Clinical basics

Tuberculosis: 9. Treatment

Education

Éducation

Earl Hershfield, BSc, MD

From the Department of Medicine, University of Manitoba, Winnipeg, Man.

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Series editor: *Dr. Anne Fanning, Division of Infectious Diseases, University of Alberta, Edmonton, Alta.*

Effective tuberculosis (TB) control in Canada depends on case-finding to discover infectious cases, investigation of contacts of those with TB, appropriate treatment (with drugs to which the organisms are susceptible and user-friendly regimens to encourage adherence), case holding (which includes registration of the patient and methods of ensuring that patients take their medications until they are declared cured by the appropriate health officials) and treatment of latent infection in high-risk groups. In this article I review the theoretical basis for treatment and describe a number of accepted regimens.

Antituberculosis drugs have been described in terms of their activity in 3 areas: bactericidal activity, sterilizing activity and prevention of drug resistance. Bactericidal activity is the ability of a drug to reduce the number of actively dividing bacilli during the induction (initial) phase of therapy.[1] Isoniazid is the most potent bactericidal antituberculosis agent, although rifampin and streptomycin also have some bactericidal activity. Sterilizing activity is the ability of a drug to kill semidormant bacteria. Rifampin and pyrazinamide are the most potent sterilizing drugs for TB.[2] Drug resistance* is prevented by drugs that eliminate all bacterial populations and do not allow the emergence of resistant organisms.

Effective treatment regimens are divided into 2 phases: an initial or induction phase, during which agents are used in combination to kill rapidly multiplying populations of *Mycobacterium tuberculosis* and to prevent the emergence of drug resistance, followed by a continuation phase, during which sterilizing drugs are used to kill the intermittently dividing populations.[3–6]

Adherence to the treatment regimen can be achieved by directly observed therapy (DOT), in which a health care provider watches the patient swallow each dose of medication. DOT is important in the treatment of tuberculosis because it allows for monitoring of the number of doses that an individual has taken, drawing attention immediately to those who have missed treatment and thus alerting the health care worker in charge of the particular case that the patient may be absconding from treatment. In addition, it ensures that monotherapy does not occur, which might happen if an individual is intolerant to one or more of the medications prescribed and thus consciously takes fewer of the drugs than necessary. It also allows for the extension of treatment on the basis of the number of doses missed.

DOT may be given daily or intermittently (2 or 3 times a week).[7–11] Intermittent therapy was introduced when it was shown in controlled clinical trials that therapeutic serum levels of the various antituberculosis drugs were maintained even when medications were given only 2 or 3 times a week.[12–14] Intermittent regimens have proven effective, do not have more toxic effects than daily regimens and allow drug administration to be adapted to local conditions.[14–16] All intermittent regimens must involve DOT.

*Drug resistance in TB is either initial or acquired. Initial resistance is defined as resistance to one or more drugs that is present in the infective organism at the time the patient becomes infected. Acquired resistance is defined as resistance to 1 or more drugs that develops during therapy in an infective organism that was originally sensitive to the drug or drugs being administered.

First-line medications

First-line antituberculosis medications are summarized in Table 1.[17,18]

Isoniazid

Isoniazid is the most commonly used antituberculosis drug. It is highly effective against *M. tuberculosis*, especially actively dividing bacilli. It is usually given orally, although parenteral preparations are available. The usual daily dose is 5 mg/kg for adults and 10 mg/kg for children.

Isoniazid may produce asymptomatic elevation of serum transaminases, overt hepatitis necessitating discontinuation of therapy, severe hepatitis leading to the need for liver transplantation[19] or even fatal hepatitis.[20] The risk of hepatitis is higher in older patients, those who are alcohol abusers, and Hispanic and black women in the child-bearing years.[21] Baseline measurement of liver enzymes is recommended for adults starting therapy with isoniazid. All patients taking isoniazid should be monitored clinically for adverse reactions.

Isoniazid may interfere with pyridoxine metabolism and thus produce peripheral neuropathy. This problem most commonly occurs in people who are mildly deficient in pyridoxine, such as pregnant women, ethanol abusers and malnourished patients; it may be prevented by the use of vitamin B_6 at a dose of 25–50 mg/day.[22]

Other adverse reactions associated with isoniazid include hypersensitivity reactions, such as acneiform skin rash, effects similar to those of monoamine oxidase inhibitor after the ingestion of such foods as red wine or cheese,[23] and development of antinuclear antibodies or (rarely) overt systemic lupus erythematosus.[24] Isoniazid may interfere with the metabolism of some anticonvulsants, such that the dose of either the anticonvulsant or isoniazid may need to be adjusted.

Rifampin

Rifampin is a potent agent against actively dividing intracellular and extracellular organisms and has activity against semidormant bacilli. It works primarily by inhibiting DNA-dependent RNA polymerase, blocking RNA transcription. It is usually given as a daily oral dose of 10 mg/kg.

Rifampin therapy causes a harmless red or orange discoloration of the urine and other body fluids and may stain contact lenses. Hepatotoxicity occurs less frequently than with isoniazid. Hypersensitivity reactions, thrombocytopenia, renal failure and flu-like symptoms occur only rarely; however, they seem to occur more frequently with intermittent than with daily administration. Patients who are using oral contraceptives or long-acting injectable progestin agents should be counselled about using other forms of birth control while they are receiving rifampin.[25,26] Rifampin also interacts strongly with protease inhibitors and non-nucleoside reverse transcriptase inhibitors (NNRTIs), 2 classes of potent antiretroviral agents used in combination with other agents for the treatment of HIV infection. It may be necessary to substitute rifabutin for rifampin and adjust the dose of rifabutin or the antiretroviral agents (or both).[27]

Rifabutin and rifapentine

Rifabutin is a rifamycin antibiotic with properties similar to those of rifampin. In vitro, it is more active than rifampin against mycobacteria; however, it yields lower serum levels. The usual daily dose is 300 mg by mouth. It has been used most often for the treatment or prophylaxis of infections with *Mycobacterium avium* complex, but it appears to be effective in the treatment of TB. There is cross-resistance with rifampin, and its usefulness in the treatment of rifampin-resistant TB has not been clearly demonstrated. However, because it is a less potent inducer of cytochrome P-450 metabolism, it has a role in TB therapy in cases in which drug interactions may occur, as in patients

Table 1: Doses of and common adverse reactions to first-line antituberculosis drugs*

Drug	Daily dose for adults and children, mg/kg	Usual dose, mg		Common adverse reactions†
		If given daily	If given twice weekly	
Isoniazid	5–10	300	900–1200	Hepatitis, peripheral neuropathy
Rifampin‡	10	600	600	Hepatitis, flu-like illness (reduced effect of some other drugs)
Pyrazinamide	15–30	1500	2500	Hepatitis, elevated serum level of uric acid, arthralgia
Ethambutol	15–25	800–1200	2400	Retrobulbar neuritis
Streptomycin	15–20	1000	1000	Vertigo, tinnitus, renal failure

Note: In alcoholic patients, diabetic patients and pregnant women, or if there is a concern for the patient's nutritional status, vitamin B_6 (25–50 mg/day) may be prescribed.

*Adapted from the Tuberculosis Committee of the Canadian Thoracic Society,[17] and the American Thoracic Society.[18]

†All drugs may cause rash, nausea and fever.

‡Rifabutin and rifapentine have similar properties.

with HIV co-infection who are taking protease inhibitors and NNRTIs.

Rifapentine is a long-acting rifamycin that is being studied in a clinical trial comparing once-weekly isoniazid and rifapentine with standard twice-weekly isoniazid and rifampin in the 16-week continuation phase of therapy.[28] Its exact role is not yet clear.

Pyrazinamide

Pyrazinamide is a potent sterilizing agent used in short-course regimens.[29] It is most active in acid environments, especially within macrophages. The daily dose of pyrazinamide is 15–30 mg/kg, given orally.

Hypersensitivity reactions and gastrointestinal upset may occur with pyrazinamide. Hepatotoxicity occurs infrequently with current recommended dosages. Pyrazinamide often produces elevated serum levels of uric acid, although arthralgias occur infrequently, and acute gout is rare.

Key points

Antituberculosis drugs can be characterized by their activities in 3 areas:

Area of activity	Drugs
Bactericidal	Isoniazid, rifampin, streptomycin
Sterilizing	Rifampin, pyrazinamide
Prevention of drug resistance	Isoniazid, rifampin

Ethambutol

Ethambutol is active against both intracellular and extracellular organisms. Because it inhibits the selection of resistant mutants, this drug is given as part of the initial regimen in cases in which isoniazid resistance is possible. Ethambutol is administered orally at a daily dose of 15–25 mg/kg. The higher dose is usually reserved for treatment of relapse and is reduced to 15 mg/kg after 2 months to help reduce the occurrence of ethambutol's most significant side effect, optic neuritis. The symptoms of this condition include blurred vision and colour blindness, which are reversible if they are detected early and the medication is stopped promptly. Patients taking ethambutol should have their visual acuity and colour vision checked at least monthly. Ethambutol is not usually given to children, who are too young for monitoring of visual acuity and colour vision, although a recent review suggests that it is safe for use in children.[30] Ethambutol is excreted by the kidneys, and the dosage should be reduced in renal failure.[31]

Streptomycin

Streptomycin is an aminoglycoside antibiotic that interferes with bacterial protein synthesis. It is given by injection, usually intramuscularly, at a daily dose of 15 mg/kg. Ototoxicity and nephrotoxicity are associated with administration of this drug, occurring more frequently in the elderly. Vestibular dysfunction is more common than auditory damage.

Fixed-dose combinations

When therapy is self-administered, fixed-dose combinations may be recommended to prevent monotherapy (patients selectively taking only one of the prescribed drugs) and the emergence of drug resistance.[32,33] The combination of isoniazid, rifampin and pyrazinamide (Rifater; Hoechst Marion Roussel, Laval, Que.) is available in Canada, although the combination of isoniazid and rifampin (Rifamate; Hoechst Marion Roussel, Kansas City, Mo.) is not.

Each Rifater tablet contains 50 mg of isoniazid, 120 mg of rifampin and 300 mg of pyrazinamide. The recommended quantity is 5 tablets a day for patients weighing less than 55 kg and 6 tablets a day for those weighing 55 kg or more. Because of the lower bioavailability of rifampin in the combination preparation, the tablets contain more rifampin than the recommended dose of a single-drug preparation. Fixed-dose combinations of antituberculosis drugs have the advantage of ensuring that the patient always takes more than one type of medication. The disadvantages include higher cost, the need for the patient to take many pills and the possibility of underdosing if the patient takes fewer tablets than prescribed. Fixed-dose combinations are unnecessary when treatment is administered by DOT.

Second-line medications

Second-line antituberculosis medications are summarized in Table 2.[17,18]

Cycloserine

The usual dose of cycloserine is 150–250 mg/kg daily to a maximum of 500 mg/day, given orally in divided doses. Cycloserine frequently causes dose-related neurologic or psychiatric disturbances, including headache, drowsiness, confusion, seizures or psychosis. These effects can be exacerbated by renal insufficiency but are usually reversed by discontinuation of the medication. Renal impairment decreases excretion of the drug and can exacerbate adverse reactions.

Ethionamide

Ethionamide is a derivative of isonicotinic acid that appears to interfere with peptide synthesis. The usual daily dose is 15–20 mg/kg, to a maximum of 750 mg/day, given orally in divided doses. Ethionamide frequently causes gastrointestinal side effects, such as abdominal pain, nausea,

vomiting and anorexia. Bedtime dosing, taking the medication with food or gradually increasing to the full dose may improve tolerance. Ethionamide may cause hepatitis but only rarely.

Capreomycin

Capreomycin in an injectable polypeptide antibiotic for which the mechanism of action is unknown. It is administered intramuscularly in a dose of 15–30 mg/kg daily. Nephrotoxicity occurs occasionally, resulting in reduced creatinine clearance and electrolyte disturbances. Renal function should be monitored closely, especially in elderly patients.

Kanamycin and amikacin

Kanamycin and amikacin are aminoglycosides with activity against *M. tuberculosis*. They may be administered intramuscularly or intravenously at a daily dose of 15–30 mg/kg. They have complete cross-resistance, and cross-resistance may also occur with capreomycin. Renal toxic effects occur only occasionally, whereas auditory toxic effects may be more common. Regular monitoring of hearing and renal function is recommended.

Fluoroquinolones

The fluoroquinolones are broad-spectrum antibiotics that have few serious adverse reactions. They are less effective than first-line agents in treating TB[34,35] and are mainly used in the treatment of drug-resistant disease.[36,37] When they are given singly, resistance quickly emerges.[38,39]

Four fluoroquinolones are used in the treatment of TB: ciprofloxacin, ofloxacin, levofloxacin and sparfloxacin. Ciprofloxacin and ofloxacin have similar potency. Ciprofloxacin is given orally at a dose of 500–750 mg twice a day, and the daily dose of ofloxacin is 600–800 mg/day. Levofloxacin is the L-isomer of ofloxacin and has approximately twice the potency. The maximum recommended dose is 500 mg daily, although 750 mg daily has been used by some clinicians. Sparfloxacin (daily dose 200 mg) has even greater potency than levofloxacin; however, photosensitivity reactions may occur, and patients must be instructed to avoid sunlight.[40]

Table 2: Doses of and common adverse reactions to second-line antituberculosis drugs*

Drug	Daily dose in adults and children		Recommended regular monitoring	Adverse reactions†
	Usual	Maximal		
Cycloserine	150–250 mg	500 mg	Mental status	Neurologic and psychiatric disturbance, convulsions, rash
Ethionamide	15–20 mg/kg	750 mg	Hepatic enzymes	Gastrointestinal disturbance, hepatotoxicity, hypersensitivity
Capreomycin	15–30 mg/kg	1 g	Vestibular function, audiometry, blood urea nitrogen, creatinine	Auditory, vestibular and renal toxic effects
Kanamycin, amikacin	15–30 mg/kg	1 g	Vestibular function, audiometry, blood urea nitrogen, creatinine, hepatic enzymes	Auditory and renal toxic effects; rarely, vestibular toxic effects
Fluoroquinolones				
Ciprofloxacin	500–750 mg twice daily	1 g		Gastrointestinal upset
Ofloxacin	600–800 mg	1 g		Gastrointestinal upset
Levofloxacin	500 mg	750 mg		Gastrointestinal upset
Sparfloxacin	200 mg			Gastrointestinal upset

Note: Second-line drugs are more difficult to use than first-line drugs. They should be used only when necessary and should be given and monitored by health care providers experienced in their use.
*Adapted from the Tuberculosis Committee of the Canadian Thoracic Society,[17] and the American Thoracic Society.[18]
†All of these drugs may cause rash, nausea and fever.

Principles of drug therapy

The recommended options for treating TB in adults are outlined in Table 3.[41] For all options, the initial or intensive phase of the regimen must contain at least three drugs — isoniazid, rifampin and pyrazinamide — along with either ethambutol or streptomycin if the local resistance pattern to isoniazid is not documented or is greater than 4%. Various combinations are recommended for the continuation phase of therapy (Table 3). Drug susceptibility tests should be performed on all initial isolates of *M. tuberculosis*, and DOT should be the standard method of delivery for all patients, whether the doses are given daily and intermittently.[41]

During treatment, patients should be examined at least monthly for evidence of active TB, adherence to treatment and adverse reactions to medications. Sputum specimens for acid-fast bacilli smear and culture should be obtained when the clinical situation warrants it; susceptibility testing should be repeated if cultures remain positive after 3 to 4 months of treatment.[18,42]

Special situations

Treatment failure

Treatment failure occurs when culture results continue to be positive for *M. tuberculosis* after 3 to 4 months of treatment with drugs to which the organisms are known to be susceptible. When cultures are unavailable or pending, treatment failure should also be considered when clinical deterioration occurs or the findings on chest radiography worsen. The assessment of a patient whose treatment is failing should include the following steps:

- ensure that the proper medications are being taken
- obtain repeat specimens for smear, culture and drug susceptibility
- continue the current regimen until susceptibility results are available
- rarely, determine serum drug levels to ensure proper gastrointestinal absorption.

If the patient's condition is deteriorating clinically, he or she should be given at least 2 new antituberculosis medications to which the organism is likely to be susceptible, and the regimen should be adjusted once susceptibility results are available.[18,42] The physician should never add a single drug to a failing regimen.

Relapse of disease

Relapse of TB is defined as recurrence of disease after completion of an adequate antituberculosis treatment regimen in a patient whose culture results have been negative for at least 6 months.[18] If the original organism was fully susceptible and the patient completed a regimen containing isoniazid and rifampin, the original regimen can be used, because the organism usually remains susceptible.[43] For patients who did not receive isoniazid or rifampin in the initial regimen, drug resistance to the previously prescribed medications should be presumed. In all situations, drug susceptibility tests should be performed and treatment regimens modified according to the results.

Extrapulmonary TB

Treatment regimens for extrapulmonary forms of TB are generally the same as for pulmonary TB. Bone or joint TB, tuberculous meningitis and pediatric miliary TB should be treated for at least 9 to 12 months.[18] Corticosteroids may be needed for tuberculous pericarditis and meningitis; some experts also recommend their use in miliary TB.[42]

Chronic renal failure

Antituberculosis drugs are cleared to a variable degree by hemodialysis: therefore, on days when dialysis is performed, the medications should be given after the procedure.

Isoniazid, rifampin, pyrazinamide and ethambutol can be used at normal doses in patients with renal failure. The

Table 3: Options for treatment of tuberculosis in adults*

Option	Drug combination and conditions	Frequency and duration of treatment
Option 1		
Initial phase†	Isoniazid, rifampin and pyrazinamide; self-administered	Daily for 8 wk
Continuation phase	Isoniazid and rifampin; DOT	Daily or intermittent (2 or 3 times/ wk) for 16 wk
Option 2		
Initial phase	Isoniazid, rifampin, pyrazinamide, and streptomycin or ethambutol; DOT	Daily for 2 wk
	Isoniazid, rifampin, pyrazinamide, and streptomycin or ethambutol; DOT	2 times/wk for 6 wk
Continuation phase	Isoniazid and rifampin; DOT	2 times/wk for 16 wk
Option 3		
Initial phase	Isoniazid, rifampin and pyrazinamide; self-administered	2 mo
Continuation phase	Isoniazid and rifampin; self-administered	4–7 mo

Note: DOT = directly observed therapy. For any therapeutic regimen, the physician should consult a tuberculosis medical expert if, after 3 months of treatment, the patient is symptomatic, or smear or culture yields positive results.

*Adapted from the American Thoracic Society.[18]

†Where annual incidence of isoniazid resistance is greater than 4%, add ethambutol or streptomycin until susceptibility to isoniazid and rifampin is demonstrated.

regimen should consist of 2 months of isoniazid, rifampin and pyrazinamide, followed by 4 to 6 months of isoniazid and rifampin.[32]

Liver disease

The potential for toxic effects in the liver as a result of antituberculosis drugs may be greater in patients with underlying liver disease. The doses of most antituberculosis drugs need not be reduced in these patients, but close monitoring of liver function for signs and symptoms of toxic effects is indicated.[41] In acute hepatic failure, a regimen including nonhepatotoxic drugs that are not cleared by the liver (e.g., aminoglycosides, capreomycin, ethambutol, cycloserine and the fluoroquinolones) should be used until liver function improves.

Pregnancy

Treatment for suspected or confirmed TB should not be delayed during pregnancy. Effective therapy for TB is the best way to prevent infection of the fetus and the newborn. Pyrazinamide and streptomycin are not recommended during pregnancy because of possible teratogenic effects.[18] Pyridoxine should be given to all pregnant women receiving TB therapy to prevent peripheral neuropathy from isoniazid.

Because many of the medications used to treat multidrug-resistant TB either are known to cause fetal abnormalities or have not been studied adequately, women of child-bearing age with multidrug-resistant TB should be advised to use birth control. Pregnant women with multidrug-resistant TB should be counselled about the potential effects of the medications on the fetus.

Breast-feeding

The small concentrations of antituberculosis drugs in breast milk are not toxic to the newborn. Therefore breast-feeding should not be discouraged in HIV-seronegative women. However, breast-feeding is not recommended for HIV-infected women.[44]

HIV infection

Until a few years ago, recommendations for the treatment of HIV-related TB suggested that patients receive TB medication for 9 months; however, the recommendations were modified in 1994 to state that treatment need last for only 6 months.[45] However, the new recommendations strongly advise prolonging the continuation phase of therapy if the clinical and bacteriologic response is slow or suboptimal.

Antiretroviral drugs

Two classes of drugs for the treatment of HIV infection are protease inhibitors and NNRTIs. Although these medications have reduced illness and death from HIV and are now recommended as part of multidrug regimens for all patients with AIDS,[46,47] they have an important impact on the treatment of TB because of their interactions with the rifamycins. The use of these 2 classes of drugs complicates the clinical management of HIV-infected patients who also have TB.[48] Experts familiar with the interactions should be consulted.

Multidrug-resistant TB

Multidrug-resistant TB is difficult to cure and costly to treat. If culture results remain positive after 3 to 4 months of treatment, the most recent cultures should undergo testing for susceptibility to all antituberculosis drugs. While awaiting the results of drug susceptibility testing, the patient may continue to receive the most recent treatment regimen, if his or condition is clinically stable. Alternatively, if the patient is acutely ill, at least 2 new drugs should be added to the original medications. An aminoglycoside or capreomycin should be one of the medications used, since these drugs lead to earlier sputum conversion.[49]

Patients with both TB and HIV infection, as well as those with multidrug-resistant TB, should always be treated by health care providers experienced with the medications used. All such patients should be treated by DOT. Intermittent regimens for multidrug-resistant TB have not been studied and should not be used.

Adherence

Despite the availability of highly effective regimens, cure rates may not be satisfactory. Patients often do not take the prescribed drugs regularly or long enough to achieve cure.[49]

A potentially more serious problem than noncompliance is partial adherence to a prescribed regimen. When some drugs are selectively discontinued, there is an increased risk of acquired drug resistance.

To help avoid the problem of multidrug-resistant TB in non-DOT regimens, clinicians should ideally give patients fixed-dose combinations adjusted for body weight. Fixed-dose drug combinations of isoniazid, rifampin and pyrazinamide make selective monotherapy impossible.

Conclusion

TB control programs must not only detect cases of active disease but also maintain contact with each patient until the disease is cured. Through the use of enablers, incentives, increased sensitivity to psychological, cultural and behavioural issues, and expanded use of DOT, it may be possible to keep patients on their treatment regimens for longer periods and thus to achieve lasting cure.

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Reprint requests to: *Dr. Earl Hershfield, Department of Medicine, Section of Respiratory Medicine, Respiratory Hospital, 810 Sherbrook St., Room RS115, Winnipeg MB R3A 1R8; fax 204 787-2420; ehersh@ccu.umanitoba.ca*