

Drug-Resistant Tuberculosis: New Challenges

Tuberculosis (TB), is a common, and in many cases lethal, infectious disease caused by various strains of *Mycobacterium*. A major public health problem worldwide, TB has become a global emergency. In the last decade, TB has remained one of the leading causes of death [nearly 3 million deaths annually]. World Health Organization estimates that one-third of the world's population is infected with *Mycobacterium tuberculosis*. In 2009, there were almost 9 million new cases of TB and the disease killed almost one million people around the world.

Resistance to antituberculosis drugs has been a problem since the era of chemotherapy began. After dramatic outbreaks of multidrug-resistant tuberculosis (MDR-TB) in the early 1990s, resistance was acknowledged as a global problem. The term drug-resistant tuberculosis, is used to describe all strains of TB that show resistance to one or more of the anti-tuberculous drugs. Whereas multidrug-resistant tuberculosis (MDR-TB) is defined by resistance to isoniazid and rifampicin. Extensively drug-resistant tuberculosis (XDR-TB) is defined as TB that is resistant to the first-line drugs (isoniazid, rifampicin) and also to at least one of three injectable second-line drugs (capreomycin, kanamycin and amikacin) and one of the fluoroquinolones.²

The MDR-TB prevalence is estimated to be 2% to 3% among new cases and 12% to 17% among re-treatment cases. However, due to the size of population and the number of TB cases reported annually, India ranks second among the 27 MDR-TB high burden countries worldwide after China.⁹

Genetic and molecular analysis of drug resistance in *Mycobacterium tuberculosis* suggests that resistance is usually acquired by the bacilli either by alteration of the drug target through mutation or by titration of the drug through overproduction of the target. The probability of resistance is very high for less effective antituberculous drugs such as thioacetazone, ethionamide, capreomycin, cycloserine and viomycin (10^{-3}), intermediate for drugs such as INH, streptomycin, ethambutol, kanamycin and para-aminosalicylic acid (10^{-6}) and lowest for rifampicin (10^{-8}). Consequently the probability of mutation is directly proportional to the bacterial load. A bacillary load of 10^9 will contain several mutants resistant to one or more antituberculous drugs. As the mutations conferring drug resistance are chromosomal, the likelihood of a mutant being simultaneously resistant to two or more drugs is the product of individual probabilities. Thus, the probability of multidrug-resistance is multiplicative. Resistance to a drug does not confer any selective advantage to the bacterium

unless it is exposed to that drug. Under such circumstances the sensitive strains are killed and drug resistant mutants flourish. When the patient is now exposed to a second course of drug therapy with another drug, mutants resistant to the new drug are selected, and the patient may eventually have bacilli resistant to two or more drugs. Thus, serial selection of drug resistance is the predominant mechanism for the development of drug resistant strains; the patients with drug resistant strains constitute a pool of chronic infection, which propagates primary multi-drug resistance. In addition to accumulation of mutations in the individual drug target genes, the permeability barrier imposed by *Mycobacterium tuberculosis* cell wall can also contribute to the development of low level drug resistance. Studies addressing resistance to streptomycin have found evidence of such a two-step mechanism for the development of drug resistance.

Suspicion for drug-resistant TB should be high if the patient with a prior history of TB has one or more of the following characteristics on current or prior treatment:³ large bacillary load with extensive (bilateral or cavitary) disease, lack of conversion of cultures to negative during therapy, lack of improvement or only partial improvement in TB symptoms, worsening of TB symptoms or radiograph picture, non-adherence or intermittent or erratic ingestion of prescribed anti-TB regimen, lack of directly observed therapy or poorly supervised therapy, and a history of an inappropriate treatment regimen. Clinical suspicion of drug resistance is also raised when a patient with TB without a prior history of TB, symptoms and signs has a history of one or more of the following: exposure to a person with documented drug-resistant TB, residence in or travel to a region with high rates of drug-resistant TB, residence or work in an institution or setting in which drug-resistant TB is documented, treatment of pulmonary problems with a prolonged course of multiple medicines or an injectable agent for more than a few weeks, i.e., the patient may not realise that he/she was treated for TB, treatment of a pulmonary problem with a fluoroquinolone and previous treatment for latent TB infection when signs of TB disease were not recognised.

Challenges in the management of drug-resistant TB under programme setting include expanding the MDR-TB management services in line with concept of universal access and at the same time maintaining quality of services. It can be achieved through multi-pronged efforts, such as effective human resource management, ensuring rational use of antibiotics by linking all health-care providers to flexible TB control

efforts and encouraging clinical and operational research.

For diagnosing drug resistant TB,⁴ culture dependent methods have traditionally been used. These are expensive (liquid culture systems) and time consuming (solid culture). The proportion susceptibility method is the gold standard for drug susceptibility testing. Drug resistant TB is a laboratory-based diagnosis either phenotypically, i.e. growing the bacteria (culture) or demonstrating the ability of bacteria to grow in the presence of anti-tuberculosis drugs (drug sensitivity testing) or genotypically by demonstrating presence of resistant genes using molecular methods. Conventional and new diagnostic tools used for diagnosis include solid culture medium (egg-based Lowenstein-Jensen) or agar-based 7H11/10 medium and liquid culture medium (commercial automated MGIT 960). Newer rapid diagnostic tools includes; non commercial solid culture methods — nitrate reductase assays, and non-commercial liquid culture methods, microscopic observation of drug susceptibility using 7H9 medium for both culture and DST.

Liquid culture system; automated MGIT 960 and MGIT Manual systems which detect the growth of mycobacteria as early as four days from the inoculation and DST is available in 21 to 28 days.

Molecular assays include polymerase chain reaction based technologies (line probe assay), using various modifications. These are used for detecting the presence of putative resistance genes (rpoB gene for rifampicin, katG and inhA for INH). Line probe assays are based on *in situ* hybridisation on nitrocellulose strips of specific targets genes for resistant genes these are now available for rifampicin and INH resistance (MDR-TB) and would shortly be available also for second-line anti-tuberculosis drugs. Gene Xpert technology (Cepheid) is integrated automated NAAT technology which provides result within 90 minutes. It is specific for *Mycobacterium tuberculosis* and detects resistance to rifampicin via rpoB gene.

Human immunodeficiency virus (HIV) infection *per se* does not appear to be predisposing factor for MDR-TB. Some studies show that MDR-TB is not more common among people infected with HIV. Epidemiological studies reveal that *Mycobacterium tuberculosis* strains infecting HIV patient have a different lineage, clustering pattern and dynamics than those infecting immune competent host.

Predisposing factors for the development of drug resistant TB among the HIV patients include increased susceptibility to TB, increased opportunity to acquire TB, malabsorption of anti-tuberculosis treatment (ATT), poor quality of drugs and frequent interruption of treatment with anti-retroviral therapy and ATT. Among immune suppressed patient, XDR-TB has been associated with exceptionally high mortality.⁸

Rajesh N. Solanki

Member, Editorial Board, and

Professor and Head

Department of Pulmonary Medicine

B.J. Medical College and Civil Hospital

Ahmedabad - 380 016 [Gujarat]

E-mail: ms04sec@yahoo.co.in

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