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CHALLENGES OF CURRENT TUBERCULOSIS TREATMENT TO TOTALLY DRUG RESISTANCE –TUBERCULOSIS; A REVIEW

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ABSTRACT

The resurgence of tuberculosis from a forgotten disease to a modern and resurgent pathology is a matter of serious global concern. Totally drug-resistant tuberculosis (TDR-TB) is a generic term for tuberculosis strains that are resistant to a wider range of drugs than strains classified as extensively drug-resistant tuberculosis. TDR-TB has been identified in three countries; **India**, Iran, and Italy. It is most commonly described as 'resistance to all first- and second-line drugs used to treat TB. The treatment of TDR-TB includes antibiotics with disputed or minimal effectiveness against *Mycobacterium tuberculosis* and the fatality rate is high. TDR-TB has resulted from further mutations within the bacterial genome to confer resistance, beyond those seen in XDR- and MDR-TB. Development of resistance is associated with poor management of cases. Drug resistance testing occurs in only 9% of TB cases worldwide. Without testing to determine drug resistance profiles, MDR- or XDR-TB patients may develop resistance to additional drugs. TDR-TB is relatively poorly documented, as many countries do not test patient samples against a broad enough range of drugs to diagnose such a comprehensive array of resistance. There is no therapy or formulation available for the prevention and treatment of total drug resistance tuberculosis.

KEYWORDS: Challenges to TB treatment, MDR-TB, XDR-TB and TDR-TB.

INTRODUCTION

Tuberculosis

Tuberculosis is an infectious disease, caused by the bacterium called *Mycobacterium tuberculosis*. It was first isolated by Robert Koch in 1882.[1] Tuberculosis typically attacks

the lungs, but can also affect other parts of the body. It is spread through the air when people who have an active TB infection cough, sneeze, or otherwise transmit respiratory fluids through the air.

Tuberculosis remains a global public health problem especially in developing countries. It is an airborne communicable disease caused by transmission of aerosolized droplets of *M. tuberculosis*, affecting almost all the organs of the body, the lungs being most commonly affected. Despite the availability of effective antituberculosis chemotherapy for over 60 years, the incidence of tuberculosis continues to persist. The World Health Organization (WHO) declared tuberculosis as a global emergency in 1993.[2] **India** has approximately two to three million people infected **Tuberculosis**. This public health problem is the world's largest tuberculosis epidemic. Tuberculosis (TB) is one of the world's deadliest diseases. One third of the world's population is infected with TB. In 2014, 9.6 million people around the world became sick with TB disease. There were 1.5 million TB-related deaths worldwide. TB is a leading killer of people who are HIV infected.[3] Tuberculosis holds one of the top places on the list of the main cause of death in India.[4]

Drug Resistance Tuberculosis

A person with active TB disease has drug resistant TB if the TB bacteria that the person is infected with, will not respond to, and are resistant to, at least one of the main TB drugs. There are two ways that people get drug resistant TB. Firstly, people get acquired drug resistant TB when their TB treatment is inadequate. This can be for a number of reasons, including the fact that patients fail to keep to proper TB treatment regimes. It can also be that the wrong TB drugs are prescribed, or substandard TB drugs are used for treatment. Secondly, transmitted or primary drug resistant TB, results from the direct transmission of drug resistant TB from one person to another. The occurrence and prevention of primary drug resistant TB has largely been neglected during the development of global TB control programs.[5]

Multi Drug Resistant Tuberculosis (MDR-TB)

MDR-TB infection may be classified as either primary or acquired. Primary MDR-TB occurs in patients who have not previously been infected with TB but who become infected with a strain that is resistant to treatment. Acquired MDR-TB occurs in patients during treatment with a drug regimen that is not effective at killing the particular strain of TB with which they have been infected.[6]

MDR-TB is defined as tuberculosis that is resistant to at least isoniazid and rifampicin: the two most powerful first-line treatment anti-TB drugs. This type of drug resistance, called acquired drug resistance, occurs in TB because a patient's bacterial population survives for several months during treatment. MDR-TB is a critical issue to address because it impacts various regions. MDR-TB most commonly develops in the course of TB treatment, and is most commonly due to doctors giving inappropriate treatment, or patients missing doses or failing to complete their treatment.[7]

Extensively Drug Resistant Tuberculosis (XDR –TB)

XDR TB is a rare type of MDR TB that is resistant to isoniazid and rifampin, plus any fluoroquinolone and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin).

Because XDR TB is resistant to the most potent TB drugs, patients are left with treatment options that are much less effective.[8]

Totally drug-resistant tuberculosis (TDR-TB)

TDR-TB is a generic term for tuberculosis strains that are resistant to a wider range of drugs than strains classified as extensively drug-resistant tuberculosis. TDR-TB has been identified in three countries; India, Iran and Italy. TDR-TB has resulted from further mutations within the bacterial genome to confer resistance, beyond those seen in XDR- and MDR-TB. Development of resistance is associated with poor management of cases. Drug resistance testing occurs in only 9% of TB cases worldwide. Without testing to determine drug resistance profiles, MDR- or XDR-TB patients may develop resistance to additional drugs.[9] First reports of extensively drug-resistant TB (XDR-TB) in 2006, two patients with strains having resistance to all first and second-line anti-TB drugs which were tested were reported from Italy.[10]

In 2009, 15 TB patients in Iran were reported to be resistant to all anti-TB drugs tested.[11]

New terms like "**Extremely drug resistant" (XXDR-TB)**, **"super XDR-TB"** and **"Totally drug-resistant TB"** (TDR-TB) were used to define such resistance patterns. In December 2011, clinicians in Mumbai, India described four patients with TDR-TB.[12]

Discovery of TDR-TB

The term totally drug resistant tuberculosis was invented by Iranian researchers in 2009 to describe a strain of TB that didn't respond to treatment. Whereas people with MDR-TB (resistance to 2+ first line drugs) have a 30 percent chance of dying and people with XDR-TB (resistance to all first line and most second line drugs) have a 60 percent chance of dying, its believed that people with TDR-TB have a 100 percent chance of dying.[13]

MDR-TB first emerged in the early 1990s, the first Indian cases of extensively drug-resistant (XDR)-TB were described from our centre in 2006, a few months after the initial Morbidity and Mortality Weekly Report.[14, 15]

But in just a few years the focus has switched again to TDR-TB. The first two cases of TDRTB (coined XXDR-TB) were reported by Migliori in Italy in 2007.[16]

Then, Velayati reported a cohort of 15 patients with TDR-TB from Iran in 2009. There was no further mention of TDR-TB for 3 years till our publication of the first four Indian cases. Since then we have encountered a further eight cases. These 12 patients, sadly, hold a mirror to the way MDR-TB is mismanaged in India.[17]

Causes of TDR-TB

People with TDR-TB likely originally head XDR-TB that developed into a more resistant strain, possibly when a drug regimen was misused or mismanaged. Drug resistance can develop anywhere, but is more common in places TB control programs are managed poorly: poor patient support, low-quality health care, patients prescribed wrong treatment/wrong dose/wrong amount of time on treatment, insufficient supply of drugs, and insufficient quality of drugs.[18]

TREATMENT OF TUBERCULOSIS

Current TB treatment is based on principles of combination chemotherapy. Thus, multiple drugs are used both to increase efficacy and to prevent the emergence of resistant organisms. Based on mechanism of action, TB drugs can be classified as inhibitors of: bacterial protein synthesis (aminoglycosides), electron transport across the bacterial membrane (a proposed mechanism of action for pyrazinamide), nucleic acid synthesis (rifampin, quinolones) and cell wall synthesis (isoniazid, ethambutol, ethionamide and cycloserine). Perhaps the greatest hurdle to optimal TB therapy with the current drugs is the long treatment time necessary to

achieve cure. The requirement for this long duration of treatment is generally attributed to physiologic heterogeneity of TB bacteria - that is, the hypothesis that there are subpopulations of organisms that span the spectrum from actively growing bacteria to metabolically quiescent ones. It appears that one or more of these bacterial subpopulations, although they are genetically drug-sensitive, can display phenotypic drug-resistance in response to altered environmental signals and thereby survive long periods of drug treatment in an animal or human host. These bacteria have been called "persisters".[19, 20]

Drugs having different mechanisms of action are most likely needed to kill different bacterial sub-populations. The most effective of the current TB drugs at killing actively replicating tubercle bacilli is isoniazid, while rifampin, an inhibitor of RNA synthesis, is active against both replicating and non-replicating or slowly replicating bacteria.[21]

Pyrazinamide, which is believed to act by inhibiting energy metabolism across the cell membrane, is a pro-drug requiring acidic conditions for activation. Clinical benefit from use of pyrazinamide is only seen during the first 2 months of therapy and the drug is believed to be effective against relatively slowly replicating bacilli.[22]

The combination of rifampin and pyrazinamide played a major role in shortening the duration of treatment of active disease from the original 18 to 24 months to the current 6 to 9 months.[23]

The treatment protocols for drug sensitive TB varies slightly in different parts of the world, but they are based on a combination of three, or more typically, four drugs, i.e. isoniazid, rifampin, pyrazinamide and ethambutol. These drugs offer the best combination of efficacy and tolerability amongst the available TB drugs and are therefore recommended for use as "first line" therapy. Less efficacious and tolerable drugs are used in cases of resistance to the first line drugs - and are referred to as "second line" products.[24]

They include streptomycin, capreomycin, kanamycin, amikacin, ethionamide, para-aminosalicylic acid, cycloserine, ciprofloxacin, ofloxacin, levofloxacin, moxifloxacin, gatifloxacin and clofazimine. These products have, in general, a lower therapeutic index, and almost all of them are significantly more expensive than the first line drugs.[25]

Challenges of current Anti-TB formulation

The first significant hurdle to the successful treatment of TB with current drugs is the length and complexity of the treatment protocols, which negatively impact patient adherence and play a significant role in the emergence of drug resistant TB. When delivered under a strictly regulated program, the cure rates with the standard regimen are quite high, exceeding 90%.[26, 27]

The World Health Organization has promoted a program known as Directly Observed Treatment – Short course (DOTS), which includes direct observation by trained personnel of the consumption of the TB medications. This has proven to be one of the most cost effective global health interventions available today[28] but its level of implementation varies as it is quite demanding for patients and for health care staff. Specific reasons for inadequate treatment include incomplete implementation of regimens in terms of duration of treatment, number of drugs and/or their dosages and quality. The consequences of inadequate treatment can be severe for both the individual and for public health, most significantly, the selection of strains that are resistant to one or more of the drugs used. Over the decades, resistance has appeared to each one of the existing drugs; strains that are resistant to at least isoniazid and rifampin are referred to as “multi-drug resistant” (MDR-TB).[29]

After MDR-TB a new drug resistance TB is appeared, Extensively drug-resistant TB (XDR TB). It is a rare type of MDR TB that is resistant to isoniazid and rifampin, plus any fluoroquinolone and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin).[30] The treatment regimens for MDR TB are much less well defined and tested than those for drug sensitive TB. Treatment of MDR TB must rely on second line drugs which are less effective and more toxic than first line therapy, as well as up to 110-fold more expensive overall.

The mortality rate in a outbreak of XDR approached 100%. XDR TB has thus come to worldwide attention as a major therapeutic challenge and potential threat to public health.[31, 32, 33] A second significant hurdle in the treatment of TB is the high prevalence of co-infection with M tb. and the human immunodeficiency virus (HIV). It is estimated that half the people living with HIV/AIDS develop active TB[34] approximately 12 million individuals are co-infected and roughly 15% of AIDS patients globally die of TB every year.[35] These two infections are synergistic. The risk of progression from latent TB to active disease is estimated to be on average fifty fold higher in HIV + individuals compared to HIV -, with the

risk of progression in an individual increasing in proportion to the degree of cellular immune suppression.[36, 37, 38, 39]

Interactions of rifampin, non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) with cytochrome P450 3A4, create a significant therapeutic obstacle in the treatment of patients co-infected with TB and HIV. These drug drug interactions render co-treatment with first-line TB drugs and antiretrovirals problematic in many high burden settings. Additionally, anti-retrovirals and isoniazid can both cause peripheral neuropathy, and their toxicity is enhanced when used together. Therefore, concomitant therapy with rifampin and PIs or NNRTIs is not recommended.[40, 41]

CONCLUSION

As far as, there is no cure for TDR-TB patient, hence it is not exaggeration to say that world is on danger of untreatable drug resistant tuberculosis strain. Therefore, if authorized health organization do not consider immediate action plan for such bacilli, then we may face a new outbreaks of untreatable TB.

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