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Microbiology

FACTORS CAN IMPROVE THE TREATMENT OUTCOME IN TREATMENT FAILURE PULMONARY TUBERCULOSIS PATIENTS

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Introduction:

Tuberculosis (TB) is a major global health problem and a leading cause of death in adults, especially among the economically productive age group. India accounts for the highest tuberculosis (TB) burden country approximating 20% of global TB burden. To tackle this problem, Revised National Tuberculosis Control Programme (RNTCP) based on the DOTS (Directly Observed Treatment Short course) strategy has been made available in the entire country since March 2006. According to the World Health Organization (WHO) Global Tuberculosis Report 2015, TB remains one of the world's deadliest communicable diseases. India accounts for 23% of the global burden of TB[1]. Emergence of anti tubercular drug resistance has further aggravated the public health problem. India is having the highest number of TB & MDR-TB cases among the notified TB patients in world[2]. In 2016, there were an estimated 10.4 million new TB cases worldwide. Seven countries accounted for 64% of the total burden, with India having the maximum number of TB patients, followed by Indonesia, China, Philippines, Pakistan, Nigeria and South Africa[2]. To control the increasing rate of tuberculosis; need to be focus on the factors those can improve the treatment outcome. There are some factors that can improve the tuberculosis treatment outcome; early diagnosis of tuberculosis and drug resistance, identification of non tuberculous mycobacterium (NTM), monitoring of hepatotoxicity and immune response of patients during the anti tubercular treatment.

Early diagnosis TB and drug resistance:

Timely identification of TB cases followed by treatment is important for control of TB. The emergence of drug resistance tuberculosis poses an even difficult challenge to the national TB control programme, as treating these cases is very complex, expensive and often less successful moreover patients may remain infectious for months or years despite receiving the best available therapy. Treatment outcome to various anti tubercular regimes varies from place to place and depends on many factors[3,4]. Physical and social environment of life also affects the human health, for example there are many health outcomes that are worse in slums than in neighboring urban areas or even rural areas[5,6].

Available health services throughout India are often comprised of an inconsistent patch work of public, private, and charity-based providers. Inadequate or in appropriate care at these places increases the risk of drug-resistant infections, such as multidrug-resistant TB[7]. Moreover initial resistance to various drugs may also affect treatment outcome. Initiation of chemotherapy based on drug sensitivity testing (DST) may help in achieving better outcome[8].

Non-tuberculous mycobacterial infection:

Increasing prevalence, incidence, and mortality of pulmonary infection caused by NTM species have been reported in various countries[9,10]. More than 150 species of NTM had been reported to date[11]**.** Infection by NTM species is more frequently detected in pulmonary than in extra-pulmonary infections[9,12]**.**

Diagnosis of pulmonary infection disease by NTM species was stressed upon by Griffith et al (2007)[13] and the Japanese Society for TB in 2008, (Nontuberculous Mycobacteriosis Control Committee of the Japanese Society for Tuberculosis) and it was based on clinical manifestations, such as symptoms and signs, radiological pictures of the lungs, and positive detection of NTM species. The evidence based studies should be used as a basis for determining management of patients or empiric therapy procedures for pulmonary NTM infection suspect patients according to the standard guidelines of American Thoracic Society (ATS) 2007[9,11,14]. NTM therapy depended, whether the NTM species were detected as causative pathogens, colonizers, or specimen contaminants. Before starting treatment for TB, in AFB sputum positive cases, mycobacterium tuberculosis complex should be confirmed and at the same time NTM infection should be ruled out either by conventional or new rapid available techniques. Thus physicians should consider NTM Pulmonary infection in the differential diagnosis of TB infection, because treatment guidelines for both of these diseases are different[15].

Hepatotoxicity during the ATT:

Tuberculosis and liver are related in many ways. Hepatotoxicity can occur during the treatment with various anti-tubercular drugs may precipitate hepatic injury or patients with chronic liver disease may pose special management problems. Treatment of tuberculosis in patients who already have a chronic liver disease poses various clinical challenges. There is an increased risk of drug induced hepatitis in these patients and its implications are potentially more serious in these patients as their hepatic reserve is already depleted. However, if needed hepatotoxic anti-tubercular drugs can be safely used in these patients if the number of drugs used is adjusted appropriately. Thus, the main principle is to closely monitor the patient for signs of worsening liver disease and to reduce the number of hepatotoxic drugs in the anti-tubercular regimen depending on the severity of underlying liver disease.

At present, most commonly used anti-TB drugs are more or less hepatotoxic, especially when several anti-TB drugs are used in combination. Most cases of the anti-tubercular drug related liver injury occurs within two-three months of starting the treatment[16,17]. Monitoring the degree of drug induced hepatic injury is also difficult in this group of patients as fluctuations in the biochemical indicators of liver function related to the preexisting liver disease act as a confounding factor. Therefore it becomes difficult to decide whether the derangements in liver function tests are due to the antitubercular treatment (ATT) drugs or are a manifestation of the already existing liver disease. However, need to study the patients with preexistent liver disease and toxicity of antitubercular drug during the tubercular treatment regimens and need careful monitoring for hepatotoxicity.

Due to the long duration of therapy and concurrent use of multiple drugs, adverse effects are most important clinical consideration in patients undergoing anti-TB treatment[18]. Hepatotoxicity is the most serious one, which not only leads to high morbidity and mortality, but also diminishes anti-TB treatment effectiveness owing to non-adherence[19].

Therefore patients should be frequently monitored clinically for development of new symptoms such as fatigue, nausea, abdominal pain, fever and jaundice. Liver function tests should be carried out before initiating ATT, for baseline levels as it has been seen that patients with abnormal baseline transaminases levels are at increased risk of developing hepatic injury eventually[17].

Immune response of TB patient:

Development of TB disease results from interactions among the

environment, the host, and the pathogen, and known risk factors include HIV co-infection, immunodeficiency, diabetes mellitus, overcrowding, malnutrition, and general poverty; therefore, an effective CD4 cell response determines whether the infection resolves or develops into clinically evident disease.

The protective immune response against TB is dependent upon T helper cells, since cellular immunity and production of IFN-γ by CD4+ and CD8+ T cells are critical for disease control in animals and humans[20].

Studies suggested that CD4 T cells simultaneously secrete IFN-c, TNF-a, and IL-2, which have been termed as multifunctional Th1 cells, are associated with control of chronic bacterial and viral infections[21]. Several studies have noted associations of vaccine-generated poly functional CD4 T cells with better protection against MTB challenge[22]. IFN-γ production by CD4 T cells is indeed essential for control of MTB infection, and is the only clear major anti-mycobacterial effector pathway of MTB-specific CD4 T cells .There is direct evidence that CD4 T cells can mediate control of MTB infection in an IFN-γ–independent manner[23]. A study by Srivastava et al, demonstrated that CD4 T cells must make direct contact with infected antigen presenting cells (APCs) to induce control of MTB infection. CD4 T cells must directly interact with the infected APC in order to induce control of the infection. Another study suggest the multifunctional MTB-specific CD4 T cells play an important role in protective immunity against tuberculosis[24].

Conclusion:

Monitoring of those factors in treatment non-responder patients help in the early diagnosis of the drug resistance tuberculosis, mixed infection or infection with other mycobacterium. As in the case of pulmonary TB, laboratory examination of mycobacteria is also recommended for suspect NTM pulmonary infection diseases before antibiotic therapy. Observed differences in the sensitivity of antibiotic drugs toward various NTM species helps in the treatment of NTM patients. Pulmonary TB suspect or lung comorbid diseases should be handled mainly based on the findings of virulent NTM species such as MAC, *M. abscessus*, and *M. kansasii*. For adequate patient treatment, communication between lung clinicians and clinical microbiology specialists to determine whether detected NTM species is causative pathogens, colonizers, or specimen contaminants,. Treatment of NTM infection is varied for species to species and it is recommended according to ATS guidelines.

Scheduled monitoring of liver enzymes would be effective in identifying asymptomatic liver damage, reducing hospitalization rate and improving compliance of anti-TB treatment. It is likely to alleviate hepatic-toxicity and reduce mortality. Estimation of CD4 cells can also help to evaluate the immune response and for proper management of tubercular infected patients that may be effective for the improvement of treatment outcome.

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