

Section V.

Treatment of Drug-Resistant Tuberculosis

Tuberculosis

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Principles of Treating Drug-Resistant Tuberculosis

Unlike the treatment of drug-susceptible tuberculosis (TB), developing standardized protocols for the treatment of known or suspected drug-resistant (DRTB) is not possible. Several issues are involved:

- Any treatment recommendation must take into account the drug susceptibility results of the individual isolate and prior treatment history.
- Good data are lacking on the efficacy of non-standard regimens.
- Adverse effects of second-line medications, often serious and intolerable, may preclude the use of these drugs for the recommended period of time.

Multidrug-resistant TB (MDRTB) refers to a strain of *M. tuberculosis* (*M. tb*) resistant to at least isoniazid and rifampin.

Treatment Principles

- Patients with DRTB, particularly MDRTB, should be treated under a program of directly observed therapy (DOT). If the patient is not given DOT, the compelling reason must be documented in the medical record. Some patients will need DOT twice a day.
- MDRTB treatment can be as complex as cancer chemotherapy and should not be attempted without the consultation of a specialist in MDRTB.
- There are no fully intermittent regimens at present for MDRTB treatment. However, the injectable agents may be administered intermittently during part of the treatment, and certain drugs may be given intermittently in patients with renal failure.

- Patients must be treated with a regimen of at least 3 to 5 anti-TB medications to which the strain is likely to be susceptible.
- A single anti-TB medication should never be added to a regimen that is failing (i.e., if the patient is not clinically improving or if the cultures are still positive 4 months after start of therapy). At least 2, and preferably 3, new anti-TB medications to which the strain is likely to be susceptible should be added.
- When an injectable agent is needed, begin with capreomycin as the injectable agent of choice until drug susceptibilities are known. All strain W and strain W variants are streptomycin- and kanamycin-resistant (these strains are still seen in NYC patients).
- Switch to streptomycin if the organism is susceptible. Use kanamycin if strain is susceptible to it and amikacin, but resistant to streptomycin. (Laboratories usually test for either kanamycin or amikacin susceptibility; there is cross-resistance between these 2 agents and resistance to one predicts resistance to the other.)
- Treatment for TB strains resistant to at least rifampin (mono-rifampin, or MDRTB) should be given for at least 18 months after culture conversion to negative. Consider extending therapy to 24 months after culture conversion to negative if:
 - There is cavitory or extensive disease
 - The patient is HIV positive or has risk factors for HIV infection
 - The patient is immunosuppressed
 - Time to culture conversion is prolonged
- In general, any level of resistance to an anti-TB medication, documented by a reliable mycobacteriology laboratory, indicates that the drug is unlikely to be effective. However, susceptibility testing for pyrazinamide,

ethionamide and capreomycin is often inconsistent among laboratories or even within the same laboratory. In cases of partial resistance or inconsistent results, physicians should follow the general dictum, “use the medication, but do not depend on it for success.”

- If there is mono-resistance to pyrazinamide, suspect *Mycobacterium bovis*, another member of the *M. tb* complex.
- Because the continued administration of second-line drugs may be life saving, physicians should not discontinue an anti-TB medication in a patient who has adverse reactions unless the reaction is severe or cannot be ameliorated by supportive treatment.
- Most of the medications used to treat MDRTB are known to cause fetal abnormalities or have not been studied adequately regarding their safety in pregnancy. Therefore, women of child-bearing age who have MDRTB should be strongly encouraged to use birth control methods if they are sexually active. Pregnant women with culture-proven MDRTB on treatment should be offered abortion counseling.
- Children with MDRTB should be treated with the first- and second-line drugs to which their *M. tb* strain, or that of their source case, is susceptible, including streptomycin, ethambutol and pyrazinamide. Ethambutol is bactericidal at higher doses, so daily doses up to 25 mg/kg should be used in children being treated for MDRTB. Some fluoroquinolones are not FDA-approved in children, and must be used after careful consideration of the potential risks and benefits, which should be documented in the patient record. See p. 210, Appendix I-B for dosages of second-line or reserve anti-TB drugs for treatment of MDRTB in children.

Monitoring Principles

- Sputum AFB smear and cultures should be monitored monthly for patients with isoniazid and/or rifampin resistant isolates.
- If a patient has a positive *M. tb* culture after 4 months of treatment, the most recent positive culture must be sent to the clinical laboratory for first- and second-line anti-TB drug-susceptibility testing. There are at least 2 treatment options while the drug-susceptibility results are pending:

1. If the patient is not acutely ill or clinically deteriorating, the current or most recent anti-TB regimen may be continued until the new drug susceptibility results are available. This regimen is often referred to as a “holding regimen”.
 2. If the patient is acutely ill or clinically deteriorating, at least 2 new medications should be started, based on an assessment of the other medications to which the strain is likely to be susceptible. The original medications should be continued until the new drug-susceptibility results are available.
- If a regimen is not failing (i.e., the patient shows clinical improvement and *M. tb* cultures have converted from positive to negative), but the MDRTB patient is having an adverse reaction to a specific, identifiable medication (severe enough to preclude the further use of the medication, e.g., ototoxicity from streptomycin, gout from pyrazinamide, etc.), the following treatment alternatives are available, depending on the length and success of treatment before the adverse reaction:
 1. The medication responsible for the adverse reaction may be omitted and the remainder of the anti-TB treatment regimen continued.
 2. A new, previously unused agent may be substituted for the medication responsible. (This alternative does not increase the risk for drug resistance because the prior anti-TB treatment regimen was not failing.)
 3. If the cause for the adverse reaction (e.g., hepatotoxicity, skin rash) cannot be readily identified, all medications should be discontinued and retested by reintroduction singly into a regimen trial. In some instances of severe toxicity, hospitalization for rechallenge with multiple drugs may be needed.
 - For management of TB patients who are HIV infected, treatment length and regimens are generally the same as for patients not infected with HIV. Nevertheless, HIV status should be determined for all TB patients, as many providers recommend extended treatment for these patients. In addition, if HIV infection is identified, patients can be referred for HIV treatment.

- Monthly, and as needed, clinical and laboratory monitoring should be done as per Bureau of Tuberculosis Control (BTBC) guidelines. (See p. 101; p. 208, Appendix I-A; p. 210, Appendix I-B; and information on individual drugs.)

Principles for Selected Drugs

- Most, but not all, *M. tb* strains that are resistant to rifampin are also resistant to rifabutin. However, a minority of rifampin-resistant organisms, especially those reported to be less than 50% resistant by agar proportion method, will prove sensitive to rifabutin. When there is *in vitro* sensitivity to rifabutin, it can be added to the regimen along with an injectable agent and other oral agents as outlined. However, since the effectiveness of the rifabutin cannot be relied upon due to lack of clinical data, the treatment length should be the same as for a non-rifampin based regimen (18-24 months).
- Aminoglycosides or capreomycin should be used for at least 6 months after culture conversion unless ototoxicity or nephrotoxicity develops. The continuation of aminoglycosides or capreomycin for longer than 6 months after culture conversion may be appropriate if there is extensive disease, extensive resistance to second-line drugs or slow conversion of sputum cultures. Data analyzed by the BTBC indicate that the duration of treatment with an injectable medication is the strongest predictor of culture conversion and survival in patients with MDRTB. With documented MDRTB, over-treatment is much more preferable than under-treatment, which may have dire consequences for the patient and the family.
- Injectable agents should be given 5 days a week initially. After culture conversion, dosing can be 2 to 3 times a week.
- Levofloxacin is currently the preferred fluoroquinolone for TB treatment, even in children. It is the optically active l-isomer of ofloxacin and is more active against *M. tb* than ofloxacin (which consists of equal amounts of the d- and l-isomers).

- The initial dose is 500 mg once daily, which can be increased over a 2-week period to 750-1,000 mg once daily as tolerated, since higher doses may be more bactericidal.
- Levofloxacin has been associated with a decreased incidence of adverse effects compared to the older fluoroquinolones. In general, the adverse effects profile is similar to the other fluoroquinolones.
- Levofloxacin is a category C drug in pregnancy and should only be used if the potential benefit to the mother justifies the potential risk to the fetus.
- When used in children, the potential benefit must justify the potential risk.
- When used in pregnant women and children, the patient and/or caregiver should be educated about the risks and benefits; this should be documented in the medical record.
- Cross-resistance has been demonstrated among levofloxacin, ofloxacin, ciprofloxacin and the newer fluoroquinolones.
- Levofloxacin should not be considered as first-line treatment in patients with drug-susceptible organisms unless they are intolerant of other first-line drugs.

Suggested Regimens for Specific Drug Resistance Patterns

The following suggested regimens are guidelines only (see p. 86, Table V-1). In reality, the options are seldom clear cut, as many patients will have already received trials of some of the medications and may have had them added one at a time to previous regimens. Furthermore, opinions vary on the best medications to use for an individual patient. Expert consultation should be sought for individuals with confirmed or suspected MDRTB.

Table V-1

Suggested Regimens for Treatment of Drug-Resistant Tuberculosis

Resistance Pattern	Initial Phase		Continuation Phase		Total Length
	Drugs	Duration	Drugs	Duration	
Isoniazid ± Streptomycin	Option A: Rifampin/Pyrazinamide/ Ethambutol	2 months	Rifampin/Pyrazinamide/ Ethambutol	4-7 months	6-9 months. Extend to 9 months if still culture positive at 2 months. Preferred regimen even in pregnancy
	If extensive disease, consider adding a 4th agent such as Fluoroquinolone or Injectable Agent				
	Option B: Rifampin/Ethambutol/ Pyrazinamide	2 months	Rifampin/Ethambutol	7 months	9 months
For Isoniazid/Pyrazinamide ± Streptomycin use option C	Option C: Rifampin/Ethambutol + Fluoroquinolone or Injectable Agent	2 months	Rifampin/Ethambutol + Fluoroquinolone or Injectable Agent	10 months	12 months
Rifampin ± Streptomycin	Option A: Isoniazid/Pyrazinamide/ Ethambutol/Injectable Agent + Fluoroquinolone	2-3 months after culture conversion	Isoniazid/Pyrazinamide/ Ethambutol ± Fluoroqui- nolone	12-14 months	18 months Preferred regimen
	Option B: Isoniazid/Pyrazinamide/ Streptomycin (if no Streptomycin resistance) ± Ethambutol	2-3 months after culture conversion	Isoniazid/Pyrazinamide/ Streptomycin ± Ethambutol	3-5 months	9 months
Pyrazinamide ± Streptomycin	Isoniazid/Rifampin/ Ethambutol	2 months	Isoniazid/Rifampin	7 months	9 months
Isoniazid/Ethambutol ± Streptomycin	Rifampin/Pyrazinamide/ Fluoroquinolone ± Injectable Agent	2-3 months after culture conversion	Rifampin/Pyrazinamide/ Fluoroquinolone	7-9 months	9-12 months or 6 months after culture conversion, whichever is longer
Isoniazid/Rifampin ± Streptomycin	Pyrazinamide/Ethambutol/ Fluoroquinolone/Injectable Agent	6 months after culture conversion	Pyrazinamide/Ethambutol/ Fluoroquinolone	12-18 months	18-24 months after culture conversion
Isoniazid/Rifampin/ Ethambutol ± Streptomycin	Pyrazinamide/fluoroquinolone/ Injectable Agent plus at least 1-2 2nd line agents to which strain is susceptible	6 months after culture conversion	Pyrazinamide/ Fluoroquinolone plus at least 1-2 2nd line agents to which strain is susceptible	12-18 months	18-24 months after culture conversion
Isoniazid/Rifampin/ Pyrazinamide ± Streptomycin	Ethambutol/Fluoroquinolone/ Injectable Agent plus at least 1-2 2nd line agents to which strain is susceptible	6 months after culture conversion	Ethambutol/ Fluoroquinolone plus at least 1-2 2nd line agents to which strain is susceptible	12-18 months	18-24 months after culture conversion
Isoniazid/Rifampin/ Pyrazinamide/Ethambutol ± Streptomycin	Fluoroquinolone/Injectable Agent plus at least 2-3 2 nd line agents to which strain is susceptible	6 months after culture conversion	Fluoroquinolone plus at least 2-3 2nd line agents to which strain is susceptible	12-18 months	18-24 months after culture conversion
Isoniazid/Rifampin/Ethambutol/ Streptomycin/Kanamycin/ Ethionamide/Rifabutin ± Pyrazinamide (strain W and W variants)	Fluoroquinolone/Injectable Agent plus at least 2-3 agents to which strain is susceptible	6 months after culture conversion	Fluoroquinolone plus at least 2-3 2nd line agents to which strain is susceptible	12-18 months	18-24 months after culture conversion
Isoniazid/Rifampin/Ethambutol/ Streptomycin/Fluoroquinolone + second-line reserve injectable agent ± Pyrazinamide (i.e. extreme drug resistant TB (XDRTB))	Any 3-4 drugs to which strain is susceptible. Linezolid & Clofazimine may be necessary.	Until culture conversion	Any 3-4 drugs to which strain is susceptible. Linezolid & Clofazimine may be necessary.	Unknown	At least 24 months after culture conversion

Isoniazid Resistance (with or without Streptomycin Resistance)

Regimens

- *Option A.* Use rifampin, pyrazinamide and ethambutol for the duration of treatment. This is the preferred regimen even for pregnant patients, as relapse rates with rifampin and ethambutol are high. Extend to 9 months if the patient is still culture positive at 2 months. If a fluoroquinolone or injectable agent has been used (in patients with extensive disease or slow conversion of sputum cultures), it may be discontinued 2 months after culture conversion.
- *Option B.* If a patient was treated with pyrazinamide for at least 2 months and the drug was discontinued, treat with rifampin and ethambutol for an additional 7 months.
- *Option C.* If pyrazinamide cannot be used because of drug resistance or intolerance, a regimen of rifampin and ethambutol, along with a fluoroquinolone or an injectable agent, should be used for a 12-month period. The use of rifampin and ethambutol alone is not recommended because of high relapse rates on this regimen.

If resistance to isoniazid (with or without streptomycin resistance) is discovered after the patient has been taking isoniazid, rifampin, pyrazinamide and ethambutol for 1 to 3 months, and the patient has extensive disease requiring the addition of a fourth agent, a single medication can be added if the patient has responded to treatment and is smear negative for acid-fast bacilli. **This does not violate the rule of “do not add a single drug to a failing regimen.”**

- High dose isoniazid is **not** recommended.

Length of Treatment

For both patients who are HIV negative and HIV positive:

- *Option A.* 6-9-month regimen; the 9-month regimen should be given to those who are still culture positive 2 months after starting treatment. This is the only regimen that can be given intermittently; 3 times a week is preferred for all patients.
- *Option B.* 9-month regimen
- *Option C.* 12-month regimen

Isoniazid and Ethambutol Resistance (with or without Streptomycin Resistance)

Regimens

- Use rifampin, pyrazinamide and a fluoroquinolone, along with an appropriate aminoglycoside or with capreomycin. Use capreomycin or an aminoglycoside other than streptomycin if streptomycin resistance is known at the start of treatment.
- If resistance to isoniazid and ethambutol (with or without streptomycin resistance) is discovered after the patient has been taking isoniazid, rifampin, pyrazinamide and ethambutol for 1-3 months, discontinue isoniazid and ethambutol. Continue rifampin and pyrazinamide, adding at least a fluoroquinolone and possibly an injectable agent such as capreomycin or an appropriate aminoglycoside.

Length of Treatment

- Nine to 12-month regimen, or 6-month regimen after culture conversion, whichever is longer.

An aminoglycoside or capreomycin may be discontinued 2 to 3 months after culture conversion to negative. However, in patients with extensive disease or slow conversion of sputum cultures, the injectable should be used for 6 months after culture conversion.

Rifampin Resistance (with or without Streptomycin Resistance)

Regimens

- *Option A.* Use isoniazid, pyrazinamide and ethambutol, along with an appropriate aminoglycoside or with capreomycin. Use capreomycin or an aminoglycoside other than streptomycin if streptomycin resistance is known at the start of treatment. If the patient has received 10 days or more of isoniazid and rifampin alone, add a fluoroquinolone to the regimen.
- *Option B.* If there is no streptomycin resistance, use isoniazid, pyrazinamide and streptomycin. This regimen, studied in patients who are HIV-negative, is the only non-rifamycin-containing regimen that has been shown to have high efficacy when used for less than 1 year.

Streptomycin was administered daily or intermittently for the entire 9 months in one study. It can be used in patients who are HIV positive with tuberculosis, who are on any antiretroviral treatment, without dose adjustments of anti-TB meds or HIV medications.

Some experts recommend an 18-month regimen of isoniazid/ethambutol as an option, in which streptomycin is used for 2 to 3 months post culture conversion. In NYC, most rifampin-resistant TB is seen in persons infected with HIV in whom this regimen has not been studied. Use pyrazinamide throughout the entire treatment if this regimen is used.

- Isoniazid, pyrazinamide, ethambutol and a fluoroquinolone in a 12-month regimen, while recommended in the new American Thoracic Society/Centers for Disease Control and Prevention (CDC)/Infectious Diseases Society of America guidelines, is not recommended by the BTBC.

Length of Treatment

For both patients who are HIV negative and HIV positive:

- *Option A.* Eighteen months total treatment with isoniazid, pyrazinamide, ethambutol and an aminoglycoside or capreomycin. If an aminoglycoside or capreomycin has been used, it may be discontinued 2 to 3 months after culture conversion. However, in patients with extensive disease or slow conversion of sputum cultures, use the injectable for 4 to 6 months after culture conversion; after this point, dosing for the injectable can be 2 to 3 times per week.
- *Option B.* Use isoniazid, pyrazinamide and streptomycin for a total of 9 months of treatment. After culture conversion, dosing for the injectable can be 2 to 3 times a week for the total duration of treatment.
- Surgery should be considered if a patient's cultures fail to convert to negative after 4 months of appropriate treatment (See p. 95.)

Isoniazid and Rifampin Resistance (with or without Streptomycin Resistance)

Regimens

- Use pyrazinamide, ethambutol and a fluoroquinolone, along with an appropriate aminoglycoside or capreomycin. Use capreomycin or an aminoglycoside other than streptomycin if streptomycin resistance is known at the start of treatment.
- If resistance to isoniazid and rifampin (with or without streptomycin resistance) is discovered after the patient has been taking isoniazid, rifampin, pyrazinamide and ethambutol for 1 to 3 months, discontinue isoniazid and rifampin. Continue pyrazinamide and ethambutol, and add at least 2 drugs — a fluoroquinolone along with an appropriate aminoglycoside or capreomycin to the regimen.

Length of Treatment

- Eighteen months after culture conversion
- Patients with extensive cavitory disease or with prolonged time to culture conversion, patients who are HIV positive, other immunosuppressed patients and patients with behavioral risk factors for HIV infection who decline HIV testing may need to have treatment extended to 24 months after culture conversion.
- The aminoglycoside or capreomycin can usually be discontinued 6 months after culture conversion.
- However, in some patients, especially those with extensive disease, slow conversion of sputum cultures or extensive second-line drug resistance, the injectable can be used for longer than 6 months after culture conversion.
- Intermittent dosing for the injectable may be used after culture conversion.
- Resistance to rifampin is generally associated with cross-resistance to rifabutin and rifapentine. When rifampin resistance is present but *in vitro* susceptibility to rifabutin is reported and this drug is added to the regimen, treatment should be the same as in the case of rifampin resistance.

- Surgery should be considered if a patient's cultures fail to convert to negative after 4 months of appropriate treatment. (See p. 95.)

Isoniazid, Rifampin and Ethambutol Resistance (with or without Streptomycin Resistance)

Regimens

- Use pyrazinamide and a fluoroquinolone, along with an appropriate aminoglycoside or with capreomycin; **in addition**, use 1 to 2 other second-line agents to which the strain is known or likely to be susceptible (e.g., ethionamide, cycloserine or para-aminosalicylic acid). Use capreomycin or an aminoglycoside other than streptomycin if streptomycin-resistance is known at the start of treatment. Use rifabutin if susceptibility to it has been documented.
- If resistance to isoniazid, rifampin and ethambutol (with or without streptomycin resistance) is discovered after the patient has been taking isoniazid, rifampin, pyrazinamide and ethambutol, discontinue isoniazid, rifampin and ethambutol. Continue pyrazinamide and add a fluoroquinolone to the regimen along with an appropriate aminoglycoside or capreomycin, and 1 to 2 other agents to which the strain is known or likely to be susceptible.
- Assess a new specimen, if available, for acquisition of pyrazinamide resistance as this may have been acquired while the patient was being treated with first-line drugs.

Length of Treatment

- Eighteen months after culture conversion
- Patients with extensive cavitary disease or with prolonged time to culture conversion; patients who are HIV positive, immunosuppressed or have behavioral risk factors for HIV infection and decline HIV testing may need to have treatment extended to 24 months after culture conversion.
- The aminoglycoside or capreomycin can usually be discontinued 6 months after culture conversion.

- However, in some patients (especially those with extensive disease, slow conversion of sputum cultures or extensive second-line drug resistance) the injectable can be used for longer than 6 months after culture conversion.
- Intermittent dosing for the injectable may be used after culture conversion.
- Resistance to rifampin is generally associated with cross-resistance to rifabutin and rifapentine. When rifampin resistance is present but *in vitro* susceptibility to rifabutin is reported and this drug is added to the regimen, treatment should be the same as in the case of rifampin resistance.
- Surgery should be considered if a patient's cultures fail to convert to negative after 4 months of appropriate treatment (see p. 95).

Isoniazid, Rifampin and Pyrazinamide Resistance (with or without Streptomycin Resistance)

Regimens

- Use ethambutol and a fluoroquinolone along with an appropriate aminoglycoside or with capreomycin. In addition, use 1 to 2 other second-line agents to which the strain is known or likely to be susceptible. Use capreomycin or an aminoglycoside other than streptomycin if streptomycin resistance is known at the start of treatment. Use rifabutin if susceptibility to the drug has been documented.
- If resistance to isoniazid, rifampin and pyrazinamide (with or without streptomycin resistance) is discovered after the patient has been taking isoniazid, rifampin, pyrazinamide and ethambutol, discontinue isoniazid, rifampin and pyrazinamide. Continue ethambutol, and consider increasing its dosage (25 mg/kg). Add a fluoroquinolone to the regimen, along with an appropriate aminoglycoside or capreomycin, and 1 to 2 other agents to which the strain is known or likely to be susceptible (e.g., ethionamide and para-aminosalicylic acid).

Assess a new specimen, if available, for acquisition of ethambutol resistance as it may have been acquired while the patient was being treated with first-line drugs.

Length of Treatment

- Eighteen months after culture conversion
- Patients with extensive cavitary disease or with prolonged time to culture conversion, patients who are HIV positive, other immunosuppressed patients and patients with behavioral risk factors for HIV infection who decline HIV testing may need to have treatment extended to 24 months after culture conversion.
- The aminoglycoside or capreomycin can usually be discontinued 6 months after culture conversion.
- However, in some patients (especially those with extensive disease, slow conversion of sputum cultures or extensive second-line drug resistance) the injectable can be used for longer than 6 months after culture conversion.
- Intermittent dosing for the injectable may be used after culture conversion.
- Resistance to rifampin is generally associated with cross-resistance to rifabutin and rifapentine. When rifampin resistance is present but *in vitro* susceptibility to rifabutin is reported and this drug is added to the regimen, treatment should be the same as in the case of rifampin resistance.
- Surgery should be considered if a patient's cultures fail to convert to negative after 4 months of appropriate treatment. (See p. 95).

Isoniazid, Rifampin, Pyrazinamide and Ethambutol Resistance (with or without Streptomycin Resistance)

Regimens

- Use a fluoroquinolone, along with an appropriate aminoglycoside or with capreomycin. In addition, use at least 2, and preferably 3, other second-line agents to which the strain is known or likely to be susceptible. Use capreomycin or an aminoglycoside other than streptomycin if streptomycin resistance is known at the start of treatment. Use rifabutin if susceptibility to the drug has been documented.
- If resistance to isoniazid, rifampin, pyrazinamide and ethambutol (with or without streptomycin resistance) is discovered after the patient has been taking isoniazid, rifampin, pyrazinamide

and ethambutol, discontinue all 4 drugs. Start a regimen of a fluoroquinolone, along with an appropriate aminoglycoside or capreomycin, and at least 2, and preferably 3, other agents to which the strain is known or likely to be susceptible (e.g., ethionamide, cycloserine and para-aminosalicylic acid).

Length of Treatment

- Eighteen months after culture conversion
- Patients with extensive cavitary disease or with prolonged time to culture conversion, patients who are HIV positive, other immunosuppressed patients and patients with behavioral risk factors for HIV infection who decline HIV testing may need to have treatment extended to 24 months after culture conversion.
- In both of the above situations, the aminoglycoside or capreomycin may be discontinued 6 months after culture conversion. However, in some patients (especially those with extensive disease or slow conversion of sputum cultures), the injectable should be used for longer than 6 months after culture conversion. Intermittent dosing of the injectable may be used after culture conversion.
- Resistance to rifampin is generally associated with cross-resistance to rifabutin and rifapentine. When rifampin resistance is present but *in vitro* susceptibility to rifabutin is reported and this drug is added to the regimen, treatment should be the same as in the case of rifampin resistance.
- Surgery should be considered if a patient's cultures fail to convert to negative after 4 months of appropriate treatment (See p. 95).

Isoniazid, Rifampin, Ethambutol, Streptomycin, Kanamycin, Ethionamide and Rifabutin Resistance ("Strain W")

Regimens

- In patients suspected of having this strain, start with a regimen of isoniazid, rifampin and pyrazinamide (in the event the strain is found to be susceptible to these medications), plus 3 other anti-TB medications to which the strain is likely to be susceptible. The 3 addi-

tional medications that have been used with success are fluoroquinolones, cycloserine (in conjunction with vitamin B₆) and intramuscular or intravenous capreomycin. Currently, the BTBC uses levofloxacin as the fluoroquinolone of choice.

- If this strain is confirmed, discontinue rifampin and treat with pyrazinamide (if susceptible), levofloxacin, cycloserine and capreomycin. Three other anti-TB medications that may have a role in the treatment of this strain are ethionamide, para-aminosalicylic acid and clofazimine, although the antituberculous activity of the latter is questionable (see p. 95). Do not use amikacin with this strain, as there is cross-resistance to kanamycin. If necessary, use isoniazid intermittently at a high dosage (900 mg twice a week), because this strain is resistant only to low levels of isoniazid. However, do not rely on the effectiveness of isoniazid.

Length of Treatment

- Eighteen months after culture conversion.
- Patients with extensive cavitory disease or with prolonged time to culture conversion, patients who are HIV positive, other immunosuppressed patients and patients with behavioral risk factors for HIV infection who decline HIV testing therapy may need to have treatment extended to 24 months after culture conversion.
- The aminoglycoside or capreomycin can usually be discontinued 6 months after culture conversion. However, in some patients (especially those with extensive disease, slow conversion of sputum cultures or extensive second-line drug resistance), the injectable can be used for longer than 6 months after culture conversion. Intermittent dosing for the injectable may be used after culture conversion.
- This strain is resistant to rifabutin.
- Surgery should be considered if a patient's cultures fail to convert to negative after 4 months of appropriate treatment (see p. 95).

Isoniazid, Rifampin, Ethambutol, Streptomycin, Fluoroquinolone Resistance (with or without either Pyrazinamide or several injectable agents)

Regimen

- Use any 3 to 4 drugs to which the organism is susceptible.
- Inhaled gamma interferon may be considered for select patients with pulmonary disease who are still AFB smear- and culture-positive. Consultation with the BTBC Director must occur.
- Surgical intervention should be considered early in the course of treatment (see p. 95).

Length of Treatment

- At least 24 months after culture conversion

Use of Newer Fluoroquinolones for Treating Tuberculosis

Several fluoroquinolones that have been approved in the last few years have potential use in treating TB. The ones most commonly used in patients with active and latent TB are levofloxacin, moxifloxacin and, until recently, gatifloxacin.

Moxifloxacin was approved in 1999 for the treatment of respiratory tract infections in adults. Many *in vitro* and animal studies have shown its potent activity against *M. tb*. The drug has been chosen by the CDC and the Global Alliance for Tuberculosis Drug Development for further study as an anti-TB agent—Phase II and Phase III clinical trials are underway. The major issue with using moxifloxacin in treating TB is a lack of data on safety and clinical efficacy for prolonged use.

Gatifloxacin also shows *in vitro* activity against *M. tb*; however, it has greater potential for cardiotoxicity than moxifloxacin and can cause hypoglycemia in the elderly and diabetic patients on oral hypoglycemic agents. Therefore, when it is necessary to use a newer generation fluoroquinolone, moxifloxacin is the preferred agent. Furthermore, the manufacturer has recently made a voluntary withdrawal of gatifloxacin from the worldwide market.

Levofloxacin, at present, remains the fluoroquinolone of choice; its safety profile for long-term use is documented over several years in patients with DRTB who are intolerant to isoniazid or a rifamycin.

To provide comparable levofloxacin exposures associated with clinical effectiveness and safety in adults, children 5 years or older need a daily dose of 10 mg/kg whereas children 6 months to younger than 5 years should receive 10 mg/kg every 12 hours.

The following patients are potential candidates for moxifloxacin during TB treatment:

- Adults and children with MDRTB who are not tolerating levofloxacin but may still be a candidate for a fluoroquinolone (e.g., an adverse reaction is unlikely to occur with a different one)
- Adults and children with MDRTB that is resistant to most first- and second-line drugs and for whom a regimen of 3 to 4 drugs cannot be identified.

To date, there is no evidence for the use of fluoroquinolones as a single agent for treatment of latent tuberculosis infection (LTBI) due to a multidrug-resistant organism. It is recommended that if a fluoroquinolone is used for LTBI, it be used in combination with another agent. However, in select situations, moxifloxacin may be used as a single agent after consultation with the BTBC Director.

Toxicities of Fluoroquinolones

Adverse events can vary markedly among the different fluoroquinolones, which most commonly cause nausea, vomiting, diarrhea (*often due to C. difficile*) and abdominal pain. Current data suggest that the newer ones, especially in high-dose regimens, cause a higher incidence of these adverse effects than do older agents such as ciprofloxacin and ofloxacin. Cholestasis, hepatitis and hepatic failure have been infrequently reported. Reversible transaminase elevation may occur in up to 2% to 3% of patients.

Some common adverse effects (phototoxicity, central nervous system effects and inhibition of drug metabolism) are associated with structural

features of the fluoroquinolones. Most adverse effects, including gastrointestinal problems and chondrotoxicity/arthropathy, have not been attributed to specific structural features of the fluoroquinolones.

Of the newer fluoroquinolones in use, levofloxacin is cleared by the kidney and is the preferred agent for patients with hepatic insufficiency; however, it should be used with caution. In patients with renal failure, the interval between doses of levofloxacin should be increased. Moxifloxacin is mostly cleared by the liver and therefore may be the preferred fluoroquinolone in a patient with renal insufficiency.

Fluoroquinolones can cause hypersensitivity reaction either after a single dose or multiple doses. Treatment should be discontinued at the first appearance of a skin rash, jaundice or any other sign of hypersensitivity.

Photosensitivity and Cardiotoxicity

Although fluoroquinolones are generally considered to have favorable adverse event profiles, 2 potentially serious adverse events—photosensitivity and QT interval prolongation—have been associated with certain drugs in the class.

- Photosensitivity is defined as a non-immunological, light-activated irritation that occurs after exposure to a photoactive chemical. This is an infrequent adverse event of most fluoroquinolones; however, the incidence varies according to the individual drug.

Phototoxicity has been described with all fluoroquinolones except moxifloxacin, but appears to occur most frequently in derivatives that have a halogen atom at C-8.

- Some second-generation fluoroquinolones have been associated with prolonged QT intervals and the potential for ventricular tachyarrhythmia. Cardiac events, such as QT prolongation and the potential for ventricular tachyarrhythmia, are most notably associated with the use of levofloxacin and moxifloxacin.

Tendinopathy/Tendinitis

Fluoroquinolone-induced tendinopathy is diagnosed by a sudden onset of swelling and tenderness concurrent with or shortly after fluoroquinolone therapy. There is tendon

rupture in about 33% of all cases. The main site affected is the Achilles tendon: however, it has been reported in the shoulder, knee, hand and plantar aponeuroses. Achilles tendon ruptures have been noted even months after drug discontinuation.

No correlation between duration of treatment and the incidence of tendinopathy has been observed; however, symptom severity is proportional to treatment duration. Uncomplicated tendinitis generally occurs after less than 5 days of therapy and tendon rupture more frequently when therapy lasts longer than 3 weeks.

Concomitant use of corticosteroids is considered to be a risk factor for developing tendinopathy while taking fluoroquinolones, especially in the elderly (older than 65 years). Treatment involves discontinuation of the fluoroquinolone and resting the tendons. Physical therapy may be needed early in treatment and may be prolonged.

Hypoglycemia and Hyperglycemia

All fluoroquinolones can cause hypoglycemia and hyperglycemia: however, such effects on blood sugar are believed to be rare despite the widespread use of these agents. Changes in blood sugar are believed to be due to interaction between ciprofloxacin and glyburide at the cytochrome P450 level. Several recent reports have indicated that the newer generation fluoroquinolones, specifically gatifloxacin, can cause severe symptomatic hypoglycemia in patients with type 2 diabetes who are taking oral hypoglycemic agents, especially the elderly.

There are more recent reports of severe hypoglycemia and hyperglycemia with gatifloxacin alone, particularly in elderly, non-diabetic patients. A possible mechanism for this phenomenon is that gatifloxacin (which is excreted by the kidneys) may accumulate in the elderly, who may experience an age-related decline in renal function. Since fluoroquinolones are generally used for prolonged periods in TB treatment, we do not recommend the use of gatifloxacin for TB. Patients on fluoroquinolones should be closely monitored, including having their blood glucose monitored regularly.

Long-Term Use of Fluoroquinolones

Although fluoroquinolones generally appear to be safe for long-term use, several studies

have documented that the incidence of adverse effects for ciprofloxacin is highest in the first 7 to 10 days of therapy. These studies are limited by the definition of long-term use (usually 1 month or 3 months).

In 1991, the use of first generation fluoroquinolones was reviewed in over 100 patients with mycobacterial disease who were given fluoroquinolones in addition to other drugs for a prolonged period of time. Most reactions were mild and reversible, and were similar for both ciprofloxacin and ofloxacin. Drug therapy was discontinued in 3 patients. Similar results were found in research examining the use of fluoroquinolones for leprosy.

Moxifloxacin

Little data is available on the use of moxifloxacin for prolonged periods. Most adverse events reported in moxifloxacin trials are described as mild to moderate in severity and required no treatment; the drug was discontinued due to adverse reactions thought to be drug-related in 3.8% of patients.

Moxifloxacin has been shown to prolong the QT interval on electrocardiogram in some patients. Due to the lack of clinical experience with the drug in patients with known prolongation of the QT interval, uncorrected hypokalemia and/or patients receiving class IA (e.g., quinidine, procainamide) or class III (e.g., amiodarone, sotalol) antiarrhythmic agents, the drug should be avoided in these populations.

There are no pharmacokinetic studies of moxifloxacin in combination with other drugs that prolong the QT interval such as cisapride, erythromycin, antipsychotics and tricyclic antidepressants. An additive effect of moxifloxacin and these drugs cannot be excluded; therefore, it should be used with caution when given concurrently with these drugs.

The effect of moxifloxacin on patients with congenital prolongation of the QT interval has not been studied; however, it is expected that these individuals may be more susceptible to drug-induced QT prolongation. Because of limited clinical experience, moxifloxacin should be used with caution in patients with ongoing pro-arrhythmic conditions such as clinically significant bradycardia and acute myocardial ischemia.

Moxifloxacin is non-formulary at present in the BTBC chest centers and requires approval of the Bureau Director prior to use. The BTBC does not recommend routine EKG testing of patients on moxifloxacin unless clinically indicated.

Adverse reactions occurring in greater than or equal to 1% of moxifloxacin treated patients that may be at least possibly drug-related are:

- Nausea (8%)
- Diarrhea (6%)
- Dizziness (3%)
- Headache (2%)
- Abdominal pain (2%)
- Vomiting (2%)
- Taste alteration (1%)
- Abnormal liver function test results (1%)
- Dyspepsia (1%)

Linezolid

Linezolid belongs to a new class of antibiotics, the oxazolidinones, and was approved by the FDA in 2000 for treatment of infections with resistant gram-positive organisms. *In vitro* studies have shown that linezolid is active against *M. tb*, including strains resistant to many first-line anti-TB drugs. Linezolid may be used as part of a regimen for treating patients with MDRTB and persistent positive sputum cultures (whose treatment options are severely limited) and who also:

- Are already prescribed a regimen to which the organism is susceptible
- Have extensive second-line drug resistance or are intolerant to many second-line drugs
- Are on DOT
- May not be surgical candidates
- Have no other treatment options

Linezolid is available for oral use as well as for intravenous administration. A dose of 600 mg twice a day has been used with good response. Food delays absorption, but does not lower peak plasma concentrations. The drug is partly metabolized in the liver and does not affect the cytochrome P450 enzyme system; it is excreted in the urine. The linezolid oral suspension contains phenylalanine and should not be given to patients with phenylketonuria.

Side effects of linezolid include:

- Myelosuppression (including anemia, leukopenia, pancytopenia and thrombocytopenia)
- Hemolytic anemia
- Diarrhea
- Nausea, vomiting (patients who have recurrent nausea and vomiting, unexplained acidosis or a low bicarbonate level should receive immediate medical attention to rule out lactic acidosis)
- Liver function test elevations
- Tongue discoloration
- Severe hypertension (if taken concomitantly with large amounts of tyramine)
- Peripheral neuropathy, including optic neuritis (in patients who have taken linezolid longer than the maximum recommended 28 days; optic neuropathy may be reversible upon discontinuation, but peripheral neuropathy may be irreversible)

Administration of vitamin B₆ (daily dose, 25 mg/day) may ameliorate some of these adverse reactions, though this remains controversial. A complete blood count should be obtained every 1 to 2 weeks, especially in those with pre-existing myelosuppression, and those receiving concomitant drugs that induce bone marrow suppression. CBC and SMA-18 profile should be monitored every 2 to 4 weeks, vision should be monitored every month and patients should overall be monitored post-treatment per BTBC protocol.

Note: Linezolid is a reversible, non-selective inhibitor of monoamine oxidase and therefore may interact with adrenergic and serotonergic agents. Co-administration of drugs containing:

- Pseudoephedrine
- Phenylpropanolamine
- Selective serotonin reuptake inhibitors
- Possibly other antidepressants

should be undertaken with caution, as serotonin syndrome may occur, manifesting as cognitive dysfunction, hyperpyrexia, hyperreflexia and incoordination; such patients may need referral to a psychiatrist. The benefit of taking linezolid with these drugs must be weighed against these risks.

In summary, the current cost and high rate of adverse effects of linezolid preclude its widespread use. Linezolid use must be approved by the BTBC Director.

Clofazimine

Clofazimine (an FDA-approved drug previously on the BTBC formulary) has been used, when absolutely necessary, in BTBC chest centers for many years to treat MDRTB. Since it has *in vitro* activity against *M. tb* and some non-mycobacterium TB (*mycobacterium avium* complex [MAC]), this drug has been used in the treatment of drug-resistant *M. tb* and non-tuberculous mycobacteria patients.

In November of 2004, Novartis Pharmaceutical Corporation discontinued commercial distribution of clofazimine in the United States due to the company's implementation of a compassionate care program for the treatment of leprosy (Hansen's disease). The FDA has now made clofazimine available under an Investigational New Drug (IND) application for these uses and in order to use this drug for a patient, an IND application has to be sent to the FDA.

The Office of Medical Affairs is responsible for obtaining clofazimine for BTBC patients. Once a patient is approved by the FDA to receive it, a unique IND number is assigned to the patient and a 60-day supply of the drug is sent to the BTBC. The bottle with that IND number is specifically for use by that patient only and a new supply has to be requested every 60 days. The Office of Medical Affairs should be contacted 30 days prior to the prescription expiring so that arrangements can be made to have clofazimine available.

Yearly updates must be sent to the FDA for continued use, and the physician caring for the patient must document the continued use of the drug, its risks and benefits, and the patient's agreement to continue with the medication. The patient should be informed of this process (and sign a brief consent form), and monitored monthly or more frequently for sputum conversion, continued need for the drug and side effects, which frequently include:

- Pink to brownish-black discoloration of the skin; the degree of discoloration is dose-related and is most pronounced on exposed parts of the body
- Ichthyosis and dry skin; pruritis and non-specific rash
- Reversible, dose-related red-brown discoloration of the conjunctiva, cornea and lacrimal fluid
- GI side effects such as abdominal and epigastric pain, diarrhea, nausea, vomiting and GI intolerance
- Nervous system effects (reported in less than 1% of patients) such as dizziness, drowsiness, fatigue, headache, giddiness, neuralgia and taste disorders

Monitoring and Post-Treatment Evaluation

Patients being treated for DRTB should be monitored during treatment as outlined on p. 101. For information on adverse reactions in patients taking second-line anti-TB medications, (see p. 210, Appendix I-B). After completing treatment, patients with MDRTB should be evaluated at 4, 8, 12, 18 and 24 months after completion of therapy, as described on p. 115 and on p. 116, Table VI-2.

Surgery for Pulmonary Tuberculosis

Surgery is not a first-line option in the treatment of TB because, in most cases, pulmonary TB is curable using modern drug regimens. Surgery is, however, one of the last alternatives available for individuals with MDRTB strains in whom chemotherapy has failed or is not possible because of a lack of sufficient and effective medications.

Indications for Surgery

In consultation with medical and surgical experts, surgery can and should be considered as an adjunct to chemotherapy when all of the following criteria are met:

- Adequate first- and second-line regimens of anti-TB medications have failed to cure, or to cause *M. tb* cultures to convert to negative within 4 to 6 months.
- Sufficient medications are available to treat the patient post-operatively.
- The disease is sufficiently localized to allow lobectomy or pneumonectomy.
- The remaining lung tissue is relatively free of disease.
- The patient has an acceptable surgical risk, with sufficient pulmonary reserve to tolerate the resection.

Some clinical circumstances, such as major bronchial obstruction, severe hemoptysis or bronchopleural fistula are additional possible indications for surgery.

Protocol for Surgery Referral

- Referrals for surgery should be made on an individual basis, and should be reviewed and coordinated by the BTBC Director or the Director of Medical Affairs.
- Chest center physicians may refer a patient for a CT scan when necessary, after consulting with the physician-in-charge.
- As part of the medical/surgical evaluation, all of the following should be documented:
 - Failure to cure TB, as evidenced by persistent positive *M. tb* sputum cultures or reversion from negative to positive cultures, despite the best treatment regimen possible and every effort to achieve adherence to treatment, including the use of DOT
 - Diagnostic evaluation that shows the majority of disease is anatomically localized, allowing surgical resection
 - Appropriate evaluation proving that the patient has an acceptable surgical risk
- Even after lung resection, the patient must complete a full course of treatment (18 to 24 months after culture conversion) with medications to which the *M. tb* strain is susceptible. If the patient is culture negative after surgery, then the date of surgery is considered to be the conversion date.

Key Sources

- Caminero JA. Treatment of multidrug-resistant tuberculosis: evidence and controversies. *Int J Tuberc Lung Dis*. 2006 10:829-837.
- Chan ED, Laurel V, Strand MJ, et.al. Treatment and outcome analysis of 205 patients with multidrug-resistant tuberculosis. *Am J Respir Crit Care Med*. 2004 15;169:1103-1109.
- Chien S, Wells TG, Blumer JL, Kearns GL, Bradley JS, Bocchini JA Jr, Natarajan J, Maldonado S, Noel GJ. Levofloxacin pharmacokinetics in children. *J Clin Pharmacol*. 2005 45(2):153-160.
- Francis J. Curry National Tuberculosis Center and California Department of Health Services. Drug-Resistant Tuberculosis: A Survival Guide for Clinicians. San Francisco, CA: Francis J. Curry National Tuberculosis Center and California Department of Health Services, 2004.
- Iseman MD. Treatment of multidrug-resistant tuberculosis. *N Engl J Med*. 1993;329:784-791.
- Ntziora F, Falagas ME. Linezolid for the treatment of patients with mycobacterial infections: a systematic review. *Int J Tuberc Lung Dis*. 2007 Jun;11(6):606-11. Review. Erratum in: *Int J Tuberc Lung Dis*. 2007;11(8):936.
- Peloquin CA. Therapeutic drug monitoring in the treatment of tuberculosis. *Drugs*. 2002;62:2169-2183.
- von der Lippe B, Sandven P, Brubakk O. Efficacy and safety of linezolid in multidrug resistant tuberculosis (MDR-TB)-a report of ten cases. *J Infect*, 2006 52(2):92-96.
- World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis. WHO/HTM/TB/2006.361. Geneva, Switzerland: World Health Organization; 2006. Available at: http://whqlibdoc.who.int/publications/2006/9241546956_eng.pdf

