Management of Drug-Resistant TB with Individualised DST- The Way Forward?

Tanu Singhal*, Neha Gupta**

**Extent of the Problem**

India has the largest TB epidemic in the world with almost 1000 TB related deaths everyday or 2 deaths every 3 minutes. Drug resistance is assuming increasing proportions with the prevalence of multi drug resistant (MDR) tuberculosis (defined as TB resistant to at least both isoniazid (H) and rifampicin (R)) approaching 1.5-2.7% in new and 13-17% in previously treated cases.\(^1\) The exact burden of extensively drug resistant (XDR) tuberculosis (defined as MDR strains with additional resistance to any fluoroquinolone (FQ) and at least one of the three second-line antituberculosis injectable agents (IA) —ie, amikacin, kanamycin, or capreomycin) is unknown but estimated to be 10% of all MDR cases.\(^1\) In 2012, totally drug resistant (TDR) or XXDR tuberculosis (defined as TB resistant to all drugs that can be tested in the laboratory) was reported from Mumbai.\(^2\)

In their article, Soman et al have coined the terms MDR+ and pre XDR TB.\(^3\) It is a meaningful step, since a significant proportion of drug resistant cases in India fall somewhere in between MDR and XDR TB. A study from Tuberculosis Research Centre, Chennai reported that of the 1498 strains of MDR tuberculosis isolated between 2001-2004 from all across India, 44.8% were resistant to second line drug (SLD). Prevalence of ethionamide resistance was 32.7%, ofloxacin resistance 16.4% and kanamycin resistance 11.3%; 4.6% strains were XDR.\(^4\) Udwadia et al have reported rise in FQ resistance in MTB isolates from 3% in 1996 to 35% in 2004.\(^5\) Recent data will be more dismal. This increase in FQ resistance can be attributed to indiscriminate use of quinolones in community acquired infections, use of these drugs upfront along with other first line anti TB treatment and last but not the least, adding these drugs as single agents to failing regimes. A two week course of quinolones is enough to lead to emergence of resistance in M.Tb later.\(^6\) Rifampicin coadministration with moxifloxacin induces enzymes that are involved in the biotransformation of moxifloxacin resulting in reduced moxifloxacin plasma concentrations.\(^7\) Rifampicin results in efflux of ofloxacin if given simultaneously in rifampicin resistant strains.\(^8\)

**Drug Susceptibility Testing (DST) for Anti Tubercular Drugs**

The reliability of phenotypic susceptibility testing for antituberculous drugs varies greatly. The WHO has classified drugs in various DST categories on the basis of published data, multicentre lab review, stability of drug powder, inter observer method agreement, reproducibility/reliability of DST and clinical outcome data.\(^9\) The reliability is highest for H and R (Category I) followed by pyrazinamide, ethambutol, streptomycin, kanamycin, amikacin, capreomycin (II), then ofloxacin and ciprofloxacin (III), moxifloxacin, levofloxacin, ethionamide, Para-amino salicylic acid (PAS), cycloserine (IV) and all other drugs category V. It is due to this varying reliability/reproducibility of DST that most labs do not have the expertise to do DST, the terminology of TDR tuberculosis has not gained widespread acceptance and
recommendations for drug therapy are not based entirely on susceptibility results. It is notable that the susceptibility tests in the study by Soman et al were performed in a lab that has now been accredited for second line DST. The results of this study with susceptibility based treatment provide new crucial clinical outcome data that validates the reliability of the current phenotypic tests.

Genotypic methods for resistance determination are now widely available as Hain line probe assay (LPA) and Gene Xpert MTB/RIF. Genotypic tests detect resistance in clinical specimens/cultures very quickly as compared to phenotypic tests which helps in designing an early appropriate regimen. Mutational analysis also provides a clue - presence of KatG mutation denotes resistance to high dose INH while inhA mutation indicates possible cross resistance to ethionamide. The type of rpoB mutation can indicate suitability of inclusion of rifabutin in a MDR/XDR drug regime.**

**Treatment of MDR/XDR TB**

Recent guidelines from Caminero et al recommend use of at least 4 active drugs to which the isolate is likely to be susceptible. The choice of these drugs is based on efficacy, adverse effects, cost, previous drug exposure, and susceptibility. An injectable second line drug (capreomycin/kanamycin/amikacin in that order), a newer fluoroquinolone (high dose levofloxacin/moxifloxacin) along with the oral group 4 drugs (ethionamide, cycloserine and PAS in that order) are the recommended agents. The use of the category 5 drugs is recommended in only special situations (clofazimine, coamoxiclav, linezolid, meropenem, clarithromycin and thioacetazone in that order; each drug counted as half a drug). The guidelines also recommend addition of high dose isoniazid, pyrazinamide and a newer fluoroquinolone to the regime even if they are tested resistant (though they should not be counted).

In their study, with careful selection of drugs based primarily on susceptibility, Soman at el have achieved treatment outcomes that are superior to that reported in literature. While recognizing the fact that careful follow up, counseling and extrapulmonary TB in more than half the study patients may have also been contributory factors, this approach appears pretty robust. Singhal et al have also reported satisfactory outcomes in 13/14 children in Mumbai with MDR+ and pre XDR TB using similar susceptibility based treatment. The avoidance of drugs which tested resistant on DST (even newer FQ) in both these studies contributed in reducing pill burden, cost of therapy and adverse effects. At the same time, in view of new data that achievable drug levels in serum with moxifloxacin are higher than the FQ MIC’s in most phenotypically resistant strains, addition of moxifloxacin to all MDR and XDR regimes despite documented phenotypic/genotypic resistance seems reasonable at this time. It may also be possible to reduce the dose of linezolid from 600 mg/day (as used in the study) to 300 mg/day to further reduce side effects.

The current RNTCP regime for treatment of MDR cases consists of pyrazinamide, levofloxacin, ethionamide, ethambutol, kanamycin and cycloserine. If the susceptibility patterns seen in this study are representative of what is happening all over the country, then this regime is inadequate with possibly only two active drugs. Inclusion of PAS and clofazimine in the regime may be a superior option.

**Conclusions**

The problem of drug resistance in TB is likely to increase over time. We have to be better prepared to handle this menace. Development of more accurate and reproducible testing methods, establishing more reference labs for DST, generation of susceptibility data from the entire country that will help design better empirical regimes, collation of clinical outcome data and finally developing and making available new drugs are important steps in this direction. Equally or possibly more important are addressing issues that lead to drug resistance with special emphasis on weight-based dosages and restricting fluoroquinolone overuse.

**References**

8. Louw GE, Warren RM, van Pittius NCG et al. Rifampicin reduces susceptibility to ofloxacin in rifampicin-resistant Mycobacterium


