

CHAPTER 8

Mono- and poly-resistant strains (drug-resistant tuberculosis other than MDR-TB)

8.1 Chapter objectives

This chapter describes the recommended treatment strategies for patients with drug-resistant TB other than MDR-TB. These include patients with mono-resistant TB and patients with poly-resistant TB other than MDR-TB. Mono-resistance refers to resistance to a single first-line drug, and poly-resistance refers to resistance to two or more first-line drugs.

8.2 General considerations

WHO does not recommend the inclusion of specific efforts to diagnose mono- and poly-resistant strains of TB in routine DOTS programmes. However, cases with mono- or poly-resistance will be identified during the course of case-finding for MDR-TB. Treatment of patients infected with mono- or poly-resistant strains using standardized short-course chemotherapy has been associated with increased risk of treatment failure and further acquired resistance, including the development of MDR-TB (1–2). While the likelihood of poor outcomes is relatively low with many types of mono- and poly-resistance (i.e. the majority of patients with mono- or poly-resistant strains will be cured with short-course chemotherapy), programmes can use different regimens based on DST patterns as described below.

8.3 Consequences for reporting

Patients whose regimens require minor adjustments (with no risk of amplification that would require the use of an empirical regimen for MDR-TB) should be recorded in the traditional District Tuberculosis Register. These regimens are considered “modifications” of Category I or Category II treatment. They are not classified as Category IV treatments, which are regimens designed to treat MDR-TB. The adjustment should be noted in the comments section of the Register and the adjusted treatment continued for the indicated length of time.

8.4 Treatment of patients with mono- and poly-resistant strains

Definitive randomized or controlled studies have not been performed to determine the best treatment for various patterns of drug resistance, except for

streptomycin resistance. The recommendations in these guidelines are based on evidence from the pre-rifampicin era, observational studies, general principles of microbiology and therapeutics in TB, extrapolations from established evidence and expert opinion. When a decision has been made to modify standard short-course chemotherapy, the most effective regimen should be chosen from the start to maximize the likelihood of cure; effective drugs should not be withheld for later use.

Table 8.1 gives suggested regimens for different DST patterns. When using this table, it is essential to consider whether resistance has been acquired to any of the drugs that will be used in the recommended regimen.

- **Development of further resistance.** Further resistance should be suspected if the patient was on the functional equivalent of only one drug for a significant period of time (usually considered as one month or more, but even periods of less than one month on inadequate therapy can lead to resistance). Sometimes resistance develops if the patient was on the functional equivalent of two drugs, depending on the drugs concerned. For example, pyrazinamide is not considered a good companion drug to prevent resistance. If a patient was receiving functionally only rifampicin and pyrazinamide in the initial phase (because of resistance to isoniazid and ethambutol), resistance to rifampicin may develop. Thus, it is crucial to consider which functional drugs the patient received between the time of DST specimen collection and the time of the new regimen design (i.e. consider whether resistance has developed to any of the functional drugs).
- **DST results.** The DST result that prompts a change in treatment may not accurately reflect the bacterial population at the time it is reported since it reflects the bacterial population at the time the sputum was collected. The regimens in Table 8.1 are based on the assumption that the pattern of drug resistance has not changed during this interval. Table 8.1 should therefore *not* be used if further resistance to any of the agents in the suggested regimen is suspected. It is also important to note that a high level of confidence in the laboratory is needed for effective use of Table 8.1.

Table 8.1 assumes that pyrazinamide susceptibility is being tested, which is not the case for many countries. If DST of pyrazinamide is not being carried out, pyrazinamide cannot be depended upon as being an effective drug in the regimen. In such situations, regimens from Table 8.1 that assume the TB strain to be resistant should be used. Some clinicians would add pyrazinamide to those regimens because a significant percentage of patients could benefit from the drug.

The design of regimens for mono- and poly-resistant cases of TB requires experience; it is recommended for programmes with good infrastructure and capable of treating MDR-TB. Individually designed treatments for mono- and poly-resistance are often decided by a review panel that meets

TABLE 8.1 **Suggested regimens for mono- and poly-drug resistance^a**
(when further acquired resistance is not a factor and laboratory results are highly reliable)

PATTERN OF DRUG RESISTANCE	SUGGESTED REGIMEN	MINIMUM DURATION OF TREATMENT (MONTHS)	COMMENTS
H (± S)	R, Z and E	6–9	A fluoroquinolone may strengthen the regimen for patients with extensive disease.
H and Z	R, E and fluoroquinolones	9–12	A longer duration of treatment should be used for patients with extensive disease.
H and E	R, Z and fluoroquinolones	9–12	A longer duration of treatment should be used for patients with extensive disease.
R	H, E, fluoroquinolones, plus at least 2 months of Z	12–18	An injectable agent may strengthen the regimen for patients with extensive disease.
R and E (± S)	H, Z, fluoroquinolones, plus an injectable agent for at least the first 2–3 months	18	A longer course (6 months) of the injectable agent may strengthen the regimen for patients with extensive disease.
R and Z (± S)	H, E, fluoroquinolones, plus an injectable agent for at least the first 2–3 months	18	A longer course (6 months) of the injectable agent may strengthen the regimen for patients with extensive disease.
H, E, Z (± S)	R, fluoroquinolones, plus an oral second-line agent, plus an injectable agent for the first 2–3 months	18	A longer course (6 months) of the injectable agent may strengthen the regimen for patients with extensive disease.

H = isoniazid; R = rifampicin; E = ethambutol; Z = pyrazinamide; S = streptomycin

^a Adapted from *Drug-resistant tuberculosis: a survival guide for clinicians* (3)

periodically. The panel consists of specialized personnel who are trained in the treatment of drug-resistant TB. The panel reviews the treatment history, DST patterns and the possibility of strains of *M. tuberculosis* having acquired new resistance, and then determines the regimen.

Box 8.1 provides an example to illustrate the risk of additional acquired resistance while awaiting DST results.

BOX 8.1**Example of regimen design for mono- and poly-resistant strains**

This example is from a setting where representative DRS data indicate that 85% of failures of Category I have MDR-TB. A patient who has received a Category I regimen of HRZE has a culture sent for DST at month 3 of treatment because of a positive smear. The intensive phase is continued for an additional month, at which time the smear is negative, and the patient is placed on the continuation phase of treatment with HR. The DST returns in month 4 of treatment with resistance to HE and susceptibility to S. DST is not known for Z. The patient is sputum smear-positive at month 4. What regimen should be used?

Answer: The patient has been on at least one month of functional monotherapy with R, and if the Z is resistant he or she may have been on monotherapy with R for four months. In this case, **do not use Table 8.1** to design the regimen; instead, assume the patient may have now developed resistance to R, and design a Category IV regimen based on the principles for MDR-TB regimen design described in Chapter 4.

References

1. Quy HT et al. Drug resistance among failure and relapse cases of tuberculosis: is the standard re-treatment regimen adequate? *International Journal of Tuberculosis and Lung Disease*, 2003, 7(7):631–636.
2. Tuberculosis Research Centre, Chennai, India. Low rate of emergence of drug resistance in sputum positive patients treated with short course chemotherapy. *International Journal of Tuberculosis and Lung Disease*, 2001, 5(1):40–45.
3. *Drug-resistant tuberculosis: a survival guide for clinicians*. San Francisco, Francis J. Curry National Tuberculosis Center and California Department of Health Services, 2004.