

CHAPTER 11

Initial evaluation, monitoring of treatment and management of adverse effects

11.1 Chapter objectives

This chapter provides information on the identification and management of adverse effects caused by second-line antituberculosis drugs. It addresses the following:

- monitoring requirements for the treatment of drug-resistant TB,
- monitoring actions for early detection of adverse effect detection,
- adverse effects associated with different second-line drugs,
- strategies for the treatment of adverse effects.

11.2 Pretreatment screening and evaluation

The required initial pretreatment clinical investigation includes a thorough medical history and physical examination. The recommended initial laboratory evaluations are shown in Table 11.1. The initial evaluation serves to establish a baseline and may identify patients who are at increased risk for adverse effects or poor outcomes. The monitoring of treatment and the management of adverse effects may have to be more intensive in patients with pre-existing conditions or conditions identified at the initial evaluation (diabetes mellitus, renal insufficiency, acute or chronic liver disease, thyroid disease, mental illness, drug or alcohol dependence, HIV infection, pregnancy, lactation and others). The management of MDR-TB when these conditions exist is described in Chapter 9. Methods of avoiding pregnancy during treatment for women of childbearing age should be discussed.

11.3 Monitoring progress of treatment

Patients should be monitored closely for signs of treatment failure. Clinically, the most important way to monitor response to treatment is through regular history-taking and physical examination. The classic symptoms of TB – cough, sputum production, fever and weight loss – generally improve within the first few months of treatment and should be monitored frequently by health-care providers. The recurrence of TB symptoms after sputum conversion, for example, may be the first sign of treatment failure. For children, height and weight should be measured regularly to ensure that they are grow-

ing normally. A normal growth rate should resume after a few months of successful treatment.

Objective laboratory evidence of improvement often lags behind clinical improvement. The chest radiograph may be unchanged or show only slight improvement, especially in re-treatment patients with chronic pulmonary lesions. Chest radiographs should be taken at least every six months, when a surgical intervention is being considered, or whenever the patient's clinical situation has worsened. *The most important objective evidence of improvement is conversion of the sputum smear and culture to negative.* While sputum smear is still useful clinically because of its much shorter turnaround time, sputum culture is much more sensitive and is necessary to monitor the progress of treatment. Sputum examinations are also dependent on the quality of the sputum produced, so care should be taken to obtain adequate specimens.

Sputum conversion is slower in MDR-TB than in drug-susceptible TB. Paucibacillary culture results should not be automatically regarded as negative when treating MDR-TB. Acquired drug resistance and treatment failure often begin with the growth of one or two colonies on a sputum culture. Culture conversion should not be considered to be equivalent to cure. A certain proportion of patients may initially convert and later revert to positive sputum culture. The factors associated with this reversion and its implications are under study.

Sputum smears and cultures should be monitored closely throughout treatment. These guidelines recommend that the tests be performed monthly before smear and culture conversion, with conversion defined as two consecutive negative smears and cultures taken 30 days apart. After conversion, the minimum period recommended for bacteriological monitoring is monthly for smears and quarterly for cultures (Table 11.1). Programmes with adequate culture capacity may choose to do cultures more frequently, every 1–2 months, after conversion.

Specimens for monitoring do not need to be examined in duplicate, but doing so can increase the sensitivity of the monitoring.

For patients who remain smear- and culture-positive during treatment or who are suspects for treatment failure, DST can be repeated. It is usually not necessary to repeat DST within less than three months of completion of treatment.

11.4 Monitoring for adverse effects during treatment

Close monitoring of patients is necessary to ensure that the adverse effects of second-line drugs are recognized quickly by health-care personnel. The ability to monitor patients for adverse effects daily is one of the major advantages of DOT over self-administration of MDR-TB treatment.

The majority of adverse effects are easy to recognize. Commonly, patients will volunteer that they are experiencing adverse effects. However, it is important to have a systematic method of patient interviewing since some patients

may be reticent about reporting even severe adverse effects. Other patients may be distracted by one adverse effect and forget to tell the health-care provider about others. DOT workers should be trained to screen patients regularly for symptoms of common adverse effects: rashes, gastrointestinal symptoms (nausea, vomiting, diarrhoea), psychiatric symptoms (psychosis, depression, anxiety, suicidal ideation), jaundice, ototoxicity, peripheral neuropathy and symptoms of electrolyte wasting (muscle cramping, palpitations). DOT workers should also be trained in simple adverse effect management and when to refer patients to a nurse or physician.

Laboratory screening is invaluable for detecting certain adverse effects that are more occult. The recommendations in Table 11.1 are an estimate of the minimal frequency of essential laboratory screening based on the experience of several DOTS-Plus projects (1). More frequent screening may be advisable, particularly for high-risk patients.

Nephrotoxicity is a known complication of the injectable drugs, both of the

TABLE 11.1 **Monitoring during treatment of drug-resistant TB**

MONITORING EVALUATION	RECOMMENDED FREQUENCY
Evaluation by clinician	At baseline, and at least monthly until conversion, then every 2–3 months
Screening by DOT worker	At every DOT encounter
Sputum smear and cultures	Monthly until conversion, then monthly smears and quarterly cultures. (Note: some programmes may choose to do smears and cultures monthly)
Weight	At baseline and then monthly
Drug susceptibility testing (DST)	At baseline in programmes doing individualized treatment or in programmes doing standardized treatments that need to confirm MDR-TB. For patients who remain culture-positive, it is not necessary to repeat DST within less than 3 months of treatment
Chest radiograph	At baseline, and then every 6 months
Serum creatinine	At baseline, then monthly if possible while receiving an injectable drug
Serum potassium	Monthly while receiving an injectable agent
Thyroid stimulating hormone	Every 6 months if receiving ethionamide/protonamide and/or PAS; and monitor monthly for signs/symptoms of hypothyroidism
Liver serum enzymes	Periodic monitoring (every 1–3 months) in patients receiving pyrazinamide for extended periods or for patients at risk for or with symptoms of hepatitis
HIV screening	At baseline, and repeat if clinically indicated
Pregnancy tests	At baseline for women of childbearing age, and repeat if indicated

aminoglycosides and of capreomycin. This adverse effect is occult (not obviously noted by taking the history of the patient or by physical examination) in onset and can be fatal. The optimal timing for checking serum creatinine is unknown, but most current treatment programmes for drug-resistant TB check serum creatinine at least monthly. In addition, patients with a history of renal disease (including co-morbidities such as HIV and diabetes), advanced age or any renal symptoms should be monitored more closely, particularly at the start of treatment. An estimate of the glomerular filtration rate may help to further stratify the risk of nephrotoxicity in these patients (see Chapter 9, section 9.7).

Electrolyte wasting is a known complication of the antituberculosis injectable drugs, most frequently with capreomycin. It is generally a late effect occurring after months of treatment, and is reversible once the injectable drug is suspended. Since electrolyte wasting is often occult in the early stages and can be easily managed with electrolyte replacement, serum potassium should be checked at least monthly in high-risk patients, and in all those taking capreomycin (2).

Hypothyroidism is a late effect provoked by PAS and ethionamide. It is suspected by clinical assessment and confirmed by testing the serum level of thyroid stimulating hormone (TSH). The use of these agents together can produce hypothyroidism in up to 10% of patients (3). Since the symptoms can be subtle, it is recommended that patients are screened for hypothyroidism with a serum TSH at 6–9 months, and then tested again every 6 months or sooner if symptoms arise. The dosing of thyroid replacement therapy should be guided using serum levels of TSH.

11.5 Management of adverse effects

Second-line drugs have many more adverse effects than the first-line anti-tuberculosis drugs. Management of adverse effects is possible even in resource-poor settings (3). Proper management of adverse effects begins with patient education. Before starting treatment, the patient should be instructed in detail about the potential adverse effects that could be produced by the prescribed drug regimen, and if and when to notify a health-care provider.

Table 11.2 reports the number and percentage of patients who had a particular adverse event, observed in the first five GLC-approved projects. The percentage of events may vary depending on the regimens used (for example, among patients using both ethionamide and PAS, a high proportion may develop a rate of hypothyroidism above 3.5%). Nonetheless, Table 11.2 provides DR-TB control programmes with an indication of the expected prevalence of adverse effects. Complete discontinuation of therapy because of adverse effects is rare and applied to only 2% of the patients in this report.

Prompt evaluation, diagnosis and treatment of adverse effects are extremely important, even if the adverse effect is not particularly dangerous. Patients

TABLE 11.2 **Frequency of common adverse effects among 818 patients in five DR-TB control programme sites (1)**

ADVERSE EVENT	NO. AFFECTED (%)
Nausea/vomiting	268 (32.8)
Diarrhoea	173 (21.1)
Arthralgia	134 (16.4)
Dizziness/vertigo	117 (14.3)
Hearing disturbances	98 (12.0)
Headache	96 (11.7)
Sleep disturbances	95 (11.6)
Electrolyte disturbances	94 (11.5)
Abdominal pain	88 (10.8)
Anorexia	75 (9.2)
Gastritis	70 (8.6)
Peripheral neuropathy	65 (7.9)
Depression	51 (6.2)
Tinnitus	42 (5.1)
Allergic reaction	42 (5.1)
Rash	38 (4.6)
Visual disturbances	36 (4.4)
Seizures	33 (4.0)
Hypothyroidism	29 (3.5)
Psychosis	28 (3.4)
Hepatitis	18 (2.2)
Renal failure/nephrotoxicity	9 (1.1)

may have significant fear and anxiety about an adverse effect if they do not understand why it is happening. These emotions in turn may augment the severity of the adverse effect, as in the case of nausea and vomiting. Long periods of time without medical evaluation also promote feelings of isolation and abandonment by the health-care system.

If the adverse effect is mild and not dangerous, continuing the treatment regimen, with the help of ancillary drugs if needed, is often the best option. In patients with highly resistant TB, a satisfactory replacement drug may not be available, so that suspending a drug will make the treatment regimen less potent. Some adverse effects may disappear or diminish with time, and patients may be able to continue receiving the drug if sufficiently motivated.

The adverse effects of a number of second-line drugs are highly dose-dependent.

Reducing the dosage of the offending drug is another method of managing adverse effects but only in cases where the reduced dose is still expected to produce adequate serum levels and not compromise the regimen. With cycloserine and ethionamide, for example, a patient may be completely intolerant at one dose and completely tolerant at a slightly lower dose. Unfortunately, given the narrow therapeutic margins of these drugs, lowering the dose may also

affect efficacy, so every effort should be made to maintain an adequate dose of the drug according to body weight. Lowering the dose by more than one weight class should be avoided (see Annex 2 for weight classes and dosing).

Pyridoxine (vitamin B₆) should be given to all patients receiving cycloserine or terizidone to help prevent neurological adverse effects. The recommended dose is 50 mg for every 250 mg of cycloserine (or terizidone) prescribed.

Psychosocial support is an important component of the management of adverse effects. This is one of the most important roles played by DOT workers, who educate patients about their adverse effects and encourage them to continue treatment. Patient support groups are another means of providing psychosocial support to patients.

Table 11.3 summarizes the common adverse effects, the likely responsible agents and the suggested management strategies.

Management often requires the use of ancillary medications to eliminate or lessen the adverse effects. DR-TB control programmes should, if at all possible, have a stock of ancillary medications available for health-care providers to prescribe to patients free of charge. Table 11.4 is a list of indications and commonly used medications for the management of adverse reactions. The list is an example of a formulary that programmes may want to have available and will assist programmes in planning the respective drug management and budgeting. However, programmes may choose to have available alternative medications in the same class as those in the list, or other medications not listed here, depending on the treatment methods in a particular country.

In addition, it is recommended that all laboratory testing for the monitoring of therapy, pregnancy testing, HIV screening and contraceptive methods be offered free of charge.

11.6 Summary

The timely and intensive monitoring for, and management of, adverse effects caused by second-line drugs are essential components of DR-TB control programmes. Poor management of adverse effects increases the risk of default or irregular adherence to treatment, and may result in death or permanent morbidity. The health-care worker of the control programme should be familiar with the common adverse effects of MDR-TB therapy. Patients experiencing adverse effects should be referred to health-care workers who have experience in treating the adverse effects. It is rarely necessary to suspend antituberculosis drugs completely. Ancillary drugs for the management of adverse effects should be available to the patient and without charge. Despite the many challenges, programmes in resource-poor areas can successfully monitor and manage large cohorts of patients when appropriate human and financial resources are available, and DOT workers and health-care workers are properly trained.

TABLE 11.1.3 Adverse effects, suspected agent(s) and management strategies

ADVERSE EFFECT	SUSPECTED AGENT(S) ^a	SUGGESTED MANAGEMENT STRATEGIES	COMMENTS
Seizures	Cs H, fluoro- quinolones	<ol style="list-style-type: none"> 1. Suspend suspected agent pending resolution of seizures. 2. Initiate anticonvulsant therapy (e.g. phenytoin, valproic acid). 3. Increase pyridoxine to maximum daily dose (200 mg per day). 4. Restart suspected agent or reinstitute suspected agent at lower dose, if essential to the regimen. 5. Discontinue suspected agent if this can be done without compromising regimen. 	<ol style="list-style-type: none"> 1. Anticonvulsant is generally continued until MDR-TB treatment is completed or suspected agent discontinued. 2. History of previous seizure disorder is not a contraindication to the use of agents listed here if a patient's seizures are well controlled and/or the patient is receiving anticonvulsant therapy. 3. Patients with history of previous seizures may be at increased risk for development of seizures during MDR-TB therapy.
Peripheral neuropathy	Cs, H S, Km, Am, Cm, Vi, Eto/Pto, fluoro- quinolones	<ol style="list-style-type: none"> 1. Increase pyridoxine to maximum daily dose (200 mg per day). 2. Change injectable to capreomycin if patient has documented susceptibility to capreomycin. 3. Initiate therapy with tricyclic antidepressants such as amitriptyline. Non-steroidal anti-inflammatory drugs or acetaminophen may help alleviate symptoms. 4. Lower dose of suspected agent, if this can be done without compromising regimen. 5. Discontinue suspected agent if this can be done without compromising regimen. 	<ol style="list-style-type: none"> 1. Patients with co-morbid disease (e.g. diabetes, HIV, alcohol dependence) may be more likely to develop peripheral neuropathy, but these conditions are not contraindications to the use of the agents listed here. 2. Neuropathy may be irreversible; however, some patients may experience improvement when offending agents are suspended.

TABLE 11.3 Adverse effects, suspected agent(s) and management strategies (continued)

ADVERSE EFFECT	SUSPECTED AGENT(S) ^a	SUGGESTED MANAGEMENT STRATEGIES	COMMENTS
Hearing loss	S, Km, Am, Cm, Clr	<ol style="list-style-type: none"> 1. Document hearing loss and compare with baseline audiometry if available. 2. Change parenteral treatment to capreomycin if patient has documented susceptibility to capreomycin. 3. Increase frequency and/or lower dose of suspected agent if this can be done without compromising the regimen (consider administration three times per week). 4. Discontinue suspected agent if this can be done without compromising the regimen. 	<ol style="list-style-type: none"> 1. Patients with previous exposure to aminoglycosides may have baseline hearing loss. In such patients, audiometry may be helpful at the start of MDR-TB therapy. 2. Hearing loss is generally not reversible. 3. The risk of further hearing loss must be weighed against the risks of stopping the injectable in the treatment regimen.
Psychotic symptoms	Cs, H, fluoro-quinolones, Eto/Pto	<ol style="list-style-type: none"> 1. Stop suspected agent for a short period of time (1–4 weeks) while psychotic symptoms are brought under control. 2. Initiate antipsychotic therapy. 3. Lower dose of suspected agent if this can be done without compromising regimen. 4. Discontinue suspected agent if this can be done without compromising regimen. 	<ol style="list-style-type: none"> 1. Some patients will need to continue antipsychotic treatment throughout MDR-TB therapy. 2. Previous history of psychiatric disease is not a contra-indication to the use of agents listed here but may increase the likelihood of psychotic symptoms developing during treatment. 3. Psychotic symptoms are generally reversible upon completion of MDR-TB treatment or cessation of the offending agent.

Depression	<p>Socio-economic circumstances, chronic disease, Cs, fluoro-quinolones H, Eto/Pto</p> <ol style="list-style-type: none"> 1. Improve socioeconomic conditions. 2. Group or individual counselling. 3. Initiate antidepressant therapy. 4. Lower dose of suspected agent if this can be done without compromising the regimen. 5. Discontinue suspected agent if this can be done without compromising regimen. 	<ol style="list-style-type: none"> 1. Socioeconomic conditions and chronic illness should not be underestimated as contributing factors to depression. 2. Depressive symptoms may fluctuate during therapy and may improve as illness is successfully treated. 3. History of previous depression is not a contraindication to the use of the agents listed but may increase the likelihood of depression developing during treatment.
Hypo-thyroidism	<p>PAS, Eto/Pto</p> <ol style="list-style-type: none"> 1. Initiate thyroxine therapy. 	<ol style="list-style-type: none"> 1. Completely reversible upon discontinuation of PAS or ethionamide/protionamide. 2. The combination of ethionamide/protionamide with PAS is more frequently associated with hypothyroidism than the individual use of each drug.
Nausea and vomiting	<p>Eto/Pto, PAS, H, E, Z</p> <ol style="list-style-type: none"> 1. Assess for dehydration; initiate dehydration if indicated. 2. Initiate antiemetic therapy. 3. Lower dose of suspected agent, if this can be done without compromising regimen. 4. Discontinue suspected agent if this can be done without compromising regimen – rarely necessary. 	<ol style="list-style-type: none"> 1. Nausea and vomiting universal in early weeks of therapy and usually abate with time on treatment and adjunctive therapy. 2. Electrolytes should be monitored and repleted if vomiting is severe. 3. Reversible upon discontinuation of suspected agent. 4. Severe abdominal distress and acute abdomen have been reported with the use of clobazamine. Although these reports are rare, if this effect occurs, clobazamine should be suspended.

TABLE 11.3 Adverse effects, suspected agent(s) and management strategies (continued)

ADVERSE EFFECT	SUSPECTED AGENT(S) ^a	SUGGESTED MANAGEMENT STRATEGIES	COMMENTS
Gastritis	PAS, Eto/Pto	<ol style="list-style-type: none"> H2-blockers, proton-pump inhibitors, or antacids. Stop suspected agent(s) for short periods of time (e.g, one to seven days). Lower dose of suspected agent, if this can be done without compromising regimen. Discontinue suspected agent if this can be done without compromising regimen. 	<ol style="list-style-type: none"> Severe gastritis, as manifested by haematemesis, melaena or haematechezia, is rare. Dosing of antacids should be carefully timed so as to not interfere with the absorption of antituberculosis drugs (take 2 hours before or 3 hours after antituberculosis medications). Reversible upon discontinuation of suspected agent(s).
Hepatitis	Z, H, R, Eto/Pto, PAS, E, fluoro-quinolones	<ol style="list-style-type: none"> Stop all therapy pending resolution of hepatitis. Eliminate other potential causes of hepatitis. Consider suspending most likely agent permanently. Reintroduce remaining drugs, one at a time with the most hepatotoxic agents first, while monitoring liver function. 	<ol style="list-style-type: none"> History of previous hepatitis should be carefully analysed to determine most likely causative agent(s); these should be avoided in future regimens. Generally reversible upon discontinuation of suspected agent.
Renal toxicity	S, Km, Am, Cm, Vi	<ol style="list-style-type: none"> Discontinue suspected agent. Consider using capreomycin if an aminoglycoside had been the prior injectable in regimen. Consider dosing 2 to 3 times a week if drug is essential to the regimen and patient can tolerate (close monitoring of creatinine). Adjust all TB medications according to the creatinine clearance. 	<ol style="list-style-type: none"> History of diabetes or renal disease is not a contraindication to the use of the agents listed here, although patients with these co-morbidities may be at increased risk for developing renal failure. Renal impairment may be permanent.

<p>Electrolyte disturbances (hypokalaemia and hypomagnesaemia)</p>	<p>Cm, Km, Am, S</p>	<ol style="list-style-type: none"> 1. Check potassium. 2. If potassium is low also check magnesium (and calcium if hypocalcaemia is suspected). 3. Replace electrolytes as needed. 	<ol style="list-style-type: none"> 1. If severe hypokalaemia is present, consider hospitalization. 2. Amiloride 5–10 mg QD or spironolactone 25 mg QD may decrease potassium and magnesium wasting and is useful in refractory cases.
<p>Optic neuritis</p>	<p>E</p>	<ol style="list-style-type: none"> 1. Stop E. 2. Refer patient to an ophthalmologist. 	<ol style="list-style-type: none"> 1. Usually reverses with cessation of E. 2. Rare case reports of optic neuritis have been attributed to streptomycin.
<p>Arthralgias</p>	<p>Z, fluoro-quinolones</p>	<ol style="list-style-type: none"> 1. Initiate therapy with non-steroidal anti-inflammatory drugs. 2. Lower dose of suspected agent, if this can be done without compromising regimen. 3. Discontinue suspected agent if this can be done without compromising regimen. 	<ol style="list-style-type: none"> 1. Symptoms of arthralgia generally diminish over time, even without intervention. 2. Uric acid levels may be elevated in patients on pyrazinamide. Allopurinol appears not to correct the uric acid levels in such cases.

^a See list of drug abbreviations, page vi.

Fluoroquinolones = Cfx, Ofx, Lfx, Gfx, Mfx

Note: Drugs in bold type are more strongly associated with the adverse effect than drugs not in bold.

TABLE 11.4 Commonly used ancillary medications

INDICATION	DRUG
Nausea, vomiting, upset stomach	Metoclopramide, dimenhydrinate, prochlorperazine, promethazine, bismuth subsalicylate
Heartburn, acid indigestion, sour stomach, ulcer	H2-blockers (ranitidine, cimetidine, famotidine, etc.), proton pump inhibitors (omeprazole, lansoprazole, etc.) Avoid antacids because they can decrease absorption of fluoroquinolone
Oral candidiasis (non-AIDS patient)	Fluconazole, clotrimazole lozenges
Diarrhoea	Loperamide
Depression	Selective serotonin reuptake inhibitors (fluoxetine, sertraline), tricyclic antidepressants (amitriptyline)
Severe anxiety	Lorazepam, diazepam, clonazepam
Insomnia	Dimenhydrinate
Psychosis	Haloperidol, thiorazine, risperidone (consider benzotropine or biperiden to prevent extrapyramidal effects)
Seizures	Phenytoin, carbamazepine, valproic acid, phenobarbital
Prophylaxis of neurological complications of cycloserine	Pyridoxine (vitamin B ₆)
Peripheral neuropathy	Amitriptyline
Vestibular symptoms	Meclizine, dimenhydrinate, prochlorperazine, promethazine
Musculoskeletal pain, arthralgia, headaches	Ibuprofen, paracetamol, codeine
Cutaneous reactions, itching	Hydrocortisone cream, calamine, caladryl lotions
Systemic hypersensitivity reactions	Antihistamines (diphenhydramine, chlorpheniramine, dimenhydrinate), corticosteroids (prednisone, dexamethasone)
Bronchospasm	Inhaled beta-agonists (albuterol, etc.), inhaled corticosteroids (beclomethasone, etc.), oral steroids (prednisone), injectable steroids (dexamethasone, methylprednisolone)
Hypothyroidism	Levothyroxine
Electrolyte wasting	Potassium and magnesium replacement

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