

CHAPTER 9

Treatment of drug-resistant tuberculosis in special conditions and situations

9.1 Chapter objectives

This chapter outlines the management of drug-resistant TB in the following special conditions and situations:

- pregnancy,
- breastfeeding,
- contraception,
- children,
- diabetes mellitus,
- renal insufficiency,
- liver disorders,
- seizure disorders,
- psychiatric disorders,
- substance dependence.

HIV infection is addressed separately in Chapter 10.

9.2 Pregnancy

All female patients of childbearing age should be tested for pregnancy upon initial evaluation. Pregnancy is not a contraindication for treatment of active drug-resistant TB, which poses great risks to the lives of both mother and fetus (1–2). However, birth control is strongly recommended for all non-pregnant women receiving therapy for drug-resistant TB because of the potential consequences for both mother and fetus resulting from frequent and severe adverse drug reactions.

Pregnant patients should be carefully evaluated, taking into consideration gestational age and severity of the drug-resistant TB. The risks and benefits of treatment should be carefully considered, with the primary goal of smear conversion to protect the health of the mother and child, both before and after birth. The following are some general guidelines.

- **Start treatment of drug resistance in second trimester or sooner if condition of patient is severe.** Since the majority of teratogenic effects occur in the first trimester, therapy may be delayed until the second trimester. The decision to postpone the start of treatment should be agreed by both

patient and doctor after analysis of the risks and benefits. It is based primarily on the clinical judgment resulting from the analysis of life-threatening signs/symptoms and severity/aggressiveness of the disease (usually reflected in extent of weight loss and lung affection during the previous weeks). When therapy is started, three or four oral drugs with demonstrated efficacy against the infecting strain should be used and then reinforced with an injectable agent and possibly other drugs immediately postpartum (3).

- **Avoid injectable agents.** For the most part, aminoglycosides should not be used in the regimens of pregnant patients and can be particularly toxic to the developing fetal ear. Capreomycin may carry the same risk of ototoxicity but is the injectable drug of choice if an injectable agent cannot be avoided.
- **Avoid ethionamide.** Ethionamide can increase the risk of nausea and vomiting associated with pregnancy, and teratogenic effects have been observed in animal studies. If possible, ethionamide should be avoided in pregnant patients.

9.3 Breastfeeding

A woman who is breastfeeding and has active drug-resistant TB should receive a full course of antituberculosis treatment. Timely and properly applied chemotherapy is the best way to prevent transmission of tubercle bacilli to her baby.

In lactating mothers on treatment, most antituberculosis drugs will be found in the breast milk in concentrations that would equal only a small fraction of the therapeutic dose used in an infant. However, any effects on infants of such exposure during the full course of MDR-TB treatment have not been established. Therefore, when resources and training are available, it is recommended to provide infant formula options as an alternative to breastfeeding. When infant formula is provided, fuel for boiling water and the necessary apparatus (stove, heating pans and bottles) must also be provided, as well as training on how to prepare and use the infant formula. All this should be free of charge to poor patients, and DR-TB control programmes should therefore budget in advance for the estimated number of patients who might need this support.

The mother and her baby should not be completely separated. However, if the mother is sputum smear-positive, the care of the infant should be left to family members until she becomes sputum smear-negative, if this is feasible. When the mother and infant are together, this common time should be spent in well-ventilated areas or outdoors. In some settings, the mother may be offered the option of using a surgical mask or an N-95 respirator (see Chapter 15) until she becomes sputum smear-negative.

9.4 Contraception

There is no contraindication to the use of oral contraceptives with the non-rifamycin containing regimens. Patients who vomit directly after taking an oral contraceptive can be at risk of decreased absorption of the drug and therefore of decreased efficacy. These patients should be advised to take their contraceptives apart from times when they may experience vomiting caused by the antituberculosis treatment. Patients who vomit at any time directly after, or within the first two hours after, taking the contraceptive tablet, should use a barrier method of contraception until a full month of the contraceptive tablets can be tolerated.

For patients with mono- and poly-resistant TB that is susceptible to rifampicin, the use of rifampicin interacts with the contraceptive drugs resulting in decreased efficacy of protection against pregnancy. A woman on oral contraception while receiving rifampicin treatment may choose between two options: following consultation with a physician, use of an oral contraceptive pill containing a higher dose of estrogen (50 µg); or use of another form of contraception.

9.5 Children

Children with drug-resistant TB generally have primary resistance transmitted from an index case with drug-resistant TB. When DST is available it should be used to guide therapy, although children with paucibacillary TB are often culture-negative. Nevertheless, every effort should be made to confirm drug-resistant TB bacteriologically by the use of DST and to avoid exposing children unnecessarily to toxic drugs.

The treatment of culture-negative children with clinical evidence of active TB disease and contact with a documented case of drug-resistant TB should be guided by the results of DST and the history of the contact's exposure to antituberculosis drugs (also see Chapter 14) (4).

There is only limited reported experience with the use of second-line drugs for extended periods in children. The risks and benefits of each drug should be carefully considered in designing a regimen. Frank discussion with family members is critical, especially at the outset of therapy. MDR-TB is life-threatening, and no antituberculosis drugs are absolutely contraindicated in children. Children who have received treatment for drug-resistant TB have generally tolerated the second-line drugs well (4–5).

Although fluoroquinolones have been shown to retard cartilage development in beagle puppies (6), experience with the use of fluoroquinolones has not demonstrated similar effects in humans (7–8). It is considered that the benefit of fluoroquinolones in treating MDR-TB in children outweighs any risk. Additionally, ethionamide, PAS and cycloserine have been used effectively in children and are well tolerated.

In general, antituberculosis drugs should be dosed according to body weight (see Table 9.1). Monthly monitoring of body weight is therefore especially important in paediatric cases, with adjustment of doses as children gain weight (9).

All drugs, including the fluoroquinolones, should be dosed at the higher end of the recommended ranges whenever possible, except ethambutol. Ethambutol should be dosed at 15 mg/kg, and not at 25 mg/kg as sometimes used in adults with MDR-TB, as it is more difficult to monitor for optic neuritis in children.

In children who are not culture-positive initially, treatment failure is difficult to assess. Persistent abnormalities on chest radiograph do not necessarily signify a lack of improvement. In children, weight loss or, more commonly, failure to gain weight adequately, is of particular concern and often one of the first (or only) signs of treatment failure. This is another key reason to monitor weight carefully in children.

TABLE 9.1 Paediatric dosing of second-line antituberculosis drugs (4, 10)

DRUG	DAILY DOSE (MG/KG)	FREQUENCY	MAXIMUM DAILY DOSE
Streptomycin	20–40	Once daily	1 g
Kanamycin	15–30	Once daily	1 g
Amikacin	15–22.5	Once daily	1 g
Capreomycin	15–30	Once daily	1 g
Ciprofloxacin	20–40	Twice daily	2 g
Ofloxacin	15–20	Twice daily	800 mg
Levofloxacin	7.5–10	Once daily	750 mg
Moxifloxacin	7.5–10	Once daily	400 mg
Gatifloxacin	7.5–10	Once daily	400 mg
Ethionamide	15–20	Twice daily	1 g
Protonamide	15–20	Twice daily	1 g
Cycloserine	10–20	Once or twice daily	1 g
<i>P</i> -aminosalicylic acid	150	Twice or thrice daily	12 g

Anecdotal evidence suggests that adolescents are at high risk for poor treatment outcomes. Early diagnosis, strong social support, individual and family counselling and a close relationship with the medical provider may help to improve outcomes in this group.

9.6 Diabetes mellitus

Diabetic patients with MDR-TB are at risk for poor outcomes. In addition, the presence of diabetes mellitus may potentiate the adverse effects of antituberculosis drugs, especially renal dysfunction and peripheral neuropathy. Diabetes must be managed closely throughout the treatment of drug-resistant TB. The health-care provider should be in close communication with the physician who manages the patient's diabetes. Oral hypoglycaemic agents are not contraindicated during the treatment of drug-resistant TB but may require the patient to

BOX 9.1**Example of regimen design for paediatric cases**

A mother who has been following treatment for MDR-TB for 9 months has been smear- and culture-negative for 6 months. She brings her child to the health centre for evaluation. The child is 14 months old and weighs 6.9 kg. She had BCG at birth and now presents with 4 months of failure to thrive, poor appetite and intermittent low grade fever for 3 months. Tuberculin (PPD) skin testing is 16 mm, and chest radiography reveals hilar adenopathy but no infiltrates. There are no other known TB contacts. TB was first diagnosed in the mother shortly after giving birth to the child; she is a patient who had both Category I and II treatment failure. Her resistance pattern from the start of treatment for drug-resistant TB is:

- Resistance to H,R,Z,E,S
- Susceptible to Am-Cm-Ofx-Eto
- DST to PAS and Cs not done

What advice and regimen do you prescribe for the child?

Answer: It should be well explained to the mother that the child very likely has TB, most probably MDR-TB. If available, DST should be attempted (see Chapter 14). While waiting for the DST results, or if the diagnostic procedure is not available, the child should be started on an empirical regimen based on the DST pattern of the mother. The following regimen is indicated:

injectable agent-fluoroquinolone-Eto(Pto)-Cs

or

injectable agent-fluoroquinolone-PAS-Cs

The injectable agent can be any drug except S, in this case Km, Cm or Am.

To illustrate dose calculation, the example for the regimen of Km-Ofx-Pto-Cs is given below. Both the low and high doses for the child's weight are calculated; a convenient dosing is then chosen between the two numbers (if necessary a pharmacist can mix the exact dose so that any milligram amount can be selected, and dosing is not limited to $\frac{1}{4}$ or $\frac{1}{2}$ tablets):

Kanamycin: (15 mg x 6.9 kg = 103 and 30 mg x 6.9 kg = 207). Select a dose between the two numbers e.g. **200 mg per day, single dose.**

Ofloxacin: (15 mg x 6.9 kg = 103 and 20 mg x 6.9 kg = 138). A convenient dosing is 100 mg/day; this is the full daily dose. Table 9.1 indicates that the daily dose is given in divided doses, so the patient would receive **50 mg ($\frac{1}{4}$ tablet) in the morning and 50 mg ($\frac{1}{4}$ tablet) in the evening.**

Protonamide: (15 mg x 6.9 kg = 103 and 20 mg x 6.9 kg = 138). A convenient dosing is 125 mg/day; this is the full daily dose. Table 9.1 indicates that the daily dose is given in divided doses, so the patient would receive **62.5 mg ($\frac{1}{4}$ tablet) in the morning and 62.5 mg ($\frac{1}{4}$ tablet) in the evening.**

Cycloserine: (15 mg x 6.9 kg = 103 and 20 mg x 6.9 kg = 138). A convenient dosing is 125 mg/day. This is the full daily dose. Table 9.1 indicates that the daily dose is given in divided doses, so the patient would receive **62.5 mg ($\frac{1}{4}$ capsule) in the morning and 62.5 mg ($\frac{1}{4}$ capsule) in the evening.**

AS THE CHILD GAINS WEIGHT THE DOSES WILL HAVE TO BE ADJUSTED (CHECK WEIGHT EVERY MONTH)

increase the dosage. Use of ethionamide or prothionamide may make it more difficult to control insulin levels. Creatinine and potassium levels should be monitored more frequently, often weekly for the first month and then at least monthly thereafter.

9.7 Renal insufficiency

Renal insufficiency caused by longstanding TB infection itself or previous use of aminoglycosides is not uncommon. Great care should be taken in the administration of second-line drugs in patients with renal insufficiency, and the dose and/or the interval between dosing should be adjusted according to Table 9.2.

9.8 Liver disorders

The first-line drugs isoniazid, rifampicin and pyrazinamide are all associated with hepatotoxicity. Of the three, rifampicin is least likely to cause hepatocellular damage, although it is associated with cholestatic jaundice. Pyrazinamide is the most hepatotoxic of the three first-line drugs. Among the second-line drugs, ethionamide, prothionamide and PAS can also be hepatotoxic, although less so than any of the first-line drugs. Hepatitis occurs rarely with the fluoroquinolones.

Patients with a history of liver disease can receive the usual drug-resistant TB chemotherapy regimens provided there is no clinical evidence of chronic liver disease, hepatitis virus carriage, past history of acute hepatitis or excessive alcohol consumption. However, hepatotoxic reactions to antituberculosis drugs may be more common in these patients and should be anticipated.

In general, patients with chronic liver disease should not receive pyrazinamide. All other drugs can be used, but close monitoring of liver enzymes is advised. If significant aggravation of liver inflammation occurs, the drugs responsible may have to be stopped.

Uncommonly, a patient with TB may have concurrent acute hepatitis that is unrelated to TB or antituberculosis treatment. In this case, clinical judgement is necessary. In some cases, it is possible to defer antituberculosis treatment until the acute hepatitis has been resolved. In other cases when it is necessary to treat drug-resistant TB during acute hepatitis, the combination of four non-hepatotoxic drugs is the safest option.

9.9 Seizure disorders

Some patients requiring treatment for drug-resistant TB will have a previous or current medical history of a seizure disorder. The first step in evaluating such patients is to determine whether the seizure disorder is under control and whether the patient is taking anti-seizure medication. If the seizures are not under control, initiation or adjustment of anti-seizure medication will be

TABLE 9.2 **Adjustment of antituberculosis medication in renal insufficiency^a**

DRUG	CHANGE IN FREQUENCY?	RECOMMENDED DOSE ^b AND FREQUENCY FOR PATIENTS WITH CREATININE CLEARANCE <30 ml/min OR FOR PATIENTS RECEIVING HAEMODIALYSIS
Isoniazid	No change	300 mg once daily, or 900 mg three times per week
Rifampicin	No change	600 mg once daily, or 600 mg three times per week
Pyrazinamide	Yes	25–35 mg/kg per dose three times per week (not daily)
Ethambutol	Yes	15–25 mg/kg per dose three times per week (not daily)
Ciprofloxacin	Yes	1000–1500 mg per dose three times per week (not daily)
Ofloxacin	Yes	600–800 mg per dose three times per week (not daily)
Levofloxacin	Yes	750–1000 mg per dose three times per week (not daily)
Moxifloxacin	No change	400 mg once daily
Gatifloxacin	Yes	400 mg per dose three times per week (not daily)
Cycloserine	Yes	250 mg once daily, or 500 mg/dose three times per week ^c
Terizidone	–	Recommendations not available
Protionamide	No change	250–500 mg per dose daily
Ethionamide	No change	250–500 mg per dose daily
<i>P</i> -aminosalicylic acid ^d	No change	4 g/dose, twice daily
Streptomycin	Yes	12–15 mg/kg per dose two or three times per week (not daily) ^e
Capreomycin	Yes	12–15 mg/kg per dose two or three times per week (not daily) ^e
Kanamycin	Yes	12–15 mg/kg per dose two or three times per week (not daily) ^e
Amikacin	Yes	12–15 mg/kg per dose two or three times per week (not daily) ^e

a Adapted from *Treatment of tuberculosis* (11).

b To take advantage of the concentration-dependent bactericidal effect of many antituberculosis drugs, standard doses are given unless there is intolerance.

c The appropriateness of 250 mg daily doses has not been established. There should be careful monitoring for evidence of neurotoxicity (if possible measure serum concentrations and adjust accordingly).

d Sodium salt formulations of PAS may result in an excessive sodium load and should be avoided in patients with renal insufficiency. Formulations of PAS that do not use the sodium salt can be used without the hazard of sodium retention.

e Caution should be used with the injectable agents in patients with renal function impairment because of the increased risk of both ototoxicity and nephrotoxicity.

needed before the start of drug-resistant TB therapy. In addition, any other underlying conditions or causes of seizures should be corrected.

Cycloserine should be avoided in patients with active seizure disorders that are not well controlled with medication. However, in cases where cycloserine is a crucial component of the treatment regimen, it can be given and the anti-seizure medication adjusted as needed to control the seizure disorder. The risks and benefits of using cycloserine should be discussed with the patient and the decision on whether to use cycloserine made together with the patient.

In mono- and poly-resistant cases, the use of isoniazid and rifampicin may interfere with many of the anti-seizure medications. Drug interactions should be checked before their use (see Annex 1 for drug interactions).

Seizures that present for the first time during antituberculosis therapy are likely to be the result of an adverse effect of one of the antituberculosis drugs. More information on the specific strategies and protocols to address adverse effects is provided in Chapter 11.

9.10 Psychiatric disorders

It is advisable for psychiatric patients to be evaluated by a health-care worker with psychiatric training before the start of treatment for drug-resistant TB. The initial evaluation documents any existing psychiatric condition and establishes a baseline for comparison if new psychiatric symptoms develop while the patient is on treatment. Any psychiatric illness identified at the start of or during treatment should be fully addressed. There is a high baseline incidence of depression and anxiety in patients with MDR-TB, often connected with the chronicity and socioeconomic stress factors related to the disease.

Treatment with psychiatric medication, individual counselling and/or group therapy may be necessary to manage the patient suffering from a psychiatric condition or an adverse psychiatric effect caused by medication. Group therapy has been very successful in providing a supportive environment for MDR-TB patients and may be helpful for patients with or without psychiatric conditions. (Adequate measures to prevent infection risk should be in place for the group therapy.)

The use of cycloserine is not absolutely contraindicated for the psychiatric patient. Adverse effects from cycloserine may be more prevalent in the psychiatric patient, but the benefits of using this drug may outweigh the potentially higher risk of adverse effects. Close monitoring is recommended if cycloserine is used in patients with psychiatric disorders.

All health-care workers treating drug-resistant TB should work closely with a mental health specialist and have an organized system for psychiatric emergencies. Psychiatric emergencies include psychosis, suicidal ideation and any situation involving the patient's being a danger to him or herself or others. Additional information on psychiatric adverse effects is provided in Chapter 11, Table 11.3.

9.11 Substance dependence

Patients with substance dependence disorders should be offered treatment for their addiction. Complete abstinence from alcohol or other substances should be strongly encouraged, although active consumption is not a contraindication for antituberculosis treatment. If the treatment is repeatedly interrupted because of the patient's dependence, therapy should be suspended until successful treatment or measures to ensure adherence have been established. Good DOT gives the patient contact with and support from health-care providers, which often allows complete treatment even in patients with substance dependence.

Cycloserine will have a higher incidence of adverse effects (as in the psychiatric patient) in patients dependent on alcohol or other substances, including a higher incidence of seizures. However, if cycloserine is considered important to the regimen, it should be used and the patient closely observed for adverse effects, which are then adequately treated.

9.12 HIV-infected patients

Given the important interaction between HIV infection and drug-susceptible and drug-resistant TB, a full chapter (Chapter 10) is devoted to this subject.

References

1. Figueroa-Damián R, Arredondo-García JL. Neonatal outcome of children born to women with tuberculosis. *Archives of Medical Research*, 2001, 32(1):66–69.
2. Brost BC, Newman RB. The maternal and fetal effects of tuberculosis therapy. *Obstetrics and Gynecology Clinics of North America*, 1997, 24(3):659–673.
3. Duff P. Antibiotic selection in obstetric patients. *Infectious Disease Clinics of North America*, 1997, 11(1):1–12.
4. Swanson DS, Starke JR. Drug resistant tuberculosis in pediatrics. *Pediatric Clinics of North America*, 1995, 42(3):553–581.
5. Mukherjee JS et al. Clinical and programmatic considerations in the treatment of MDR-TB in children: a series of 16 patients from Lima, Peru. *International Journal of Tuberculosis and Lung Disease*, 2003, 7(7):637–644.
6. Takizawa T et al. The comparative arthropathy of fluoroquinolones in dogs. *Human and Experimental Toxicology*, 1999, 18(6):392–329.
7. Warren RW. Rheumatologic aspects of pediatric cystic fibrosis patients treated with fluoroquinolones. *Pediatric Infectious Disease Journal*, 1997, 16(1):118–122.
8. Hampel B, Hullmann R, Schmidt H. Ciprofloxacin in pediatrics: worldwide clinical experience based on compassionate use – safety report. *Pediatric Infectious Disease Journal*, 1997, 16(1):127–129.

9. Loebstein R, Koren G. Clinical pharmacology and therapeutic drug monitoring in neonates and children. *Pediatric Review*, 1998, 19(12):423–428.
10. Siberry GK, Iannone R, eds. *The Harriet Lane handbook*, 15th ed. Baltimore, Mosby, 2000.
11. Centers for Disease Control and Prevention, American Thoracic Society, Infectious Diseases Society of America. Treatment of tuberculosis. *Morbidity and Mortality Weekly Report*, 2003, 52(RR11):1–77.