Drug-resistant tuberculosis – A ticking time bomb!

Historical evidence suggests that tuberculosis (TB) is probably the most significant challenge ever imposed on humankind by nature. Many millennia without specific therapy for TB have recorded catastrophic loss of human lives. During the last five decades, we have achieved significant milestones in our fight against TB with highly efficacious standardized antituberculous therapy provided through high-priority national health programs as a result of which there has been significant reduction in morbidity and case fatality rates across the world. In spite of the above progress, an estimated 2 billion people have infection with *Mycobacterium tuberculosis* and about 1.7 million people die every year globally.

The emergence of drug-resistant TB in recent years is one of the most important factors that has diminished our success stories in TB management. Although a large proportion of TB cases are susceptible to first-line antituberculous drugs, some strains are resistant to one or more of these drugs resulting in adverse outcomes. By definition, multidrug-resistant TB (MDR-TB) is when the *Mycobacterium tuberculosis* strain causing disease is resistant to at least isoniazid and rifampicin. Extensively drug-resistant TB (XDR-TB) is when the MDR strain is also resistant to one of injectable second-line drugs and any of the fluoroquinolones.

According to a report by the WHO in 2010, an estimated 3.6% of (new) TB cases globally (total of 440,000) were MDR-TB.[1] This is an underestimation of true global burden of MDR-TB due to nonavailability of reliable data from many countries. Indian statistics on drug-resistant TB emerges predominantly from a drug resistance surveillance conducted by the Revised National Tuberculosis Control Program (RNTCP) in only three states (Gujarat, Maharashtra, and Andhra Pradesh) in 2008.[2] According to this surveillance report, MDR-TB represented an estimated 2.3% of new TB cases and 17% of retreatment cases. These figures indicate the existence of about 100,000 MDR-TB cases in the country. In this scenario, the RNTCP was swift enough to address this massive public health problem by establishing DOTS-plus services in 2010. Since then, programmatic management of drug-resistant TB has shown a rapid progress across the country, through the provision of expensive second-line drugs free of cost, extensive laboratory expansion, and public–private partnership. Despite this prioritized approach, further progress in the management of MDR/XDR-TB is marred by several challenges. The paucity of human resources and huge funding for expensive second-line drugs and quality-assured laboratory facility are few administrative challenges. Above all, individual patients’ experience through a 2-year long course of treatment with toxic drugs, i.e., adverse drug reaction (ADR), is the most important challenge that every physician struggles to tackle.

In this issue, Piparava et al. reported treatment outcomes and ADRs of directly observed treatment (DOT)-plus regimen for MDR-TB. Although the target for treatment success in MDR-TB is around 75%, studies showed that the success rate ranged from 35% to 65% globally.[3-5] The most recent annual report by the RNTCP showed that the national average of treatment success rate was 47%.[6] According to the same report, another 20% died during treatment, 19% defaulted, and about 10% had treatment failure. The outcomes reported by Piparava et al. are consistent with the national data. Although adverse outcomes of managing drug-resistant TB are explainable by a multitude of factors, the single most important determinants are incidence and characteristics of ADR during the treatment.

However, there are no enough data on the incidence of adverse drug effects, their severity, and factors that predict their occurrence in individual patients. Most studies have profiled the adverse drug effects as one of many secondary objectives, and hence, true pattern of occurrence is far from our understanding. Very few studies have addressed this issue by defining adverse effects of second-line anti-TB drugs and objectively assessing the causality and severity of these effects. Piparava et al., in their study, have carefully chosen and administered validated tools and have shown that a majority of ADRs are only mild and “possibly” caused by one or more anti-TB drugs. This is in contrast to some retrospective studies where the data were not descriptive on ADRs and were more “subjective,” often overestimating the burden of ADRs in the management of drug-resistant TB.

Despite the above-mentioned strengths, this study has limitations. The data reported by Piparava et al. reflect a single-center experience with a relatively small sample...
of MDR-TB patients. The study did not include patients with other types of drug-resistant TB, namely, mono- or polyresistance TB and XDR TB. These limitations make it difficult to generalize the data to a larger population. Another important limitation is that the study design was restricted to descriptive statistics, giving information only on the incidence and characteristics of ADRs and other outcomes. It could have been useful if the authors had inferred on clinical and other risk factors for adverse outcomes. Such results could have given strategic advice to readers on the management of drug-resistant TB.

In the above context, it is imperative to believe that we need more data to meet the challenges faced in the management of drug-resistant TB. Despite India accounting for 99,000 cases of MDR-TB, there is a paucity of local data on treatment outcomes. This situation has forced program managers to depend on western data for strategic planning and implementation of DOTS-plus services. There are several challenges in conducting clinical trials in TB. Securing access to the standard of care requires the involvement of the national TB program heads once the study design is identified. This requires collaboration with concerned stakeholders and is a challenge, especially while testing a novel TB regimen. Identifying clinical trial sites with experienced PI and infrastructure can be cumbersome. A major issue could be well-trained accredited laboratory with experience in mycobacteriology sampling.

Operational research initiatives by the RNTCP in recent years have just started to yield results with more data emerging from various centers. However, these initiatives are at times counterweighed by a shortage of workforce and funds, lack of expertise among clinicians in epidemiology, and time constraints in busy centers. A sustained commitment by the policymakers, staff training, and dedicated team for data management may improve research and innovation in TB control. A robust research culture facilitating evidence-based decision-making at the highest level is the need of the hour.