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Editorial

Therapeutic drug monitoring: The future of tuberculosis management

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Tuberculosis (TB), a communicable disease, is a major global cause of illness and mortality. In 2020, India contributed 26% to the global incidence of TB. Most persons who develop tuberculosis can be cured and infection transmission reduced if diagnosed early and treated with first-line ant-TB drugs for six months.[1,2] Today with advances in medicine, we are moving towards individualized medicine.

Therapeutic Drug Monitoring (TDM) is one tool that may individualize TB pharmacotherapy. It typically includes drug concentration measurements in serum specimens collected between 2 and 6 hours following dosage of the drug or drugs in concern. The dried blood spot analysis (DBSA) method, which collects a drop of blood from a finger prick on a card that can be shipped by mail at room temperature, has made sample collection easier.[3] TDM cannot predict who will fail, relapse, or be cured; nevertheless, it can help doctors make timely and informative judgments about the need for dose modifications when they are indicated.[3,4]

TDM may be beneficial in the following conditions or scenarios.[4]

1. TB patients in whom TB treatment had a poor therapeutic response despite compliance and a fully drug-susceptible Mycobacterium tuberculosis strain.
2. Patients with severe gastrointestinal abnormalities, such as chronic diarrhea with malabsorption, severe gastroparesis, and short bowel syndrome.
3. Drug-drug interactions: Among anti-TB drugs, rifampicin accelerates the metabolism of several other drugs.
4. Impaired renal clearance: Patients with renal insufficiency, patients on peritoneal dialysis, and critically ill patients on continuous renal replacement.
5. People living with HIV (PLHIV infection and diabetes mellitus.
6. Patients on anti-TB treatment with second-line drugs.

Thus, some common scenarios where TDM may be helpful would be (1) patients with a delayed sputum conversion or treatment failure that is not due to noncompliance or drug resistance; (2) patients with medical disorders that are suspected of causing subtherapeutic or toxic drug levels (e.g., impaired renal function); and (3) patients with drug-resistant TB undergoing treatment.[4]

Another group of patients is the obese patients, where the optimum dosage of anti TB drugs may be higher than

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the current recommendation. For example, the maximum recommended daily doses of Isoniazid (INH) and rifampicin are 300 mg and 600 mg, respectively. This dose in a 90 kg person would be 3.33 mg/kg for INH and 6.67 mg/kg for rifampicin which are below their recommended doses (INH-4-6 mg/kg, Rifampicin – 8-12 mg/kg) as per body weight.[5]

The maximum safe dose of first-line anti TB drugs is yet to be searched. Charlotte Seijger et al. in their decade long experience of high dose rifampicin in tuberculosis patients, concluded that daily rifampicin dosages of up to 32 mg/kg are tolerated well for the whole duration of treatment by these patients.[6]

In their study on intermittent anti-TB chemotherapy, Geetha Ramachandran et al. reported suboptimal concentrations of rifampicin in 91% of TB patients and found it to be one of the factors associated with poor treatment outcomes.[7] Also, suboptimal peak concentrations of rifampicin and pyrazinamide are main predictors of therapy failure or death in children with TB.[8]

Dose titration with TDM: INH and Rifampicin are the two main first-line anti TB drugs. Their doses may be titrated as follows if their serum levels are suboptimal. Follow-up levels can be checked 24 hours after a dose adjustment is made.

Table 1: Isoniazid and Rifampin expected peak concentrations and recommended doseadjustment[9]

Medication expected peak serum concentration (Cmax) Range	Dose adjustment when below the peak
Isoniazid - daily (3-6 μg/ml)	Increase daily dose from 300 mg to 450 mg
Rifampin - (8-24 μg/ml)	Increase dose from 600 mg to 900 mg

The potential importance of TDM in drug-resistant TB can be gauged by the fact that current WHO guidelines (2019) recommend TDM for second-line anti TB drugs when the dose is at the upper and lower ends of the weight band. This recommendation has been made to reduce the adverse therapeutic effects of both excess and under-exposure (especially for injectable agents, linezolid, and fluoroquinolones).[10]

Titrating the doses of anti-TB drugs with TDM may optimize the efficacy of the drug regime and decrease the potential of adverse drug reactions in carefully selected patients. However, the facilities of TDM for anti TB drugs are very limited at present.

24^{th} March is designated globally as world TB Day, and this year, i.e., 2022, the theme for the world TB day is 'Invest to End TB. Save Lives'. The theme is appropriate in the context of the inclusion of TDM in the programmatic management of TB. The Indian National TB Elimination Program (NTEP) needs to include and provide facilities for TDM of anti TB drugs, at least at the intermediate reference laboratories (IRLs). The inclusion of this advanced biochemical investigation necessitates the need to rope in medical biochemistry specialized doctors in the program to complement the existing medical microbiologist at the IRLs. This expansion of laboratory services in the NTEP is essential for the overall advancement of the program towards more evidence-based management of tuberculosis.

Thus, therapeutic drug monitoring may represent the future of tuberculosis management, be it individualized or standardized as in the programmatic setup.

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Conflicts of Interest

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