Canadian Tuberculosis Standards

7th Edition

Chapter 5: Treatment of Tuberculosis Disease

Public Health Agency of Canada

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CHAPTER 5

TREATMENT OF TUBERCULOSIS DISEASE

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KEY MESSAGES/POINTS

- Treatment of active TB should include two effective drugs at all times, and in the initial phase (first 2 months) at least three effective drugs are recommended.

- Treatment should be guided by the results of drug sensitivity testing, which should be performed for all patients with culture-confirmed disease.

- All patients with active TB in Canada should be treated with a regimen of isoniazid (INH), rifampin (RMP), pyrazinamide (PZA) and ethambutol (EMB) initially. If the isolate causing disease is fully susceptible to all first-line drugs, the EMB can be stopped, and PZA should be given for the first 2 months. After that it is recommended that only INH and RMP be given for the remainder of therapy – usually another 4 months.

- Therapy is prolonged to 9 months if there are risk factors for relapse. These include persistent presence of cavity on the chest x-ray after 2 months or at the end of effective anti-TB therapy, persistent smear and/or culture positivity after 2 months of therapy, or HIV coinfection.

- Providers who are initiating TB therapy should provide comprehensive, patient-centred care and be able to monitor that 100% of prescribed doses are taken. Directly observed treatment (DOT) is one method to achieve this and is recommended at a minimum for patients with risk factors for non-adherence, or population groups with historically increased rates of treatment failure or relapse or with inadequate rates of treatment completion, defined as default rates of 5% or greater. It is recommended that all jurisdictions across Canada have the capacity to provide DOT.

- Therapy can be given 5 days per week in the initial 2 months, then three times per week if DOT is used, to facilitate treatment supervision. Therapy that is self-administered should be taken daily.

- Fixed-dose combination (FDC) preparations of multiple TB medications are not recommended.

- Treatment of active disease in pregnant or breastfeeding women should be the same as the standard regimen.

- The same drugs, dosing and duration as in the standard regimen are recommended for treatment of active disease in patients with renal insufficiency. However, prolonged dosing intervals are recommended for PZA and EMB from daily to three times per week.

- Therapeutic drug monitoring (TDM) is not available in Canada but is available in the United States. The impact of TDM on important outcomes is unknown. Nevertheless, TDM should be considered for patients with renal or hepatic insufficiency, HIV coinfection or known malabsorption.
- Treatment of drug-resistant, HIV-associated, extrapulmonary and pediatric TB is described in separate chapters.

FUNDAMENTALS OF TREATMENT OF TB DISEASE

These fundamentals are discussed in a number of other excellent sources, and interested readers are referred to these references.[1-6]

OBJECTIVES OF TREATMENT OF DISEASE

There are three fundamental objectives of treatment of active TB. It is useful to understand these objectives, as each one is achieved by different TB drugs or combinations of drugs:

1. Rapid killing of TB bacilli, to produce rapid improvement in the clinical condition of the patient and thereby prevent complications (reduce morbidity), prevent death (reduce mortality) and prevent transmission (reduce contagiousness).
2. Prevent the emergence or worsening of drug resistance.
3. Prevent the relapse of disease after completion of therapy and achieve long-lasting cure.

PRINCIPLES OF TREATMENT OF DISEASE

Therapy is given in two phases: initial intensive, and continuation.

In the initial phase multiple effective drugs are used in combination to achieve the first and second objective. On the basis of results of randomized trials, this phase should last 2 months, and the drugs should preferably be given daily.

The second objective is addressed by the continuation phase, during which only two drugs are usually given. The length of this phase is variable, depending on indicators of risk of relapse, on the drugs given in the initial phase and on the results of pre-treatment drug susceptibility testing. Therapy can be daily or intermittent.

Optimal therapy to achieve all three treatment objectives for patients of all ages, with disease at any site, should be guided by the results of drug susceptibility testing. This reinforces the importance of microbiologic confirmation of the diagnosis of TB disease. Patients with suspected active TB should always have multiple specimens sent for microbiologic investigation before treatment is started. (See Chapter 3, Diagnosis of Active Tuberculosis and Drug Resistance.)

It is recommended that at least two effective drugs should be used at all times. If drug susceptibility testing results are pending then more drugs may be needed to ensure that at least two are likely to be effective.

In the initial intensive phase, particularly when bacillary load is high (see below), three likely effective drugs should be used to prevent emergence of drug resistance.

A decision to initiate TB treatment implies a commitment to ensure that therapy is not interrupted or irregular at any time, until the planned date of treatment completion. Therefore, it is recommended that all necessary measures be taken to avoid patient drop-out or loss to follow-up, or interruption of drug supply. If patients experience adverse events, an alternative therapy should be initiated promptly. Practitioners who cannot guarantee adequate monitoring and supervision of therapy should refer the patients immediately to centres where this can be assured.

PREVENTION OF DRUG RESISTANCE

Drug resistance is discussed in detail in Chapter 8, Drug-Resistant Tuberculosis. However, to understand the rationale for many of the principles above it is useful to understand how drug resistance develops. In brief, all patients with active disease harbour at least a few bacilli which have undergone spontaneous mutations to produce resistance to each anti-TB drug.[7,8] The mutation rate for each TB drug has been established from *in-vitro* experiments.[7,8] Therapy with a single drug will lead to the uninhibited growth of bacilli carrying the mutation to this drug while all other bacilli are eradicated.[9] This means that within 2-3 months of the start of monotherapy all bacteria will carry this mutation, and clinically the patient will be fully resistant to that drug.[10] Fortunately, the mutations to different drugs are independent, so treatment with two drugs will usually mean that the mutants with resistance to one drug are killed by the other drug, unless the total number of bacilli is very high.[9]

Experimental studies have established the total number of bacilli present with each type of TB lesion or extent of disease.[7] Using this, and the spontaneous mutation rate, it is possible to calculate the probability that treatment with one, two or three drugs will lead to the emergence of drug resistance as a result of natural or spontaneous mutations, even in a patient who takes all doses properly. As seen in Table 1, monotherapy will not lead to the emergence of resistance in a patient with latent TB but is very likely to do so with minimal active TB. On the other hand, two effective drugs will be adequate for many patients with active TB but not for patients with more extensive disease.

Table 1. Probability of drug resistance emerging if TB with different bacillary loads is treated with different numbers of drugs[9]

Number of TB bacilli (TB infection/disease state)	Probability of resistance by number of drugs in treatment		
	1 drug	2 drugs	3 drugs
10^3 (latent infection)	0	0	0
10^4 (latent infection)	0	0	0
10^6 (smear-negative culture-positive)	50%	0	0
10^8 (single cavity)	100%	50%	0
10^{10} (several cavities)	100%	100%	0
10^{12} (very extensive disease)	100%	100%	1%

DRUGS USED IN TREATMENT

Anti-TB drugs are divided into two broad groups.

First-line drugs (FLD)

Four drugs are classified as FLD in Canada, because all are effective, can be taken orally and are well tolerated (or at least better tolerated than the second-line drugs).

Second-line drugs (SLD)

The SLD include the fluoroquinolones, all injectables and many "older" TB drugs that were used in the 1950s and 1960s but were abandoned because of relatively poor efficacy and/or greater toxicity.[4]

Evidence about the action and the role in therapy of each drug comes from *in-vitro* and animal studies as well as from multiple randomized trials. Table 2 summarizes the doses, with daily or thrice weekly schedules, of the four FLD and the most commonly used SLD.

Table 2. Recommended drug doses for daily and intermittent therapy in adolescents and adults[1,6]*

	Daily		Thrice weekly	
	By weight	**Max (mg)**	**By weight**	**Max (mg)**
First-line drugs				
INH	5 mg/kg	300	10 mg/kg	600
RMP	10 mg/kg	600	10 mg/kg	600
PZA	20-25 mg/kg	2000	30-40 mg/kg	4000
EMB	15-20 mg/kg[†]	1600	25-40 mg/kg	2400
Second-line drugs				
Fluoroquinolones[‡] – moxifloxacin, levofloxacin		400 / 750-1000		¶ / ¶
Injectables – amikacin[§]	15 mg/kg as single dose	**		¶

INH = isoniazid, RMP = rifampin, PZA = pyrazinamide, EMB = ethambutol

*For doses in children see Chapter 9.

[†]EMB dosing: optimal dosing is unclear. It is clear that eye toxicity is dose dependent, and its risk is higher at 25 mg/kg than at 15 mg/kg.

[‡]Fluoroquinolones: gatifloxacin is not recommended in Canada because of dysglycemia problems. This drug has been used in recent trials and is still used in some countries.

[§]Amikacin: Of the injectables amikacin is preferred for use in Canada because of the ready availability of the drug, familiarity with its use by clinicians, nurses and pharmacists, and the ability to measure serum drug concentration in many facilities. Streptomycin (SM) is not available in Canada but may be preferred in some low- and middle-income countries as rates of toxicity are similar and costs may be lower.

[¶]There are inadequate data from randomized trials on the use of fluoroquinolones or injectables as part of intermittent regimens. If these drugs are needed because of intolerance or resistance to first-line drugs, daily therapy is suggested

**Initial dosage if renal function is normal. Dosing should be adjusted based on peak and trough serum levels in consultation with a pharmacist.

Isoniazid (INH)

This agent was first introduced in 1952 and is still a cornerstone of modern TB therapy. It has very powerful early bactericidal activity, meaning that it is highly effective in rapid killing of bacteria in the first few days. Hence, the drug is important in achieving Objective 1, above. It is also effective in preventing the emergence of resistance, although its role in preventing relapse is unclear. If INH is not given for the full duration of therapy, then therapy should be prolonged. If INH is not given at all, therapy should be for at least 12 months. Pyridoxine (vitamin B6) should routinely be added for patients with diabetes, renal failure, malnutrition, substance abuse or seizure disorders or for women who are pregnant or breastfeeding, because of the increased risk of symptoms related to pyridoxine deficiency in these patients. A pyridoxine dose of 25 mg is sufficient; higher doses may interfere with INH activity.

Rifampin (RMP)

This drug, introduced in 1968, is the most potent anti-TB drug available. Its use allows shortening of the regimen to a total of 9 months (or less if PZA is also used). The drug has good bactericidal activity (Objective 1), prevents acquired drug resistance (Objective 2) and is very important in preventing relapse (Objective 3). Current doses are based on studies performed in the 1960s, when the lowest effective dose was used because of the high cost of the drug. Case series have reported low RMP drug concentrations in 40%-50% of patients taking standard doses[11,12] and in patients with poor treatment outcomes.[13,14] This has given rise to the hypothesis, being tested in ongoing trials, that RMP at higher doses would be more effective. When the results of these trials are available it is possible that RMP dosing recommendations will change.

If RMP is not given for the full duration of therapy, then therapy should be prolonged. If RMP is not given at all, therapy should be for at least 18 months.

Rifabutin (RBT)

This rifamycin has similar activity *in vitro* against *M. tuberculosis* as RMP but causes much less upregulation of the cytochrome p450 system and so results in fewer drug interactions. Hence, RBT is commonly used for HIV-infected or transplant patients, as the regimens they are often taking may be profoundly affected by RMP, but not by RBT. Hematologic toxicity is more common with this drug.

Rifapentine (RPT)

This rifamycin has a half-life that is 5 times longer than RMP, which allows the drug to be given only once a week. However, in randomized trials, HIV-infected patients who received the drug, plus INH, once weekly in the continuation phase had significantly higher rates of failure, relapse and acquired drug resistance.[15] Hence, it is not recommended for use in the treatment of active TB at this time. In addition, RPT is available in Canada only through application for the treatment of an individual patient by means of the Special Access Program (at: http://www.hc-sc.gc.ca/dhp-mps/acces/drugs-drogues/sapg3_pasg3-eng.php).

Pyrazinamide (PZA)

This drug is also bactericidal but appears to provide benefit only in the first 2 months of therapy (Objective 1). In randomized trials, use of PZA in the continuation phase did not reduce relapse rates,[5,6] and the drug appeared to offer no protection against the development of resistance.[5]

If PZA is not given for the entire first 2 months, the total duration of therapy should be 9 months.

Ethambutol (EMB)

This is the least effective of the four FLD for bactericidal activity (Objective 1) or prevention of relapse (Objective 3), but it is effective in preventing the emergence of drug resistance (Objective 2). If a previously untreated patient has unrecognized INH resistance and is given only INH, RMP and PZA for the first 2 months then RMP resistance could emerge, given the inability of PZA to protect against the emergence of resistance. Hence, EMB is added in the initial phase whenever there is any suspicion of initial drug resistance and while the results of drug susceptibility testing (DST) are pending. In Canada EMB is recommended as part of standard initial therapy if the prevalence of INH resistance in the population group to which the patient belongs is 4% or more.

If the strain is fully susceptible, the duration of therapy is no different whether EMB is given or not.

Fluoroquinolones (FQN)

Currently these drugs are still considered second-line drugs, i.e. they are alternative medications for TB rather than part of standard first-line treatment, even though they are highly efficacious for TB,[16,17] are taken orally and are well tolerated. Indications for the use of FQN include drug resistance or intolerance of FQN. A number of ongoing trials are testing the use of FQN as part of first-line therapy to reduce the total duration of therapy. When the results are available, recommendations for use of the drugs as first-line therapy may change.

Injectables

The injectables include streptomycin, amikacin, kanamycin and capreomycin. SM is still used as part of first-line therapy in a few countries, but the inconvenience and pain of daily injections, plus higher rates of toxicity, have relegated SM to second- line drug status. This drug is not available in Canada. On the basis of expert opinion, the Canadian Thoracic Society suggests that of all the injectables amikacin is preferred for use in Canada, because it is available in most hospitals, providers (including pharmacists) are familiar with the drug, and drug concentrations are readily available, reducing risk of toxicity.

THERAPEUTIC REGIMENS

These regimens and the underlying evidence are discussed in more detail in two other excellent publications.[4,6]

STANDARD REGIMEN

RECOMMENDATION

As summarized in Table 3, standard therapy for patients with drug-sensitive TB or expected drug-sensitive TB (while DST results are pending) is INH, RMP, PZA and EMB for the first 2 months followed by INH and RMP for 4 more months.

(Strong recommendation, based on strong evidence)

EMB may not be needed if the likelihood of INH monoresistance or other forms of resistance is less than 4%. There are few situations in which one can confidently predict such a low likelihood of any resistance, especially since the prevalence of resistance has risen steadily over the last

40 years in all populations with access to treatment. EMB could be avoided in some Aboriginal populations and elderly Canadians who acquired TB infection during the pre-antibiotic era, as they usually have such a low prevalence of drug resistance. EMB can be discontinued as soon as DST results are available if the organisms are shown to be fully susceptible.

Table 3.   Treatment regimens recommended by the Canadian Thoracic Society for adults with fully susceptible (or expected to be fully susceptible) disease

	Initial phase (first 2 months)	Continuation phase
Standard		
Regimen 1	INH RMP PZA EMB* daily (or 5 days/week)	INH RMP for 4 months daily (or 3 times/week)[†]
Regimen 2	INH RMP EMB* daily (or 5 days/week)	INH RMP for 7 months daily (or 3 times/weekly)
Elderly (>65) or other risk factor for hepatotoxicity		
	INH RMP EMB* daily (or 5 days/week)	INH RMP for 7 months daily (or thrice weekly)
Pregnant		
	INH RMP PZA EMB[†] or INH RMP EMB* daily (or 5 days/week),	INH RMP for 7 months *if PZA not used and for 4 months if PZA used in first 2 months* daily (or thrice weekly)

*EMB can be stopped as soon as the DST results are available if pan sensitive. PZA is continued for the full 2 months.

[†]Three times weekly preferred over twice weekly for programmatic reasons. If patients miss a single dose while receiving thrice weekly therapy they effectively receive twice weekly therapy, which is still adequate. If they miss a dose of twice weekly therapy they effectively receive once weekly therapy which is inadequate. HIV-negative patients with minimal disease (e.g. initially smear-negative but culture-positive) or known to be reliable with DOT may be considered for twice weekly therapy in the continuation phase.

ROUTES OF ADMINISTRATION

Therapy for TB is effective and most readily administered by the oral route. When necessary, all of the oral forms of anti-TB medication can be administered by means of nasogastric or feeding tube. The tablets can be crushed and mixed with water, or suspensions of the medications can be prepared to make delivery easier. Only INH, RMP, the injectable agents and the FQN are available for parenteral administration. In patients for whom parenteral medications are needed, consultation with a TB specialist is recommended.

PROLONGING THE CONTINUATION PHASE

In a recent meta-analysis, among patients with initially fully susceptible strains, relapse was less than 1% following treatment with RMP-containing regimens lasting 8 months or more, compared with 4% following 6-month regimens.[18] To prolong therapy in all patients in order to achieve a 3% reduction in relapse would expose many patients needlessly to prolonged therapy. However, risk factors for relapse have been identified. These include having more extensive disease and/or cavities on a chest x-ray in the first 2 months of therapy,[19] being culture-positive after 2 months of therapy[19] or having a cavity on chest x-ray at the end of treatment.[20]

> **RECOMMENDATION**
>
> **In patients with any of the above risk factors, the continuation phase should be prolonged from 4 to 7 months, to provide a total of 9 months of therapy.**
>
> *(Strong recommendation, based on moderate evidence)*

There is also evidence from a recent meta-analysis that among HIV-infected individuals not taking antiretroviral therapy, relapse rates are significantly lower with 9 months of anti-TB therapy than 6 months[21] (see Chapter 10, Tuberculosis and Human Immunodeficiency Virus).

INTERMITTENT THERAPY

Many randomized trials have demonstrated that intermittent regimens have excellent results in patients with drug-sensitive TB.[5,9] Intermittent therapy should be used only with DOT, which it facilitates by reducing the number of times that patients need to be observed taking medications. If therapy is self-administered, all drugs should be taken daily.[6]

Findings from a recent systematic review and meta-analysis of randomized trials of RMP-containing regimens[18] and related recommendations from the World Health Organization (WHO)[6] are summarized on the following page.

1. No randomized trials have evaluated the efficacy of RMP-containing regimens given twice weekly from the outset or after an initial 2 weeks of daily therapy.

   These regimens are not recommended.

   (Strong recommendation, based on strong evidence)

2. RMP-containing regimens given three times weekly from the outset or after an initial 2 weeks of daily therapy had somewhat higher failure and relapse rates, and significantly higher rates of acquired drug resistance in a pooled meta-analysis of randomized trials. This finding has also been seen in cohort studies.[22,23]

   - **In the initial intensive phase daily therapy is recommended. This can be given 5 days per week, if therapy is given by DOT.**

     (Strong recommendation, based on moderate evidence)

   - **When daily DOT in the initial phase is difficult, patients may be treated with thrice weekly therapy if they are HIV-uninfected, have a low bacillary load (i.e. have non-cavitary, smear-negative disease initially) and have demonstrated excellent adherence to their DOT in the first 2 weeks.**

     (Conditional recommendation, based on moderate evidence)

3. Many studies have evaluated different schedules of therapy in the continuation phase, after daily therapy for the first 2 months. These have included daily as well as once, twice or thrice weekly schedules.

   - **Once weekly regimens are inadequate and should not be used.**

     (Strong recommendation, based on strong evidence)

   Treatment outcomes were similar with all other schedules of drug administration.

- **If DOT is used, then thrice weekly therapy is preferred in the continuation phase.[6]**

    (Conditional recommendation, based on moderate evidence)

This is based mostly on practical considerations: if a patient given a twice weekly regimen misses a single dose, then effectively he or she will receive once weekly therapy, which is inadequate. If a patient receiving thrice weekly intermittent therapy misses a single dose they are effectively receiving twice weekly therapy, which is still acceptable.

- **When thrice weekly DOT in the continuation phase is difficult, patients may be treated with twice weekly therapy if they are HIV-uninfected and have demonstrated excellent adherence to their DOT to date.**

    (Conditional recommendation, based on moderate evidence)

- **Intermittent therapy is not recommended for HIV-infected people** (following WHO guidelines, see Chapter 10, Tuberculosis and Human Immunodeficiency Virus).

FIXED-DOSE COMBINATION (FDC)

Fixed-dose combination tablets containing two or more of the first-line drugs have been manufactured for over 30 years, and the WHO recommends their use.[6] A combination of INH/RMP/PZA is available in Canada. In theory these formulations should prevent monotherapy – from physician or patient error, or patient selection of only some of their medication. Since there are many fewer tablets with FDCs than separate formulations in the initial phase (see Figure 1) they may be preferred by patients.

Figure 1. Typical number of tablets taken for active TB treatment with FDCs (on left) or separate drug formulations (on right)

A recent systematic review and meta-analysis of 15 randomized trials comparing FDCs with separate formulations found no significant differences in rates of failure, relapse, acquired drug resistance, treatment completion or adverse events.[24] None of the five studies that assessed patient adherence favoured FDCs. Patient satisfaction was assessed in only two of the 15 studies and was significantly better with FDCs in one of these two studies, but not the other.

On the basis of this evidence, use of FDCs is not recommended.

(Strong recommendation, based on strong evidence)

TREATMENT OF ACTIVE TB IN THE ELDERLY (AND OTHERS AT MODERATE TO HIGH RISK OF HEPATOTOXICITY)

PZA is the most toxic of the standard first-line drugs and the most common cause of drug-induced hepatotoxicity in patients treated for TB disease.[25,26] Therefore, it may be better to avoid PZA in patients at risk of hepatotoxic effects, such as the elderly or patients with pre-existing mild-moderate liver dysfunction.

(Conditional recommendation, based on moderate evidence)

If PZA is not given in the first 2 months then the total duration of therapy should be a minimum of 9 months. If the risk of non-adherence is judged to be low, the lower risk of toxicity may justify the longer therapy.

TREATMENT OF ACTIVE TB IN THOSE WITH SEVERE LIVER DISEASE

In patients with severe liver disease, use of RMP, or INH or PZA is risky, because any of these three drugs can cause drug-induced hepatotoxicity and dramatically worsen the patient's condition. All three should be avoided if possible, although because RMP is such a potent and effective drug and hepatotoxicity is rare with RMP alone,[25,26] its use may be considered in people with more extensive disease (smear-positive and/or cavitary disease) or more serious forms of extrapulmonary disease.

A suggested regimen is an FQN plus EMB plus an injectable (amikacin) for the first 2 months followed by an FQN and EMB for a total of 18 months.

(Conditional recommendation, based on weak evidence)

As above, RMP may be added but with careful monitoring of liver enzymes and function.

TREATMENT OF ACTIVE TB WITH RENAL INSUFFICIENCY AND DIALYSIS

In patients with creatinine clearance that is impaired but above 30% of normal, the need for adjustment of drug dosing or frequency is unclear. It is suggested that all drugs can be given in normal doses and frequency, but with careful monitoring for toxicity. If creatinine clearance is less than 30% of normal then, as summarized in Table 4, EMB and PZA can be used but at reduced doses because they are excreted by the kidney.

It is preferable to reduce the frequency of administration of these drugs rather than reduce the doses, as the peak serum concentrations are key to their bactericidal effects. Visual toxicity from EMB is more common in patients with renal insufficiency. Monitoring serum concentrations will be very useful to ensure that adequate, yet safe, doses are given. INH and RMP are safe to give in the usual doses since these drugs are metabolized mostly by the liver. The use of injectables (streptomycin, amikacin, kanamycin and capreomycin) should be avoided if possible

in patients with impaired renal function, as these drugs are excreted by the kidney and may cause worsening renal function as well as other toxicities.[1,6]

In patients undergoing dialysis, INH and RMP may be given in the usual doses since they are not appreciably affected by dialysis. EMB and PZA are dialyzable and should be given in standard doses three times per week after dialysis (see Table 4). Ideally, all medications could be given together (including INH and RMP) right after dialysis; this facilitates DOT. When uncertainties arise, the patient should be referred to a TB specialist.

Peritoneal dialysis

There are no data on the pharmacokinetic characteristics of first-line TB drugs in patients receiving peritoneal dialysis. Hence, the standard dosing and schedule are recommended, but patients should be closely monitored, and therapeutic drug monitoring (i.e. measurement of serum drug concentrations) should be considered.

Table 4. Recommended doses of TB drugs in renal failure[1,6]

	Clearance by kidney	Normal dose	Creatinine clearance <30%* or hemodialysis[†]
INH	No	5 mg/kg daily	No change
RMP	No	10 mg/kg daily	No change
PZA	Metabolites	20-25 mg/kg daily	25-35 mg three times per week
EMB	Yes	15-20 mg/kg daily	15-25 mg three times per week
Levofloxacin	Partial	750-1000 mg/daily	Give usual dose, but only three times/week[‡]
Amikacin	Yes	15 mg/kg daily	12-15 mg two or three times per week

*Insufficient data if creatinine clearance >30% but <60%. Give standard doses, but monitor closely.

[†]No data on pharmacokinetics if patient is undergoing peritoneal dialysis. Give doses as for hemodialysis but monitor closely.

[‡]Renal clearance of moxifloxacin is less, but dosing interval is not established.

TREATMENT OF ACTIVE TB IN PREGNANCY AND BREASTFEEDING

The risk of untreated active TB to a pregnant woman and her fetus is far greater than the risk of the toxic effects of the drugs used in its treatment. In a pregnant woman with active TB it is recommended that effective therapy be administered promptly. TB is not an indication for the termination of pregnancy.[6]

> **RECOMMENDATION**
>
> **INH, RMP and EMB are considered safe in pregnancy, so all three should be used as initial treatment.**
>
> *(Strong recommendation, based on strong evidence)*

Pyridoxine (vitamin B6) should be given.[1,6] The WHO recommends use of PZA in pregnancy,[6] although there remains some uncertainty about its safety in pregnancy.[1] To date there have been no reports of teratogenicity even though this drug has been given to millions of pregnant women worldwide.

RECOMMENDATION

Hence, PZA can be given in women with extensive disease and/or women who do not tolerate any of the other FLD.

(Conditional recommendation, based on moderate evidence)

Most second-line agents are not considered safe in pregnancy,[4] either because of known teratogenicity or inadequate data indicating safety. FQN are best avoided during pregnancy and breastfeeding. The use of injectables (streptomycin, amikacin, kanamycin and capreomycin) is contraindicated because of the effects on the fetus, including eighth cranial nerve palsies, deafness and teratogenic effects.[4] These drugs should only be considered for use in specific instances after consultation with a TB specialist.

Specific information regarding the effects of anti-TB drugs in breastfed children is available at the Drugs and Lactation Database, LactMed, of the United States Library of Medicine's Toxicology Data Network: http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT. Mothers receiving treatment for TB can safely breastfeed but should be given pyridoxine (vitamin B6) supplements. At most, 3% of the maternal dose is excreted in breast milk.[27] The resulting amounts ingested by the newborn baby will not produce toxic effects. It is important to remember that the amount ingested in maternal milk would not constitute an effective dose for treatment or prophylaxis in a nursing infant, even in a newborn.[27]

INTERACTIONS OF TB MEDICATIONS WITH OTHER DRUGS AND FOOD

Significant interactions may occur between TB medications and other medications. The absorption of some TB drugs may be adversely affected by food. A list of significant interactions is available from the Heartland National TB Center, Texas, at: http://www.heartlandntbc.org/products/tuberculosis_medication_drug_and_food_interactions.pdf.

The most important cause of interactions with other medications is RMP, which causes upregulation of cytochrome p450 hepatic metabolism. Most of these drug interactions can be managed by adjusting the dosage according to measured drug concentrations (e.g. phenytoin), by monitoring the clinical effect of these drugs (e.g. international normalized ratio for warfarin) or by substituting certain drugs (e.g. antiretroviral regimens, see Chapter 10, Tuberculosis and Human Immunodeficiency Virus). In some patients the drug interactions are not manageable or could result in serious consequences, such as a patient receiving immune suppressive therapy following solid organ transplantation. In these patients, RBT may be used in place of RMP, although it should be remembered that RBT has a higher rate of adverse events than RMP, particularly hematologic events.[1]

ADJUNCTIVE USE OF CORTICOSTEROIDS

Corticosteroids should be used only when adequate anti-TB therapy is also being administered. In randomized trials adjunctive use of corticosteroids improved survival in patients with TB meningitis[28,29] and improved survival and reduced the need for pericardiectomy in patients with TB pericarditis.[30] Two reviews suggest that prednisone in doses of 40-80 mg/day for 6-12 weeks is likely to be effective,[31,32] but the optimal dose and duration of treatment are not well defined. Corticosteroids, in replacement doses, may also be of clinical value in cases of TB-caused adrenal insufficiency and in cases of life-threatening disseminated disease if there is concern about adrenal insufficiency. In a meta-analysis of three small randomized trials of patients with tuberculous pleurisy, corticosteroids resulted in more rapid resolution of symptoms and pleural fluid, but there was no evidence of long-term benefits.[33]

RECOMMENDATION

Adjunctive corticosteroids (in addition to effective anti-TB therapy) are recommended for patients with TB meningitis and TB pericarditis.

(Strong recommendation, based on strong evidence)

RECOMMENDED FOLLOW-UP DURING TREATMENT AND MANAGEMENT OF ADVERSE EVENTS

HOSPITALIZATION

Although frequently diagnosed in hospital, TB is largely managed in the outpatient setting. With increasing age, patients with TB are more likely to have severe disease or to require additional medical services not directly related to TB and thus require hospital treatment.

TB patients should be hospitalized in facilities capable of providing adequate airborne isolation and staffed by experienced personnel knowledgeable in the management of TB (see Chapter 15, Prevention and Control of Tuberculosis Transmission in Health Care and Other Settings).

INDICATIONS FOR HOSPITALIZATION

- Investigation and/or treatment of symptoms, i.e. fever, life-threatening hemoptysis, malaise/cachexia.

- Establishment of an acceptable therapeutic regimen in patients with significant drug-related adverse events or with known/suspected drug resistance.

- Drug desensitization.

- Management of associated medical conditions complicating the diagnosis of TB, i.e. congestive heart failure, HIV infection, respiratory failure.

- Provision of airborne isolation if this cannot be effectively provided as an outpatient.

- Involuntary admission when other measures such as DOT are unsuccessful.

ROUTINE OUT-PATIENT FOLLOW-UP

There is no published evidence regarding the impact of follow-up on patient outcomes. Hence, the following is suggested by the Canadian Thoracic Society (CTS), based on expert opinion.

Follow-up during active TB treatment should be at least monthly, to assess adherence and response to therapy, and to detect adverse events: response to treatment should be gauged clinically, radiographically and microbiologically. Of these methods, microbiologic monitoring is considered the most reliable.[9] Patients who are sputum direct smear AFB positive should have one weekly smear examination to assess response to therapy and contagiousness (see Chapter 15) until smear-negative. When sputum direct smears are AFB negative, one culture should be done at the end of the second month of therapy to assess risk of relapse, then again towards the end of therapy. If a patient is suspected of failing therapy, two sputum smears and cultures (with DST if culture-positive) should be done. Chest radiography should be performed after 2 and 6 months of therapy to assess response, potential complications and risk of relapse.

ACHIEVING COMPLETION OF THERAPY AND DIRECTLY OBSERVED TREATMENT (DOT)

Poor adherence to prescribed anti-TB therapy is the most common cause of treatment failure and is difficult to predict, although some risk factors have been identified.

> **The decision by a care provider to initiate treatment of active TB implies a commitment to ensure that all the recommended doses are taken without interruption. The goal of active TB treatment is to take 100% of prescribed doses. This is best done by providing a comprehensive, patient-centred treatment program.[34]**
>
> *(Conditional recommendation, based on weak evidence)*

This means not only careful monitoring of adherence and response to the treatment regimen but also providing multi-disciplinary support for all problems facing the patients.[35] Key elements include use of incentives and enablers, nursing care, coordinating care for other medical problems, social service support such as for child care, housing assistance, referral for treatment of substance abuse and providing transportation where possible. For patients receiving self-administered therapy this would also include monitoring and reinforcement of adherence through measures such as detailed inquiry, reinforcement of prompts to take the medications at every follow-up visit, use of tick-off calendars, linking medication taking to a specific event in the daily routine, routine pill counts or daily cell phone text reminders. Adequate resources are needed to achieve this. In many jurisdictions the public health department can and does play an important role in monitoring and enhancing adherence to treatment.

DOT is one method to monitor and enhance adherence to therapy and has been the subject of considerable debate. In its simplest form DOT involves watching the patient swallow each dose of medication to support higher completion rates. This can be achieved through paid TB program staff at a health facility or outreach workers, or through volunteers such as family or friends. Many studies, including randomized trials, cohort and ecologic studies, have examined this question. Six high-quality trials have directly compared treatment completion in all patients with TB disease randomly assigned to self-administered or directly observed treatment.[36-41] Pooled treatment success with DOT was 68% (95% confidence interval 61%, 76%) compared with 67% (62%, 72%) with self-administered therapy. Treatment completion was significantly superior with DOT compared with self-administered therapy in only one study, in which DOT was supervised by a family member.[36] In one of the remaining negative trials, completion rates were substantially, but not significantly, greater in the arm with community-based DOT.[40] In three of the six trials DOT was facility-based (i.e. patients had to travel to a clinic daily to get their medications).

The majority of the published cohort[42-54] and ecologic[55-61] studies, including a recent Canadian study,[62] have reported an association of improved treatment outcomes, or other TB control parameters, with use of DOT. Many of these studies reported on DOT programs that were community-based (rather than facility-based), used non-family members to supervise/support treatment, included outreach to locate patients who were lost to follow-up and had high completion rates – over 90%. However, confounding and other sources of bias were major limitations of these observational studies.

The studies that are considered to have the strongest designs provide reasonably consistent evidence that the use of DOT for all patients adds little to enhance treatment completion. However, only one of these trials was conducted in a high-income country, none involved North American style DOT programs, none of the trials involved children or adolescents, and the completion rates were all suboptimal with respect to current standards of treatment in Canada. Hence, the generalizability of these results to Canadian settings may be questioned, particularly with respect to children or adolescents. Taken together, the CTS believes that the overall evidence supporting the use of DOT for all patients in all settings (universal DOT) should be considered weak.

RECOMMENDATIONS

Close supervision and monitoring of medication is considered essential for all TB patients. It is recommended that all jurisdictions have the capacity to provide DOT. The need for DOT should be considered for each patient. An additional advantage of DOT is the closer monitoring of side-effects for all patients. At a minimum, individuals with known risk factors for non-adherence[63] and/or whose TB has major individual and public health implications if they fail treatment should be considered for DOT throughout their treatment.

Individual risk factors:

- disease due to multidrug-resistant organisms;
- treatment failure or documented relapsed disease;
- injection drug use/other substance abuse;
- homelessness or unstable housing;
- suspected non-adherence or previous non-adherence;
- major mental illnesses; and
- children and adolescents.

As well, routine use of DOT should be strongly considered in populations with previously documented high rates of non-completion. This is defined as a benchmark of 5% or more of patients who had outcomes of default, lost to follow-up, transfer out without known outcomes or were otherwise not accounted for. If this benchmark is not met, then the CTS suggests that programs strongly consider adoption of universal DOT for their population in addition to other program enhancements to provide comprehensive care.

THERAPEUTIC DRUG MONITORING

There are several clinical situations in which the monitoring of serum concentrations of TB drugs might be helpful. These include coinfection of patients with gastrointestinal disease or HIV (in whom malabsorption of drugs is common),[64] liver or renal dysfunction (resulting in reduced excretion) or drug-resistant TB (for which optimization of every available drug is crucial). At the present time there is no laboratory in Canada that offers this service. Serum samples must be sent to the Florida Infectious Disease Pharmacokinetics Laboratory (http://idpl.cop.ufl.edu) or the National Jewish Health in Denver, CO (http://www.nationaljewish.org/). Information about the timing of blood draws, processing and shipping of samples is available from the websites of the two laboratories offering this service.

A systematic review of 66 studies of therapeutic drug monitoring, which involved 2,938 patients, has recently been completed. It found 27 studies with 1,025 patients that reported RMP concentrations; these were low in 63% (95% confidence interval 51%, 74%). Twenty-seven studies with 812 patients reported INH concentrations, which were low in 38% (27%, 50%) of patients. Of the 66 studies, none evaluated the impact of monitoring on patient outcomes, and only three evaluated the impact on patient management (J Minion, personal communication).

On the basis of this evidence, therapeutic drug monitoring is suggested for patients with risk factors for altered drug absorption or metabolism and excretion.

(Conditional recommendation, based on weak evidence)

ADVERSE EVENTS

Recognition and appropriate management of adverse drug reactions is an essential part of the treatment program. Physicians and nurses responsible for the treatment of TB should be well acquainted with these reactions (Table 5). Any possible adverse event should be carefully evaluated in order to identify other potential causes or to identify the responsible drug, which is not easy with multiple-drug regimens. It is very important to avoid unnecessary cessation of a first-line drug, as the efficacy of the treatment will be less, the duration longer and the toxicity of a replacement drug possibly worse than that of the drug that was stopped. Once a serious adverse reaction is clearly attributed to any anti-TB drug, the patient should not receive this agent again.

Table 5. Adverse events of first- and second-line drugs[6]

	Common adverse events	Uncommon but important adverse events	Rank for probability of hepatitis*	Rank for probability of rash
First-line drugs				
INH	Rash, hepatitis, neuropathy	CNS toxicity, anemia	2	3
RMP	Drug interactions, rash	Hepatitis, 'flu-like illness, neutropenia, thrombocytopenia	3	1
PZA	Hepatitis, rash, arthralgia	Gout	1	2
EMB	Eye toxicity	Rash	4	4
Second-line drugs				
Fluoroquinolones	Rash	Tendonitis, tendon rupture, QT interval prolongation		
Amikacin	Nephrotoxicity, ototoxicity			

CNS = central nervous system

*1 = most likely / 4 = least likely

Serious adverse reactions (death, life-threatening event, hospitalization, disability) associated with any anti-TB drug should be reported to local public health departments and to Health Canada's Canadian Adverse Drug Reaction Monitoring Program. To report these on-line, see http://www.hc-sc.gc.ca/dhp-mps/medeff/databasdon/index-eng.php and follow the links.

INH

INH may produce liver dysfunction ranging from asymptomatic, mild elevation of the serum transaminases to liver failure. Risk factors for hepatotoxicity include older age,[26,65] daily alcohol consumption[64] and pre-existing liver disease,[26,66] particularly hepatitis C.[65] INH may interfere with pyridoxine metabolism and cause peripheral neuropathy or other significant reactions (i.e. psychotic episodes). Rash may also occur, as may nausea and vomiting, especially with intermittent regimens administered in combination with RMP. Finally, patients may also note fatigue, drowsiness, headaches or mild hair loss.

RMP

The most important adverse reactions with RMP are hypersensitivity reactions and drug interactions. Hypersensitivity reactions to RMP include skin rash, fever, abdominal pain, thrombocytopenia and a rare hypotensive reaction similar to anaphylactic shock. RMP induces hepatic microsomal enzymes and accelerates the clearance of many drugs metabolized by the liver. These include estrogens, coumadin, anticonvulsants, glucocorticoids, digoxin, antiarrhythmics, sulfonylureas, theophylline, cyclosporin, methadone and ketoconazole. Women using hormonal contraceptives should be advised to use alternative forms of birth control while receiving RMP.

RMP alone is rarely hepatotoxic,[67,68] but combined with INH there is a slightly increased incidence of liver toxicity than with either drug alone.[69] Patients receiving RMP should be informed that their saliva and urine may become orange/red in color but that this is of no significance. Those wearing soft contact lenses should be advised that the drug may lead to permanent discoloration of the lenses from pigmented tears.

PZA

PZA is the most common cause of drug-induced hepatotoxicity and rash in patients taking standard initial therapy.[25] In up to 11% of people taking PZA arthralgias will develop; these can be very painful but are easily managed with non-steroidal anti-inflammatory drugs. Almost invariably PZA will cause elevation of serum uric acid levels, but acute gout is rarely seen except in patients with pre-existing gout. Gastrointestinal upset may also occur with PZA.

EMB

Visual impairment manifested by decreases in visual acuity, visual fields or colour vision is the most significant adverse effect of EMB. Risk factors include higher doses (e.g. 25 mg/kg), older age and renal impairment. In a recent review, incidence was 2 per 1,000 patients taking 15-25 mg/kg for 2-8 months.[70]

Patients should be advised to report any change in vision immediately. Patients who will take EMB for longer than just the initial phase should be referred to an ophthalmologist for periodic assessment of visual acuity, colour vision and visual fields. Monthly nursing assessment of visual acuity and red-green colour discrimination is recommended. EMB-related optic neuritis is usually reversible if the drug is stopped promptly, although resolution can take several months. EMB should be used with caution in children who are too young for monitoring, although a recent review suggests that its use is safe in children.[71] Other side effects, such as rash may also occur.

SUGGESTED MANAGEMENT OF COMMON ADVERSE REACTIONS

Appropriate management of adverse reactions is complicated. If there is uncertainty, consultation with a TB specialist is recommended.

Management of presumed TB drug-induced rash

All of the TB drugs may cause rash, although some cause rash more frequently than others. Mild itching or slight rash may be treated symptomatically without changing TB treatment. It is important to remember that failure and relapse rates are higher with alternative regimens; hence, any decision to stop the first-line drugs should never be made lightly. However, if the rash is generalized, particularly if associated with involvement of mucous membranes, wheezing, hypotension etc, then the following are suggested (based entirely on expert opinion).

RECOMMENDATIONS

(All conditional recommendations, based on very weak evidence)

- Stop all current drugs, and immediately start at least two alternative TB medications: a fluoroquinolone plus an injectable or an oral second-line agent.
- Review the history carefully, especially with regard to other possible causes of rash, such as food allergies or other drugs taken, including over-the-counter and herbal remedies.
- When rash has resolved restart one TB drug. Give the drug judged least likely responsible but also one of the most effective TB drugs. If history is unclear (which is the norm) give INH.
- Wait 2 to 3 days to verify if rash recurs with INH before starting the second drug – RMP.
- If there is no rash after 2-3 days of RMP give EMB.
- If there is no rash with EMB, assume that the rash was due to PZA. The decision to rechallenge with PZA depends on the need for PZA and the severity of the initial allergic reaction.

If the rash recurs with one agent, then discontinue that drug permanently and start all remaining drugs. Adjust the regimen according to which drug was permanently stopped.

MANAGEMENT OF PRESUMED TB DRUG-INDUCED HEPATITIS

Drug-induced hepatitis can be caused by PZA, INH or RMP, in that order of probability. Diagnosis may be difficult, as symptoms are nonspecific. A feeling of being unwell may be the first sign of impending hepatitis. If the serum transaminase level (aspartate aminotransferase or alanine aminotransferase [ALT]) exceeds five times the upper limit of normal or clinical jaundice develops then the following are suggested (based on entirely on expert opinion).

RECOMMENDATIONS

(All conditional recommendations, based on very weak evidence)

- Stop PZA, INH and RMP, and immediately start at least two alternative TB medications: an FQN plus an injectable, or an FQN plus an oral second-line agent.

- Review the history carefully, especially with regard to other possible causes of hepatotoxicity, such as alcohol or other drugs taken, including over-the-counter and herbal remedies. Check viral serologies (hepatitis A, B and C).

- When transaminases have returned to normal restart one of the three TB drugs stopped earlier. Give RMP, as this drug is the least likely to be responsible and is the most effective TB drug.

- Wait 2 weeks to verify that transaminases remain normal with RMP before starting INH. If initial hepatotoxicity was very severe (ALT >1,000 U/L) it may be wiser not to rechallenge with PZA or with INH; fatalities have been reported with INH rechallenge in this situation. This depends on the need for these two drugs. Consult with a TB specialist.

- If RMP and INH are restarted and transaminases remain normal, assume that the hepatitis is due to PZA. Do NOT rechallenge with PZA.

If hepatitis recurs with one agent, then discontinue that drug permanently and start all remaining drugs. Adjust regimen according to which drug was permanently stopped.

FOLLOW-UP AFTER TREATMENT

As a general rule, patients who have completed treatment and are judged to be cured do not need follow-up after treatment. For patients with HIV/TB or drug-resistant TB, or in whom adherence was at all questionable, regular follow-up every 6 months for 2 years is suggested. All patients should be told to return at any time in the future for evaluation of symptoms that suggest disease relapse, such as persistent cough or fever, hemoptysis or unexplained weight loss.

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