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Totally Drug-Resistant Tuberculosis (TDR-TB): An Overview

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ABSTRACT

Tuberculosis (TB) is as old as the mankind. Though the disease was known since ancient times, the organism causing TB was described only a century ago by Robert Koch on March 1882. On the 20th of November 1944, the first successful anti-tubercular chemotherapy was administered using streptomycin. This was followed by the invention of P-aminosalicylic acid (1949), isoniazid (1952), pyrazinamide (1954), cyclosporine (1955), ethambutol (1962) and rifampicin; 1963.The term 'totally drug resistant' has not been clearly defined for tuberculosis. While the concept of 'total drug resistance' is easily understood in general terms, in practice, *in-vitro* drug susceptibility testing (DST) is technically challenging. The term "Totally Drug–Resistant Tuberculosis (TDR-TB)"for TB strains that showed *in-vitro* resistance to all first and second line drugs tested (isoniazid, rifampicin, streptomycin, ethambutol, pyrazinamide, ethionamide, para-aminosalicylic acid, cycloserine, ofloxacin, amikacin, ciprofloxacin, capreomycin, kanamycin). The primary results using transmission and atomic force microscopes confirmed morphological variation in TDR-TB isolates. Till today, many reviews on tuberculosis drug resistance in M. tuberculosis were published. There are little evidence and much controversy regarding the treatment of TDR-TB.

INTRODUCTION

Tuberculosis (TB) is as old as the mankind. Though the disease was known since ancient times, the organism causing TB was described only a century ago by Robert Koch on March 1882. On the 20th of November 1944, the first successful anti-tubercular chemotherapy was administered using streptomycin. This was followed by the invention of P-aminosalicylic acid (1949), isoniazid (1952), pyrazinamide (1954), cyclosporine (1955), ethambutol (1962) and rifampicin; 1963. Multidrug-resistant TB (MDR-TB) is caused by an organism that is resistant to at least isoniazid and rifampin, the two most potent TB drugs(1). XDR-TB is defined as "resistant to at least rifampicin and isoniazid among the first line- antitubercular drugs in addition to resistant to any fluoroquinolones i.e. ofloxacin, ciprofloxacin and levofloxacin, and at least one of the three injectable second-line anti-TB drugs i.e. amikacin, kanamycin, and capreomycin(2).Within a year of the first reports of extensively resistant TB (XDR-TB) in 2006, isolated cases were reported in Italy that had resistance to all first-line anti-TB drugs (FLD) and second-line anti-TB drugs (SLD) that were tested. In 2009, a cohort of 15 patients in Iran was reported which were resistant to all anti-TB drugs tested. The terms 'extremely drug resistant' ('XXDR-TB') and 'totally drug-resistant TB' ('TDR-TB') were given by the respective authors reporting this group of patients. Recently, a further 4 patients from India with 'totally drug resistant tuberculosis ('TDR-TB') were described, with subsequent media reports of a further 8 cases (3).

Definition: 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(4).The term "Totally Drug–Resistant Tuberculosis (TDR-TB)"for TB strains that showed *in-vitro* resistance to all first and second line drugs tested (isoniazid, rifampicin, streptomycin, ethambutol, pyrazinamide, ethionamide,para-aminosalicylicacid, cycloserine, ofloxacin, amikacin, ciprofloxacin, capreomycin, kanamycin) (5). 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. The United Nations' Special Programme for Research and Training in Tropical Diseases has set up a TDR Tuberculosis Specimen Bank to archive specimens of TDR-TB. TDR-TB has been identified in three countries; India, Iran, and Italy. The emergence of TDR-TB has been documented in four major publications. However, it is not yet recognised by the World Health Organization (4,12-14). TDR-TB is an iatrogenic disease that represents a failure of physicians, public and private, and a failure of public health. These patients have slipped through the cracks in India's TB control programme and it is informative to analyse where we have collectively failed them.(6).

Treatment of TDR -TB patients:

In some study, it was noted that TDR-TB patients remained smear and culture positive after 18 months median treatment despite second line drugs. Even changing the treatment to co-amoxiclav (625 mg per 8 h) or clarithromycin(1,000 mg/day-1) along with high dose of isoniazid(15 mg/kg-1) led to no improvement. Majority of cases were expired or remained positive in the next 4 years of follow-up (5).

TDR -TB study at cellular level:

The primary results using transmission and atomic force microscopes confirmed morphological variation in TDR-TB isolates. Aconsiderable number of bacilli were round (35%), oval (15%) or even multiple branching forms. In addition, various type of cell division i.e., symmetrical, asymmetrical and budding were found in their exponential phase of growth. The cell wall was significantly thicker than MDR-TB isolates and recently, pilli like structure (10-15%) that protruded from the head, tail or side poles of the bacilli were also detected (5).

Spread of TB (in general to all TB types):

Drug-susceptible TB and Drug-resistant TB are spread the same way. TB bacteria are put into the air when a person with TB disease of the lungs or throat coughs, sneezes, speaks, or sings. These bacteria can float in the air for several hours, depending on the environment. Persons who breathe in the air containing these TB bacteria can become infected.

TB is not spread by:

- ❖ Shaking someone's hand
- ❖ Sharing food or drink
- ❖ Touching bed linens or toilet seats
- ❖ Sharing toothbrushes
- ❖ Kissing (7).

Symptoms to all TB cases:

The general symptoms of TB disease include a feeling of sickness or weakness, weight loss, fever, and night sweats. The symptoms of TB disease of the lungs may also include coughing, chest pain, and coughing up blood. Symptoms of TB disease in the other parts of the body depends on the area affected (7).

Types of drug resistance (A general approach):

Antibiotic resistance in *M. tuberculosis* develops primarily through mutations in chromosomal genes. Drug resistance is of two type: 1) **Primary resistance** and 2) **Acquired resistance** (8).

Mechanism of *M. tuberculosis* drug resistance:

Some of the ways the tubercle bacillus acquires drug resistance are:

✪ **Cell wall**: The cell wall of *M. tuberculosis* consists of complex lipids, and it acts as a permeability barrier from drugs.

✪ **Drug modifying & inactivating enzymes**: The *M. tuberculosis* genome codes for certain enzymes that make it drug resistant. The enzymes usually phosphorylate, acetylate, or adenylate the drug compounds.

✪ **Drug efflux systems**

✪ **Mutations:** Spontaneous mutations in the *M. tuberculosis* genome can give rise to proteins that make the bacterium drug resistant, depending on the drug action (1).

Causes of drug resistance:

- ✓ Genetic factors
- ✓ Factors related to previous anti-TB treatment
- ✓ Lack of laboratory diagnostic facilities (9).

Risk factors for developing the MDR-TB, TDR-TB, and XDR-TB:

Drug resistance is more common in people who:

- ➢ Do not take their TB medicines regularly
- ➢ Do not take all of their TB medicines as prescribed by their doctor
- ➢ Develop TB disease again, after having taken TB medicine in the past
- ➢ Come from areas of the world where drug-resistant TB is common
- ➢ Have spent time with someone known to have drug-resistant TB disease (7).
- ➢ Other factors that may be responsible for increased risk of resistant TB are co-infection with HIV, socio-economically deprived groups in slums, prisons, correctional facilities, day care centers, intravenous drug abusers, anticancer therapy patients, and patients with diabetes mellitus (8).

Solutions to TDR-TB:

✪ Laboratory capacity needs to be urgently increased. MDR, XDR, and TDR-TB remain essentially microbiological diagnoses. In the 27 high-burden countries for MDR-TB, only 1% of cases received a DST in 2008. It is one of those sad TB paradoxes that India, which bears the lion's share of the world's TB burden, has only one of the 26 supranational reference laboratories (SRLN), while the majority are concentrated in the European Union and the USA, despite only1% of the 9 million new TB cases in 2007 occurring in these regions.

✪ DST should be offered early to all patients whose condition fails to respond to DOTS instead of subjecting them to category 2 treatment.

✪ DOTS plus needs to move beyond the pilot study stage to broader implementation, despite the staggering additional finances involved. India's huge MDR-TB population has waited too long for this basic injustice to be redressed.

✪ New drugs are desperately needed. The two most promising candidates are in the pipeline, TMC207 and OPC67863.

✪ Sadly, still several years away from clinical use. Till then, it is even more imperative that we do not squander available drugs with inappropriate prescriptions.(6).

TB prevention and adjuncts to therapy:

The largest potential impact on TB control would come from effective vaccines to prevent all forms of TB. Combining chemotherapy with various with various vaccines has the theoretical potential to contribute to the increased effectiveness of drug regimens, to provide alternative strategies for limiting the duration of infectiousness of patients with TB (10).

Prevention of TB (FOR XDR, MDR, TDR-TB in general approach):

There are several ways that drug resistance to TB, and drug resistance in general, can be prevented:

❖ Rapid diagnosis & treatment of TB: One of the greatest risk factors for drug resistant TB is problems in the treatment and diagnosis, especially in the developing countries. If TB is identified and treated soon, drug resistance can be prevented.

❖ Completion of treatment: Previous treatment of TB is an indicator of MDR-TB. If the patient does not complete his/her antibiotic treatment, or if the physician does not prescribe the proper antibiotic regimen, resistance can develop. Also, drugs that are of poor quality or less in quantity, especially in developing countries, contribute to MDR-TB.

❖ Patients with HIV/AIDS should be identified and diagnosed as soon as possible. They lack the immunity to fight the TB infection and are at great risk of developing drug resistance.

❖ Identify contacts that could have contracted TB: i.e. family members, people in close contact, etc.

❖ Research: Much research and funding is needed in the diagnosis, prevention and treatment of TB(1).

Consequences about TDR-TB:

The authors have rightly pointed out that patients with MDR tuberculosis only should be treated within the confines of government sanctioned DOTS-plus programmes to prevent the emergence and spread of this form of tuberculosis. Nonetheless, the report has highlighted the issue of drug resistance in India that includes the possibility of resistance to many drugs and the problem of wrong treatment by some private practitioners, private and corporate hospitals. However, the authors should not have used the term "TDR-TB", particularly when their laboratory is not even accredited to carry out such DST for second-line anti-TB drugs. Further, genotypic DST analysis for various drugs carried out by the laboratory has not even been validated (11).

CONCLUSION

By referencing the sources mentioned below and reviewing papers, we come to across to the fact that Totally-drug Resistant Tuberculosis is still increasing at very slow rate. Till today, many reviews on tuberculosis drug resistance in *M. tuberculosis* were published. There are little evidence and much controversy regarding the treatment of TDR-TB. Approaches such as DOTS-Plus may have to be employed to effectively control MDR-TB, XDR-TB and ultimately TDR-TB. We should apply the latest techniques and findings related to TDR-TB in order to decrease the mortality rate. If new TB drugs and rapid diagnostics are not developed and implemented shortly, TDR –TB will be an expanding fraction of TB cases.

REFERENCES

1. Available from :[https://en.wikipedia.org/wiki/Multi-drug-resistant_tuberculosis]
2. Available from :[http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.523.6703&rep=rep1&type=pdf]
3. Available from :[http://www.who.int/tb/challenges/xdr/xdrconsultation/en/]
4. Available from :[https://en.wikipedia.org/wiki/Totally_drug-resistant_tuberculosis]
5. Available from :[http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3631557/pdf/ijcem0006-0307.pdf]
6. Available from :[http://www.tbonline.info/media/uploads/documents/thoraxjnl-2012-20166.pdf]
7. Available from :[http://www.cdc.gov/tb/publications/factsheets/drtb/mdrtb.pdf]
8. Available from :[http://medind.nic.in/ibr/t05/i3/ibrt05i3p121.pdf]
9. Available from :[http://icmr.nic.in/ijmr/2004/1009.pdf]
10.Available from :[http://jid.oxfordjournals.org/content/197/11/1493.full.pdf+html]
11. Available from :[http://medind.nic.in/ibr/t12/i4/ibrt12i4p190.pdf]
12. Available from:[Migliori GB, De Iaco G, Besozzi G, Centis R, Cirillo DM. First tuberculosis cases in Italy resistant to all tested drugs. Euro Surveill. 2007;12(20):pii=3194. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=3194
13 Available from:[*Katherine Rowland (13 January 2012). "Totally drug-resistant TB emerges in India". Nature.*

14 Available from:[*Velayati, A. A.; Masjedi, M. R.; Farnia, P.; Tabarsi, P.; Ghanavi, J.; Ziazarifi, A. H.; Hoffner, S. E. (2009). "Emergence of New Forms of Totally Drug-Resistant Tuberculosis Bacilli: Super Extensively Drug-Resistant Tuberculosis or Totally Drug-Resistant Strains in Iran". Chest* ***136*** *(2): 420–425. doi:10.1378/chest.08-2427.PMID 19349380.*