Drug-Resistant Tuberculosis:
10 Principles for Effective Management

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Multidrug-resistant (MDRTB) and extensively drug-resistant TB (XDR-TB) are demanding conditions to treat and are best managed by a specialist with experience in treating such severe forms of TB. Alternatively, such patients are best referred to the national TB program (RNTCP) where they are now offered the standardised Category 4 or Category 5 treatment depending on whether they are MDR or XDR, respectively. So, GPs should always seek help in the management of MDR and XDR-TB.

MDR-TB refers to *M. tuberculosis* resistance to at least isoniazid and rifampicin, the two key first-line antibiotics. Extensively drug-resistant (XDR) TB disease, which causes even more-severe disease manifestations, is not only resistant to isoniazid and rifampicin, but also any fluoroquinolone and any of the three injectable second-line antibiotics.

Even in the best hospitals, under optimal conditions, global treatment success rates are in the vicinity of 60% for MDR-TB and 44% for XDR-TB. Errors in treatment amplify resistance and convert MDR strains to XDR-TB and beyond. The 10 principles outlined here maximise the chances of successful outcome.

PRINCIPLE 1: Plan your regimen based on a careful drug history coupled with the drug susceptibility test (DST) report from a reliable, quality assured, laboratory. DST requires liquid cultures, supplemented with rapid molecifular tests such as Xpert MTB/RIF, and line probe assays (Hain Genotype MTBDRplus for first-line drugs, and Hain Genotype MTBDRsl for second-line drugs).

PRINCIPLE 2: Include the right number of drugs (**Table** shows the available drugs, categorized into groups by WHO). Too many drugs risks toxicity, while too few increases the risk of treatment failure. WHO recommends 4 new drugs (to which the TB bacteria are sensitive) while a more recent article suggests 6 drugs may be ideal.

PRINCIPLE 3: Select drugs from the following groups when composing the regimen:

i. include any first-line drugs to which the patient is still sensitive e.g., ethambutol or pyrazinamide. These should be included but not "counted" as one of the 4 new drugs.

ii. use a Group A fluoroquinolone (FQ). Levofloxacin and moxifloxacin are the preferred FQ's. The exact doses are unclear but most experts feel up to 1000mg of levofloxacin and 600mg of moxifloxacin per day might be ideal.

iii. use a Group B 2nd line injectable aminoglycoside to which the organism is sensitive. The injectable should be used for at least 6-8 months, ideally 5 days a week.

iv. add Group C drugs to make up the desired 5 drugs in the regimen. These drugs (e.g., cycloserine, ethionamide) are bacteriostatic and have considerable toxicity. The WHO recommends that ethionamide, being the most effective, should be introduced first.

v. add other Group C or D3 drugs if the requisite number of drugs has not been met yet, depending on disease burden and pattern of resistance. The most effective but most toxic drug in this group is linezolid. This drug should, however, be used with great caution because of the high risk of toxicity. Toxicities frequently encountered include peripheral neuropathy, anemia and optic neuritis. Clofazamine is an old but useful drug and should be added to most regimens. Meropenem-clavulanate is extremely expensive and since it is administered intravenously, ideally needs a IV port to be inserted, which adds to the cost. The new 2016 WHO guidelines differ from the earlier guidelines in that they have specifically dropped clarithromycin (which is useful for *Mycobacterium avium complex* (MAC) infections but not for *M. tuberculosis*), and amoxicillin/clavulanate (which has no anti-mycobacterial activity on its own).

vi. try and access new drugs (D2) for highly resistant strains. Bedaqualine (Sirturo®) and Delamanid (Deltyba®) are both difficult to access in India, but should be considered for 6 months for highly resistant strains or treatment failures

Table. WHO classification of TB drugs used for MDR-TB[1]

A. Fluoroquinolones[2]		Levofloxacin	Lfx
		Moxifloxacin	Mfx
		Gatifloxacin	Gfx
B. Second-line inhectable agents		Amikacin	Am
		Capreomycin	Cm
		Kanamycin	Km
		(Streptomycin)[3]	(S)
C. Other core second-line agents[2]		Ethionamide / Prothionamide	Eto / Pto
		Cycloserine / Terizdone	Cs / Trd
		Linezolid	Lzd
		Clofazimine	Cfz
D. Add-on agents (not part of the core MDR-TB regimen)	**D1**	Pyrazinamide	Z
		Ethambutol	E
		High-dose isoniazid	Hh
	D2	Bedaquilline	Bdq
		Delamanid	Dlm
	D3	Para-aminosalicylic acid	PAS
		Imipenem-cilastatin[4]	Ipm
		Meropenem[4]	Mpm
		Amoxicillin-clavulante[4]	Amz-Civ
		(Thioacetazone)[5]	(T)

1. This regrouping is intended to guide the design of conventional regimens; for shorter regimens lasting 9-12 months the composition is usually standardised (See WHO MDR-TB guidelines)
2. Medicines in Groups A and C are shown by decreasing order of usual preference for use
3. Refer to the WHO guidelines for the conditions under which streptomycin may substitute other injectable agents. Resistance to streptomycin alone does not qualify for the definition of extensively drug-resistant TB (XDR-TB)
4. Carbapenems and clavulanate are meant to be used together; clavulanate is only available in formulations combined with amoxicillin
5. HIV-status must be tested and confirmed to be negative before thioacetazone is started

Source: WHO, Geneva http://www.who.int/tb/MDRTBguidelines2016.pdf

PRINCIPLE 4: Treat for the right duration. The current WHO recommendation for total duration of treatment stands at around 22 months. The Bangladesh regimen, which WHO calls the Shorter MDR-TB regimen, is an exciting new development, which attempts to shorten the duration of treatment to just 9-12 months. According to the updated 2016 WHO guideline, in selected patients with rifampicin-resistant or MDR-TB who have not been previously treated with second-line drugs and in whom resistance to fluoroquinolones and second-line injectable agents has been excluded or is considered highly unlikely, this shorter regimen of 9-12 months may be used instead of a conventional regimen. Sadly, a majority of Indian MDR-TB patients are likely to have been already treated before seeing a specialist, and hence it is unlikely this regimen would work in a high burden country like India.

PRINCIPLE 5: Use the right doses at the highest end of the range to compensate for the inherent weakness of these drugs. Bear in mind that wrong doses contribute to treatment failure and toxicity. Therapeutic drug monitoring (TDM) is useful but is available in no more than a handful of centres across the world.

PRINCIPLE 6: Treatment should be administered daily (no role for intermittent therapy here) and ideally under close supervision (e.g., directly observed therapy). Regular cultures are necessary to monitor treatment efficacy.

PRINCIPLE 7: Monitor closely for toxicity. Major adverse effects (including life threatening ones) occur in as many as 40-60% of MDR and XDR cohorts and must be anticipated and carefully monitored for.

PRINCIPLE 8: Early surgery should be considered whenever feasible. Indeed, the more resistant strain, the lower the threshold for surgery. Surgery must be performed by an experienced surgeon in the patient with localised disease, with enough respiratory reserve to withstand this often high-risk procedure.

PRINCIPLE 9: Empathise, support and motivate. This prolonged and toxic treatment will only succeed with patient-centric support from the treating physician.

PRINCIPLE 10: Address the social determinants and comorbid conditions that often accompany TB. TB is a social disease and a holistic approach that attempts to improve the general poverty, malnutrition, smoking, biomass exposure, and diabetes that often co-exist is of vital importance. ■

SUGGESTED READING:

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Multidrug-Resistant Tuberculosis (MDR TB)—Fact Sheet

1 How does drug resistance happen?

Resistance to anti-TB drugs can occur when these drugs are misused or mismanaged. Examples include when patients do not complete their full course of treatment; when health-care providers prescribe the wrong treatment, the wrong dose, or length of time for taking the drugs; when the supply of drugs is not always available; or when the drugs are of poor quality.

2 Who is at risk for getting MDR TB?

Drug resistance is more common in people who:

- Do not take their TB medicine regularly
- Do not take all of their TB medicine as told by their doctor or nurse
- Develop TB disease again, after having taken TB medicine in the past
- Come from areas of the world where drug-resistant TB is common
- Have spent time with someone known to have drug-resistant TB disease

3 How can MDR TB be prevented?

The most important thing a person can do to prevent the spread of MDR TB is to take all of their medications exactly as prescribed by their health care provider. No doses should be missed and treatment should not be stopped early. Patients should tell their health care provider if they are having trouble taking the medications. If patients plan to travel, they should talk to their health care providers and make sure they have enough medicine to last while away.

Health care providers can help prevent MDR TB by quickly diagnosing cases, following recommended treatment guidelines, monitoring patients' response to treatment, and making sure therapy is completed.

Another way to prevent getting MDR TB is to avoid exposure to known MDR TB patients in closed or crowded places such as hospitals, prisons, or homeless shelters. If you work in hospitals or health-care settings where TB patients are likely to be seen, you should consult infection control or occupational health experts. If the patient with DR-TB wears a mask he/she can reduce the transmission of TB to household contacts.

Source: CDC, USA http://www.cdc.gov/tb/publications/factsheets/drtb/mdrtb.htm