

Multidrug - Resistant Tuberculosis (MDR-TB): Epidemiology, Mechanisms of Drug Resistance

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Abstract: Multidrug-resistant tuberculosis (MDR-TB) is caused by *Mycobacterium tuberculosis* resistant to both isoniazid and rifampicin with or without resistance to other drugs. World-wide, about 3% of all newly diagnosed patients and a considerably higher proportion of patients who have previously received antituberculosis treatment have MDR-TB. While host genetic factors may probably contribute, irregular, incomplete and inadequate treatment is the single most important factor resulting in the development of MDR-TB. Management of MDR-TB is a challenge as it requires prolonged use of expensive second-line drugs that are not widely available with a significant potential for toxicity. Furthermore, centres equipped with reliable laboratory service for mycobacterial culture and *in vitro* sensitivity testing are seldom available. Given these constraints, the best method to contain this menace appears to be.

Key Words : Multidrug-resistant tuberculosis, MDR-TB, epidemiology, diagnosis, drug resistance mechanisms.

Introduction

Globally, tuberculosis (TB) is considered to be a major public health hazard. According to the recent estimates, in 2000 there were an estimated 8.3 million new cases of TB worldwide; 95% of TB cases and 98% of TB deaths are in developing countries^{1,2}. With the availability of definitive antituberculosis treatment and the introduction of "short-course treatment", cure for TB became a reality. However, there has been a global resurgence of TB with the advent of HIV infection-the acquired immunodeficiency syndrome (AIDS) pandemic^{3,4}.

Definition

Isoniazid, and rifampicin are the keystone drugs in the management of TB. While resistance to either of them may be managed with other first line drugs, resistance to both isoniazid and rifampicin (MDR-TB) demands treatment with second-line drugs with limited sterilising capacity that are not suitable for short-course treatment⁵. It is possible to strictly define a given isolate of *Mycobacterium tuberculosis* as "multidrug-resistant" only after performing mycobacterial culture and *in vitro* sensitivity testing. The term MDR-TB has been used in this review in the strict sense of the definition referring to isolates resistant to both isoniazid and rifampicin with or without resistance to other drugs since the therapeutic implications are different. Presently, the terms resistance among new cases, and resistance among previously treated patients are preferred over the older terms such as primary and acquired resistance as these are more precise.

Epidemiology

World : Though earlier studies suggested that drug resistance was a potential problem, it was the emergence of MDR-TB in the USA in the 1990s which attracted the attention². The report by the World Health Organization (WHO)-International Union Against Tuberculosis and Lung Disease (IUATLD) Global Project on Anti-tuberculosis Drug Resistance Surveillance between 1994 and 1997 which describes the prevalence of resistance to four first-line antituberculosis drugs in 35 countries⁶. In this study⁶ resistance to antituberculosis drugs was found in all 35 countries surveyed suggesting that it is a global problem. The median prevalence of acquired MDR-TB was 13%, with a range of 0% (Kenya) to

54.4% (Latvia). Subsequently, WHO-IUATLD survey (6) was extended to define this problem further⁷. Between 1996 and 1999, patients in 58 geographic sites were surveyed⁸. The median prevalence of MDR-TB among new cases of tuberculosis was only 1%, but the prevalence was much higher in Estonia (14.1%), Henan Province in China (10.8%), Latvia (9%), the Russian oblasts of Ivanovo (9%) and Tomsk (6.5%), Iran (5%), and Zhejiang Province in China (4.5%). Results of resistance surveys from 64 countries, together with data predictive of resistance rates from 72 others suggest that an estimated 273,000 new cases of MDR TB occurred worldwide in 2000 and constituted 3.2% of all new TB cases (8). Further details are expected to be known in the third report on the Antituberculosis drug resistance in the world that is likely to be available on-line soon.

India : Reliable data on the epidemiology of MDR-TB are lacking from India⁹. In India, prevalence of primary MDR-TB in newly diagnosed cases has been observed to be 3.4% or less^{5,9}. Data meticulously collected at the Tuberculosis Research Centre (TRC), Chennai over the last three decades suggest that MDR-TB levels in newly diagnosed patients has been 1% or less^{5,9,10}.

Prevalence of MDR-TB among previously treated patients has been observed to be higher ranging from 9% to 80%^{5,9,10}. However, caution has to be exercised in interpreting the prevalence figures published in studies with a small sample size because of inherent methodological concerns.

Biologic and Molecular Basis of Drug Resistance

Spontaneous chromosomally borne mutations occurring in *Mycobacterium tuberculosis* at a predictable rate is thought to confer resistance to antituberculosis drugs^{5,12,13}. A characteristic feature of these mutations is that they are unlinked. Thus, resistance to a drug is usually not associated with resistance to an unrelated drug. This means that, if mutations causing resistance to isoniazid occur in about 1 in 10⁶ replications of bacteria, the probability of spontaneous mutations causing resistance to both isoniazid and rifampicin would be 10⁶ x 10⁶ = 1 in 10¹⁴. Given that this number of bacilli cannot be found even in patients with extensive cavitary pulmonary tuberculosis (a tuberculosis cavity usually contains 10⁷ to 10⁸ bacilli), the chance of spontaneous dual resistance developing is practically remote^{5,12,13}. Thus, the fact that mutations are "unlinked", forms the scientific basis of antituberculosis chemotherapy. Currently, the primary mechanism of multiple drug

resistance in tuberculosis is due to perturbations in the individual drug target genes. Table 1 lists the molecular mechanisms of antituberculosis drug resistance that are considered to be important^{5,12,13}. Multidrug transporters comprise four families of transmembrane efflux proteins that actively pump out a broad range of structurally unrelated compounds from the interior of the cell, using either proton motive force or ATP supplied energy⁵. The potential contribution of these multidrug transporter proteins in the causation of MDR-TB merits further evaluation. These transmembrane efflux proteins also appear to be novel target for drug therapy in future⁵.

Table 1 : Molecular mechanisms implicated in antituberculosis drug resistance.

Drug	Gene(s) involved in drug resistance
Isoniazid	Enoyl acp reductase (<i>inhA</i>)
	Catalase-peroxidase (<i>katG</i>)
	Alkyl hydroperoxide reductase (<i>ahpC</i>)
	Oxidative stress regulator (<i>oxyR</i>)
Rifampicin	RNA polymerase subunit B (<i>rpoB</i>)
Pyrazinamide	Pyrazinamidase (<i>pncA</i>)
Streptomycin	Ribosomal protein subunit 12 (<i>rpsL</i>)
	16s ribosomal RNA (<i>rrs</i>)
	Aminoglycoside phosphotransferase gene (<i>strA</i>)
Ethambutol	Arabinosyl transferase (<i>emb A,B and C</i>)
Fluoroquinolones	DNA gyrase (<i>gyr A and B</i>)

Adapted from reference 5

Potential Causes of Drug Resistance

Various factors have been implicated in the causation of MDR-TB⁵. These are discussed below.

Genetic factors : Though there is some evidence to postulate host genetic predisposition as the basis for the development of MDR-TB, it has not been conclusive⁵. It is likely that these loci for the alleles linked with them play a permissive role in conferring increasing susceptibility to the development of MDR-TB.

Factors related to previous antituberculosis treatment:

Incomplete and inadequate treatment : Review of published literature strongly suggests that the most powerful predictor of the presence of MDR-TB is a history of treatment of tuberculosis. Irregular, incomplete, inadequate treatment appears to be the most common means of acquiring drug resistant organisms. Use of single drug to treat TB is another common predisposing cause in the India setting. This could have occurred because of ignorance; use of penicillin/streptomycin combinations; use of rifampicin for other diseases; and economic constraints. There is also the risk of use of unreliable drugs with poor bioavailability. Use of antituberculosis drugs by unqualified persons or alternative medicine practitioners resulting in bizarre regimens for inadequate periods.

Poor treatment compliance : The change over from fully supervised sanatorium treatment to unsupervised domiciliary treatment has affected compliance significantly. Poor compliance with treatment is also an important factor in the development of acquired drug resistance. Non-compliance with prescribed treatment is often underestimated by the physician and is difficult to predict. The drug defaulter, just like placebo reactor is not a consistent or readily identified person. In the west, demographic factors such as age, sex marital status, education level and socio-economic status have not been found to correlate with the degree of compliance. On the other hand, certain factors such as psychiatric illness, alcoholism, drug addiction and homelessness do predict

non-compliance. This may not be entirely true in the Indian context and the relevance of these factors in the Indian scenario merits further study⁵.

Lack of laboratory diagnostic Facilities : Good, reliable laboratory support is seldom available in developing nations, the areas where MDR-TB is a major health hazard. When facilities for culture and sensitivity testing are not available, therapeutic decisions are most often made by algorithms or inferences from previous treatment¹⁴. Programmatic approach has been observed to fail in some settings and published data suggest that standard short-course chemotherapy, based on first-line drugs, is an inadequate treatment for some patients with drug-resistant TB^{15,16}. Although the DOTS strategy is the basis of good TB control, the strategy should be modified in some settings to identify drug-resistant cases sooner, and to make use of second-line drugs in appropriate treatment regimens^{17,18}.

Predictors for the development of MDR-TB : In most of the published studies, previous history of tuberculosis and past history of antituberculosis treatment have been implicated in the causation of MDR-TB⁵.

Implications for treatment

Second-line drugs are very difficult to obtain in small towns and rural areas in India. Therefore, reliable supply of drugs is a difficult problem. Moreover, there is a wide variation in the price range between different pharmaceutical brands. Reliable pharmacokinetic data regarding bioavailability of most of these formulations is not available either. Moreover, there is no assurance that the most expensive brand names have the best bioavailability profile. Even considering the cheapest brand names available, the cost of drug treatment alone is much beyond the means of the average Indian patient. Therefore, long term compliance is not very good. All these factors constitute significant therapeutic challenges for the clinicians treating MR-TB in the field setting. Population migration due to poverty to seek better job opportunities, because of natural disasters, wars political instability and regional conflicts also create mobile populations. These factors make treatment of MDR-TB difficult, as it is not easy for persons who are forced to move for any of a variety of reasons to complete 24 months of treatment⁵.

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IMSA News

IMSA Chapter Activities (April to June 2005)

Delhi Chapter

- 30.4.2005 : Dr. Ram Raj Singh, USA, "Indian Rheumatology-has its time come too late in th world".
- 7.5.2005 : Dr. S.J. Gupta, "Case presentation".
- 2.6.2005 : Dr. Prathiba Saran, "Recent advances in ophthalmology".

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- 8.5.2005 : Dr. P.C. Rajaram, "Value of ultrasonography in musculo skeletal and soft tissue lesions in the face".
- 12.6.2005 : Dr. Arun Balakrishnan, "Bio activity based screening of novel molecules towards drug development

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For registration contact : Dr. S.S. Sethi President - IAALS, Convenor and Chairman at abroad address under intimation to IMSA Headquarter

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Dr. Tarun Gupta has been conferred '*Distinguished Service Award*' by the Indian Medical Association New Delhi.

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