Let's Talk TB

A Series on Tuberculosis, A Disease That Affects Over 2 Million Indians Every Year

Management of Drug-Resistant Tuberculosis: Q&A for Primary Care Physicians

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Abstract

Drug-resistant TB (DR-TB) is a serious and growing threat in India, especially in urban areas such as Mumbai. Multidrug-resistant TB (MDR-TB) is resistance to two of the most important first-line anti-TB drugs – isoniazid and rifampicin. Some patients develop more severe forms of DR-TB. Extensively drug-resistant TB (XDR-TB) is resistance to isoniazid and rifampicin, plus any fluoroquinolone, and at least one of 3 injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin). DR-TB occurs when patients fail to complete first-line drug therapy, have relapse, or newly acquire it from another person with DR-TB. If patients have any risk factors for drug-resistance, or live in a high MDR-TB prevalence area (e.g., Mumbai city), or do not respond to standard drug therapy, they must be investigated for MDR-TB using drug-susceptibility tests (DST) like GeneXpert, line probe assays, and liquid cultures. MDR-TB requires long-term and specialized treatment. So, patients should be referred to specialists, either in the private sector, or in the public sector where free MDR treatment is available. This Q&A covers commonly asked questions by the primary care doctor about identification and referral of patients with suspected or confirmed DR-TB.

Key words: tuberculosis; treatment; drug regimen; adherence, MDR-TB, XDR-TB

Q: WHAT IS MDR-TB AND WHY DOES IT MATTER?

MDR-TB is caused by TB bacteria that are resistant to at least isoniazid (INH) and rifampicin (RIF), the two most potent TB drugs in the standard, short-course TB treatment. According to WHO, India had an estimated 62,000 MDR-TB cases among notified pulmonary TB patients.[1] However, this number is likely to be an underestimate, as privately treated TB patients may not be notified.

Early diagnosis of MDR-TB is critical because the treatment regimen required is entirely different from standard, first-line anti-TB therapy (ATT). Treatment of MDR-TB is much longer (at least 2 years), more toxic, and very expensive. Even with correct management, mortality rates can approach 50%. Specialized care, therefore, is very important, and treatment must be guided by drug-susceptibility testing (DST) results.

Q: WHAT IS XDR-TB AND HOW COMMON IS IT?

XDR-TB is more severe resistance than MDR-TB. XDR-TB occurs when TB bacteria become resistance to INH and rifampicin, plus any fluoroquinolone (e.g., moxifloxacin or levofloxacin), and at least one of 3 injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin). Treatment of XDR-TB should never be done in primary care settings. Specialist treatment is mandatory. XDR-TB and pre-XDR TB increasingly seen in cities such as Mumbai, but are considered rare at the national level in India.[2-4]

Q: WHAT IS TOTALLY DRUG-RESISTANT TB (TDR-TB)?

Some hospitals, including in Mumbai, have reported a few cases where TB bacteria were found to be resistant to all of the drugs tested (first and second line).[3] Such resis-

tant strains have also been reported in other countries. While WHO does not recognize TDR-TB as a specific category, it is important to acknowledge the emergence of very extreme forms of DR-TB, where no drug therapy might work, and mortality rates are exceedingly high.

Q: WHEN SHOULD YOU SUSPECT DRUG-RESISTANT TB IN YOUR PATIENT?

DR-TB is more common in patients who:

- Do not take their TB medications regularly (i.e., in patients who are poorly adherent to ATT)
- Do not respond to standard ATT: they may be getting adequate treatment in the right doses during the intensive treatment, but show no clinical improvement. These patients may be persistently sputum AFB positive despite 2 months of adequately dosed drugs.
- Develop TB disease again, after having taken ATT in the past (i.e., in any patient with recurrence or relapse)
- Come from areas of India (e.g., Mumbai) where drug-resistant TB is widespread
- History of exposure to a patient with pulmonary DR- TB.

Q: IF YOU SUSPECT DR-TB IN YOUR PATIENT, HOW CAN YOU CONFIRM IT? WHAT ARE THE METHODS AVAILABLE FOR DRUG-SUSCEPTIBILITY TESTING (DST)?

The WHO recently announced the post-2015 "End TB Strategy".[5] A key component of this strategy is the push towards 'universal DST' which means that all TB patients should get a DST done at the time of their diagnosis. At the very least, all patients with history of previous TB treatment, treatment failure or recurrence, must undergo DST. In cities such as Mumbai, it is important to get a DST on ALL TB patients, regardless of risk factors.

DST can be done using two methods: genotypic and phenotypic. Genotypic methods are based on molecular tests that detect mutations in TB bacteria that confer drug-resistance. For example, mutations in the rpoB gene of *M. tuberculosis* is strongly associated with rifampicin resistance. Genotypic tests include Xpert MTB/RIF (GeneXpert), and Hain Genotype MTBDRplus (a commercial line probe assay). Phenotypic methods are based on detection of culture growth with and without TB drugs added to the culture media. Phenotypic methods include solid and liquid cultures. While solid cultures can take up to 2 months, liquid cultures (e.g., MGIT culture) can produce results within 2 weeks.

According to International Standards for TB Care (ISTC), DST should be performed at the start of therapy for all previously treated patients.[6] Patients who remain sputum smear-positive at completion of the intensive phase of treatment and patients in whom treatment has failed, have been lost to follow-up, or relapsed following one or more courses of treatment should always be assessed for drug resistance. For patients in whom drug resistance is considered to be likely, an Xpert MTB/RIF® test should be the initial diagnostic test, as per WHO policy.[6,7]Line-probe assay or liquid culture and DST to at least isoniazid and rifampicin should be performed promptly if rifampicin resistance is detected. If MDR-TB is detected, DST to second line TB drugs especially fluoroquinolones and injectable drugs is required for correct management.

For DST, both WHO and ISTC recommend Xpert MTB/RIF® test as the initial diagnostic test because it can rapidly detect rifampicin resistance within 90 minutes with high accuracy, and allow clinicians to initiate empiric MDR therapy, pending confirmation with cultures.[7] Hence in areas (e.g., Mumbai) where levels of primary drug resistance are high, it is imperative to send out the sputum (in pulmonary TB) and/or other samples from appropriate sites (in extra-pulmonary TB) for an Xpert MTB/RIF test.

Line-probe assays (e.g., Hain Genotype MTBDRplus) or liquid culture and DST should then be performed promptly if rifampicin resistance is detected using Xpert MTB/RIF. Once culture and DST results are obtained, MDR therapy can be customized to the patient's drug-susceptibility profile, and must include a combination of at least 5 drugs to which the TB bacilli are still sensitive. The algorithm for DST is shown in the graphic (**on the next page**).

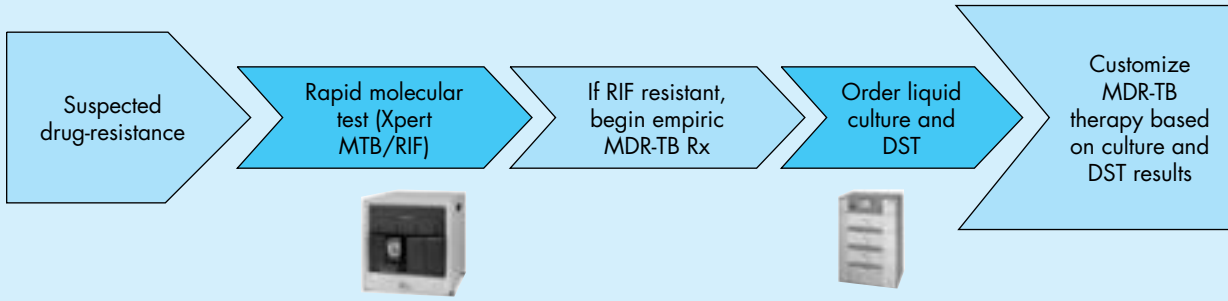
Q: IS IT IMPORTANT TO ALWAYS SEND A SAMPLE FOR MGIT CULTURE?

Yes, especially if you are suspecting MDR-TB in your patient, or practising in an area of high prevalence of MDR-TB. The liquid culture is the gold standard for the diagnosis of TB, and MDR-TB. Every other test is compared against the liquid culture. Since culture results can take a few weeks, it is important to send out cultures early on in the treatment for the following reasons:

- It is the gold standard for the confirmation of TB itself.
- Both pulmonary and extra-pulmonary samples can be subjected to culture
- Culture confirms the diagnosis of TB as opposed to atypical mycobacteria or nocardiosis (smear microscopy may still be positive in the latter two)
- A positive culture can be subjected to a line probe assay for an early diagnosis of MDR-TB.
- Cultures are the only tests that assay a variety of first and second line drugs, and confirm MDR and XDR-TB.

When you practice in a high-prevalence area of TB, you will save a lot of time for the patient by sending out

Algorithm for Drug-Susceptibility Testing (DST)



cultures early on in the treatment. In a scenario where the patient turns out to have drug-sensitive strains on a culture, you can rest assured you are on the right track, and the money spent on culture and first-line DSTs was worth it. If the patient turns out drug-resistant, then you have saved an enormous amount of time of the patient on diagnosis, and appropriate individualised treatment by the concerned specialist.

Q: WHEN SHOULD YOU REFER THE PATIENT TO A SPECIALIST?

- To confirm the diagnosis of TB, if in doubt
- To obtain invasive samples for testing (e.g., bronchoalveolar lavage, or pleural biopsy)
- To get a treatment plan, if the patient has co-morbidities like diabetes, immunosuppressive conditions, etc. Remember diabetes triples the risk of developing TB, and increase the severity of TB too. Conversely TB can worsen blood glucose control as well, in patients with TB.
- To decide on addition of steroids to an ATT regimen
- If adverse effects are unmanageable at primary care level
- If drug-resistant TB is confirmed (through molecular or culture tests), for a management and monitoring plan
- If lung resection surgery is indicated for any reason, be it for the diagnosis or treatment of the tuberculosis.

Patients can be referred to specialists in either the private/public sector. The Revised National TB Control Program (RNTCP) in India is steadily increasing its capacity to offer MDR-TB therapy via Programmatic Management of Drug-resistant TB (PMDT) centers and hospitals, where free MDR-TB therapy is available. This is a useful option for patients unable to afford private care.

Q: WHAT ARE THE COMMONEST MANAGEMENT ERRORS THAT CAN RESULT IN ACQUIRED DRUG-RESISTANCE?

- Addition of a single drug to a failing regimen. Many physicians add a quinolone to the 4 first-line drugs (HRZE) when the standard therapy does not result in improvement. This is wrong, and believed to be one of the causes of high fluoroquinolone resistance in MDR-TB of late.
- Prescribing only 2 or 3 drugs in the intensive phase. The intensive phase should always have 4 drugs. Otherwise, the bacteria mutate and develop resistance.
- Prescription of second-line drugs in the first instance. Some physicians have the mistaken perception that second-line drugs are more potent than first-line medication. In fact they are less effective (and more toxic) drugs, and should be reserved only for patients with DR-TB, or first-line drug intolerance.
- Prescribing total drugs for an inadequate duration – e.g., 2 to 4 months, instead of the minimum of 6 months.
- Under-dosing of first-line medication is another common problem – many physicians prescribe drug 'kits' or fixed dose combinations (FDCs), in the belief that everyone falls in a fixed weight category. This is obviously not the case. A significant number of patients with TB are significantly underweight and overweight too, and this needs appropriate adjustment of dosing.
- Sometimes, patient switch between doctors, and if the new doctor changes the regimen without adequate drug-susceptibility information, then this might result in inappropriate regimens that increase risk of resistance.
- Patients may feel better and decide to stop taking medications. Premature stoppage occurs, with disastrous consequences on cure, and of course increased risk of drug-resistant bacilli.
- Drug-related side effects (if not adequately counselled on at the outset) is another common reason for non-adherence, and possible treatment default.
- Stigma of the disease and sometimes cost (though not very high for first-line drugs) has been a reason for non-adherence and treatment default in the past.
- Finally, personal/social issues like village travel, death in the family etc. have also been reasons for patients in-

terrupting their treatment at crucial stages (especially intensive phase), with resultant disastrous consequences.

Q: IS IT PROPER TO TREAT MDR-TB (ONCE CONFIRMED) IN GENERAL PRACTICE?

No, this is not advisable for the following reasons:

- MDR and XDR-TB do not have a simple, standardised treatment plan. Drug therapy needs to be customized to the individual patient's DST profile.
- The cost and duration of treatment are significant, and need to be appropriately counselled on.
- The side effects of the various drugs are significant and common, and often difficult to manage. Hospitalization may be required to manage severe cases.
- A significant number of patients default on treatment, spreading the disease further. Hence significant time needs to be spent with the patient, something not easy in a primary care practice.
- A lot of treatment is based on experience of the specialist and his ability to counsel patients and their care-givers appropriately. Early detection and treatment of XDR is also very critical here.
- Finally, a significant number of patients may benefit with surgery in MDR-TB. Examples include decortications, lobectomy and pneumonectomy. Decisions regarding this should be taken by a respiratory physician early in the treatment course, in consultation with an experienced thoracic surgeon. These are decisions beyond the purview of primary care.

Q: IS IT PROPER TO MONITOR MDR-TB TREATMENT IN PRIMARY CARE?

Absolutely, yes. Every patient trusts his or her GP the most, and especially if the GP is competent to manage drug-sensitive TB well, and alert to refer to a specialist when required. These qualities in a GP increase trust by the patient. The patient with MDR-TB will always need a primary care physician to monitor her disease, especially sputum cultures when appropriate, drug-related side effects, communication with the specialist on need for interval bronchoscopies (to ascertain culture status in lung MDR-TB), and decisions on major surgery. Your patient will value your role here.

Q: IN THE ABOVE CONTEXT, WHAT ARE THE SECOND-LINE DRUGS FOR TB AND THEIR SIDE EFFECTS?

Group 1 are the first-line drugs: isoniazid, rifampicin, ethambutol, pyrazinamide

Group 2

Aminoglycosides: (any one drug to be used) Streptomycin, Kanamycin, Amikacin, Capreomycin

- 15 mg/kg/day
- Monitor creatinine, vestibular and ototoxicity
- Check for giddiness, Romberg's sign, tinnitus or reduced hearing as early signs of ototoxicity
- Most MDR-TB patients are streptomycin resistant too, so avoid using streptomycin in an empiric MDR regimen
- Kanamycin and Amikacin exhibit some cross-resistance
- Capreomycin exhibits no cross-resistance
- Patients who are unable to take regular intramuscular injections (up to 6 months at least), may need to take intravenous amikacin through a PICC line

Group 3

Fluoroquinolones (ofloxacin, levofloxacin and moxifloxacin) – any one to be used

- Usually cross-resistant to each other, except for moxifloxacin which can still exhibit activity despite resistance to other fluoroquinolones
- Giddiness, headache and GI upsets are the commonest side effects
- Teratogenic effects
- Concern in small children with growing cartilage

Group 4 – less potent oral agents

Thioamides (ethionamide and prothionamide)

- 15 – 20 mg/kg/day (max 1 gm/day)
- Epigastric discomfort – hence start with 250 mg twice daily initially and then increase the dose if tolerated.
- Hypothyroidism
- Hypoglycaemia
- Teratogenic effects
- Cross-resistance between drugs

Cyloserine and Terizidone

- 10- 20 mg/kg/day
- Altered behaviour, mood swings, suicidal tendencies
- Giddiness, seizures
- Avoid in alcoholics, epileptics and mental illness
- Slurred speech

Para-aminosalicylic acid (PAS)

- 150mg/kg/day in 2 divided doses
- GI upsets
- Avoid the sodium salt in patients needing salt restriction
- Hypothyroidism

Group 5 – Drugs for whom anti-tuberculosis action has not been documented in clinical trials

- Thioacetazone
- Clofazimine
- Linezolid
- Amoxycillin-clavulanic acid
- Clarithromycin
- Imipenam – cilastatin
- High dose isoniazid

New TB drugs for MDR-TB that are not approved for clinical use in India

Two new drugs are now available for TB: bedaquiline and delamanid. Clinical trials on these drugs are ongoing and approval by the Indian regulatory agency is expected in future. Currently, these drugs should

NOT be used by primary care providers. They might be available for specialist use on compassionate grounds.

Bedaquiline:

- SIRTURO® by Janssen Therapeutics ™ (bedaquiline; https://www.sirturo.com/) is a diarylquinoline antimycobacterial drug indicated as part of combination therapy in adults (≥18 years) with pulmonary multi-drug resistant tuberculosis (MDR-TB).
- SIRTURO was the first new TB drug with a novel mechanism of action to be made available for more than 40 years and was granted accelerated approval by the United States FDA. It is still in Phase III trials.
- SIRTURO is restricted for use only when an effective treatment regimen cannot otherwise be provided.

Delamanid:

- Delamanid (also known by its trade name, Deltyba® by Otsuka Pharmaceutical Co., Ltd) is a drug in the nitroimidazole class.
- Delamanid is a new potential option for people with MDR-TB who lack effective, tolerable treatments.
- Delamanid was granted conditional approval by the European Medicine Agency in April 2014. Information about this new drug is limited, since it has only been through Phase IIb trial and studies for safety and efficacy.

Interim policy guidance on these new drugs is available from WHO.[8]

Q: WHAT ARE THE THINGS TO REMEMBER WHEN CHECKING THE PRESCRIPTION OF A SPECIALIST FOR MDR-TB?

- As a GP, your role is paramount. A good primary care physician can be alert to wrong prescriptions and remind a specialist at times, that the direction or plan of treatment is wrong. Remember you see the patient far more frequently than the specialist.
- Check that at least 4 new drugs have been commenced, preferably one from Group 2 and 3, and 2 more, from **Group 3, 4** or **both** (depending on whether the patient has MDR, XDR or TDR TB)
- Check that none of the drugs are contra-indicated for your patient:

- Hearing loss pre-existing	- Chronic kidney disease
- Mental illness	- Pre-existing seizure disorder
- Visual disturbances	- Pre-existing sever gastritis

- Do a skin sensitivity test before administering the aminoglycoside the first time.
- A drug that was used within a previous failing regimen should never be used again if possible, and should not be counted in the total of 4 drugs for re-treatment.
- Monitor CBC and platelets in patient on linezolid
- Monitor for visual disturbances in patient on linezolid.

Q: QUESTIONS YOU NEED TO ASK THE SPECIALIST PERIODICALLY DURING THE TREATMENT OF MDR-TB?

- Is the patient non-infectious?
- When do you next need a sputum/bronchoscopic sample for AFB culture?
- When should the next round of chest x-rays be done?
- Is a CT scan chest indicated, and if so, for what purpose?
- If there is a persistent cavity despite clinical improvement, how can we ensure the patient is still not harbouring active infection? (usually a bronchoscopic aspirate is indicated here)
- What is the likely total cost of treatment, excluding any surgery?
- Is the patient a candidate for surgery, and if so what is the likely cost?
- How long do you expect the entire duration of treatment to last?

It is very important to ask these questions, since the same message (specialist's) needs to be constantly reinforced by the primary care physician as well, to ensure better adherence at all stages of treatment.

All in all, remember that treating and supervising MDR-TB management in clinical practice is a big responsibility and needs commitment and time. If you are unable to manage the same, refer to an appropriate specialist. Never feel you will lose your patient that way. Your role to monitor for side effects is paramount; so too your role in ensuring adherence. Patients are ever-grateful when they are referred to the right specialists. Their confidence in you (as their primary care physician) will only increase. ■

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