne disease which spreads from one to other by droplets. When these droplets are inhaled by a person, the bacteria reach to alveoli by alveolar macrophages in the lungs. Based on type of response and infection time TB is progressed to types.[20]

Primary Tuberculosis
It is a primary infection by the tubercle bacilli in host, commonly takes place in children. Bacilli is engulfed by alveolar macrophages. They multiply and it further leads to sub pleural focus of tuberculous pneumonia in the lower lobe or the upper lobe called Ghon focus. Hilar lymph nodes are also engaged. Ghon focus with the enlargement of hilar lymph nodes is called primary complex. It is about 3-8 weeks rom infections.

Post Primary Type
TB is caused by reactivation of latent infection. It affects the upper lobes of the lungs. Where lesions undergo necrosis and tissue destruction, leading to cavitation.

Extra Pulmonary TB
It is the haematogenic spread of M.tuberculosis. Which includes anatomical site in the body.

DIAGNOSIS
It should be noticed some aspects while the diagnosis of tuberculosis. They are Symptoms, History of exposure, Tuberculin test, Chest X-ray, Sputum test. [21]

History of Exposure
Should possess accurate medical history of the patient while treating and diagnosing. Early intervention is needed.

Tuberculin Skin Test
Tuberculin test is done to the patient suspected of latent TB. It is otherwise known as purified protein derivative, (PPD). PPD is by cultivating mycobacteria. Test is conducted by Monteux method. In Monteux, 0.1ml of 5 tuberculin units of purified protein is injected intra-cutaneous into the surface of the forearm. If induration is 6mm in diameter then it is confirmed as a positive test. If it exceeds 6mm then it is confirmed that patient having HIV positive, immuno-compromised or an organ transplant. If it is 10mm or more than that then there is high risk of TB and it is due to mostly patients suffering from diabetes mellitus, chronic renal failure, malignant conditions like leukaemia, lymphoma.

Chest X ray
Infected person with latent TB, chest x ray shows normal. With this preventive medication is prescribed. If there is inflammation in the lungs, there will be an abnormal shadow is visible on chest-x-ray. To this people diagnostic tests and treatment are often necessary.[22]

Sputum smear microscopy
At first sample is collected from the infected person by coughing. A thin layer of sample is placed on the slide and a series of stains are applied on the sample, further it is examined under the microscope. [23]

DIAGNOSING TB OUTSIDE THE LUNGS BIOPSY
It is a technique in which removal of tissue for histological examination from a living person. Sample is taken from the affected area and sent to histopathology lab for examining whether the presence of TB causing bacteria.

Urine culture
Bacteria in the kidney region are identified by this test.

Lumbar puncture
From brain a little amount of fluid around the spine called cerebro spinal fluid is taken and performed test.

CT scan
This test used to diagnose the disease might spread in the body and also in lungs

MRI
It is used to perform the test for TB in the brain and spine.

TB Interferon gamma release assays (IGRAs)
This is a very accurate test which is used to measure the immune response of a person to the bacteria. The cytokines which are generated by immune system, are detected by this test and are called as interferon gamma cytokine. By collecting blood sample from an infected person and it is mixed with varying substances to identify the cytokines.[24]

Fluorescent microscopy
This test is achieved by illuminating the sample with a quartz halogen or high pressure mercury vapour lamp. And the presence of bacteria is examined.

Serological tests for TB
These tests are conducted by detecting antibodies in the blood samples from the infected person. But there is no accurate result, so WHO has warned these tests not to be performed. [25]

PREVENTION
It is preventable, curable disease when it is detected and addressed early. Its prevalence is poor in developed nations.

Tuberculosis vaccine
Tb can be controlled by Bacillus Calmette-Guerin (BCG) vaccination. This vaccine is delivered to infants in disease prevalent countries. In countries like the UK where it is less frequent it is given to those who are at risk. Monteux skin test is carried out to check for latent tuberculosis before the vaccine is given. Person affected with latent tuberculosis vaccination is not recommended.

Prevention of transmission of infection
Patients are isolated and they should be invited to follow some precautionary measures. They are being away from crowded areas, mouth and nose should be closed with a napkin while sneezing and coughing, sharing beds and room should avoid with uninfected persons, Latent infections should be treated, proper precautions and maintain hygienic conditions.

MANAGEMENT
Treatment of Tuberculosis is based on the types and also drug combinations and dosages are varied for the type of TB. Treatment of TB mainly consists of an initial phase that is for 2-3 months and continuous phase for 4-6 months. Drugs which are using the treatment are classified into 2 types. They are first line drugs and second line drugs taken into account their efficacy and toxicity. [26] The first line drugs are isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin, highly efficient and less toxic. Whereas, second line drugs are highly toxic and less efficient. They are para-amino salicylic acid, ethionamide, thiacetazone, cycloserine, kanamycin, amikacin, ofloxacin, clarithromycin, capreomycin, ciprofloxacin. [27]

New Onset
In world of 1/3 of the population are infected by mycobacterium tuberculosis. About 8.8 million patients were diagnosed with active TB and 1.6 million patients die because of TB. TB becomes more epidemic by the human immuno-deficiency virus. About 28% of patients are HIV positive. The current first line drugs for TB should be taken at least 6 months for high cure rates. [28]

Multi -Drug Resistant TB
MDR-TB is termed as resistance to both type drugs and also not for other drugs. In India MDR-TB is for about 2.8% of all the new TB cases and 12-17% retreatment cases in varied states. Depending on WHO, India has the highest number of MDR-TB cases in South East Asia. The regimen should have up to 4 drugs which are most effective. Have to avoid combinational cross resistance drugs DOTS-PLUS programme started in the year 2000 to identify and treat MDR-TB. And guidelines got updated in 2010. Which are under the WHO guidelines. Hence there is a potential work to treat the disease accurately with high efficiency drugs having less toxicity and high efficacy. [29]

Extensively drug resistant TB: (XDR-TB)
It is a disease which is caused by the bacteria that are resistant to the Anti-TB drugs. XDR-TB is identified by misusing multidrug resistant regimen. The XDR-TB is difficult to treat, which has a rapid course and high mortality. These drugs are more expensive and efficacy and drugs like TMC-207 (bedaquiline), PA-824 (Pretomanid) is an experimental anti-tuberculosis drug. Whereas MDR-TB regimen has stopped due resistance amplification XDR-TB is detected.

Treatment in pregnant women
People with pregnant having tuberculosis should not be delayed to take treatment. They are treated with INH and should receive pyridoxine for 10-25 mg/day.

Treatment of breastfeeding women
All anti-TB drugs are compatible with the breast feeding women, and complete course is taken, but the child should be under observation. Child should have BCG vaccination and if there is, active disease than at the 6 month isoniazid is used as preventive treatment.

Chemoprophylaxis
Chemoprophylaxis is included with the administration of antitubercular drugs to prevent the development of active infection. The mostly used appreciated drug with superior efficacy, bioavailability and less toxicity is isoniazid. And it is initiated in patients having latent tuberculosis tested as a positive result of the tuberculin test.

Treatment includes regimens
1. Administering INH daily in 5mg/kg for 9 months. 2. Cost-effective regimen INH for 6months. Patients with HIV infection, just have to administer the drug for a period of 9 months.[29]
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SCENARIO OF TB IN THE WORLD

Global Scenario
Tuberculosis is most pandemic disease according to WHO. Among 15 countries, 13 are in Africa with high TB cases and along with these six Asian countries like Bangladesh, China, India, Indonesia, Pakistan and Philippines are more prevalent with tuberculosis. On March 2010 WHO fact sheet stated that 1/3 of the population in the world are affected by tuberculosis, based on this survey people in the world are infected with TB bacilli in every second and also HIV infection which weakens the immune system badly, which leads to death with having both TB and HIV. In Africa HIV is the lead factor which is the reason for increasing the TB since 1990. In 2008 fact sheets stated that there were about 9.37 million TB cases in Africa region and also in the South East Asian region. In 2008 about 1.3 million were dead because of TB and increasing death rate is more in the South East Asian region and the highest mortality rate is in the African region. In 1993 global community rises against tuberculosis and TB is declared as a global emergency by WHO and the main aim is to decrease the mortality and death rate of TB. For basics of TB cases regarding cure and treatment a strategy is recognized internationally named Directly Observed Treatment-Short Course (DOTS). This program is not a clinical perspective to the patients, but it is a management strategy for the public which includes the case-detection through quality assured bacteriology, political commitment, adequate drug supply, recording systems, short course chemotherapy, sound reporting. In 1995 to 2008 36 million were treated and 6 million deaths were prevented in DOTS programme. World is widely about 85% of the treatment success rate is achieved by the DOTS program in 2007. Half of the world is badly suffering from poverty; this was the main reason for easy adaptability of the communicable and spreadable diseases, due to lack of having clean infrastructure and medical help. Whereas 6 of 14 million deaths are caused due communicable disease, which results in 42% of the disability. In South-East Asian region about 3.6 million people are evaluated having HIV/AIDS. This is the region having complex heterogeneous HIV epidemic conditions at diverse stages. When coming to the Indian about 2/3 of the population are evaluated to HIV and in which 6 states in south and northeast and also in Indonesia prevalence of HIV is very low, and whereas in Bangladesh and Nepal, increasing HIV prevalence. Owing to intravenous drug users HIV is more epidemic in these countries.[30]

Indian Scenario
India is populous country in the world but it is the highest burden of TB. According to World Health Organization TB statistics for India for 2016 is estimated at 2.79 million cases of TB and along with HIV and TB about 87000 million cases. MDR/RR-TB is about 147,000 million cases. It is estimated about 40% Indian population is infected with TB bacteria.[31,32]

PROGRAMMES OF TB IN INDIA

Revised National Tuberculosis Control Program
This program was initiated to notice cases earlier and treat them in the year 1962.

District Tuberculosis Program
To coordinate and supervise the program this state level program is started.

Nikshay
In 2012 web based reporting was started to manage drug resistant TB services.

TB control objectives
- By detecting the case and treating it to pursue worthful DOTS. Making dots available to poor.
- With TB-HIV joint activities, DOTS and other approaches we can face TB-HIV, MDR-TB.

- Conspire with other health services to build up the health system.
- Involve all health care providers, public non-governmental and private, by scaling up approaches based on a public private mix, to ensure adherence to the worldwide standards of TB care.
- Engaging people in TB awareness work will involve scaling up of community TB care, creating demand through context specific advocacy communication and social mobilization.
- Encouraging research of new drugs and vaccines is necessary.[33]

PROGRESS AND THE CHALLENGES

Second largest DOTS program is considered in India, due which case-detection rate is 68% (2007) and treatment success rate is 86% in 2006. Success rate had increased from 25% to 86% and death rates decreased to 4% from 29%. To gain the TB control objective, threat of multidrug resistance, India is employed hard. Drug resistant TB had become further major problem, which is observed due to resistant to second line drugs. In India, prevalence of XDRTB is low, but the potential threat cannot be ignored. Drugs for TB are available outside the RNTCP without any restrictions and lack of standardized regimens. Treatments led to drug resistant TB. The best TB- treatment programme is Resistance National Tuberculosis Control Programme. Absence of primary prevention and effective vaccine is the main drawbacks. The program does not see any steps to identify and actively treat latent infections mainly people who are circulating the bacteria amongst susceptible population.[34]

RESEARCH

Owing to limitations of BCG Vaccine, researches are continued for new TB vaccines. Numerous potential compounds are in phase I and II clinical trials. 2 main activities are used to improve the efficacy of available vaccines. Adding a sub-unit of BCG is the first strategy, 2nd strategy is to develop new and better live vaccines. Latent and active disease is expected to be cured by vaccines. Vaccine development needs different economic models for further development. Bedaquiline & delamind are studied along with other medications for multidrugresistant tuberculosis.[35]

CONCLUSION

Evident which was given in above information, we have come to the conclusion that to be aware of the TB and should possess the complete and clear knowledge of this dreadful disease. There is a proverb said by famous poet Robert Frost, "...Miles to go before I sleep", regarding this we have have gone for eradicating TB in the world. By 2050 TB should be eliminated with the strategy "STOP TB", of WHO. [36] We have to step forward to strengthen our surveillance programs to evaluate the obligation of TB including childhood, HIV/MDR-TB, XDR-TB and there is a terrible need to modulate the use of first and second line drugs. These drugs should therefore not be sold as over the counter drugs. In all developing countries including India, local government should encourage the manufacturing of the antithetical drugs and also the government should come forward to invest the new drugs which possess high efficacy and less toxicity with minimum MIC value which works efficiently.

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