DRUG-RESISTANT TUBERCULOSIS

A SURVIVAL GUIDE FOR CLINICIANS

Arnold Schwarzenegger, Governor
STATE OF CALIFORNIA

S. Kimberly Belshé, Secretary
CALIFORNIA HEALTH & HUMAN SERVICES AGENCY

Sandra Shewry, Director
DEPARTMENT OF HEALTH SERVICES
Drug-Resistant Tuberculosis

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Introduction to This Survival Guide

THE PROBLEM OF DRUG-RESISTANT TB

Drug-resistant tuberculosis (TB) is a relatively new phenomenon that now occurs throughout the world. Quite simply, drug-resistant TB has been caused by inadequate therapy for drug-susceptible TB. Three terms describe its variations:

1. **Mono-resistant:** Resistant to only 1 anti-tuberculosis drug
2. **Multidrug-resistant (MDR):** Resistant to at least isoniazid (INH) and rifampin (RIF), considered to be the 2 most effective anti-tuberculosis drugs
3. **Poly-resistant:** Resistant to more than 1 anti-tuberculosis drug, but not the combination of INH and RIF

The problem of drug-resistant TB is growing in several hot spots throughout the world. Without a concerted global effort to combat MDR-TB, the disease will pose a serious public health threat for generations to come. Drug-resistant TB devastates not only individuals and their families, but also imposes enormous burdens on overextended public health systems that lack the resources needed to contain it.

THE NEED FOR EXPERTISE

Expertise in managing drug-resistant and MDR cases of TB in the United States is limited. The most widely publicized U.S. outbreaks of MDR-TB were described in the late 1980s and early 1990s, primarily in congregate living settings where immunosuppressed patients were not prescribed (or failed to complete) adequate therapy. The outbreaks spread within health care facilities and prisons to normal hosts, including health care workers. Unfortunately, drug resistance was simultaneously developing abroad and most drug resistance in the U.S. is now associated with foreign-born status and history of previous TB treatment (see Chapter 1, *Epidemiology and Background*). Consequently, jurisdictions across the country are confronting the need to build their capacity to successfully diagnose and treat these complex cases.

The Tuberculosis Control Branch of the California Department of Health Services (CDHS) has developed a systematic approach to consultation on cases of drug-resistant TB in California. The CDHS model builds on the experience and shared expertise of two successful programs: the Texas Department of State Health Services and the Los Angeles County MDR-TB Unit. To complement its service, CDHS collaborated with the Francis J. Curry National Tuberculosis Center (CNTC) in San Francisco to develop this resource guide: *Drug-Resistant Tuberculosis: A Survival Guide for Clinicians*. Recognizing the national need for such a resource, CDHS and CNTC are disseminating the *Guide* to jurisdictions and providers across the country.
DESCRIPTION OF THE GUIDE AND TARGET AUDIENCE

The Guide contains information and user-friendly tools and templates for use by any clinician who participates in the management of patients with drug-resistant TB. From physicians to pharmacists, infection control practitioners to public health nurses, the Guide arms all health care providers in the fight against drug-resistant TB.

The 10 chapters and 15 appendices cover major topics pertaining to epidemiology, diagnosis, treatment, medications, monitoring, special situations, adverse reactions, case management, legal issues, and treatment of contacts. While readers are encouraged to review all sections of the Guide, each section is designed to be self-contained. For example, when a reader needs details about specific anti-tuberculosis drugs, he/she can refer to Chapter 4, Medication Fact Sheets, to find the properties and details of individual drugs. When a patient is experiencing a potential side effect, the reader can turn to Chapter 7, Adverse Reactions, for a review of response to toxicity or to Chapter 4 for the individual fact sheets about the medications the patient is receiving. Appendix 15 contains 4 case examples that highlight pitfalls and common errors in the management of drug-resistant cases. The index and Appendix 14, Frequently Asked Questions (FAQs), provide the reader with resources for quickly finding answers to the most commonly asked questions.

Although conceived in California, the Guide is designed for a national audience of providers in both the public and private sectors of health care. Authors and reviewers from all national geographic areas contributed to its content. When considering the recommendations presented in this Guide, users are advised to consult the policies and protocols of their local jurisdictions.

The authors of this Guide acknowledge that hard data are often lacking to assist clinicians in the management of MDR-TB. Many of the drugs used to treat drug-resistant TB are not even Food and Drug Administration (FDA)-licensed for these indications. Examples include amikacin, all of the fluoroquinolones, and rifabutin. Much-needed research is currently underway to more thoroughly document the clinical efficacies of various treatment regimens for drug-resistant TB and MDR-TB. This Guide presents the best practice strategies available when the Guide was compiled in mid-2004 and, in many cases, is based on expert opinion, given the paucity of randomized controlled trials in this area. The experience of managing large volumes of patients with drug-resistant TB constitutes expertise in this field.

The following are a few examples of elements of drug-resistant TB care that vary among experts (there are no randomized controlled trials to support any of these preferences):

- **Duration of daily aminoglycoside/capreomycin therapy:** Assuming good clinical and microbiologic response, some experts feel comfortable using daily injectable therapy for as little as a month or 2 before changing to 3 times weekly therapy. Others use 6 months of daily therapy (barring toxicity or renal impairment) before changing to intermittent therapy.
- **Total duration of injectable drug therapy:** The most quoted guideline recommends 4–6 months of aminoglycoside/capreomycin therapy. All experts
would use longer injectable therapy if there was delayed response to therapy or if there were fewer than 3–4 oral drugs remaining in the regimen. Some experts routinely use the injectable drug 12 months from the time of culture conversion.

- **Dose of aminoglycoside/capreomycin**: The standard daily/intermittent dose for the aminoglycosides is 15mg/kg/dose. Some authors use up to 25 mg/kg/dose for intermittent therapy and tolerate peak levels up to 65–80 mcg/ml. Experts who treat with longer courses of injectable drugs are comfortable with peak levels as low as 20–35 mcg/ml. **Note**: Doses achieving lower levels than these will not achieve the desired effect in the regimen and may lead to amplification of resistance.

- **Number of drugs in the regimen**: Older recommendations suggested that a regimen of 2–3 drugs to which the isolate is susceptible was acceptable. Newer series suggest that better outcomes are associated with more drugs. Expert opinion varies: some begin with 4–6 drugs to which the isolate is susceptible with the goal of using 3–4 oral drugs to complete the therapy. Others would initially use as many drugs as are available. This strategy allows room to eliminate drugs from the regimen as toxicity develops and as more susceptibility results become available.

- **Use of therapeutic drug monitoring (TDM)**: Several indications for use of TDM are universally agreed upon: 1) aminoglycoside/capreomycin levels in the setting of renal impairment, change in renal function or concerns about ototoxicity; 2) routine cycloserine levels to keep the level below 35 mcg/ml (associated with marked increase risk of CNS toxicity); and 3) ethambutol level monitoring in the setting of renal impairment (increased risk of ophthalmic toxicity). TDM is also used by some providers who are concerned about possible malabsorption of drugs (especially in failing treatment regimens, patients with HIV, patients with history of stomach surgery, patients with extremely low body mass index, and those with other diarrheal processes). Some experts use TDM routinely and serially, especially for monitoring the levels of injectable drugs.

- **Duration of therapy**: Some experts recommend 18–24 months of therapy total, and some treat 18–24 months from the time of culture conversion. Pediatric series have used shorter durations of therapy.

- **Treatment of MDR-LTBI and use of window prophylaxis for MDR-TB contacts**: Some providers use fluoroquinolone monotherapy for MDR-LTBI, some use 2-drug therapy, and some experts and jurisdictions would never use window prophylaxis for contacts to MDR-TB, while others would treat the most at-risk individuals with 2 drugs to which the isolate is susceptible.

Managing drug-resistant TB is extremely challenging. National guidelines call for treatment of drug-resistant TB to be provided by or in close consultation with experts. Regardless of their individual styles, the experts in treatment of drug-resistant TB have developed insight from treating many different patients in different situations. This *Guide* should be considered a supplemental resource to expert consultation. Contact information for expert resources can be found in Appendix 1.
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
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<tr>
<td>ad</td>
<td>right ear</td>
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<td>AFB</td>
<td>acid-fast bacilli</td>
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<td>AIDS</td>
<td>acquired immunodeficiency syndrome</td>
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<td>AK</td>
<td>amikacin</td>
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<td>ALT</td>
<td>alanine aminotransferase</td>
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<td>ANA</td>
<td>antinuclear antibodies</td>
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<td>as</td>
<td>left ear</td>
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<td>AST</td>
<td>aspartate aminotransferase</td>
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<td>ATS</td>
<td>American Thoracic Society</td>
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<td>BAL</td>
<td>bronchoalveolar lavage</td>
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<td>BCG</td>
<td>bacille Calmette-Guérin</td>
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<tr>
<td>BID</td>
<td>twice a day</td>
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<td>BUN</td>
<td>blood urea nitrogen</td>
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<tr>
<td>Ca</td>
<td>calcium</td>
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<td>CAPD</td>
<td>continuous ambulatory peritoneal dialysis</td>
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<td>CBC</td>
<td>complete blood count</td>
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<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
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<td>California Department of Health Services</td>
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<td>CM</td>
<td>capreomycin</td>
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<td>CNS</td>
<td>central nervous system</td>
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<td>CNTC</td>
<td>Francis J. Curry National Tuberculosis Center</td>
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<td>CS</td>
<td>cycloserine</td>
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<td>CSF</td>
<td>cerebrospinal fluid</td>
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<td>CXR</td>
<td>chest x-ray</td>
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<td>DOT</td>
<td>directly observed therapy</td>
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<td>ethionamide</td>
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<td>FDA</td>
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<td>fluoroquinolone</td>
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<td>gastrointestinal</td>
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<td>HAART</td>
<td>highly active antiretroviral therapy</td>
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<td>high efficiency particulate air</td>
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<td>Hgb</td>
<td>hemoglobin</td>
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<td>human immunodeficiency virus</td>
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<td>isoniazid</td>
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<td>International Union Against Tuberculosis and Lung Disease</td>
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<td>intravenous</td>
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<td>levofloxacin</td>
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<td>latent tuberculosis infection</td>
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<td><em>Mycobacterium avium</em> complex</td>
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<td><em>Mycobacterium bovis</em></td>
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<td>M. tuberculosis</td>
<td><em>Mycobacterium tuberculosis</em></td>
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<td>MDR-TB</td>
<td>multidrug-resistant tuberculosis (resistant to at least isoniazid and rifampin)</td>
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<tr>
<td>Mg</td>
<td>magnesium</td>
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<td>MIC</td>
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<td>NSAID</td>
<td>nonsteroidal anti-inflammatory drug</td>
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<td>nontuberculous mycobacteria</td>
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<td>Plt</td>
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<tr>
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<tr>
<td>PPD</td>
<td>purified protein derivative (TST)</td>
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<tr>
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<td>PRUCOL</td>
<td>Permanent Residence Under Color of Law</td>
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<tr>
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<td>every morning</td>
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<td>qd</td>
<td>once a day</td>
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<tr>
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<td>every evening</td>
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<td>qid</td>
<td>four times a day</td>
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<tr>
<td>QT</td>
<td>the interval from the beginning of the QRS complex to the end of the T wave on an electrocardiogram</td>
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<td>RFB</td>
<td>rifabutin</td>
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<tr>
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<td>SGPT</td>
<td>serum glutamic-pyruvic transaminase</td>
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<td>SIRE</td>
<td>streptomycin, isoniazid, rifampin, ethambutol</td>
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<td>SM</td>
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<td>SSRI</td>
<td>selective serotonin reuptake inhibitor</td>
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<td>tuberculosis</td>
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<td>TID</td>
<td>three times a day</td>
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<td>thyroid stimulating hormone</td>
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<td>tuberculin skin test</td>
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Epidemiology & Background

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Tuberculosis is an ancient disease that has caused inestimable suffering and claimed millions of lives over the centuries.

Some of TB’s more famous casualties include Anton Chekov, Frederick Chopin, Robert Louis Stevenson, George Orwell, and Charlotte and Emily Brontë. It is little wonder that the discovery of effective anti-tuberculosis drugs in the 1940s was hailed as a medical milestone.

Tragically, in the last 20 years, the misuse of these “miracle” drugs has resulted in a new public health nightmare: drug-resistant TB.

- **One in three** individuals worldwide is infected with *Mycobacterium tuberculosis*.
- Among those infected with *M. tuberculosis*, approximately **50 million** are infected with drug-resistant strains.
- In the United States, drug resistance in foreign-born persons with TB is much more common than in U.S.-born persons, corresponding to the higher rates of drug resistance in the countries of origin. In 2003 more than three fourths of multidrug-resistant TB (MDR-TB) cases in the U.S. were among foreign-born persons.

MDR-TB is a strain that is resistant to at least isoniazid and rifampin.

**Two Types of Drug-Resistant Cases: New and Previously Treated**

**Drug resistance in a new TB case:** Presence of a resistant strain of *M. tuberculosis* in a newly diagnosed TB patient who has not previously been treated with TB drugs (or therapy of less than 1 month duration). These patients were likely to have been infected with a strain that was already drug-resistant. These cases are sometimes referred to as “primary drug resistance.”

**Drug resistance in a previously treated TB case:** Presence of a resistant strain in a TB patient who has previously received at least 1 month of TB therapy. These cases are likely to have been initially infected with a drug-susceptible *M. tuberculosis* strain, but during the course of anti-tuberculosis treatment, drug resistance emerged (sometimes referred to as “secondary drug resistance”).

Without molecular fingerprinting of original and subsequent isolates, it is impossible to discern whether previously treated patients have always been infected with drug-resistant strains, were reinfected with a new drug-resistant strain (primary resistance), or whether their strains evolved on treatment (secondary resistance). Hence the current terminology: drug resistance in new vs. previously treated cases.
Global Burden of Drug Resistance

Accurate data regarding rates of drug resistance are not universally available. Prior to 1994, rates of drug resistance were mostly based on non-standardized, non-representative samples. Starting in 1994, the World Health Organization (WHO) began to systematically sample countries or regions in order to better assess rates of drug-resistant TB. WHO surveyed 77 geographical regions between 1999 and 2002, and reported the following findings:

- Drug resistance to anti-tuberculosis drugs was found among TB cases in 74 of 77 geographical settings (96%), representing all regions of the world.
- Several regions (such as Cuba, Hong Kong SAR, Thailand, and the U.S.) have shown significant improvement in rates of resistance among new cases, but many regions have not. Even areas with relatively low prevalence of drug resistance have experienced dramatic increases in recent years. For example, in New Zealand the percentage of new TB cases that were resistant to at least 1 TB drug has more than doubled, from 4.8% in 1996 to 11.4% in 2001. From 1996 to 2000, drug resistance among new cases in Norway increased from 10.9% to 24.4%.
- **Between 1999 and 2002, the incidence of MDR-TB among previously treated cases of TB was alarmingly high in several “hot spots,” including Kazakhstan (56.4%), Lithuania (53.3%), and the Russian Federation – Tomsk Oblast (43.6%).** Between 1994 and 2000, Estonia's rates of MDR among previously treated cases more than doubled, from 19.2% to 45.3%.

MDR-TB: A Staggering Cost for a Small Percentage of TB Cases

In the year 2000, there were an estimated 273,000 new cases of MDR-TB in the world (representing 3.2% of all new TB cases). This figure is in contrast to the 1960s, when rifampin was introduced and not a single MDR case had yet been documented. Appropriate care of these MDR-TB patients would cost more than the care of all drug-susceptible cases combined.
### Table 1.

**Rates of MDR-TB Among New Cases of TB in Selected Countries/Regions**

<table>
<thead>
<tr>
<th>Country/Region</th>
<th>Year</th>
<th>% of MDR among New Cases</th>
<th>% of any resistance (1 or more drugs) among New Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kazakhstan</td>
<td>2001</td>
<td>14.2</td>
<td>57.1</td>
</tr>
<tr>
<td>Israel</td>
<td>2000</td>
<td>14.2</td>
<td>31.2</td>
</tr>
<tr>
<td>Russian Fed. – Tomsk Oblast</td>
<td>2002</td>
<td>13.7</td>
<td>37.3</td>
</tr>
<tr>
<td>Uzbekistan – Karakalpakstan</td>
<td>2001</td>
<td>13.2</td>
<td>48.1</td>
</tr>
<tr>
<td>China – Liaoning</td>
<td>1999</td>
<td>10.4</td>
<td>42.1</td>
</tr>
<tr>
<td>Lithuania</td>
<td>2002</td>
<td>9.4</td>
<td>29.2</td>
</tr>
<tr>
<td>Latvia</td>
<td>2000</td>
<td>9.3</td>
<td>31.7</td>
</tr>
<tr>
<td>China – Henan</td>
<td>2001</td>
<td>7.8</td>
<td>29.9</td>
</tr>
<tr>
<td>Ecuador</td>
<td>2002</td>
<td>6.6</td>
<td>23.4</td>
</tr>
<tr>
<td>Turkmenistan – Dashoguz</td>
<td>2001</td>
<td>3.8</td>
<td>30.5</td>
</tr>
<tr>
<td>India – North Arcot</td>
<td>1999</td>
<td>2.8</td>
<td>27.7</td>
</tr>
<tr>
<td>Mexico (Baja CA, Oaxaca, Sinaloa)</td>
<td>1997</td>
<td>2.4</td>
<td>14.1</td>
</tr>
<tr>
<td>United States</td>
<td>2001</td>
<td>1.1</td>
<td>12.7</td>
</tr>
</tbody>
</table>

Source: WHO


### Table 2.

**Rates of MDR-TB Among Previously Treated Cases of TB in Selected Countries/Regions**

<table>
<thead>
<tr>
<th>Country/Region</th>
<th>Year</th>
<th>% of MDR among Previously Treated Cases</th>
<th>% of any resistance (1 or more drugs) among Previously Treated Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kazakhstan</td>
<td>2001</td>
<td>56.4</td>
<td>82.1</td>
</tr>
<tr>
<td>Lithuania</td>
<td>2002</td>
<td>53.3</td>
<td>67.9</td>
</tr>
<tr>
<td>Estonia</td>
<td>2000</td>
<td>45.3</td>
<td>58.1</td>
</tr>
<tr>
<td>Russian Fed. – Tomsk Oblast</td>
<td>2002</td>
<td>43.6</td>
<td>60.7</td>
</tr>
<tr>
<td>Russian Fed. – Orel Oblast</td>
<td>2002</td>
<td>42.4</td>
<td>73.3</td>
</tr>
<tr>
<td>Uzbekistan – Karakalpakstan</td>
<td>2001</td>
<td>40.2</td>
<td>79.4</td>
</tr>
<tr>
<td>Egypt</td>
<td>2002</td>
<td>38.2</td>
<td>68.2</td>
</tr>
<tr>
<td>China – Henan</td>
<td>2001</td>
<td>36.6</td>
<td>60.8</td>
</tr>
<tr>
<td>Latvia</td>
<td>2000</td>
<td>27.1</td>
<td>38.1</td>
</tr>
<tr>
<td>Ecuador</td>
<td>2002</td>
<td>24.8</td>
<td>47.4</td>
</tr>
<tr>
<td>Mexico (Baja CA, Oaxaca, Sinaloa)</td>
<td>1997</td>
<td>22.4</td>
<td>41.1</td>
</tr>
<tr>
<td>United States</td>
<td>2001</td>
<td>5.2</td>
<td>18.8</td>
</tr>
</tbody>
</table>
Several international organizations are working to control and prevent TB, including:

- **Stop TB**, a partnership hosted by the WHO, dedicated to accelerating social and political action to stop the unnecessary spread of TB around the world.
- **International Union Against Tuberculosis and Lung Disease (IUATLD)** has a worldwide focus, with a particular emphasis on low-income countries and on promoting national autonomy by developing, implementing, and assessing anti-tuberculosis and respiratory health programs.
- **Médecins Sans Frontières** (Doctors Without Borders) brings health care for chronic diseases to remote, isolated areas where resources and training are limited.
- The **Green Light Committee** works with the pharmaceutical industry to provide concessially-priced second-line anti-tuberculosis drugs to DOTS-Plus pilot projects meeting the standards outlined in the *Guidelines for Establishing DOTS-Plus Pilot Projects for the Management of MDR-TB*.
- **Partners In Health** (PIH) establishes long-term relationships with sister organizations based in settings of poverty. PIH has developed groundbreaking TB treatment projects in Siberian prisons, Peruvian slums, and rural Haiti.

Along the U.S.–Mexico border, a number of organizations and collaborations exist to address TB control:

- **CureTB** (operated from the San Diego TB Control Program) and **TBNNet** (operated by the Migrant Clinicians Network in Austin, Texas) are designed to improve continuity of care and access to health care for TB patients who move between Mexico and the U.S.
- **Ten Against Tuberculosis** (TATB) is a major collaboration for the organizations in the 10 border states that are working to control and prevent TB.

Additionally, many state health department TB control programs participate in these efforts.

*See Appendix 2, Contact Information for Selected Organizations Working to Control and Prevent TB in the International Arena.*
In 2003: 14,874 TB cases (5.1 per 100,000) were reported in the U.S.

- Among the cases reported that were new cases (no previous history of TB): 7.9% were isoniazid (INH)-resistant and 0.9% were caused by MDR-TB strains.
- Among the cases reported with previously treated TB: 12.6% were INH-resistant and 3.6% were caused by MDR-TB strains.

The number of MDR-TB cases in the U.S. has declined steadily over the past decade (see Figure 1) after aggressive public health intervention in the early 1990s. Completion of therapy by DOT and effective infection control measures have helped to control the spread of MDR-TB in immunocompromised and hospitalized individuals.

In 2002, 42 states reported INH-resistant TB cases; 28 states reported MDR-TB.

- California, New York, and Texas contribute the highest number of TB cases and drug-resistant TB cases to the U.S. total, accounting for 79 of the 148 MDR-TB cases reported in 2002.

- California reported 21% of all cases and 27% of MDR-TB cases in 2002, while New York reported only 9.5% of cases, but 19% of MDR-TB cases.
- In California, MDR-TB cases increased from 30 in 2001 to 42 in 2002. Given the lengthy period of treatment, the prevalence of MDR-TB cases can be more than twice the number of new cases reported in a given year.
- In 2003, 86 of 114 (75%) U.S. MDR cases were foreign-born. In California, more than 85% of MDR cases were foreign-born. In 1993, 31% of patients with MDR-TB in the U.S. were foreign-born, and the percentage has gradually increased to the current level (CDC unpublished data).
Figure 1.


- Persons with no prior history of TB
- Persons with prior history of TB
Of the foreign-born patients diagnosed with MDR-TB in the U.S. in 2002–2003, 80% were born in only 12 countries. Table 3 shows the drug resistance pattern for the top 12 countries of origin for U.S. cases of drug-resistant TB. Younger patients, patients who have recently immigrated, and patients previously treated for TB will have higher rates of resistance.

Table 3.


<table>
<thead>
<tr>
<th>Country of origin</th>
<th>Total TB cases*</th>
<th>MDR</th>
<th>Any resistance</th>
<th>INH resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mexico</td>
<td>2833</td>
<td>46</td>
<td>529</td>
<td>254</td>
</tr>
<tr>
<td>Philippines</td>
<td>1322</td>
<td>27</td>
<td>251</td>
<td>216</td>
</tr>
<tr>
<td>Vietnam</td>
<td>991</td>
<td>10</td>
<td>268</td>
<td>161</td>
</tr>
<tr>
<td>India</td>
<td>901</td>
<td>14</td>
<td>147</td>
<td>103</td>
</tr>
<tr>
<td>China</td>
<td>578</td>
<td>16</td>
<td>104</td>
<td>70</td>
</tr>
<tr>
<td>Haiti</td>
<td>411</td>
<td>5</td>
<td>56</td>
<td>47</td>
</tr>
<tr>
<td>Republic of Korea</td>
<td>318</td>
<td>9</td>
<td>48</td>
<td>38</td>
</tr>
<tr>
<td>Peru</td>
<td>260</td>
<td>17</td>
<td>72</td>
<td>47</td>
</tr>
<tr>
<td>Ecuador</td>
<td>253</td>
<td>0</td>
<td>20</td>
<td>11</td>
</tr>
<tr>
<td>Guatemala</td>
<td>248</td>
<td>2</td>
<td>31</td>
<td>16</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>210</td>
<td>1</td>
<td>29</td>
<td>21</td>
</tr>
<tr>
<td>Honduras</td>
<td>204</td>
<td>6</td>
<td>23</td>
<td>12</td>
</tr>
</tbody>
</table>

* Total cases with positive cultures and initial susceptibilities performed.
TB Drugs and the Development of Resistance

With the widespread and sometimes incorrect use of anti-tuberculosis treatment, the drug resistance situation has changed dramatically. Resistance to streptomycin was documented shortly after it was introduced as monotherapy for TB in the U.S. in the 1940s. When a single drug is used to treat a large bacillary load of TB organisms, the susceptible organisms are killed, and gradually, the resistant strains multiply and constitute a greater percentage of the population. Subsequently, the patient experiences clinical, microbiologic, and treatment failure.

Multidrug regimens soon became the recommended treatment standard in order to prevent the selection of drug-resistant strains. By 1972, rifampin (RIF) became regularly utilized in anti-tuberculosis regimens, and overall resistance to anti-tuberculosis drugs was uncommon. From 1985 to 1992, TB incidence increased in the U.S. and outbreaks of drug-resistant and MDR-TB occurred. In 1993, the Centers for Disease Control and Prevention (CDC) initiated a national surveillance program for drug resistance to monitor trends and inform interventions.

### Clinical Use of Anti-Tuberculosis Drugs in the U.S.

<table>
<thead>
<tr>
<th>Year</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>1943</td>
<td>Streptomycin</td>
</tr>
<tr>
<td>1946</td>
<td>Para-aminosalicylic Acid</td>
</tr>
<tr>
<td>1952</td>
<td>Isoniazid / Pyrazinamide</td>
</tr>
<tr>
<td>1962</td>
<td>Ethambutol</td>
</tr>
<tr>
<td>1967</td>
<td>Rifampin</td>
</tr>
</tbody>
</table>
Evolution and Genetic Basis of Drug-Resistant TB

- Mutations that confer resistance to anti-tuberculosis drugs occur spontaneously and independently.
- Wild-type TB strains are those that have not previously been exposed to anti-tuberculosis drugs.
- Within wild-type *M. tuberculosis* populations, small populations of mutants are found to be resistant to anti-tuberculosis drugs. In a given wild-type population:
  - $3.5 \times 10^{-6}$ are resistant to INH.
  - $1.2 \times 10^{-8}$ are resistant to RIF.
  - $3.1 \times 10^{-5}$ are resistant to ethambutol (EMB).
  - $3.8 \times 10^{-6}$ are resistant to streptomycin (SM).
- Resistance to more than 1 TB drug is even rarer (as resistance to the various drugs is not linked genetically). Inherent resistance to more than 1 TB drug is the product of the rates of the individual drugs.
  - **INH and RIF**: $3.5 \times 10^{-6} \times 1.2 \times 10^{-8}$ equals $4.2 \times 10^{-14}$
- Before the clinical use of TB drugs, *M. tuberculosis* strains were susceptible to the newly discovered anti-tuberculosis drugs.
- Prior to the use of anti-tuberculosis therapy, an individual would need to be infected with a very large population of *M. tuberculosis* to contain any drug-resistant organisms, much less any that would be clinically significant.

Selection of the naturally occurring drug-resistant mutants by inadequate TB treatment will cause the population of *M. tuberculosis* bacteria to become increasingly drug-resistant.

- A large body of knowledge has been accumulated regarding the molecular basis for drug resistance of *M. tuberculosis*.
- Known mutations account for most resistance of strains of *M. tuberculosis* to INH, RIF, pyrazinamide (PZA), SM, EMB, and fluoroquinolones. (See Table 4.)
- Some strains are drug-resistant and do not have any of the known mutations.
### MUTATIONS

<table>
<thead>
<tr>
<th>Anti-tuberculosis drug</th>
<th>Gene mutated</th>
<th>% of mutations</th>
<th>Product of that gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>katG</td>
<td>40–60%</td>
<td>Catalase-peroxidase (activates INH)</td>
</tr>
<tr>
<td>Isoniazid – ethionamide</td>
<td>inhA</td>
<td>15–43%</td>
<td>Reductase analog (Mycolic acid synthesis)</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>ahpC</td>
<td>10%</td>
<td>Hydroperoxidase reductase</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>kasA</td>
<td>unknown</td>
<td>Carrier protein synthase</td>
</tr>
<tr>
<td>Rifampin</td>
<td>rpoB</td>
<td>&gt;96%</td>
<td>Subunit of RNA polymerase</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>pncA</td>
<td>72–97%</td>
<td>Pyrazinamidase</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>embB</td>
<td>47–65%</td>
<td>Arabinosyltransferase</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>rpsL</td>
<td>70%</td>
<td>Ribosomal protein S12</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>rrs</td>
<td>70%</td>
<td>16S rRNA</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>gyrA</td>
<td>75–94%</td>
<td>DNA gyrase A subunit</td>
</tr>
</tbody>
</table>
Factors That Create Resistance

In a previously treated TB case, factors that create or amplify drug resistance include:

- The patient may not take all the drugs prescribed, due to any of the following factors:
  - Lack of resources
  - Intolerance/toxicity
  - Misunderstanding
  - Interrupted drug supply
  - Disbelief of the diagnosis
  - Disbelief of the efficacy or necessity of the treatment
  - Chaotic lifestyle; substance abuse
  - Cultural issues
  - Pregnancy
  - Neuropsychiatric disease

- There may be a dispensing or administration error of a correct dose.
- The patient may not be prescribed a large enough dose to be effective.
- The patient may not absorb the full dose of medication and/or have disease in areas where the penetration of 1 or more of the drugs may be impaired.
- The provider may not prescribe an adequate TB regimen.
- The patient’s organism may already be resistant to 1 of the TB drugs prescribed, leaving an unrecognized suboptimal TB regimen.
- The patient may have been incorrectly diagnosed as having latent TB infection (LTBI), rather than active TB, and treated with monotherapy.
- The TB patient may be taking therapy for another disease. That therapy may coincidentally contain a single drug active against TB (rifampin in an HIV patient for Mycobacterium avium complex [MAC] prophylaxis; repeated courses of a fluoroquinolone for community-acquired pneumonia).
- The patient may take TB medicines available without a prescription.
- The TB medicines may interact with other drugs being taken by the patient.

If the patient starts an effective TB regimen and then stops taking all the TB drugs at the same time, the population of bacteria usually remains susceptible. This is one of the major advantages of DOT: either the patients take all the drugs or none of the drugs. This is also the benefit of combination formulations such as INH/RIF or INH/RIF/PZA in a single product. The patient either takes all drugs or none—reducing risk of development of resistance.

Clinically significant drug resistance usually emerges after 1–2 months of administration of an inadequate drug regimen.
Summary

There are 2 types of drug-resistant TB cases: “new cases” (infected by an already drug-resistant strain) and “previously treated” TB cases.

Drug-resistant TB is found throughout the world. Hot spots include: Kazakhstan, Lithuania, Estonia, Russian Federation (Tomsk Oblast), China, Ecuador, and Israel.

Although MDR-TB in the U.S. has declined over the last decade, 42 states reported drug-resistant cases in 2002. California, New York, and Texas have the highest numbers of cases.

The incidence of drug-resistant TB in the U.S. is highest among foreign-born cases.

Sustained political will, significant resources, and efficient TB control programs are required to reverse the trend of TB drug resistance.

Mutations leading to drug-resistant M. tuberculosis occur spontaneously and independently. The tiny populations of inherently resistant mutants are easily treated during appropriate multidrug TB regimens. Inadequate TB treatment or inadvertent mono-drug therapy allows for the proliferation and eventual clinical significance of drug-resistant populations.
References


- Cole ST, Institut Pasteur; Eisenach KD, University of Arkansas for Medical Sciences; McMurray DN, Texas A&M University Health Science Center; Jacobs WR Jr, Albert Einstein College of Medicine; eds. *Tuberculosis and the Tubercle Bacillus.* Washington, DC: ASM Press; 2004.


Diagnosis

Risk Assessment
Risk Factors
Questions to Ask Patients
Laboratory Diagnosis
Susceptibility Testing
Interpretations
Methods
Variation in Results
Use of Strain Typing
References
The first step in diagnosing drug-resistant TB is to recognize that the patient is at risk and to expedite the laboratory diagnosis of TB.

The diagnosis of tuberculosis (TB) frequently requires a high index of suspicion, especially in low prevalence areas. Once TB is considered, sputum or other specimens for acid-fast bacilli (AFB) smear, growth detection, and susceptibility testing are collected. The possibility of drug-resistant TB should be considered simultaneously with specimen collection and selection of the initial treatment regimen. Failure to consider the possibility of drug-resistant TB until drug susceptibility tests return weeks to months later can result in unnecessarily inadequate drug regimens.

Risk Assessment for Drug Resistance

Rapid identification of drug resistance in a patient with TB is critical in order to:

- Treat the patient with the most appropriate empiric regimen.
- Minimize transmission.
- Minimize potential drug side effects.
- Provide the best chance of cure.
- Prevent further drug resistance.
- Offer appropriate care to contacts.

Predicting who is at risk prior to the return of susceptibility test results is the first step in early detection of drug resistance.

The most important predictors of drug-resistant TB are:

- A **previous episode** of TB treatment
- **Progressive** clinical and/or radiographic findings while on TB therapy
- **Origin** from, **history of residence** in, or **frequent travel** to a region/country with high rates of drug resistance
- **Exposure to an individual with infectious drug-resistant TB**, including in facilities where drug resistance has occurred; e.g., correctional institutions, homeless shelters, or other congregate settings
Risk Factors in Persons WITH a History of TB

**Suspicion for drug-resistant TB should be HIGH** if the patient has 1 or more of the following characteristics on current or prior treatment:

- Large bacillary load with extensive (bilateral or cavitary) disease
- Lack of conversion of cultures to negative during therapy
- Lack of improvement or partial improvement in TB symptoms
- Worsening of TB symptoms or radiograph findings
- Nonadherence or intermittent or erratic ingestion of prescribed anti-TB regimen
- Lack of directly observed therapy (DOT) or poorly supervised therapy
- History of an inappropriate treatment regimen, including:
  - Administration of single drug therapy
  - Too few effective drugs
  - Inadequate drug doses

Risk Factors in Persons WITHOUT Prior TB History

**Clinical suspicion of drug resistance** should occur when a patient with TB symptoms and signs has a history of 1 or more of the following:

- Exposure to a person with documented drug-resistant TB
- Residence in or travel to a region with high rates of drug-resistant TB
- Residence or work in an institution or setting in which drug-resistant TB is documented
- Treatment of pulmonary problems with a prolonged course of multiple medicines or an injectable agent for more than a few weeks in a foreign country; i.e., the patient may not realize that he/she was treated for TB
Questions to Ask Your Patient

Soliciting history of previous TB treatment requires a great deal of patience and attention to detail. In a culturally sensitive and confidential setting, allow plenty of time, utilize an accurate and unbiased medical interpreter (if necessary), and be willing to repeat or rephrase a question to obtain the information. Give the patient encouragement to reveal accurate information by asking and responding in a non-judgmental manner. Ask the patient if he/she has ANY written information regarding his/her treatment, any old radiographs, etc.

- Have you been told you had TB before?
- Have you been treated for TB?
- Have you received injections for a lung problem?
- Have you purchased and used medicated cough syrups in a foreign country?

If Yes:

- Where were you treated?
- What drugs did you receive?
- How many different drugs? How many pills each day? What size and colors were the pills/capsules?
- Did you receive injections?
- How long were you on treatment?
- When did you start?
- When did you stop? Why did you stop (completed treatment, adverse reaction)?
- It’s hard to remember to take medicine everyday. Did you take medications daily? Every pill?
- TB medicine is expensive. Were you ever without medication? Did you miss medication sometimes? How often?
- Did health care workers observe you taking your medications?
- Did your urine turn orange?
- Did you improve?
- Did you ever have a sputum examined? What was the result?
- If positive, did your sputum turn to negative?
- Did your doctor ever tell you: That you had to be treated for TB longer? That you had a return of TB? That you had drug resistance?
- Did your TB symptoms return after finishing treatment?
If the patient was previously treated for TB in the U.S. or Mexico, records detailing his/her treatment should be obtained from the local jurisdiction or CureTB (see Appendix 2, Contact Information for Selected Organizations Working to Control and Prevent TB in the International Arena). If the patient was treated in Western Europe or by a private provider in a developed country, records may be available and should be sought. Appendix 3, International Resources for TB Treatment and Policies, lists websites that may be helpful in identifying TB policies in selected countries.

If No:

- Have you been exposed to or had contact with anyone with TB?
- If yes, when was that?
- What is that patient’s name and birthdate? Where was he/she treated? How long was he/she treated? Was he/she cured?
- Did you have a skin test? Do you know the results?
- Did you have a chest x-ray? Do you know the results?
- Did you receive medications to prevent TB? If so, what drugs and for how long? Did you come to a clinic for the medications where a health care worker observed you take the pills, or did a health care worker meet you and provide medications?
- Did you have cough, fever, weight loss, or other symptoms?
- If yes, when did those symptoms start?
- Have you ever given sputum specimens to check for TB?

Obtain records when possible regarding treatment of a presumed source case.
Laboratory Diagnosis

The role of the laboratory is critical in the diagnosis of active TB and even more so for drug-resistant TB. Definitive diagnosis of drug-resistant TB requires that *M. tuberculosis* be isolated and drug susceptibility results be completed and conveyed to the clinician. Prompt turnaround time for laboratory results is of paramount importance in rapid diagnosis and appropriate treatment of multidrug-resistant TB (MDR-TB).

Growth detection and identification of *M. tuberculosis* may take a few weeks. Drug susceptibility testing of a TB isolate requires an additional 2–3 weeks. Slow growth of some mycobacteria (a common characteristic noted in many MDR-TB strains) further lengthens the time to identification and susceptibility testing. Delays in the return of reports of culture confirmation and susceptibility results will delay identification of patients with drug-resistant TB and initiation of appropriate treatment.

To ensure rapid diagnosis of *M. tuberculosis* and drug-resistant TB, the following turnaround times—set by national standards—should be achieved by laboratories:

**National Standards for Laboratory Turnaround Times**

- **Clinical specimens should reach the laboratory within 24 hours of collection.**
- **AFB smear reports should reach physicians within 24 hours of specimen receipt in the laboratory.**
- **Positive culture identification should occur within 14 days of specimen collection.**
- **Isolate should be definitively identified as *M. tuberculosis* within 17–21 days of specimen collection.**
- **Antibiotic susceptibility results should be reported to the physician within 28 days of specimen collection.**

Because successful treatment of drug-resistant TB depends on susceptibility test results of the *M. tuberculosis* isolate, **second-line susceptibility tests should be requested as soon as drug resistance is suspected or identified.** Consult with the laboratory about which second-line susceptibility tests (if any) are performed and which reference laboratory it is using. See Appendix 4, *Laboratory Resources* for tests performed by some of the public health and reference laboratories. Clinicians should contact their state or local TB programs or an expert in MDR-TB for assistance in identifying a qualified public health/reference laboratory, if necessary. In some jurisdictions, rapid molecular methods are available to rapidly diagnose some drug resistance.
If drug resistance is strongly suspected based on the patient’s prior treatment history or exposure to drug-resistant disease, concerns should be discussed immediately with the laboratory director.

Molecular susceptibility testing or conventional direct susceptibilities can sometimes be performed upon request, which may hasten the results. (See Appendix 4, Laboratory Resources, and Appendix 5, Direct Method.) Second-line susceptibility tests should be ordered even before the first-line results have been returned in these circumstances. The laboratory should notify the clinician of preliminary results as soon as it is confident of the validity and not wait for final confirmation.

- When drug resistance to more than 1 first-line drug is found, susceptibility tests should be requested for the full spectrum of second-line agents. Amikacin or kanamycin, capreomycin, ofloxacin or levofloxacin, and ethionamide are the minimum second-line drugs. Fewer laboratories perform testing against cycloserine, para-aminosalicylate (PAS), rifabutin, and other agents, but these too may be required.
- Timely and frequent communication with the laboratory is essential. If the laboratory that cultured the isolate has limited capacity for susceptibility testing, the provider should arrange to send the isolate to a reference laboratory immediately.
- The clinician should know the name, telephone number, and contact person for each laboratory that will process and perform drug susceptibility testing on isolates for patients with suspected drug resistance.

FALSE-POSITIVE RESULTS

- If the diagnosis of drug-resistant TB is highly unlikely, discuss the possibility of a false-positive result with the laboratory and reiterate that drug resistance should be confirmed by a second method or by a second laboratory. The laboratory should automatically consider that possibility when more than 1 unrelated patient specimen processed in close proximity by date or test assay has the same resistant susceptibility pattern. Other clues include the diagnosis of TB in patients very unlikely to have TB, only 1 positive culture among several specimens collected, and discrepant results among different cultures from the same patient. Reports describing pseudo-outbreaks and misdiagnosis of drug-resistant TB have attributed false-positive results to:
  - Mislabling of specimens in the laboratory, clinic, ward, or bronchoscopy suites
  - Malfunctioning ventilation hoods
  - Contaminated tubing, bulbs, reagents, etc.
  - Malfunction of radiometric test systems
Susceptibility Testing

SUSCEPTIBILITY INTERPRETATIONS

The interpretation of susceptibility testing results for mycobacteria is somewhat different than that for most other pathogens. In the latter case, the clinician compares the minimum inhibitory concentration (MIC) of the pathogen with the achievable serum level. If a safe dose of the antibiotic will kill the bacteria in the patient, the drug can be successfully used. The interpretation of susceptibility testing for mycobacteria is not as straightforward. Several variables complicate the interpretation of susceptibility testing for mycobacteria: 1) mycobacteria may be either within or outside of human cells; 2) they have a long generation time and may exist in a dormant or active state; and 3) they live in tissues that may have variable penetration of drug.

In mycobacterial susceptibility interpretation, clinical trials have ascertained that when more than 1% of organisms within a population are mutants resistant to a given drug, clinical success is less likely. The concentration that constitutes the break-point between a resistant and susceptible strain is called the “critical concentration.” The critical concentration is the level of drug that inhibits a wild-type (a strain which has not been exposed to TB drugs) M. tuberculosis strain, but does not appreciably suppress the growth of a resistant strain. The critical concentration depends on the medium used for growth detection of M. tuberculosis.

The agar proportion method using Middlebrook 7H10 agar was used for the early clinical efficacy trials. In the U.S., this method is used as the standard by which to compare all newer susceptibility methods. Each method sets the critical concentration for each drug based on M. tuberculosis growth compared to growth on 7H10 agar. (See Appendix 6, Critical Concentrations.)

If more than 1% of the strain’s population grows at the critical concentration of the drug for that particular medium, consider the isolate to be resistant to that drug and plan on using other drugs. (Be aware that isoniazid [INH] could be tested at both low and high level and it may be possible to still use INH in the event of low-level INH resistance.)
SUSCEPTIBILITY METHODS

Susceptibility testing of mycobacteria utilizes the same solid media, broths, and inoculation methods as culture techniques. The systems are supplemented with anti-tuberculosis drugs. Growth of the organisms in the presence of anti-tuberculosis drugs is compared to controls in order to interpret susceptibility or resistance. (For examples and details about susceptibility testing and each of the following methods, see Appendices 5–11.)

**Proportion method:** The clinical specimen (direct method) or a subculture of mycobacterial growth (indirect method) is used to inoculate agar plates containing either a TB drug or no drug (control). The growth of colonies on the drug-containing plates is compared to the control plate as a proportion (percent resistance). This process typically takes at least 3–4 weeks. (See Appendix 8, *Proportion Method*.)

**Direct method:** The clinical specimen (usually AFB smear-positive sputum) is processed and then inoculated directly onto agar plates containing various TB drugs. (See Appendix 5, *Direct Method*.)

**Indirect method:** After the *M. tuberculosis* grows from a clinical specimen, a suspension is prepared and inoculated onto drug-containing agar plates or into broth bottles or tubes. (See Appendix 9, *Indirect Method*.)

**Broth methods:** *M. tuberculosis* is grown in vials/tubes of broth containing either the critical concentration of an anti-tuberculosis drug or no drug (control). The growth of the organism in the drug-containing bottles is compared to the growth in the control vial/tube. Broth methods are preferred for first-line testing as they are much faster than the proportion method using agar media (typically 5–10 days).

**BD BACTEC 460TB method:** *M. tuberculosis* is grown in vials of broth containing $^{14}$CO$_2$-labeled substrate. The BD BACTEC 460TB system is well standardized and very reliable; however, it is a radioactive test system and requires the use of needles/syringes and is not fully automated. (See Appendix 10, *BD BACTEC 460TB Method*.)

**Newer broth methods:** In order to avoid use and disposal of radioactive materials, other broth systems have been developed that use pressure change, or fluorescent or colorimetric changes to detect mycobacterial growth in a fully automated system. In contrast to the BD BACTEC 460TB system, the laboratory community has less experience with these newer assays. (See Appendix 11, *Newer Broth Methods*.)

**Molecular methods:** DNA is extracted from the organisms and amplified. Mutations causing drug resistance are detected. (See Appendix 7, *Molecular Methods*.)
Variation in Results

Discrepancies in test results can occur between different laboratories. Reasons include:

- Some strains of *M. tuberculosis* have MICs that are close to the critical concentration. Long experience has shown that the reproducibility for testing of these strains can be poor.
- The different laboratories may not have actually used the same specimen.
- Errors can occur during drug susceptibility testing:
  - Failure to use a standardized inoculum (well-dispersed suspension)
  - Failure to add a drug to a vial
  - Adding the wrong drug or concentration
  - Failure to recognize a mixed infection (*M. tuberculosis* and a non-tuberculous mycobacterium [NTM]), which is more difficult to detect in broth systems
  - Failure to recognize contamination with another organism, which is more difficult to recognize in broth systems
- Changes in drug activity or support of mycobacterial metabolism can occur between different lots of culture media. Ideally, laboratories should check new batches of medium ingredients to verify that the medium they produce has the same drug activity as previous, validated lots of medium.
- If a subculture is tested, it may not represent the entire initial population.

Because the ramifications of rifampin resistance or MDR are so significant, always have the resistance pattern confirmed by the public health laboratory.

- Scrutinize results and assess whether they fit the clinical and epidemiological picture.
- Talk to the laboratorian and discuss reasons for conflicting results.
  - Ask how the laboratory ruled out any mixed infection with non-tuberculous mycobacteria.
  - Ask how the laboratory ruled out any contamination with non-AFB organisms.
  - If in doubt, your public health laboratory should repeat the test using the most recent isolate available.
USE OF STRAIN TYPING IN DIAGNOSIS

Molecular typing of *M. tuberculosis* strains can be useful in providing evidence to:

- Confirm an outbreak or cluster of related cases in a recent chain of transmission.
- Evaluate the possibility of a false-positive culture.
- Help distinguish between relapse or reinfection in a case with recurrent TB.
- Document the amplification of initial monoresistance to MDR.

New and rapid methods for detection of drug-resistant TB have recently been developed. Isolates with matching strain types can have different drug susceptibility patterns. This is because TB due to a specific strain may initially be susceptible to a panel of drugs, but with inappropriate or inadequate treatment, the population of resistant organisms will flourish. **The genotype does not change because drug resistance has developed.**

### Summary

**Patients at highest risk of drug-resistant TB are those who:**
- Previously have been treated for TB.
- Came from or traveled to regions/countries with high rates of drug resistance.
- Have been exposed to individuals with drug-resistant TB.

**Each TB patient should be assessed for risk of drug resistance.**

**The laboratory is crucial in the diagnosis and management of drug-resistant TB.**

**Drug-resistant TB should be confirmed by a public health laboratory or experienced reference laboratory.**

**Proper control of TB transmission requires timely performance of all laboratory testing and close communication between the clinician and the laboratory.**


Treatment

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An empiric expanded TB regimen is appropriate for patients at high risk for drug resistance, especially if they are seriously ill or have extensive disease.

Diagnosis and Early Detection

The first step in the management of drug-resistant tuberculosis (TB) is to recognize that the patient is at risk of harboring drug-resistant *M. tuberculosis*. As described in Chapter 2, *Diagnosis*, suspect underlying drug resistance in the following situations:

- Patients in whom TB treatment is failing (i.e., are not showing significant clinical, radiographic, and bacteriologic improvement by the third month of therapy)
- Persons who have been previously treated for TB
- Contacts to drug-resistant cases of TB
- Persons who were born in countries or reside in settings where drug-resistant TB is prevalent

If a patient is suspected of harboring drug-resistant *M. tuberculosis* based on treatment failure, a history of previous therapy, or epidemiologic information, consider use of an empirically expanded regimen, particularly if the patient is seriously ill and/or has extensive disease (increased risk of relapse and failure).

The treatment regimen can be changed once the results of drug-susceptibility tests are available. Given the importance of having susceptibility results, every effort should be made to obtain specimens for culture and drug-susceptibility testing.
High-Risk Groups

TREATMENT FAILURE

Recognition of a Failing Regimen

Treatment failure is defined as continued or recurrently positive cultures in a patient receiving appropriate chemotherapy. Studies have demonstrated that approximately 90–95% of patients with drug-susceptible pulmonary TB will be culture-negative after 3 months of treatment with a regimen that contains isoniazid (INH) and rifampin (RIF).

A treatment regimen has failed when sputum cultures remain positive after 4 months of treatment or become positive again after a period of negative cultures. However, the possibility of a failing treatment regimen should be considered well before 4 months of treatment. Patients who are not clinically improving and/or remain smear-positive during the first months of treatment should be considered for the possibility of drug resistance.

There are several potential reasons for treatment failure:

- Nonadherence to the treatment regimen
- Acquired drug resistance
- Malabsorption of drugs
- Reinfection with a new strain of M. tuberculosis
- Inadequate treatment regimen

The Clinician’s Response to Treatment Failure

Determine the cause of treatment failure:

- Verify drug-susceptibility results by reviewing written reports or discussing the results with the laboratory.
- Perform repeat drug-susceptibility testing to determine if drug resistance has developed while on therapy. However, patients with treatment failure should be assumed, until proven otherwise, to have drug-resistant organisms.
- Treat persons who were being treated with self-administered therapy with directly observed therapy (DOT).
- In patients who were being treated with DOT, measurement of drug serum concentrations may be indicated, particularly if drug resistance has developed on therapy or there are risk factors for malabsorption.
Consider a Treatment Regimen Change

If treatment failure is presumed to be due to underlying drug resistance and the patient does not have severe TB, either initiate an empiric regimen (see Starting an Expanded Empiric Treatment Regimen) or wait for the results of drug-susceptibility testing.

If the patient is seriously ill or has a positive sputum acid-fast bacilli (AFB) smear, start and continue an empiric regimen until drug-susceptibility test results are available.

Never add a single drug to a failing regimen.

PERSONS WHO HAVE RELAPSED AFTER PRIOR TREATMENT

Relapse occurs when a patient who has completed TB therapy and has documented negative sputum cultures either becomes culture-positive again or experiences clinical or radiographic deterioration consistent with active TB.

Persons who have been treated previously for TB and subsequently relapse are at increased risk of presenting with drug-resistant organisms. Numerous studies have identified previous treatment as one of the greatest risk factors for the acquisition of drug-resistant TB.

Acquired drug resistance is more likely in persons who were not treated initially with DOT. In patients who received DOT and were adherent to therapy, the risk of developing acquired resistance is small unless the patient has advanced HIV infection and received highly intermittent therapy (e.g., weekly or twice weekly).

As with treatment failures, there are several possible causes for relapse:

- Nonadherence to the treatment regimen
- Acquired drug resistance
- Malabsorption of drugs
- Reinfection with a new strain of *M. tuberculosis*
- Inadequate treatment regimen
Re-Treatment Options

In patients who relapse after initial treatment with a regimen that included INH, RIF, pyrazinamide (PZA), and ethambutol (EMB) administered under direct observation, initiate re-treatment with the same 4-drug regimen pending the results of drug-susceptibility tests.

If the patient previously received any self-administered therapy or an inappropriate treatment regimen, consider use of an expanded treatment regimen. An expanded regimen is indicated especially in patients with impaired immunity, limited respiratory reserve, central nervous system involvement, or other life-threatening circumstances.

Ideally, at least 2, preferably 3, new drugs that are added to the standard 4-drug treatment regimen should be ones that the patient has not received previously.

CONTACTS OF A DRUG-RESISTANT CASE WITH ACTIVE DISEASE

Consider the infectious period of the source case, and tuberculin skin test (TST) conversion of the contact, to confirm when infection was likely to have occurred. If the source case had progressive drug resistance, consider the susceptibility pattern of the source case at the time of exposure.

Assume that the secondary case has the same pattern of drug resistance as the source case, unless there is evidence to the contrary.

In general, base the empiric treatment regimen on the drug-susceptibility pattern of the source case. If drug-susceptible disease is documented subsequently, switch to a standard 4-drug treatment regimen.

PERSONS WHO COME FROM REGIONS WHERE DRUG-RESISTANT TB IS PREVALENT

In situations where data about a region’s prevalence of drug resistance is lacking or possibly inaccurate, consider using an expanded regimen by adding 2–3 additional drugs to the treatment regimen in patients who are seriously ill and at risk of dying from TB. (See Appendix 3, International Resources for TB Treatment and Policies.)
Starting an Expanded Empiric Treatment Regimen

The decision to start an expanded empiric regimen will be determined by the level of suspicion for drug-resistant TB and the severity of illness in the TB suspect. When suspicion for drug-resistant TB is high (e.g., previous treatment, especially if self-administered, a close contact to a case with confirmed drug-resistant TB), then an expanded treatment regimen may be warranted. In addition, when a patient is suspected of having drug-resistant disease and has life-threatening TB, use an expanded treatment regimen. An expanded empiric regimen usually consists of the 4 first-line drugs and 2 or more additional drugs. When extensive disease or resistance is suspected, do not limit the empiric regimen to just 6 drugs.

There are situations where it may be more appropriate to initiate a 4-drug (first-line) regimen or defer treatment completely until drug-susceptibility results are available. This is particularly true if an inappropriate regimen may risk amplification of drug resistance. If few treatment options remain, definitive treatment may be the patient’s last chance for cure. This is an appropriate option only if the patient is not particularly ill and can be isolated to prevent infection of contacts.

An Expanded Treatment Regimen*

When an expanded treatment regimen is warranted, the following regimen is recommended:

- INH
- RIF
- EMB
- PZA
- A fluoroquinolone
- An injectable agent (because of the frequency of streptomycin [SM] resistance in the world, better alternatives would be capreomycin or amikacin)
- Consider use of ethionamide, cycloserine, or PAS

When choosing the injectable agent and other second-line drugs, consider:

- The previous treatment history of the patient
- The drug resistance pattern of the source case
- The likely patterns of resistance in a specific region

* When extensive resistance or disease is present or the patient is seriously ill, do not limit the empiric regimen to 2–3 additional drugs.
Selection and Dosing of Individual Drugs—Building the Regimen

The choice of drugs for the treatment of drug-resistant TB will depend on:

- The pattern of drug resistance
- Which drugs have been taken previously
- Whether the patient has underlying medical conditions
- The adverse effects associated with the drug

The number of drugs required to cure multidrug-resistant TB (MDR-TB) is not known. Most studies that have been published have used 4–6 drug regimens. Table 1 lists most published series of MDR-TB treatment and outcomes. These regimens have resulted in cure in 56–83% of the patients. The outcome of treatment is likely to vary depending on the number of drugs to which the isolate is resistant, the drugs used, the duration of therapy, the extent of disease, and the presence of other medical conditions, such as HIV infection.

Unfortunately, recommendations for MDR-TB are based on expert opinion rather than data from randomized controlled trials.

The following predictors have been noted in small trials or series:

Predictors of a good outcome include:

- Susceptibility to and use of PZA and/or EMB
- Susceptibility to and use of a fluoroquinolone
- Sputum culture conversion by 2 months
- Surgical resection

Predictors of failure include:

- History of previous therapy
- Greater number of drugs to which the organism is resistant
- Presence of caviation on the chest radiograph
- Positive cultures at 2–3 months
<table>
<thead>
<tr>
<th>Study site, study dates, study design, and citation</th>
<th>Number of patients and comments</th>
<th>Mean number of drugs to which the isolate was resistant</th>
<th>Mean number of drugs given</th>
</tr>
</thead>
<tbody>
<tr>
<td>NJMRC** Denver, CO (1973–1983) Retrospective chart review Goble 1993</td>
<td>N = 171 (134 eligible for outcome analysis) Mean inpatient stay &gt;7 months</td>
<td>6 drug resistance</td>
<td>6 drugs</td>
</tr>
<tr>
<td>Bellevue Hospital, New York (1983–1994) Retrospective chart review Park 1996</td>
<td>N = 173</td>
<td>37% 2 drugs 26% 3 drugs 37% ≥ 4 drugs</td>
<td>Not reported</td>
</tr>
<tr>
<td>Istanbul, Turkey (1992–1999) Retrospective chart review Tahaoglu 2001</td>
<td>N = 158 Mean inpatient stay 200 days</td>
<td>4.4 drug resistance</td>
<td>5.5 drugs 4.4 effective drugs</td>
</tr>
<tr>
<td>Florida (1994–1997) Retrospective chart review Narita 2001</td>
<td>N = 81 39 patients managed at specialized TB hospital; 42 managed in the community Outpatients who survived &gt; 2 mo included in outcome analysis</td>
<td>4.8 drug resistance Community management: 3.2 drugs Hospital management: 6.6 drugs</td>
<td>Effective drugs: Community management: 2.9 drugs Hospital management: 5.5 drugs</td>
</tr>
<tr>
<td>NJMRC** Denver, CO (1983–1998) Retrospective chart review Chan 2004</td>
<td>N = 205 Mean inpatient stay 93 days</td>
<td>6 drug resistance</td>
<td>6 drugs</td>
</tr>
</tbody>
</table>

* Statistically significant on multivariate analysis  ** National Jewish Medical and Research Center  *** Treatment with 2 or more drugs to which the isolate was susceptible
<table>
<thead>
<tr>
<th>HIV status</th>
<th>Outcomes</th>
<th>Variables associated with good outcome*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not reported</td>
<td>37% mortality (all causes) 21% mortality (TB) 65% initial culture conversion (56% cure; 9% relapse)</td>
<td>History of exposure to fewer drugs Female gender</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>52% HIV+ 24% unknown</td>
<td>58% mortality (all causes) 20% mortality (TB)</td>
<td>HIV seronegative status Appropriate therapy*** Isolated pulmonary involvement Cavitary disease at diagnosis (HIV-)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>86% HIV+ 7% unknown</td>
<td>83% mortality (all causes) 20% mortality (TB)</td>
<td>Capreomycin use CD4 lymphocyte &gt; 200 Fluoroquinolone use INH use</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>89% HIV+</td>
<td>58% mortality (all causes) 45% mortality (TB) 63% initial response 50% overall response</td>
<td>Appropriate therapy*** for &gt; 2 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0% HIV+</td>
<td>4% mortality 77% overall success 49% cure</td>
<td>Lack of previous fluoroquinolone use Younger age Resistance to more than 5 drugs</td>
</tr>
<tr>
<td>Community management:</td>
<td>32% mortality (all causes, all patients) Community management: 45% mortality 48% cure</td>
<td></td>
</tr>
<tr>
<td>48% HIV+ 32% unknown</td>
<td>Hospital management: 41% HIV+ 5% unknown</td>
<td>Treatment at specialized TB hospital</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.3% HIV+ 13% unknown</td>
<td>23% mortality (all causes) Of n = 66 completing &gt; 4 mo treatment, 83% probable cure</td>
<td>Pyrazinamide use, if susceptible Ethambutol use, if susceptible</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not reported</td>
<td>25% mortality (all causes) 12% mortality (TB) 75% long-term favorable outcome</td>
<td>Surgical resection Fluoroquinolone use</td>
</tr>
</tbody>
</table>
When choosing anti-tuberculosis drugs, begin with any first-line drugs that are available, and then add a fluoroquinolone and an injectable agent (Figure 1).

**BUILDING A TREATMENT REGIMEN FOR MDR-TB**

**Step 1**
- **Use any available**
  - **First-line drugs**
    - Pyrazinamide
    - Ethambutol
  - **Fluoroquinolones**
    - Gatifloxacin
    - Levofloxacin
    - Moxifloxacin
  - **Injectable agents**
    - Amikacin
    - Capreomycin
    - Streptomycin
    - Kanamycin

**Step 2**
- **Pick one or more of these**
  - **Oral second-line drugs**
    - Cycloserine
    - Ethionamide
    - PAS

**Step 3**
- **Consider use of these**
  - **Third-line drugs**
    - Clofazimine
    - Imipenem
    - Linezolid
    - Macrolides
    - Amoxicillin/clavulenate
    - High-dose isoniazid

When developing a treatment regimen for patients with MDR-TB, begin with any first-line agents that are available and then add a fluoroquinolone and an injectable agent. Additional oral second-line drugs should be added to have a total of 4–6 drugs available. In patients with highly resistant organisms, alternative third-line drugs (*in vitro* activity against *M. tuberculosis*, limited clinical experience) may be needed. These should be chosen in consultation with someone who has experience using these drugs to treat MDR-TB.
SPECIFIC DRUGS

Fluoroquinolones

There are few clinical data to help decide which fluoroquinolone to choose. Levofloxacin has been used extensively for the treatment of drug-resistant TB. Limited data suggest that levofloxacin may be more efficacious than ofloxacin when treating drug-resistant TB. Ciprofloxacin is the least potent of the available fluoroquinolones. Moxifloxacin and gatifloxacin have better *in vitro* activity against *M. tuberculosis*, compared with levofloxacin, ofloxacin, and ciprofloxacin.

Future studies should help to define which of the available fluoroquinolones would be the best choice when treating drug-resistant TB.

The dose of levofloxacin has been successfully increased to 1.0 gram/day or more on a case-by-case basis and tolerated well. Patients should be initially treated with 500 mg daily, and the dose gradually escalated over a few weeks as tolerated. The doses of moxifloxacin and gatifloxacin should not be increased beyond their Food and Drug Administration (FDA)-recommended doses because of the possibility of more drug-related toxicities.

Aminoglycosides and Polypeptides

When choosing an aminoglycoside or polypeptide agent, weigh the cost and toxicity profiles of the different drugs.

SM and kanamycin are the least expensive. There is a large amount of clinical trial data to support the use of SM. However, SM resistance is one of the most common forms of resistance found in the world.

Amikacin has excellent *in vitro* activity against *M. tuberculosis*, but it is more expensive than SM and some authorities (and patients) say that intramuscular SM is less painful than amikacin. However, it is easier to obtain amikacin serum concentrations than SM, kanamycin, or capreomycin concentrations, and amikacin is tolerated well for long periods.

Capreomycin is also expensive, but the drug has been well tolerated when given for long periods of time. Significant electrolyte disturbances can occur with capreomycin (as well as the aminoglycosides), so close monitoring is required.

An injectable drug is administered 5–7 times weekly by IM injection or via indwelling catheter during the initial phase. After 2–6 months, the injectable drug is given 3 times weekly. The injectable drug should be continued at least 6 months and longer if the patient has extensive disease, slow microbiologic response, or extensive resistance.
Additional Oral Second-Line Drugs

The drugs para-aminosalicylate (PAS), ethionamide, and cycloserine are generally bacteriostatic (ethionamide may be weakly bactericidal at higher doses). There are few data supporting one drug over the other in terms of efficacy. The decision of which drug(s) to use is often based on the side effect profile of the drug and the ability to measure drug serum concentrations in the case of cycloserine.

When INH resistance occurs at low concentrations, the organism may also be resistant to ethionamide. In this situation, ethionamide may not be the best choice of second-line drugs unless the organism has been shown to be susceptible with in vitro testing.

Alternative or Third-Line Drugs

In this Guide, we refer to third-line anti-tuberculosis drugs (e.g., imipenem, clofazimine, amoxicillin/clavulanate potassium, clarithromycin, azithromycin, and linezolid) as those that have demonstrated in vitro activity against M. tuberculosis, but for which there are little clinical data supporting their use. Most of these drugs are expensive and, in some cases, require intravenous administration. Third-line drugs should only be used in consultation with an expert in the treatment of drug-resistant TB.

Several novel agents are currently being studied and have promise for treatment of drug-resistant TB. Compounds containing a nitroimidazopyran nucleus appear to inhibit the synthesis of protein and cell wall lipid both in replicating and static M. tuberculosis. Thiolactomycin and related analogues inhibit fatty acid and mycolic acid biosynthesis and have had activity against drug-resistant M. tuberculosis strains.
Table 2.
CROSS-RESISTANCE FOR ANTI-TUBERCULOSIS DRUGS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cross-resistance</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>Ethionamide</td>
<td>Cross-resistance to ethionamide may occur when there is low-level resistance to isoniazid.</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Rifamycins</td>
<td>Cross-resistance among the rifamycin class of drugs is typical. In a few strains that are resistant to rifampin, rifabutin may retain susceptibility <em>in vitro</em>.</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Streptomycin</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Amikacin</td>
<td>Kanamycin</td>
<td>High likelihood of cross-resistance since it is associated with the same mutation.</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>Amikacin</td>
<td>High likelihood of cross-resistance since it is associated with the same mutation.</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Other fluoroquinolones</td>
<td>In general, there is a complete class effect cross-resistance among fluoroquinolones <em>in vitro</em>. However, data suggest that the more potent fluoroquinolones (i.e., moxifloxacin and gatifloxacin) may continue to demonstrate some activity despite <em>in vitro</em> resistance to ofloxacin.</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>PAS</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Ethionamide</td>
<td>Isoniazid</td>
<td>Cross-resistance to isoniazid may occur when there is low-level resistance to ethionamide.</td>
</tr>
<tr>
<td>Clofazimine</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>
AVOID DRUGS THAT HAVE BEEN USED PREVIOUSLY TO TREAT THE PATIENT’S TB

Data from National Jewish Medical and Research Center suggest that patients who have taken a drug for over 1 month in the past have less effect from that drug, even if in vitro susceptibility tests demonstrate the isolate to be susceptible. Despite this, most experts recommend that first-line drugs with documented susceptibility be included in the treatment regimen.

CONSIDER SIDE EFFECTS WHEN CHOOSING DRUGS

For example, in someone with depression, it may be desirable to avoid cycloserine. When possible, try to avoid using drugs that have similar toxicity profiles. For example, the combination of PAS and ethionamide increases the risk of hypothyroidism. On the other hand, in some patients there is no choice because these may be the only drugs to which the isolate is susceptible, and hypothyroidism can easily be managed with the addition of thyroid replacement medications until treatment completion. Additionally, in persons with renal or hepatic disease, certain drugs may be easier to use or safer. Ultimately, the safest and most effective drugs to complete the treatment regimen should be chosen. It is important to recognize that some drugs, such as the aminoglycoside/polypeptide antimicrobials, will usually be stopped prior to completion of therapy. Therefore, the patient should receive a sufficient number of oral drugs from the beginning of therapy to make sure that there are at least 3–5 oral drugs remaining after the injectable is discontinued.

Ultimately, the choice of anti-tuberculosis drugs will depend on in vitro susceptibility results and, possibly, cost.

It is important to note that intolerance to one agent does not necessarily mean the patient will be intolerant to another agent. Other oral or intravenous second-line agents may be needed depending on the drug-resistance pattern. In some cases, with highly resistant organisms, the regimen may require the addition of third-line drugs.
Administration of the Treatment Regimen

Outcomes of treatment are usually worse with MDR-TB compared with susceptible disease, and drug-related toxicities are common. Although the cure rate remains high with TB caused by mono-resistant organisms, additional resistance can develop as a result of treatment errors, nonadherence to treatment, or amplification of mono-resistance. Therefore, DOT is strongly recommended for all forms of drug-resistant TB.

Treat all forms of drug-resistant TB with DOT and in consultation with experts in the treatment of resistant disease.

DOT can be delivered in the field or clinic. Although intermittent therapy is not recommended for the treatment of MDR-TB, 5-day-a-week directly observed dosing can be used for patients who are not hospitalized or institutionalized, with medications self-administered on weekends. In patients who are severely ill, treatment should be administered 7 days per week (including the injectable drugs).

ESCALATION OF DOSAGES (DRUG RAMPING)

The second-line anti-tuberculosis drugs are commonly associated with adverse effects. Some authorities recommend hospitalization at the time of initiation of therapy in order to monitor for drug toxicity or intolerance. During this period, serum drug concentrations can be determined as the dosages of the drugs are slowly increased to targeted serum concentrations. On the other hand, when resources and infrastructure are available, and transmission to contacts can be prevented, patients can be treated as outpatients and serum drug concentrations measured, if necessary. Most drugs should be started at full dose, except cycloserine, ethionamide, and PAS, in which case the dose of the drug can be increased over a 2-week period.

In some patients, beginning with a low dose and gradually increasing the dose is more acceptable and allows the clinician time to manage drug-related adverse effects. This approach of slowly escalating drug dosage is referred to as “drug ramping” and is most often used with the drugs PAS, ethionamide, and cycloserine. Examples of drug ramping can be seen in Figure 2.
The patient is begun on a low starting dose and the dose is increased every few days until the targeted dose (as mg/kg or maximum dose) is reached. The dose escalation should be completed within 2 weeks. Some patients will tolerate consolidation of cycloserine to once daily dosing (enhances adherence).
Individualized Treatment Regimens

The treatment regimen for confirmed cases of drug-resistant TB will depend on the results of drug susceptibility tests and the patient’s previous history of treatment. Once drug resistance has been documented by in vitro drug susceptibility testing, the following treatment regimens are recommended:

**MONO-RESISTANT MYCOBACTERIUM TUBERCULOSIS**

Isolated Resistance to ISONIAZID (INH)

Effective treatment regimens for patients with isolated INH-resistant TB are readily available. There are 3 options for treatment of patients with INH-resistant disease.

**Option 1:** Patients can be treated with daily RIF, EMB, and PZA, all given for 6–9 months depending on the microbiologic, clinical, and radiographic response. If a patient was initiated on a standard 4-drug regimen, INH can be stopped when resistance is documented, and RIF, EMB, and PZA continued.

**Option 2:** For patients with extensive disease, a fluoroquinolone may be added to the regimen. Continuation of INH in the setting of documented isolated resistance to INH is not necessary, given the high cure rate with the regimen described above. Treatment should continue daily for at least 6 months.

**Option 3:** If the patient does not tolerate PZA, a regimen consisting of RIF and EMB given for 12 months is effective. As in Option 2, a fluoroquinolone may be added to the regimen, especially during the initial phase of treatment. Some experts would include a fluoroquinolone for the entire course of treatment for essentially all such patients.
Isolated Resistance to RIFAMPIN (RIF)

The loss of RIF from the treatment regimen requires a longer duration of therapy. Resistance to RIF is associated in most cases with cross-resistance to rifabutin and rifampicine. In over 80% of strains where RIF resistance is documented, the strain is also resistant to rifabutin. Therefore, use rifabutin only when \textit{in vivo} susceptibility is documented. Resistance to rifampicine is universal in RIF-resistant isolates. RIF-resistant TB can be treated using at least 3 different regimens.

\textbf{Option 1:} Patients can be treated with INH, EMB, and a fluoroquinolone for 12–18 months, supplemented with at least 2 months of PZA.

\textbf{Option 2:} In patients with extensive cavitary disease, or to shorten the duration of therapy (e.g., 12 months), addition of an injectable agent to the Option 1 regimen for at least the first 2 months is recommended.

\textbf{Option 3:} Alternatively, INH, PZA, and SM (or another aminoglycoside/polypeptide) can be given for 9 months with acceptable results. However, extended use of an injectable may not be feasible for some patients.

Isolated Resistance to ETHAMBUTOL (EMB), PYRAZINAMIDE (PZA), or STREPTOMYCIN (SM)

Isolated resistance to EMB, PZA, or SM will have little impact on the efficacy of the treatment regimen. Loss of EMB or SM from the regimen will not decrease the efficacy or change the treatment duration. Loss of PZA from the regimen, however, requires prolonging the duration of therapy with INH and RIF by 3 months, for a total of 9 months of therapy.

**MULTIDRUG-RESISTANT MYCOBACTERIUM TUBERCULOSIS (MDR-TB)**

Patients with MDR-TB, defined as resistance to at least INH and RIF, should always be treated with a minimum of 4 or more drugs to which the isolate is susceptible. Treatment must be more aggressive in situations where the patient has long-standing disease (years), extensive disease, or multiple previous failed treatment efforts.

The duration of therapy will depend on the anti-tuberculosis drugs used and the extent of the disease. When treating MDR-TB, every effort should be made to use first-line agents to which \textit{in vivo} susceptibility has been demonstrated. In choosing drugs, begin with the available first-line drugs, and then add a fluoroquinolone and an injectable agent. Other oral or intravenous second-line agents may be needed, depending on the drug resistance pattern (Figure 1). Intermittent therapy should not be used in treating TB caused by multidrug-resistant organisms, except perhaps for injectable agents after an initial period (usually 2–3 months) of daily therapy. Table 3 presents recommended regimens for the treatment of drug-resistant TB.
### Table 3. TREATMENT REGIMENS FOR THE MANAGEMENT OF PATIENTS WITH DRUG-RESISTANT TB

<table>
<thead>
<tr>
<th>Pattern of drug resistance</th>
<th>Suggested regimen</th>
<th>Minimum duration of treatment (mos)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH (± SM)</td>
<td>RIF, PZA, and EMB</td>
<td>6–9</td>
<td>A fluoroquinolone (FQN) may strengthen the regimen for patients with extensive disease.</td>
</tr>
<tr>
<td>INH and PZA</td>
<td>RIF, EMB, and FQN</td>
<td>9–12</td>
<td>A longer duration of treatment should be used for patients with extensive disease.</td>
</tr>
<tr>
<td>INH and EMB</td>
<td>RIF, PZA, and EMB</td>
<td>9–12</td>
<td>A longer duration of treatment should be used for patients with extensive disease.</td>
</tr>
<tr>
<td>RIF</td>
<td>INH, EMB, FQN, plus at least 2 months of PZA</td>
<td>12–18</td>
<td>An injectable drug may strengthen the regimen for patients with extensive disease.</td>
</tr>
<tr>
<td>RIF and EMB (± SM)</td>
<td>INH, PZA, FQN, plus an injectable agent for at least the first 2–3 months</td>
<td>18</td>
<td>A longer course (6 mo) of the injectable may strengthen the regimen for patients with extensive disease.</td>
</tr>
<tr>
<td>RIF and PZA (± SM)</td>
<td>INH, EMB, FQN, plus an injectable agent for at least the first 2–3 months</td>
<td>18</td>
<td>A longer course (6 mo) of the injectable may strengthen the regimen for patients with extensive disease.</td>
</tr>
<tr>
<td>INH, EMB, PZA (± SM)</td>
<td>RIF, FQN, plus an oral second-line agent, plus an injectable agent for the first 2–3 months</td>
<td>18</td>
<td>A longer course (6 mo) of the injectable may strengthen the regimen for patients with extensive disease.</td>
</tr>
<tr>
<td>INH and RIF (± SM)</td>
<td>PZA, EMB, FQN, injectable agent ± another second-line agent</td>
<td>18–24 beyond culture conversion</td>
<td>Extended treatment is necessary to lessen the risk of relapse.</td>
</tr>
<tr>
<td>INH, RIF (± SM), and EMB or PZA</td>
<td>FQN, (EMB or PZA if available), injectable agent, plus 2 other second-line agents</td>
<td>24 beyond culture conversion</td>
<td>Consider surgery. Consider high-dose INH treatment if low-level resistance is documented.</td>
</tr>
<tr>
<td>INH, RIF, EMB, PZA (± SM)</td>
<td>FQN, injectable agent, 3 other second-line drugs</td>
<td>24 beyond culture conversion</td>
<td>Consider surgery. Consider high-dose INH treatment if low-level resistance is documented.</td>
</tr>
<tr>
<td>INH, RIF, EMB, PZA, injectables</td>
<td>3 second-line drugs, an injectable agent, plus consider third-line agent</td>
<td>24 beyond culture conversion</td>
<td>Consider surgery. Consider high-dose INH treatment if low-level resistance is documented.</td>
</tr>
<tr>
<td></td>
<td>FQN, 3 other second-line drugs, ± additional third-line agents</td>
<td>24 beyond culture conversion</td>
<td>Surgery should be performed if possible. Consider high-dose INH treatment if low-level resistance is documented.</td>
</tr>
</tbody>
</table>
Resistance to INH and RIF

A regimen consisting of PZA, EMB, and a fluoroquinolone given for a total of 18–24 months beyond culture conversion is recommended. Give an injectable agent for at least the first 6 months of therapy (longer durations may be considered in cases of extensive disease and delayed culture conversion). In patients with extensive cavitary disease, consider addition of 1 or more oral second-line drugs such as cycloserine, ethionamide, or PAS. The use of more than 1 additional oral drug should especially be entertained if there has been prior use of PZA or EMB in a failing regimen.

Resistance to INH, RIF, and EMB

A regimen consisting of PZA, a fluoroquinolone, and 2 second-line oral agents (cycloserine, ethionamide, or PAS) for 24 months beyond culture conversion is recommended. Give an injectable agent for at least the first 6 months of therapy (longer may be considered in cases of extensive disease and delayed culture conversion). In patients with extensive cavitary disease, consider an additional oral drug. Consider surgery if there is focal cavitary disease. (See Role of Surgery in the Treatment of Drug-Resistant Tuberculosis.)

Resistance to INH, RIF, and PZA

A regimen consisting of EMB, a fluoroquinolone, and 2 second-line oral agents (cycloserine, ethionamide, or PAS) for 24 months beyond culture conversion is recommended. Give an injectable agent for at least the first 6 months of therapy. Administer EMB at a higher dose of 25 mg/kg/day until culture conversion has occurred (at which point the dose should be decreased to 15 mg/kg/day). Monitor the patient monthly for evidence of optic neuritis while receiving EMB. In patients with extensive cavitary disease, consider an additional oral drug. Consider surgery if there is focal cavitary disease.

Resistance to INH, RIF, PZA, and EMB

A regimen consisting of a fluoroquinolone and 3 second-line oral agents should be given for 24 months beyond culture conversion. Give an injectable agent for at least 6 months and preferably 12 months, if tolerated. Strongly consider surgery if there is focal cavitary disease.
Resistance to All First-Line Drugs and Fluoroquinolones

The chance of cure diminishes as the patient’s isolate acquires additional resistance.

In this setting, a regimen containing an injectable agent such as an aminoglycoside or polypeptide is critical. Capreomycin can sometimes be used with an aminoglycoside, as they are different classes of drugs. Since their toxicities are additive, close monitoring of hearing, vestibular, and renal function will be required. An injectable agent should be used for at least 12 months. Additionally, at least 3 second-line oral drugs should be used. Third-line agents should also be considered. Some investigators have had success using intravenous imipenem for approximately 6 months, followed by oral amoxicillin/clavulanate potassium. Linezolid and the newer macrolides have also been utilized in this setting when in vitro susceptibility has been documented. Strongly consider surgery if there is localized disease. Treat the patient for 24 months beyond culture conversion.

Resistance to All First-Line Drugs and Injectables

The chance of cure in a patient whose isolate is resistant to so many drugs is unacceptably low. Treat the patient with all available second-line oral agents and perform surgery, whenever possible. Consider additional agents, such as intravenous imipenem or possibly linezolid, particularly if surgery is not an option. Treat these patients for 24 months beyond culture conversion.

NOTE:

Some strains of *M. tuberculosis* demonstrate resistance at low isoniazid concentrations (0.2 µg/ml), but are susceptible at higher concentrations (1.0 µg/ml). In these situations, high-dose (900 mg per day) intermittent therapy may be indicated. Use of isoniazid was associated with better survival rates in patients with the W-strain variety of multidrug-resistant *M. tuberculosis* that was susceptible to higher concentrations of isoniazid.
Guidelines for Management of Multidrug-Resistant TB

A single new drug should never be added to a failing regimen.

When initiating or revising therapy, always attempt to employ at least 3 previously unused drugs to which there is demonstrated in vitro susceptibility. One of these should be an injectable agent.

Sufficient numbers of oral drugs should be started at the onset of therapy to make sure there is an adequate regimen once the injectable agent is discontinued.

Do not limit the regimen to 3 agents if other previously unused drugs that are likely to be active are available.

Patients should receive either hospital-based or domiciliary DOT.

Intermittent therapy should not be used in treating TB caused by multidrug-resistant organisms, except perhaps for injectable agents after an initial period (usually 2–3 months) of daily therapy.

The use of drugs to which there is demonstrated in vitro resistance is not encouraged because there is little or no efficacy of these drugs (assuming the test results are accurate). In the case of low-level resistance to INH, high doses are sometimes given intermittently to complement the regimen.

Resistance to RIF is associated in most cases with cross-resistance to rifabutin and in all cases to rifapentine.

There is no cross-resistance between SM and the other injectable agents: amikacin, kanamycin, and capreomycin; however, cross-resistance between amikacin and kanamycin is nearly universal.

Determination of resistance to PZA is technically problematic and, thus, is not made in many laboratories. However, resistance to PZA is uncommon in the absence of resistance to other first-line drugs. However, PZA mono-resistance in vitro is essentially universal for Mycobacterium bovis isolates.

Role of Surgery in the Treatment of Drug-Resistant TB

Surgery is sometimes necessary to cure patients with MDR-TB. The decision to perform resectional surgery should be made in consultation with an expert in treating drug-resistant TB and should be based on the degree of underlying drug resistance, the presence of focal cavitary disease, and the patient’s ability to tolerate surgery.

Surgery should be considered:

- When cultures continue to be positive beyond 4–6 months of treatment for MDR-TB;
- and/or
- When extensive patterns of drug resistance exist that are unlikely to be cured with chemotherapy alone.

Consider surgery in patients who remain culture-positive despite 4–6 months of chemotherapy with agents that have demonstrated in vitro susceptibility.

At National Jewish Medical and Research Center, the median time to culture conversion was 2 months, with the majority of patients becoming negative by 4 months. If a patient remained culture-positive after 4 months of treatment and had high levels of drug resistance, surgery was recommended.

To maximize the potential success of surgery:

- The disease should be sufficiently localized to allow lobectomy or pneumonectomy, and the remaining lung tissue should be relatively disease-free. In all cases, the patient must represent an acceptable surgical risk and have adequate pulmonary function reserves to tolerate resectional surgery.
- Surgery should be performed by an experienced surgeon and only after several months of chemotherapy have been given. Whenever possible, the surgery should be performed after culture conversion has occurred.
- Even after successful lung resection, the patient should complete a full course of treatment. Surgery does not allow shortening of the treatment course.
Consultation with Experts

**Treatment of TB caused by drug-resistant organisms should be done by or in close consultation with an expert in the management of these difficult cases.**

Second-line regimens often present the patient’s best hope for cure, and thus, inappropriate management of a drug-resistant case can have life-threatening consequences.

The management of drug-resistant TB is often complicated by drug toxicities and long durations of therapy. Even under the best circumstances, successful treatment outcomes for drug-resistant TB are often difficult to achieve compared with drug-susceptible disease, particularly when multidrug resistance is present.

Experts in the management of drug-resistant TB provide consultation and assistance in a number of ways. Experts can:

- Help with the design of the empirical treatment regimen in patients suspected of having drug-resistant disease, and later assist with the design of the definitive treatment regimen when drug resistance has been documented.
- Help with management of toxicities and adjustments of treatment regimens when medications need to be discontinued.
- Help with decisions about when treatment should or can be modified (i.e., discontinuation of injectable drugs).
- Educate the provider about possible drug-related adverse reactions and suggest monitoring strategies.
- Provide guidance in managing contacts to drug-resistant cases.

**EXPERT CONSULTATION**

- Consult with a local or regional expert in the treatment of drug-resistant TB. Ideally, written communication will be shared for clarity of recommendations.
- Have ready access to the expert so decisions can be made in a timely manner.
- Stay in contact with the expert and communicate on a regular basis.
- Consult with expert before making changes in the treatment regimen.
- Consult expert for help in addressing slow response and managing adverse reactions.

Refer to Appendix 1, List of Expert Resources for Drug-Resistant TB.
Summary

Each patient should be assessed for risks of drug resistance: previous TB treatment, exposure to a drug-resistant case, or travel to or immigration from an area of high resistance.

An empiric expanded TB regimen is appropriate for patients at high risk for drug resistance, especially if they are seriously ill or have extensive disease.

An empiric expanded regimen should be customized based on suspected resistance patterns and the patient’s previous TB treatment. In general, an expanded empiric regimen should contain the 4 first-line TB drugs, a fluoroquinolone, and an injectable drug.

Never add a single drug to a failing regimen.

In treatment of MDR-TB, the number of drugs in the regimen depends on the susceptibility pattern, availability of first-line agents, and extent of disease.

The minimum duration of treatment for pulmonary MDR-TB is 18 months beyond culture conversion.


**AMIKACIN**

<table>
<thead>
<tr>
<th><strong>Drug Class</strong></th>
<th>Aminoglycoside</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trade Name</strong></td>
<td>Amikacin/Amikin</td>
</tr>
<tr>
<td><strong>Activity Against TB</strong></td>
<td>Bactericidal; has strong anti-TB activity. Cross-resistance with kanamycin (but not with streptomycin).</td>
</tr>
</tbody>
</table>
| **Dose (all once daily)** | **Adults:** 15 mg/kg/day, 5–7 days per week (maximum dose is generally 1 gram, but a large, muscular person could receive more and should have levels monitored). 15 mg/kg/dose, 2–3 times per week after initial period of daily administration (some experts use up to 25 mg/kg/dose for intermittent therapy; monitor levels).  
  > 59 yrs of age: 10 mg/kg/dose (max 750 mg) 5–7 times per week or 2–3 times per week after initial period.  
  Children: 15–30 mg/kg/day (max 1 gram) 5–7 days per week.  
  15–30 mg/kg/day (max 1 gram) 2–3 days per week after initial period daily.  
  Renal failure/dialysis: 12–15 mg/kg/dose 2–3 times weekly (not daily).  
  Markedly obese individuals should have an adjusted dose due to the decreased distribution of extracellular fluids in adipose tissues. Dosing based on actual weight will give supratherapeutic levels. The suggested adjusted weight is ideal body weight plus 40% of the excess weight.  
  Ideal Body Weight (Men): 50 kg plus 2.3 kg/inch over 5 ft  
  Ideal Body Weight (Women): 45 kg plus 2.3 kg/inch over 5 ft  
  Levels should be followed closely. |
| **Route of Administration** | IV or IM (intraperitoneal and intrathecal have been reported—penetrates meninges only with inflammation). Some report that it is more painful than IM streptomycin. Not absorbed orally. |
| **Preparation** | Colorless solution; 250 mg/ml (2, 3, or 4 ml vials) and 50 mg/ml (2 ml vial). For intravenous solution, mix with D5W or other solutions (in at least 100 ml of fluid for adults or 5 mg/ml for children). |
| **Storage** | Solution is stable at room temperature; diluted solution is stable at room temperature at least 3 weeks or in the refrigerator at least 60 days. |
| **Pharmacokinetics** | For intravenous administration, infuse over 60 minutes for adults; 1–2 hours for children; intramuscular absorption is complete within 4 hours and peak levels are achieved at 1–2 hours. The intravenous peak is 30–60 minutes after the infusion is complete.  
  **Peak levels** for a 15 mg/kg dose are between 35 and 45 mcg/ml.  
  **Peak levels** of 25–35 mcg/ml are acceptable if you anticipate using amikacin for more than 6 months.  
  **Peak levels** of 65–80 mcg/ml are obtained after a 25 mg/kg dose.  
  Trough levels should be < 5 mcg/ml in patients with normal renal function. |
| **Oral Absorption** | There is no significant oral absorption. Intramuscular absorption might be delayed if the same site is used consistently. |
**AMIKACIN [CONTINUED]**

<table>
<thead>
<tr>
<th>CSF Penetration</th>
<th>Penetrates inflamed meninges only.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Special Circumstances</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Use in pregnancy/breastfeeding:</strong></td>
<td>Generally avoided in pregnancy due to congenital deafness seen with streptomycin and kanamycin. Can be used while breastfeeding.</td>
</tr>
<tr>
<td><strong>Use in renal disease:</strong></td>
<td>Use with caution. Levels should be monitored for patients with impaired renal function. Interval adjustment is recommended for renal impairment or dialysis. See Dose – Renal Failure/Dialysis (previous page). The drug is not cleared by hemodialysis; see Chapter 5, Special Situations – Renal Failure.</td>
</tr>
<tr>
<td><strong>Use in hepatic disease:</strong></td>
<td>Drug levels not affected by hepatic disease (except a larger volume of distribution for alcoholic cirrhotic patients with ascites). Presumed to be safe in severe liver disease; however, use with caution—some patients with severe liver disease may progress rapidly to hepato-renal syndrome.</td>
</tr>
<tr>
<td><strong>Diuretic use:</strong></td>
<td>Coadministration of loop diuretics and aminoglycoside antibiotics carries an increased risk of ototoxicity.</td>
</tr>
<tr>
<td><strong>Adverse Reactions</strong></td>
<td>Nephrotoxicity: 9% for general population (may be lower for once-daily use, higher for prolonged use). Appears to be more nephrotoxic than streptomycin.</td>
</tr>
<tr>
<td></td>
<td>Ototoxicity: Increased with advanced age and prolonged use.</td>
</tr>
<tr>
<td></td>
<td>Local pain with IM injections.</td>
</tr>
<tr>
<td></td>
<td>Vestibular toxicity.</td>
</tr>
<tr>
<td></td>
<td>Electrolyte abnormalities, including hypokalemia and hypomagnesemia.</td>
</tr>
<tr>
<td><strong>Contraindications</strong></td>
<td>Pregnancy (congenital deafness seen with streptomycin and kanamycin use in pregnancy).</td>
</tr>
<tr>
<td></td>
<td>Hypersensitivity to aminoglycosides.</td>
</tr>
<tr>
<td></td>
<td>Caution with renal, hepatic, vestibular, or auditory impairment.</td>
</tr>
<tr>
<td><strong>Monitoring</strong></td>
<td>Monitor renal function by documenting creatinine at least monthly (more frequently if renal or hepatic impairment); document creatinine clearance if there is baseline renal impairment or any concerns; document baseline and monthly audiology exam; follow monthly electrolytes, magnesium, and calcium. Question patient regularly about vestibular complaints and perform serial vestibular exams. Document peak and trough levels at baseline if there is any question about renal function. Some experts monitor aminoglycoside levels routinely, regardless of renal function. Monitor levels serially for patients with impaired renal function.</td>
</tr>
<tr>
<td><strong>2004 Wholesale Cost,</strong> 30-day supply, 75-kg person</td>
<td>$333 (TB clinic)</td>
</tr>
<tr>
<td></td>
<td>$251 (community hospital)</td>
</tr>
<tr>
<td><strong>Patient Instructions</strong></td>
<td>Call your doctor right away if you have:</td>
</tr>
<tr>
<td></td>
<td>Problems with hearing, dizziness, or balance</td>
</tr>
<tr>
<td></td>
<td>Rash or swelling of your face</td>
</tr>
<tr>
<td></td>
<td>Trouble breathing</td>
</tr>
<tr>
<td></td>
<td>Decreased urination</td>
</tr>
<tr>
<td></td>
<td>Watery or bloody diarrhea</td>
</tr>
<tr>
<td></td>
<td>Swelling, pain, or redness at your IV site</td>
</tr>
<tr>
<td></td>
<td>Muscle twitching or weakness</td>
</tr>
<tr>
<td>AMOXICILLIN/CLAVULANATE</td>
<td></td>
</tr>
<tr>
<td>-------------------------</td>
<td></td>
</tr>
<tr>
<td><strong>Drug Class</strong></td>
<td>Penicillin/beta-lactam inhibitor</td>
</tr>
<tr>
<td><strong>Trade Name</strong></td>
<td>Augmentin</td>
</tr>
<tr>
<td><strong>Activity Against TB</strong></td>
<td>Conflicting and limited reports, but possible early bactericidal activity.</td>
</tr>
</tbody>
</table>
| **Dose**                | **Adults:** 1000 mg as amoxicillin/250 mg clavulanate 3 times daily.  
                          | **Children:** 80 mg/kg/day divided 3 times daily of the amoxicillin component.  
                          | **Renal failure/dialysis:** For creatinine clearance 10–30 ml/min dose 1000 mg as amoxicillin twice daily; for creatinine clearance < 10 ml/min dose 1000 mg as amoxicillin once daily. Hemodialysis: Single dose every 24 hours and after each dialysis session. |
| **Route of Administration** | Oral. Imipenem/cilastatin should be used if a parenteral beta-lactam drug is desired. |
| **Preparation**         | For thrice daily dosing, as the amoxicillin component: 500 mg amoxicillin/125 mg clavulanate tablets, 125 or 250 mg chew tabs, or 125 or 250 mg/5 ml suspension. |
| **Storage**             | Tablets are stable at room temperature; reconstituted suspension should be stored in the refrigerator and discarded after 10 days. |
| **Pharmacokinetics**   | Time to peak oral concentration is 60–90 minutes.  
                          | **Serum levels** of 7.1 mcg of amoxicillin were reported following a 500 mg (as amoxicillin) dose. |
| **Oral Absorption**     | Good oral absorption, best tolerated when dosed with a small amount of food. |
| **CSF Penetration**     | Approximately 5% of the plasma level reaches the CSF. |
| **Special Circumstances** | **Use in pregnancy/breastfeeding:** Probably safe in pregnancy (no known risk); can be used while breastfeeding.  
                          | **Use in renal disease:** Amoxicillin is renally excreted and the dose should be adjusted for renal failure. It is cleared by dialysis, so should be dosed after dialysis (see above).  
                          | **Use in hepatic disease:** Clavulanate is cleared by the liver, so care should be used when using in patients with liver failure. |
| **Adverse Reactions**   | Diarrhea and abdominal discomfort are most common.  
                          | Hypersensitivity.  
                          | Nausea, vomiting, and rash are also common.  
                          | Rare side effects have been reported in all other organ systems. |
Contraindications: Penicillin allergy; use with caution with cephalosporin allergies.

Monitoring: No specific monitoring is required.

2004 Wholesale Cost: $145 (TB clinic) $184 (community hospital)

Patient Instructions: May be better tolerated if taken with food. Store tablets at room temperature; store suspension in the refrigerator—throw away suspension after 10 days and refill the prescription.

Call your doctor right away if you have:
- Rash or swelling
- Trouble breathing
- Severe diarrhea
<table>
<thead>
<tr>
<th><strong>CAPREOMYCIN</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug Class</strong></td>
</tr>
<tr>
<td><strong>Trade Name</strong></td>
</tr>
<tr>
<td><strong>Activity Against TB</strong></td>
</tr>
</tbody>
</table>
| **Dose (all once daily)** | **Adults:** 15 mg/kg/day, 5–7 days per week (maximum dose is generally 1 gram, but a large, muscular person could receive more and should have levels monitored). 15 mg/kg/dose, 2–3 times per week after initial period of daily administration (some experts use up to 25 mg/kg/dose for intermittent therapy; monitor levels).  
**> 59 yrs of age:** 10 mg/kg/dose (max 750 mg) 5–7 times per week or 2–3 times per week after initial period.  
**Children:** 15–30 mg/kg/day (max 1 gram) 5–7 days per week.  
15–30 mg/kg/day (max 1 gram) 2–3 days per week after initial period daily.  
**Renal failure/dialysis:** 12–15 mg/kg/dose 2–3 times weekly (not daily).  
**Markedly obese individuals** should have an adjusted dose due to the decreased distribution of extracellular fluids in adipose tissues. Dosing based on actual weight will give supratherapeutic levels. The suggested adjusted weight is ideal body weight plus 40% of the excess weight.  
  - Ideal Body Weight (Men): 50 kg plus 2.3 kg/inch over 5 ft  
  - Ideal Body Weight (Women): 45 kg plus 2.3 kg/inch over 5 ft  
  - Levels should be followed closely. |
| **Route of Administration** | IV or IM. |
| **Preparation** | Capreomycin is available in vials of 1 gm for either IM or IV administration. The contents of the vial should be reconstituted with 2 ml or more of NS or sterile water. |
| **Storage** | Package insert indicates that reconstituted capreomycin can be stored in the refrigerator up to 24 hours prior to use. Other data suggest that it may be held for 14 days in the refrigerator or 2 days at room temperature. |
| **Pharmacokinetics** | Intramuscular peak levels are achieved at 2 hours. The intravenous peak is 30–60 minutes after the infusion is complete.  
**Peak levels** for a 15 mg/kg dose are between 35 and 45 mcg/ml.  
**Peak levels** of 25–35 mcg/ml are acceptable if you anticipate using capreomycin for more than 6 months.  
**Peak levels** of 65–80 mcg/ml are obtained after a 25 mg/kg dose.  
Trough levels should be < 5 mcg/ml in patients with normal renal function. |
| **Oral Absorption** | There is no significant oral absorption. Intramuscular absorption might be delayed if the same site is used consistently. |
### CSF Penetration

Capreomycin does not penetrate the meninges.

### Special Circumstances

**Use in pregnancy/breastfeeding:** Generally avoided in pregnancy due to congenital deafness seen with streptomycin and kanamycin. There are case reports of its safe use in pregnancy (unaffected newborns). Can be used while breastfeeding.

**Use in renal disease:** Use with caution. Levels should be monitored for patients with impaired renal function. Interval adjustment is recommended for renal impairment or dialysis. See **Dose – Renal Failure/Dialysis** (previous page) and Chapter 5, **Special Situations – Renal Failure**.

**Use in hepatic disease:** Drug levels not affected by hepatic disease (except a larger volume of distribution for alcoholic cirrhotic patients with ascites). Presumed to be safe in severe liver disease; however, use with caution—some patients with severe liver disease may progress rapidly to hepato-renal syndrome.

### Adverse Reactions

Similar to the aminoglycosides.

- Nephrotoxicity: 20–25% including proteinuria, reduced creatinine clearance, and depletion of potassium and magnesium.
- Ototoxicity: Occurs more often in elderly persons or those with pre-existing renal impairment; vestibular toxicity.
- Local pain with IM injections.
- Electrolyte abnormalities, including hypokalemia, hypocalcemia, and hypomagnesemia.
- Liver function test abnormalities when used with other TB drugs.

### Contraindications

**Hypersensitivity to capreomycin.** Most experts would not use capreomycin if vestibular side effects resulted from aminoglycoside use.

**Generally avoided in pregnancy** due to congenital deafness seen with aminoglycosides. There are case reports of its safe use in pregnancy (unaffected newborns).

### Monitoring

Monitor renal function by documenting creatinine at least monthly (more frequently if renal or hepatic impairment); document creatinine clearance if there is baseline renal impairment or any concerns; document baseline and monthly audiometry exam; follow monthly electrolytes, magnesium, and calcium. Question patient regularly about vestibular complaints and perform serial vestibular exams. Document peak and trough levels at baseline if there is any question about renal function. Some experts monitor capreomycin levels routinely, regardless of renal function. Monitor levels serially for patients with impaired renal function.

### 2004 Wholesale Cost

| 30-day supply, 75-kg person | $137 (TB clinic) | $645 (community hospital) |

### Patient Instructions

**Call your doctor right away if you have:**

- Rash
- Fever or chills
- Bleeding or bruising
- Problems with hearing, dizziness, or balance
- Decreased urination
- Trouble breathing
- Muscle weakness
- Bleeding or a lump where the shot is given
**CLOFAZIMINE**

<table>
<thead>
<tr>
<th><strong>Drug Class</strong></th>
<th>Iminophenazine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trade Name</strong></td>
<td>Lamprene</td>
</tr>
<tr>
<td><strong>Activity Against TB</strong></td>
<td><em>In vitro</em> activity against <em>M. tuberculosis</em> without much <em>in vivo</em> data. Generally reserved for cases with few other options.</td>
</tr>
<tr>
<td><strong>Dose (all once daily)</strong></td>
<td><strong>Adults</strong>: 100–300 mg daily (oral) have been used. A regimen of 300 mg daily for 2 months, followed by 100 mg daily has been used.  <strong>Children</strong>: Limited data, but doses of 1 mg/kg/day have been given.  <strong>Renal failure/dialysis</strong>: No adjustment required.</td>
</tr>
<tr>
<td><strong>Route of Administration</strong></td>
<td>Oral; not available parenterally.</td>
</tr>
<tr>
<td><strong>Preparation</strong></td>
<td>50 and 100 mg capsules.</td>
</tr>
<tr>
<td><strong>Storage</strong></td>
<td>Room temperature.</td>
</tr>
<tr>
<td><strong>Pharmacokinetics</strong></td>
<td>Tissue half-life estimated to be around 70 days.  <strong>Peak levels</strong>: 2–3 hours after a dose are expected to be 0.5–2.0 mcg/ml. Peak concentrations occur at 4–8 hours when given with food.</td>
</tr>
<tr>
<td><strong>Oral Absorption</strong></td>
<td>46–60% absorption after an oral dose.</td>
</tr>
<tr>
<td><strong>CSF Penetration</strong></td>
<td>Limited data are available regarding CNS penetration.</td>
</tr>
<tr>
<td><strong>Special Circumstances</strong></td>
<td><strong>Use in pregnancy/breastfeeding</strong>: Not recommended due to limited data (some reports of normal outcomes, some reports of neonatal deaths). Avoided with breastfeeding due to pigmentation of the infant.  <strong>Use in renal disease</strong>: No dosage adjustment required.  <strong>Use in hepatic disease</strong>: Metabolized by the liver; use caution and/or adjust the dose for severe hepatic insufficiency.</td>
</tr>
<tr>
<td><strong>Adverse Reactions</strong></td>
<td>Pink or red discoloration of skin, conjunctiva, cornea, and body fluids.  Gastrointestinal intolerance.  Photosensitivity.  Other side effects include retinopathy, dry skin, pruritus, rash and severe abdominal symptoms, bleeding, and bowel obstruction.</td>
</tr>
<tr>
<td><strong>Contraindications</strong></td>
<td>Allergy to clofazimine.</td>
</tr>
</tbody>
</table>
### Monitoring
Symptomatic monitoring.

### 2004 Wholesale Cost
| 30-day supply, 75-kg person | $21 (TB clinic)  
|                           | $29 (community hospital) |

As of 11/2004, clofazimine will not be commercially available within the U.S. After the limited remaining stock in pharmacies is exhausted, clinicians should contact the FDA’s Division of Special Pathogen and Immunologic Drug Products (301-827-2127) in order to apply for a single patient Investigational New Drug (IND).

### Patient Instructions
Take with food to avoid stomach upset and improve absorption.

This medicine may discolor your skin and body secretions pink, red, or brownish-black. This should go away after stopping the medicine, but may take a long time. Avoid the sun and use strong sunscreens.

**Call your doctor right away if you have:**
- Bloody or black stools or diarrhea
- Yellowing of your skin or eyes
- Severe nausea, vomiting, abdominal pain, cramps, or burning
- Depression or thoughts of hurting yourself
# CYCLOSERINE

<table>
<thead>
<tr>
<th><strong>Drug Class</strong></th>
<th>Analog of D-alanine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trade Name</strong></td>
<td>Seromycin</td>
</tr>
<tr>
<td><strong>Activity Against TB</strong></td>
<td>Bacteriostatic; inhibits cell wall synthesis.</td>
</tr>
</tbody>
</table>
| **Dose** | **Adults:** 10–15 mg/kg/day usually; 250 mg PO twice a day; can increase to 250 mg PO 3 times a day or 250 mg qam and 500 mg PO qhs if peak levels are kept below 35 mcg/ml.  
**Children:** 10–20 mg/kg/day divided every 12 hours (daily maximum 1 gram).  
**Vitamin B6:** All patients should receive vitamin B6 while taking cycloserine. Adults need 100–300 mg (or 50 mg per 250 mg of cycloserine) and children should receive a dose proportionate to their weight.  
**Renal failure/dialysis:** 250 mg once daily or 500 mg 3 times per week (see Chapter 5, *Special Situations – Renal Failure*); monitor drug levels to keep peak levels < 35 mcg/ml. |
| **Route of Administration** | Oral; not available parenterally. |
| **Preparation** | 250 mg capsule. |
| **Storage** | Room temperature in airtight containers. |
| **Pharmacokinetics** | Peak oral absorption usually occurs by 2 hours (may be up to 4 hours).  
Peak level should be drawn at 2 hours; if delayed absorption is suspected, a level at 6 hours will be helpful. A level at 10 hours will allow for calculation of the half-life. Allow 3–4 days of drug administration before drawing levels due to the long half-life.  
**Peak levels** are expected to be between 20 and 35 mcg/ml. CNS toxicity is associated with levels over 35 mcg/ml, but may occur even at lower levels. |
| **Oral Absorption** | Modestly decreased by food (best to take on an empty stomach); not significantly affected by antacids and orange juice. |
| **CSF Penetration** | Levels approach those in serum. |
| **Special Circumstances** | **Use in pregnancy/breastfeeding:** Not well studied, but no teratogenicity documented. Use if there are not better choices. Can be used while breastfeeding (dose the infant with vitamin B6 if breastfed).  
**Use in renal disease:** Cycloserine is cleared by the kidney and requires dose adjustment for renal failure (see above). Use with caution.  
**Use in hepatic disease:** Not associated with hepatotoxicity.  
**Ethionamide use:** May have increased toxicity when ethionamide also used. |
### Adverse Reactions
CNS toxicity, including inability to concentrate and lethargy. More serious CNS side effects, including seizure, depression, psychosis, and suicidal ideation, usually occur at peak levels > 35 mcg/ml, but may be seen in the normal therapeutic range. Other side effects include peripheral neuropathy and skin changes. Skin problems include lichenoid eruptions and Stevens-Johnson syndrome.

### Contraindications
**Significant CNS disease**, including seizure disorder, psychotic disease, or alcohol abuse.

### Monitoring
Peak levels should be obtained within the first 1–2 weeks of therapy and monitored serially during therapy. The peak level should be kept below 35 mcg/ml. The dose is generally increased if the peak is less than 15 mcg/ml, and the dose is decreased if the peak is above 40 mcg/ml. If the dose is adjusted, repeat the peak level after at least 3–4 days.

### 2004 Wholesale Cost
- 30-day supply, 75-kg person
  - $161 (TB clinic)
  - $297 (community hospital)

### Patient Instructions
Best taken on an empty stomach, with juice, or antacids. If food taken, avoid a large fatty meal. Avoid alcohol.

You must also take a high-dose vitamin B6 supplement while on this drug.

**Call your doctor right away if you have:**
- Seizures
- Shakiness or trouble talking
- Depression or thoughts of hurting yourself
- Anxiety, confusion, or loss of memory
- Personality changes, such as aggressive behavior
- Rash or hives
- Headache
<table>
<thead>
<tr>
<th><strong>Drug Class</strong></th>
<th>Unspecified</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trade Name</strong></td>
<td>Myambutol</td>
</tr>
<tr>
<td><strong>Activity Against TB</strong></td>
<td><strong>Bacteriostatic</strong> inhibitor of cell wall synthesis; bactericidal only at the high end of the dosing range. At doses used over long periods of time, ethambutol protects against further development of resistance.</td>
</tr>
</tbody>
</table>
| **Dose (all once daily)** | **Adults:** 15–25 mg/kg/day (max dose 1.6 grams). Higher doses should be used only during the initial months of therapy. For prolonged therapy, the dose should be closer to 15 mg/kg/day to avoid toxicity.  
**Children:** 15–25 mg/kg/day (max dose 1.6 grams); doses closer to 15 mg/kg/day should be used if the drug is used for more than 2 months.  
**Renal failure/dialysis:** 15–25 mg/kg/dose 3 times weekly (not daily).  
**Obesity:** Ethambutol should be dosed on lean body weight.  
Ideal Body Weight (Men): 50 kg plus 2.3 kg/inch over 5 ft  
Ideal Body Weight (Women): 45 kg plus 2.3 kg/inch over 5 ft |
| **Route of Administration** | Oral; not available parenterally. |
| **Preparation** | 100 mg tablets; scored 400 mg tablets; coated 100 mg tablets; coated, scored 400 mg tablets. |
| **Storage** | Room temperature. |
| **Pharmacokinetics** | Peak oral absorption occurs 2–4 hours after the dose. Draw a peak serum level 2–3 hours after the dose; a second sample 6 hours post-dose could be obtained if there is concern about late absorption and in order to estimate the serum half-life.  
**Peak levels** of 2–6 mcg/ml are expected. |
| **Oral Absorption** | 80% bioavailability independent of food. |
| **CSF Penetration** | Ethambutol penetrates meninges in the presence of inflammation, but does not have demonstrated efficacy in tuberculous meningitis. |
| **Special Circumstances** | **Use in pregnancy/breastfeeding:** Safe in pregnancy; can be used while breastfeeding.  
**Use in renal disease:** Use with caution—cleared by the kidneys; dose adjustment required for renal failure. Increased risk of toxicity with renal failure. If needed for use in the regimen, consider monitoring drug levels; see Chapter 5, *Special Situations – Renal Failure*.  
**Use in hepatic disease:** Safe in liver disease. |
### Adverse Reactions
Retrobulbar neuritis (dose-related—exacerbated during renal failure).

### Contraindications
Pre-existing optic neuritis; visual changes on ethambutol.

### Monitoring
Patients should be counseled to report any visual changes. Baseline and monthly visual acuity and color discrimination monitoring should be performed (particular attention should be given to individuals on higher doses or with renal impairment).

### 2004 Wholesale Cost
| 30-day supply, 75-kg person | $81 (TB clinic) | $161 (community hospital) |

### Patient Instructions
Can be taken with food or on an empty stomach.

**Call your doctor right away if you have:**
- Any problems with your eyes: vision changes, blurring, color blindness, trouble seeing, or eye pain
- Swelling of face
- Rash, hives, or trouble breathing
- Numbness, pain, or tingling in hands or feet
- Joint pain
- Fever or chills
- Nausea, vomiting, poor appetite, or abdominal pain
- Headache or dizziness
### ETHIONAMIDE

<table>
<thead>
<tr>
<th><strong>Drug Class</strong></th>
<th>Derivative of isonicotinic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trade Name</strong></td>
<td>Trecator-SC</td>
</tr>
<tr>
<td><strong>Activity Against TB</strong></td>
<td><strong>Weakly bactericidal;</strong> blocks mycolic acid synthesis.</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td><strong>Adults:</strong> 15–20 mg/kg/day frequently divided (max dose 1 gm per day); usually 500–750 mg per day in 2 divided doses or a single daily dose. <strong>Children:</strong> 15–20 mg/kg/day usually divided into 2–3 doses (max dose 1 gm per day). A single daily dose can sometimes be given at bedtime or with the main meal. Many individuals require gradual ramping up of the dose and treatment for GI upset. <strong>Vitamin B6:</strong> All patients should receive vitamin B6 while taking ethionamide. Adults need 100 mg (more if also taking cycloserine) and children should receive a dose proportionate to their weight. <strong>Renal failure/dialysis:</strong> No change.</td>
</tr>
<tr>
<td><strong>Route of Administration</strong></td>
<td>Oral; not available parenterally.</td>
</tr>
<tr>
<td><strong>Preparation</strong></td>
<td>Coated 250 mg tablet.</td>
</tr>
<tr>
<td><strong>Storage</strong></td>
<td>Store at room temperature.</td>
</tr>
<tr>
<td><strong>Pharmacokinetics</strong></td>
<td>Peak oral absorption is usually reached in 2–3 hours, but delayed absorption is common; peak levels should be drawn at 2 hours. <strong>Peak levels</strong> are typically 1–5 mcg/ml.</td>
</tr>
<tr>
<td><strong>Oral Absorption</strong></td>
<td>Erratic absorption, possibly due to GI disturbances associated with the medication.</td>
</tr>
<tr>
<td><strong>CSF Penetration</strong></td>
<td>Levels approach those in serum; one pediatric study evaluating drug levels in the CSF suggests that ethionamide should be dosed on the high end of the range for patients with meningitis.</td>
</tr>
<tr>
<td><strong>Special Circumstances</strong></td>
<td><strong>Use in pregnancy/breastfeeding:</strong> Generally avoided during pregnancy due to reports of teratogenicity; little data during breastfeeding—an estimated 20% of a usual therapeutic dose is thought to be received (dose the infant with vitamin B6 if breastfed). <strong>Use in renal disease:</strong> No precautions are required for renal impairment. <strong>Use in hepatic disease:</strong> Can cause hepatotoxicity similar to that of INH—use with caution in liver disease.</td>
</tr>
</tbody>
</table>
**ETHIONAMIDE [CONTINUED]**

| Adverse Reactions | Gastrointestinal upset and anorexia: Sometimes intolerable (symptoms are moderated by food or taking at bedtime). Metallic taste. Hepatotoxicity. Endocrine effects: Gynecomastia, hair loss, acne, impotence, menstrual irregularity, and reversible hypothyroidism—treat with thyroid replacement. Neurotoxicity (patients taking ethionamide should take high doses of vitamin B6). Side effects may be exaggerated in patients also taking cycloserine. |
| Contraindications | Sensitivity to ethionamide. |
| Monitoring | Monitor TSH for evidence of hypothyroidism requiring replacement; therapeutic drug monitoring if malabsorption suspected. Monitor liver function tests. |
| 2004 Wholesale Cost | $177 (TB clinic) $296 (community hospital) |
| Patient Instructions | Take this medicine with food. You must also take a high-dose vitamin B6 supplement while on this drug. **Call your doctor right if you have:** Any problems with your eyes: eye pain, blurred vision, color blindness, or trouble seeing Numbness, tingling, or pain in your hands or feet Unusual bruising or bleeding Personality changes such as depression, confusion, or aggression Yellowing of your skin or eyes Dark-colored urine Nausea and vomiting Dizziness Swollen breasts (in men) |
### GAMMA-INTERFERON

Gamma-interferon is an adjunctive agent rather than a true anti-microbial

<table>
<thead>
<tr>
<th><strong>Drug Class</strong></th>
<th>Cytokine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trade Name</strong></td>
<td>Actimmune</td>
</tr>
<tr>
<td><strong>Activity Against TB</strong></td>
<td>Little is known—possibly useful as an adjunctive therapy in patients failing MDR treatment. Interferon-alpha has also been used in the treatment of MDR-TB (see references).</td>
</tr>
</tbody>
</table>
| **Dose**                | **Adults:** Aerosol interferon-gamma 500 mcg (inhaled) 3 times a week or 65 mcg/m² subcutaneously every other day.  
                          | **Children:** No data on inhaled pediatric dosing. Children with chronic granulomatous disease routinely receive 50 mcg/m² subcutaneously 3 times per week. |
| **Route of Administration** | Inhaled or subcutaneously.                                               |
| **Preparation**         | 100 mcg/0.5 ml vial.                                                    |
| **Storage**             | Product should be refrigerated and not frozen or left at room temperature for a total time exceeding 12 hours. Vials should not be shaken. |
| **Pharmacokinetics**    | Data regarding inhaled use not available. Peak levels after subcutaneous administration occur in 4–13 hours; elimination half-lives of 2–8 hours have been reported. |
| **Absorption**          | Data regarding inhaled use not available. Subcutaneous absorption is slow. |
| **CSF Penetration**     | Data limited. Subcutaneous treatment was associated with clinical and radiographic improvement of MDR-TB of the brain. |
| **Special Circumstances** | **Use in pregnancy/breastfeeding:** No human data.  
                          | **Use in renal disease:** No dose adjustments required for renal impairment. Rare reports of renal insufficiency.  
                          | **Use in hepatic disease:** Can cause transaminase elevation; use with caution in liver disease. |
| **Adverse Reactions**   | When given parenterally: Arthralgia, myalgia, fatigue, fever, flu-like symptoms, headache, dizziness, injection site tenderness, rash, nausea/vomiting, or leukopenia/thrombocytopenia. Hypotension and cardiac arrhythmias have been reported. |
### GAMMA-INTERFERON [CONTINUED]

<table>
<thead>
<tr>
<th>Contraindications</th>
<th>Hypersensitivity to interferon-gamma or <em>E. coli</em> derivatives. Multiple sclerosis (associated with exacerbations of relapsing-remitting form).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monitoring</td>
<td>Monitor blood counts, and hepatic and renal functions.</td>
</tr>
<tr>
<td>Cost</td>
<td>$3,400 (subcutaneous) – $12,750 (inhaled) (community hospital)</td>
</tr>
</tbody>
</table>
| **Patient Instructions** | For injectable form: Use a different site for each injection (keep a record if necessary to avoid using the same site continuously). Taking Tylenol 4 hours before an injection may help you feel well. Many people feel achy and have chills with this medicine. Those symptoms get better as you take the medicine. Taking your shot at bedtime may also help you feel your best. **Call your doctor right away if you have:**  
  - Black, tarry stools  
  - Dizziness or trouble walking  
  - Unusual bleeding or bruising  
  - Nausea, vomiting, or diarrhea  
  - Redness or swelling at the injection site  
  - Rash |
<table>
<thead>
<tr>
<th><strong>Drug Class</strong></th>
<th>Fluoroquinolone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trade Name</strong></td>
<td>Tequin</td>
</tr>
<tr>
<td><strong>Activity Against TB</strong></td>
<td><strong>Bactericidal;</strong> has strong anti-TB activity. Inhibits DNA gyrase.</td>
</tr>
</tbody>
</table>
| **Dose (all once daily)** | **Adults:** 400 mg daily (PO or IV).  
**Children:** Limited data, but doses of 10 mg/kg (PO or IV) achieve levels similar to adult doses. (See discussion of fluoroquinolones in children in Chapter 5, *Special Situations – Pediatrics.*)  
**Renal failure/dialysis:** 400 mg load, then 200 mg daily (after dialysis) or 400 mg 3 times weekly after dialysis (see Chapter 5, *Special Situations – Renal Failure*). |
| **Route of Administration** | Oral or IV. |
| **Preparation** | 200 mg or 400 mg coated tablet (PO); 2 mg/ml (100 ml or 200 ml container) or 10 mg/ml solution (20 ml or 40 ml vials) for IV administration. An oral suspension may be available soon at 40 mg/ml. |
| **Storage** | Oral forms, undiluted solution, and pre-mixed solutions are stored at room temperature. Data not yet available on storage of a currently unlicensed oral suspension. |
| **Pharmacokinetics** | For intravenous infusion, infuse over 60 minutes (not bolus).  
**Peak levels** are achieved 1–2 hours after an oral dose.  
**Peak level** after a 400 mg oral dose is around 3.5 mcg/ml; concentration in lung tissue exceeds that of serum. |
| **Oral Absorption** | Good oral absorption: Equivalent to intravenous dosing. Given without regard for food. Should not be administered within 2 hours of ingestion of milk-based products, antacids, or other medications containing divalent cations (iron, magnesium, calcium, zinc, vitamins, didanosine, sucralfate). |
| **CSF Penetration** | CSF levels are about 50% of those in serum in animal models. |
| **Special Circumstances** | **Use in pregnancy/breastfeeding:** Fluoroquinolones are generally avoided in pregnancy AND breastfeeding due to observation of arthropathy in puppy models.  
**Use in renal disease:** Excreted primarily in the kidneys—see above for dose.  
**Use in hepatic disease:** Rarely associated with elevated transaminases. |
### Adverse Reactions
- Gastrointestinal upset.
- Prolongation of Q-T interval.
- Rare tendon rupture.
- Blood glucose disturbance.
- Vaginitis.
- Dizziness and headache.

### Contraindications
- Sensitivity to fluoroquinolones; prolonged QTc syndrome or use of other drugs that cause prolonged QTc; pregnancy.

### Monitoring
- Symptomatic monitoring.

### 2004 Wholesale Cost
- 30-day supply, 75-kg person
  - $299 (TB clinic)
  - $236 (community hospital)

### Patient Instructions
- Avoid caffeinated foods and beverages while taking this medicine; you can take gatifloxacin with food. Drink plenty of beverages. Don’t take milk-based products, antacids (especially aluminum-containing), or multi-vitamins within 2 hours of this medication. This medicine may cause sun sensitivity; use sunscreens.

**Call your doctor and stop the medicine right away if you have:**
- Pain, swelling, or tearing of a tendon (such as the back of your ankle, elbow, etc.), or muscle or joint pain
- Rashes, hives, bruising or blistering, trouble breathing, or tightness in your chest
- Diarrhea
- Yellow skin or eyes
- Anxiety, confusion, or dizziness
<table>
<thead>
<tr>
<th><strong>Drug Class</strong></th>
<th>Beta-lactam – carbapenem</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trade Name</strong></td>
<td>Primaxin</td>
</tr>
<tr>
<td><strong>Activity Against TB</strong></td>
<td><em>In vitro</em> activity—very limited clinical experience.</td>
</tr>
</tbody>
</table>
| **Dose** | **Adults:** 500–1000 mg IV every 6 hours.  
**Children:** Meropenem preferred: 20–40 mg/kg/dose IV every 8 hours, up to 2 grams per dose.  
**Renal failure/dialysis:** Adjustment in dose and interval based on severity of renal failure and body weight—for example, 500 mg every 8 hours for creatinine clearance 20–40 ml/min, 500 mg every 12 hours for creatinine clearance < 20 ml/min. |
| **Route of Administration** | IV or IM (total IM doses are not recommended more than 1.5 gm/day and are therefore not very practical for treatment of drug-resistant TB). No oral preparation. |
| **Preparation** | Lyophilized powder 1:1 ratio of imipenem and cilastatin. Vials are available 250, 500, 750 mg, or 1 gram. |
| **Storage** | Powder should be kept at room temperature; suspended product should be kept no more than 4 hours at room temperature or no more than 24 hours refrigerated. |
| **Pharmacokinetics** | Peak levels occur immediately after IV infusion and 1 hour after IM infusion.  
**Peak levels** of 35–60 mcg/ml occur after infusion of 1 gm. |
| **Oral Absorption** | No oral absorption. |
| **CSF Penetration** | Good CSF penetration, but children with meningitis treated with imipenem had high rates of seizures (meropenem preferred for meningitis and for children). |
| **Special Circumstances** | **Use in pregnancy/breastfeeding:** Little information known regarding use in pregnancy; unknown safety during breastfeeding.  
**Use in renal disease:** Dose adjustment required (see above); dose after dialysis.  
**Use in hepatic disease:** Elevated liver function tests have been noted in up to 6% of patients, but no definite liver damage has been documented. |
| **Adverse Reactions** | Diarrhea, nausea, or vomiting.  
Seizure (noted with CNS infection). |
### IMIPENEM/CILASTATIN [CONTINUED]

<table>
<thead>
<tr>
<th>Contraindications</th>
<th>Carbapenem intolerance; meningitis (use meropenem rather than imipenem).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monitoring</td>
<td>Symptomatic monitoring.</td>
</tr>
<tr>
<td>2004 Wholesale Cost</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$1,864 (TB clinic)</td>
</tr>
<tr>
<td></td>
<td>$3,000 (community hospital)</td>
</tr>
<tr>
<td>Patient Instructions</td>
<td>Make sure your doctor knows if you are also taking ganciclovir or have allergy to penicillins or cephalosporins.</td>
</tr>
<tr>
<td></td>
<td><strong>Call your doctor right away if you have:</strong></td>
</tr>
<tr>
<td></td>
<td>- Fast or irregular heartbeat</td>
</tr>
<tr>
<td></td>
<td>- Seizures</td>
</tr>
<tr>
<td></td>
<td>- Severe diarrhea (watery or bloody)</td>
</tr>
<tr>
<td></td>
<td>- Skin rash, hives, or itching</td>
</tr>
<tr>
<td></td>
<td>- Swelling in the face, throat, or lips</td>
</tr>
<tr>
<td></td>
<td>- Wheezing or trouble breathing</td>
</tr>
<tr>
<td><strong>ISONIAZID</strong></td>
<td></td>
</tr>
<tr>
<td>----------------</td>
<td></td>
</tr>
<tr>
<td><strong>Drug Class</strong></td>
<td>Isonicotinic acid hydrazide (INH)</td>
</tr>
<tr>
<td><strong>Trade Name</strong></td>
<td>INH/Isoniazid/Laniazid/Nydrazid</td>
</tr>
<tr>
<td><strong>Activity Against TB</strong></td>
<td>Bactericidal, especially for rapidly dividing cells. Affects mycolic acid (cell wall) synthesis.</td>
</tr>
</tbody>
</table>
| **Dose** | **Adults:** 5 mg/kg/day (PO or IV) up to 300 mg daily; high-dose INH (900–1500 mg twice or thrice weekly) is sometimes used, especially for patients with low-level INH resistance.  
**Children:** 10–15 mg/kg/day up to 300 mg (PO or IV); 20–30 mg/kg/dose twice or thrice weekly.  
**Renal failure/dialysis:** 300 mg once daily or 900 mg thrice weekly.  
**Vitamin B6** should be used when high-dose INH employed and in patients with diabetes, uremia, HIV infection, alcohol abuse, malnutrition, or peripheral neuropathy. Additionally, pregnant and post-partum women and exclusively breastfeeding infants should receive vitamin B6 while taking INH. |
| **Route of Administration** | Oral, intravenous, or intramuscular. |
| **Preparation** | 50 mg, 100 mg, or 300 mg scored or unscored tablets; 50 mg/5 ml oral suspension in sorbitol; solution for injection 100 mg/ml. |
| **Storage** | Suspension must be kept at room temperature. |
| **Pharmacokinetics** | Peak serum levels are achieved at 1–2 hours after the oral dose.  
Peak levels should be drawn at 1 and 4 hours; if other drug levels are being submitted, collect blood for peak serum levels 2 hours after a dose (and if desired at 6 hours after a dose in order to calculate half-life).  
**Peak level** is expected to be 3–5 mcg/ml after daily dose and 9–15 mcg/ml after twice weekly dose. |
| **Oral Absorption** | Well absorbed orally or intramuscularly; best absorbed on an empty stomach; up to 50% reduction in peak concentration with a fatty meal. |
| **CSF Penetration** | Level equivalent to plasma in inflamed meninges. 20% of levels in plasma in non-inflamed meninges. |
ISONIAZID [CONTINUED]

| Special Circumstances | Use in pregnancy/breastfeeding: Safe during pregnancy; safe during breastfeeding (both baby and mother should receive pyridoxine supplementation). Up to 20% of the infant therapeutic dose will be passed to the baby in the breast milk.  
Use in renal disease: No dose adjustment for renal failure, but pyridoxine supplementation should be used.  
Use in hepatic disease: May exacerbate liver failure. Use with caution.  
Seizure medication: Serum concentrations of phenytoin and carbamazepine may be increased in persons taking INH.  
Inclusion of INH in the regimen of patients with Strain W MDR-TB was also associated with improved outcomes. |
|---|---|
| Adverse Reactions | Hepatitis (age-related).  
Peripheral neuropathy.  
Hypersensitivity reactions.  
Other reactions, including optic neuritis, arthralgias, CNS changes, drug-induced lupus, and diarrhea and cramping with liquid product. |
| Contraindications | Patients with high-level INH resistance who have failed an INH-containing regimen should not receive INH. |
| Monitoring | Clinical monitoring of all patients on INH is essential. Routine laboratory monitoring is not recommended for patients receiving INH monotherapy. For patients receiving multiple TB drugs or other hepatotoxic drugs, or with underlying liver disease (including viral hepatitis), baseline liver function testing is recommended. Follow-up liver function testing is determined by baseline concerns and symptoms of hepatotoxicity. Therapeutic drug monitoring is recommended only for patients suspected of having malabsorption or treatment failure. Monitor levels of phenytoin or carbamazepine in patients receiving those drugs (increases phenytoin levels and risk of hepatotoxicity with carbamazepine), especially when undergoing INH monotherapy. Rifampin tends to lower levels of these drugs and balance effect of INH. |
| 2004 Wholesale Cost | $1 (TB clinic)  
$3 (community hospital) |
| Patient Instructions | Do not take this medication with a large fatty meal. If you have an upset stomach, take the medicine with a snack. If you (or your child) are taking the liquid suspension—do not put it in the refrigerator. Avoid alcohol while taking this medicine. If you need an antacid, don’t take it within an hour of this medicine. Make sure your doctor knows if you are also taking medicine for seizures. Let your doctor know if you get flushing, sweating, or headaches when eating certain cheeses or fish. Ask your doctor if you should be taking a vitamin B6 (pyridoxine supplement).  
Call your doctor right away if you have any of these side effects:  
- Loss of appetite for a few days that is not going away  
- Tiredness, weakness  
- Moderate stomach pain, nausea, or vomiting  
- Numbness or tingling of your fingers or toes  
- Blurred vision, eye pain  
- Yellow skin or eyes or dark-colored urine |
<table>
<thead>
<tr>
<th><strong>Drug Class</strong></th>
<th>Aminoglycoside</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trade Name</strong></td>
<td>Kantrex</td>
</tr>
<tr>
<td><strong>Activity Against TB</strong></td>
<td><strong>Bactericidal</strong>; has strong anti-TB activity. Cross-resistance with amikacin (but not with streptomycin); inhibits protein synthesis.</td>
</tr>
</tbody>
</table>
| **Dose (all once daily)** | **Adults**: 15 mg/kg/day, 5–7 days per week (maximum dose is generally 1 gram, but a large, muscular person could receive more and should have levels monitored).  
15 mg/kg/dose, 2–3 times per week after initial period of daily administration (some experts use up to 25 mg/kg/dose for intermittent therapy; monitor levels).  
> 59 yrs of age: 10 mg/kg/dose (max 750 mg) 5–7 times per week or 2–3 times per week after initial period.  
**Children**: 15–30 mg/kg/day (max 1 gram) 5–7 days per week.  
15–30 mg/kg/day (max 1 gram) 2–3 days per week after initial period daily.  
**Renal failure/dialysis**: 12–15 mg/kg/dose 2–3 times weekly (not daily).  
**Markedly obese individuals** should have an adjusted dose due to the decreased distribution of extracellular fluids in adipose tissues. The suggested adjusted weight is ideal body weight plus 40% of the excess weight.  
Ideal Body Weight (Men): 50 kg plus 2.3 kg/inch over 5 ft  
Ideal Body Weight (Women): 45 kg plus 2.3 kg/inch over 5 ft  
Levels should be followed closely. |
| **Route of Administration** | Intravenous or intramuscular; not absorbed orally. |
| **Preparation** | Clear colorless solution stable at room temperature; 250 mg/ml in vials of 500 mg or 1 gram; 1 gram in 3 ml vial; or 75 mg/vial for infants. Can be mixed with D5W or normal saline for intravenous infusion. Adult doses should be mixed in at least 100 ml of fluid, and pediatric doses should be mixed to a concentration of at least 5 mg/ml. |
| **Storage** | Store in the refrigerator. |
| **Pharmacokinetics** | For intravenous administration, infuse over 60 minutes for adults; 1–2 hours for children; intramuscular absorption is complete within 4 hours and peak levels are achieved at 1–2 hours. The intravenous peak is 30–60 minutes after the infusion is complete.  
**Peak levels** for a 15 mg/kg dose are between 35 and 45 mcg/ml.  
**Peak levels** of 25–35 mcg/ml are acceptable if you anticipate using kanamycin for more than 6 months.  
**Peak levels** of 65–80 mcg/ml are obtained after a 25 mg/kg dose.  
Trough levels should be < 5 mcg/ml in patients with normal renal function. |
<p>| <strong>Oral Absorption</strong> | Not absorbed orally; 40–80% of the dose is absorbed intramuscularly. |</p>
<table>
<thead>
<tr>
<th>Special Circumstances</th>
<th>Use in pregnancy/breastfeeding: Generally avoided in pregnancy due to documented congenital deafness. Can be used while breastfeeding.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Use in renal disease:</strong> Use with caution. Levels should be monitored for patients with impaired renal function. Interval adjustment is recommended for renal impairment or dialysis. See Dose – Renal Failure/Dialysis (previous page). The drug is not cleared by hemodialysis; see Chapter 5, Special Situations – Renal Failure.</td>
</tr>
<tr>
<td></td>
<td><strong>Use in hepatic disease:</strong> Drug levels not affected by hepatic disease (except a larger volume of distribution for alcoholic cirrhotic patients with ascites). Presumed to be safe in severe liver disease; however, use with caution—some patients with severe liver disease may progress rapidly to hepato-renal syndrome.</td>
</tr>
<tr>
<td></td>
<td><strong>Diuretic use:</strong> Coadministration of loop diuretics and aminoglycoside antibiotics carries an increased risk of ototoxicity.</td>
</tr>
<tr>
<td>Adverse Reactions</td>
<td>Nephrotoxicity: Appears to be more nephrotoxic than streptomycin. Ototoxicity and vestibular toxicity: Increased with advanced age and prolonged use; appears to occur slightly more commonly with kanamycin than with streptomycin and at about the same frequency as amikacin. Kanamycin seems to have slightly less vestibular toxicity.</td>
</tr>
<tr>
<td>Contraindications</td>
<td><strong>Pregnancy</strong> (congenital deafness seen with streptomycin and kanamycin use in pregnancy); <strong>hypersensitivity to aminoglycosides</strong>; caution with renal, vestibular, or auditory impairment; patients with intestinal obstructions.</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Monitor renal function by documenting creatinine at least monthly (more frequently if renal or hepatic impairment); document creatinine clearance if there is baseline renal impairment or any concerns; document baseline and monthly audiology exam. Question patient regularly about vestibular complaints and perform serial vestibular exams. Document peak and trough levels at baseline if there is any question about renal function. Some experts monitor aminoglycoside levels routinely, regardless of renal function. Monitor levels serially for patients with impaired renal function.</td>
</tr>
<tr>
<td>2004 Wholesale Cost</td>
<td>$81 (TB clinic) $89 (community hospital)</td>
</tr>
<tr>
<td>Patient Instructions</td>
<td><strong>Call your doctor right away if you have:</strong></td>
</tr>
<tr>
<td></td>
<td>- Problems with hearing, dizziness, or balance</td>
</tr>
<tr>
<td></td>
<td>- Rash or swelling of your face</td>
</tr>
<tr>
<td></td>
<td>- Trouble breathing</td>
</tr>
<tr>
<td></td>
<td>- Decreased urination</td>
</tr>
<tr>
<td></td>
<td>- Watery or bloody diarrhea</td>
</tr>
<tr>
<td></td>
<td>- Swelling, pain, or redness at your IV site</td>
</tr>
<tr>
<td></td>
<td>- Muscle twitching or weakness</td>
</tr>
<tr>
<td><strong>Drug Class</strong></td>
<td>Fluoroquinolone</td>
</tr>
<tr>
<td>----------------</td>
<td>-----------------</td>
</tr>
<tr>
<td><strong>Trade Name</strong></td>
<td>Levaquin</td>
</tr>
<tr>
<td><strong>Activity Against TB</strong></td>
<td><strong>Bactericidal</strong>; has strong anti-TB activity. Cross-resistance with other fluoroquinolones, but data suggest greater activity than ciprofloxacin or ofloxacin. Inhibits DNA gyrase.</td>
</tr>
<tr>
<td><strong>Dose (all once daily)</strong></td>
<td>Adults: For treatment of active TB: 500–1000 mg/day (PO or IV). Usually at least 750 mg/day is used and the dose can be increased to 1000 mg if tolerated. For contacts to MDR-TB: 500 mg/day if &lt; 45.5 kg (100 lbs); 750 mg/day if &gt; 45.5 kg (100 lbs). Children: 10 mg/kg/day for older children and 15–20 mg/kg/day for younger children (PO or IV) based on limited data and extrapolation from adult data (see discussion of fluoroquinolones in children in Chapter 5, <em>Special Situations – Pediatrics</em>). <strong>Renal failure/dialysis:</strong> 750–1000 mg/dose 3 times weekly (not daily).</td>
</tr>
<tr>
<td><strong>Route of Administration</strong></td>
<td>Oral or intravenous.</td>
</tr>
<tr>
<td><strong>Preparation</strong></td>
<td>Coated tablets (250 mg, 500 mg, 750 mg); solution for injection 25 mg/ml; 250 mg in 50 ml container; 500 mg in 100 ml container; 750 mg in 150 ml container. Oral suspension 25 mg/ml.</td>
</tr>
<tr>
<td><strong>Storage</strong></td>
<td>Oral forms, undiluted solution, and pre-mixed solutions are stored at room temperature. Once diluted, the solution can be kept at room temperature for 3 days, in the refrigerator for 2 weeks, or frozen for 6 months.</td>
</tr>
<tr>
<td><strong>Pharmacokinetics</strong></td>
<td>Peak oral absorption occurs at 1–2 hours. Peak levels should be drawn at 2 hours after the dose, and a trough 6–10 hours after the dose allows for calculation of the half-life. <strong>Peak levels</strong> of 8–12 mcg/ml are expected.</td>
</tr>
<tr>
<td><strong>Oral Absorption</strong></td>
<td>Excellent oral absorption. Should not be administered within 2 hours of ingestion of milk-based products, antacids, or other medications containing divalent cations (iron, magnesium, calcium, zinc, vitamins, didanosine, sucralfate).</td>
</tr>
<tr>
<td><strong>CSF Penetration</strong></td>
<td>Levels are 16–20% of those in serum.</td>
</tr>
<tr>
<td><strong>Special Circumstances</strong></td>
<td><strong>Use in pregnancy/breastfeeding:</strong> Fluoroquinolones are generally avoided in pregnancy AND breastfeeding due to observation of arthropathy in puppy models. <strong>Use in renal disease:</strong> Dosage adjustment is recommended if creatinine clearance is &lt; 50 ml/min. The drug is not cleared by hemodialysis; supplemental doses after dialysis are not necessary. (See Chapter 5, <em>Special Situations – Renal Failure.</em>). <strong>Use in hepatic disease:</strong> Drug levels not affected by hepatic disease. Presumed to be safe in severe liver disease.</td>
</tr>
</tbody>
</table>
### LEVOFLOXACIN (CONTINUED)

| **Adverse Reactions** | Nausea and bloating.  
|                       | Headache, dizziness, insomnia, or tremulousness.  
|                       | **Rare** tendon rupture, arthralgias (can usually be treated symptomatically).  
|                       | QTc prolongation.  |
| **Contraindications** | Pregnancy; hypersensitivity to fluoroquinolones; prolonged QTc.  |
| **Monitoring**        | Side effect monitoring, but no specific laboratory monitoring required.  |
| **2004 Wholesale Cost** | $147 (TB clinic)  
| 30-day supply, 75-kg person | $471 (community hospital)  |
| **Patient Instructions** | Avoid caffeinated foods and beverages while taking this medicine; you can take levofoxacin with food. Drink plenty of beverages. Don’t take milk-based products, antacids (especially aluminum-containing), or multi-vitamins within 2 hours of this medication. This medicine may cause sun sensitivity; use sunscreens.  
**Call your doctor and stop the medicine right away if you have:**  
- Pain, swelling, or tearing of a tendon (such as the back of your ankle, elbow, etc.), or muscle or joint pain  
- Rashes, hives, bruising or blistering, trouble breathing, or tightness in your chest  
- Diarrhea  
- Yellow skin or eyes  
- Anxiety, confusion, or dizziness  |
<table>
<thead>
<tr>
<th><strong>Drug Class</strong></th>
<th>Oxazolidinones</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trade Name</strong></td>
<td>Zyvox</td>
</tr>
<tr>
<td><strong>Activity Against TB</strong></td>
<td>Has <em>in vitro</em> bactericidal activity—little clinical experience; inhibits protein synthesis.</td>
</tr>
</tbody>
</table>
| **Dose**             | **Adults:** 600 mg every 12 hours or 600 mg once daily.  
|                      | **Children:** 10 mg/kg/dose every 8 hours.  
|                      | **Renal failure/dialysis:** No dose adjustment required. |
| **Route of Administration** | Oral or intravenous.                              |
| **Preparation**      | Coated tablets: 400 and 600 mg; intravenous solution: 2 mg/ml; 100, 200, or 300 mg bags. Oral powder for suspension: 100 mg/5 ml 240 ml bottle. |
| **Storage**          | Store tablet at room temperature. Reconstituted oral suspension may be stored at room temperature for 21 days. Parenteral preparation should be stored at room temperature (protect from light and do not freeze). |
| **Pharmacokinetics** | Intravenous doses are administered over 30–120 minutes.  
|                      | Peak levels are achieved 1–1.5 hours after an oral dose and \( \frac{1}{2} \) hour after an IV dose.  
|                      | Peak levels should be drawn 2 hours after an oral dose and a trough level should also be obtained.  
|                      | **Peak levels** are expected to be 12–24 mcg/ml with a trough of 2–9 mcg/ml. |
| **Oral Absorption**  | Nearly complete oral absorption.                    |
| **CSF Penetration**  | CSF levels are about \( \frac{1}{3} \) of those in serum in animal models and has been used to treat meningitis in humans. |
| **Special Circumstances** | **Use in pregnancy/breastfeeding:** Not recommended during pregnancy or breastfeeding due to limited data.  
|                      | **Use in renal disease:** No dose adjustment is recommended, but metabolites may accumulate.  
|                      | **Use in hepatic disease:** Rarely associated with increased transaminases. |
| **Adverse Reactions**| Myelosuppression.  
|                      | Diarrhea and nausea.  
|                      | Optic and peripheral neuropathy (rare). |
**LINEZOLID**

<table>
<thead>
<tr>
<th>Contraindications</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypersensitivity to oxazolidinones.</strong></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Monitoring</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Monitor CBC weekly during the initial period, then monthly, and then as needed based on symptoms; there is little clinical experience with prolonged use.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2004 Wholesale Cost</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>30-day supply, 75-kg person</strong></td>
<td></td>
</tr>
<tr>
<td>$2,183 for twice daily dose (TB clinic)</td>
<td></td>
</tr>
<tr>
<td>$3,047 for twice daily dose (community hospital)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient Instructions</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>This medicine may be taken with or without food. Try taking it with food if it bothers your stomach. Avoid food and drinks that contain tyramine: aged cheeses, dried meats, sauerkraut, soy sauce, tap beers, and red wines. Make sure your doctor knows if you’re taking medicines for colds, congestion, or depression.</td>
<td></td>
</tr>
</tbody>
</table>

**Call your doctor right away if you have any of these side effects:**

- Black, tarry stools or severe diarrhea
- Unusual bleeding or bruising
- Unusual tiredness or weakness
- Headache, nausea, or vomiting
**MOXIFLOXACIN**

<table>
<thead>
<tr>
<th><strong>Drug Class</strong></th>
<th>Fluoroquinolone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trade Name</strong></td>
<td>Avelox</td>
</tr>
<tr>
<td><strong>Activity Against TB</strong></td>
<td>Bactericidal; inhibits DNA gyrase; cross-resistance with other fluoroquinolones, but may be more active based on <em>in vitro</em> data.</td>
</tr>
</tbody>
</table>
| **Dose (all once daily)** | **Adults:** 400 mg daily (PO or IV).  
**Children:** No established dose (see discussion of fluoroquinolones in children in Chapter 5, *Special Situations – Pediatrics*).  
**Renal failure/dialysis:** No dose adjustment required. |
| **Route of Administration** | Oral or IV. |
| **Preparation** | Tablets (400 mg); aqueous solution (400 mg/250 ml) for IV injection. |
| **Storage** | Store oral and IV products at room temperature (do not refrigerate). |
| **Pharmacokinetics** | Peak absorption after an oral dose is noted in 1–3 hours.  
Peak levels should be drawn at 2 hours.  
**Peak levels** are expected to be 2.5 mcg/ml up to 4.5 mcg/ml after a 10-day course.  
Trough levels of 0.3–0.5 mcg/ml were noted. |
| **Oral Absorption** | Good oral absorption (90% bioavailable). Should not be administered within 2 hours of ingestion of milk-based products, antacids, or other medications containing divalent cations (iron, magnesium, calcium, zinc, vitamins, didanosine, sucralfate). |
| **CSF Penetration** | Good penetration in animal model studies. |
| **Special Circumstances** | **Use in pregnancy/breastfeeding:** Fluoroquinolones are generally avoided in pregnancy AND breastfeeding due to observation of arthropathy in puppy models.  
**Use in renal disease:** Excretion unchanged in the face of renal failure; no data on effect of dialysis.  
**Use in hepatic disease:** Rarely associated with hepatotoxicity; use with caution. No dose adjustment required for mild or moderate liver disease. |
| **Adverse Reactions** | Nausea and diarrhea.  
Headache and dizziness.  
**Rare** tendon rupture; arthralgias.  
Rare hepatotoxicity.  
QTc prolongation. |
### MOXIFLOXACIN (CONTINUED)

<table>
<thead>
<tr>
<th>Contraindications</th>
<th>Fluoroquinolone intolerance, pregnancy, prolonged QTc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monitoring</td>
<td>Symptomatic monitoring.</td>
</tr>
<tr>
<td>2004 Wholesale Cost</td>
<td>$306 (TB clinic)</td>
</tr>
<tr>
<td></td>
<td>$229 (community hospital)</td>
</tr>
<tr>
<td>Patient Instructions</td>
<td>Keep moxifloxacin at room temperature. Moxifloxacin can be taken with food, but do not take milk-based products, antacids (especially aluminum-containing), vitamin supplements, or sucralfate within 2 hours of this medication.</td>
</tr>
</tbody>
</table>

**Call your doctor and stop the medicine right away if you have:**

- Pain, swelling, or tearing of a tendon (such as the back of your ankle, elbow, etc.), or muscle or joint pain
- Rashes, hives, bruising or blistering, trouble breathing, or tightness in your chest
- Diarrhea
- Yellow skin or eyes
- Anxiety, confusion, or dizziness
<table>
<thead>
<tr>
<th><strong>Drug Class</strong></th>
<th>Salicylic acid – anti-folate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trade Name</strong></td>
<td>PASER</td>
</tr>
<tr>
<td><strong>Activity Against TB</strong></td>
<td>Bacteriostatic.</td>
</tr>
</tbody>
</table>
| **Dose** | Adults: 8–12 grams per day divided 2–3 times per day.  
Children: 200–300 mg/kg/day divided 2–4 times per day.  
Renal failure/dialysis: No change. |
| **Route of Administration** | Oral; not available parenterally in the U.S. |
| **Preparation** | 4 grams per packet. |
| **Storage** | Packets should be kept in the refrigerator or freezer. |
| **Pharmacokinetics** | Delayed peak concentration with the PASER formulation (the only product available in the U.S.) due to its enteric coating and sustained release (1–6 hours).  
Peak levels should be collected at 6 hours.  
**Peak levels** are expected to be 20–60 mcg/ml. |
| **Oral Absorption** | Incomplete absorption (usually 60–65%)—sometimes requires increased doses to achieve therapeutic levels. |
| **CSF Penetration** | Poorly penetrates the meninges (somewhat better with inflammation). |
| **Special Circumstances** | **Use in pregnancy/breastfeeding:** Not studied, but no teratogenicity known.  
There is little data regarding breastfeeding. In one patient, the milk concentration was 1 mcg/ml compared to a serum level of 70 mcg/ml.  
**Use in renal disease:** Inactive metabolite is cleared by the kidneys.  
The package insert says to avoid with severe renal failure. Other authorities believe it can be used with caution (no toxicity of metabolite known). See Chapter 5, Special Situations – Renal Failure.  
**Use in hepatic disease:** Use with caution; 0.5% incidence of hepatotoxicity. |
| **Adverse Reactions** | Gastrointestinal distress (less with the PASER formulation than with older preparations).  
Rare hepatotoxicity and coagulopathy.  
Reversible hypothyroidism (increased risk with concomitant use of ethionamide)—treat with thyroid replacement. |
**Contraindications**

Allergy to aspirin.

**Monitoring**

Monitor TSH, electrolytes, blood counts, and liver function tests.

**2004 Wholesale Cost**

| 30-day supply, 75-kg person | $265 (TB clinic) | $270 (community hospital) |

**Patient Instructions**

Keep the product in the refrigerator or freezer. Sprinkle granules over applesauce or yogurt or swirl in acidic juices (tomato, grape, grapefruit, cranberry, apple, or orange). Do not chew the granules. Take with food if desired. Don't use the packet if swollen or if the granules are discolored. Gastrointestinal discomfort and diarrhea usually improve over time. The shells of the granules may be seen in the stool.

**Call your doctor right away if you have any of these side effects:**

- Skin rash, severe itching, or hives
- Severe abdominal pain, nausea, or vomiting
- Unusual tiredness or loss of appetite
- Black stools or bleeding
<table>
<thead>
<tr>
<th><strong>Drug Class</strong></th>
<th>Synthetic derivative of nicotinamide</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trade Name</strong></td>
<td>Pyrazinamide</td>
</tr>
<tr>
<td><strong>Activity Against TB</strong></td>
<td><strong>Bactericidal</strong> for semi-dormant <em>M. tuberculosis</em>. Mechanism unclear.</td>
</tr>
</tbody>
</table>
| **Dose (all once daily)** | **Adults:** 20–25 mg/kg/day (max dose 2 grams).  
**Children:** 15–30 mg/kg (max dose 2 grams); some literature suggests less complete absorption in children; the American Academy of Pediatrics suggests 20–40 mg/kg/dose.  
**Renal failure/dialysis:** 25–35 mg/kg/dose 3 times per week (not daily).  
**Obesity:** Pyrazinamide should be dosed on lean body weight.  
   - Ideal Body Weight (Men): 50 kg plus 2.3 kg/inch over 5 ft  
   - Ideal Body Weight (Women): 45 kg plus 2.3 kg/inch over 5 ft |
| **Route of Administration** | Oral; not available parenterally. |
| **Preparation** | 500 mg scored or unscored tablet. |
| **Storage** | Store the tablets at room temperature. |
| **Pharmacokinetics** | Peak concentration is 1–4 hours after an oral dose.  
Peak levels should be drawn at 2 and 6 hours for therapeutic drug monitoring.  
**Peak levels** of 20–40 mcg/ml are expected after a daily dose. Pyrazinamide can be found in the urine all day long and can be an indication of adherence to therapy. |
| **Oral Absorption** | Well absorbed from the GI tract. |
| **CSF Penetration** | Levels equivalent to serum. |
| **Special Circumstances** | **Use in pregnancy/breastfeeding:** In the U.S., pyrazinamide is avoided in pregnancy for drug-susceptible disease due to lack of data regarding teratogenicity, but should be used for drug-resistant TB when the isolate is sensitive to pyrazinamide (no known teratogenicity). Can be used while breastfeeding.  
**Use in renal disease:** Cleared by the kidneys; dose 3 times a week and after dialysis.  
**Use in hepatic disease:** Use with caution; pyrazinamide is associated with hepatotoxicity in about 1% of patients. The hepatotoxicity can be quite severe and continue to worsen even after medication is stopped. |
### PYRAZINAMIDE (CONTINUED)

| **Adverse Reactions**       | Gout (hyperuricemia) and arthralgias.  
|                            | Hepatotoxicity.  
|                            | Rash.  
|                            | Photosensitivity.  
|                            | Gastrointestinal upset.  
| **Contraindications**       | **Allergy to pyrazinamide; severe gout.**  
| **Monitoring**              | Monitor transaminases; check uric acid if the patient develops arthralgias.  
| **2004 Wholesale Cost**    |  
| 30-day supply, 75-kg person | $49 (TB clinic)  
|                            | $77 (community hospital)  
| **Patient Instructions**   | May be taken with or without food; this medicine may cause a rash after sun exposure: limit your sun exposure.  
|                            | **Call your doctor right away if you have any of these side effects:**  
|                            | ■ Skin rash, severe itching, or hives  
|                            | ■ Pain or swelling in the joints  
|                            | ■ Yellowing of the skin or eyes or dark urine  
|                            | ■ Nausea or vomiting  
|                            | ■ Unusual tiredness or loss of appetite  

<table>
<thead>
<tr>
<th><strong>Drug Class</strong></th>
<th>Rifamycin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trade Name</strong></td>
<td>Mycobutin</td>
</tr>
<tr>
<td><strong>Activity Against TB</strong></td>
<td>Bactericidal; same mechanism of activity as rifampin (inhibits RNA polymerase). Less than 20% of rifampin-resistant strains are susceptible to rifabutin.</td>
</tr>
</tbody>
</table>
| **Dose (all once daily)** | Adults: 5 mg/kg/dose (max dose 300 mg, though doses up to 450 mg are sometimes used). Dose adjustments sometimes required when dosing with interacting drugs.  
Children: The pediatric dose is not established, but doses of 5–10 mg/kg/day have been used (higher doses have been recommended for children < 1 year of age). Caution should be used in very young children in whom visual changes might not be obvious.  
Renal failure/dialysis: Reduce dose by 50% for creatinine clearance less than 30 ml/minute.  
Concomitant medications: Dosage adjustment may be required, particularly with antiretroviral therapy use. |
| **Route of Administration** | Oral; not available parenterally. |
| **Preparation** | 150 mg capsule. |
| **Storage** | Capsules should be kept at room temperature. |
| **Pharmacokinetics** | Peak concentration is reached 3–4 hours after a dose.  
Peak serum level should be drawn 3 hours after the dose; a second sample 10 hours post-dose is desirable in order to estimate the serum half-life.  
Peak level should be between 0.3 and 0.9 mcg/ml. Dose adjustments should be considered for patients with levels < 0.2 or > 1.0 mcg/ml. Rifabutin concentrates in tissues: in lung tissues, levels reach 10–20 times of those in serum. |
| **Oral Absorption** | Well absorbed from the GI tract. |
| **CSF Penetration** | Penetrates inflamed meninges. |
| **Special Circumstances** | Use in pregnancy/breastfeeding: Insufficient data in pregnancy. Unknown effects from breastfeeding.  
Use in renal disease: Used without dose adjustment in renal failure.  
Use in hepatic disease: Use with caution and additional monitoring in liver disease. Dose adjustments necessary for drug interactions—especially HIV drugs. |
### RIFABUTIN [CONTINUED]

| **Adverse Reactions** | Leukopenia (dose-dependent); thrombocytopenia.  
|                       | Rashes and skin discoloration (bronzing or pseudojaundice).  
|                       | Anterior uveitis and other eye toxicities.  
|                       | Hepatotoxicity similar to that of rifampin.  
|                       | Drug interactions with many other drugs—but only 40% of those seen with rifampin.  
|                       | Rifabutin levels may be affected by other drugs.  
|                       | Arthralgias.  |

<table>
<thead>
<tr>
<th><strong>Contraindications</strong></th>
<th><strong>Rifamycin hypersensitivity.</strong> Should not be used for patients with MDR-TB unless susceptibility to rifabutin documented.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th><strong>Monitoring</strong></th>
<th>Increased liver function monitoring; monitor drug levels of interacting medications; blood counts and vision screening.</th>
</tr>
</thead>
</table>

| **2004 Wholesale Cost** | $153 (TB clinic)  
|                       | $337 (community hospital)  |

| **Patient Instructions** | May be taken with or without food; if it bothers your stomach, try taking it with food. It is normal for your urine, tears, and other secretions to turn a brownish-orange color when taking this medicine. Sometimes skin even becomes discolored. Soft contact lenses may become discolored while you are on this medicine. Make sure your doctor knows all the medicines you take, as there are many drugs that interfere with this one. Avoid the use of oral hormone-based birth control methods because rifabutin may decrease their effectiveness.  
|                          | **Call your doctor right away if you have any of these side effects:**  
|                          | ■ Any eye pain, change in vision, or sensitivity to light  
|                          | ■ Fever, chills, or sore throat  
|                          | ■ Pain or swelling in the joints  
|                          | ■ Yellowing of the skin or eyes or dark urine  
|                          | ■ Nausea or vomiting  
|                          | ■ Unusual tiredness or loss of appetite  |


# Rifampin (Rifampicin)

<table>
<thead>
<tr>
<th><strong>Drug Class</strong></th>
<th>Rifamycin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trade Name</strong></td>
<td>Rifadin</td>
</tr>
<tr>
<td><strong>Activity Against TB</strong></td>
<td>Bactericidal; inhibits protein synthesis; cross-resistance with other rifamycins.</td>
</tr>
</tbody>
</table>
| **Dose (all once daily)** | **Adults:** 10 mg/kg/dose up to 600 mg (PO or IV).  
**Children:** 10–20 mg/kg/dose up to 600 mg (PO or IV).  
**Renal failure/dialysis:** No adjustment required.  
**Concomitant medications:** Dosage adjustment may be required, particularly with antiretroviral therapy use. |
| **Route of Administration** | Oral or intravenous. |
| **Preparation** | 150 and 300 mg capsules; lyophilized powder for injection: 600 mg/vial; contents of capsules can be mixed with liquid or semi-soft vehicles. Extemporaneously prepared oral solutions have unproven homogeneity and shelf life. Immediate administration of the dose after mixing capsular contents in a vehicle is ideal. |
| **Storage** | Capsules and powder should be kept at room temperature; powder suspended in saline is stable for 24 hours; powder suspended in dextrose solutions is stable for 4 hours. |
| **Pharmacokinetics** | Peak time to concentration after an oral dose is 1–4 hours.  
Peak levels should be obtained 2 hours after a dose, and if delayed absorption is considered, a level at 6 hours should also be collected.  
**Peak levels** of 8–24 mcg/ml are expected. Dose increase should be strongly considered for low levels (but not for delayed absorption), as rifampin exhibits a dose response in treatment of TB. |
| **Oral Absorption** | Usually rapid absorption, may be delayed or decreased by high-fat meals. |
| **CSF Penetration** | Rifampin achieves only 10–20% of serum levels in CSF (may be better in the face of inflamed meninges), but this may still be an important contribution to the regimen. |
| **Special Circumstances** | **Use in pregnancy/breastfeeding:** Recommended for use in pregnancy; can be used while breastfeeding.  
**Use in renal disease:** Can be used without dose adjustment.  
**Use in hepatic disease:** Use with caution, can be associated with hepatotoxicity. |
| Adverse Reactions | Many drug interactions.  
Orange staining of body fluids.  
Rash and pruritus.  
GI upset, flu-like syndrome (usually only with intermittent administration).  
Hepatotoxicity.  
Hematologic abnormalities (thrombocytopenia, hemolytic anemia). |
| Contraindications | Rifamycin allergy; due to drug interactions, may be contraindicated with concurrent use of certain drugs. |
| Monitoring | Liver function monitoring if appropriate (if given with other hepatotoxic medications or if there are symptoms of hepatotoxicity); monitor drug levels of interacting medications. |
| 2004 Wholesale Cost | $43 (TB clinic)  
$80 (community hospital) |
| Patient Instructions | Best taken without food; if it bothers your stomach, try taking it with a small amount of food. It is normal for your urine, tears, and other secretions to turn an orange color when taking this medicine. Soft contact lenses may become discolored while you are on this medicine. Make sure your doctor knows all the medicines you take because many drugs can interfere with this one. Avoid the use of oral hormone-based birth control methods because rifampin may decrease their effectiveness.  
Call your doctor right away if you have any of these side effects:  
■ Unusual tiredness or loss of appetite  
■ Severe abdominal upset  
■ Fever or chills |
**STREPTOMYCIN**

<table>
<thead>
<tr>
<th><strong>Drug Class</strong></th>
<th>Aminoglycoside</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trade Name</strong></td>
<td>Streptomycin sulfate</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Activity Against TB</strong></th>
<th>Bactericidal; inhibits protein synthesis; no significant cross-resistance with other aminoglycosides.</th>
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</table>

<table>
<thead>
<tr>
<th><strong>Dose</strong></th>
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<tbody>
<tr>
<td><strong>Adults:</strong></td>
<td>15 mg/kg/day, 5–7 days per week (maximum dose is generally 1 gram, but a large, muscular person could receive more and should have levels monitored).</td>
</tr>
<tr>
<td></td>
<td>15 mg/kg/dose, 2–3 times per week after initial period of daily administration (some experts use up to 25 mg/kg/dose for intermittent therapy; monitor levels).</td>
</tr>
<tr>
<td></td>
<td>&gt; 59 yrs of age: 10 mg/kg/dose (max 750 mg) 5–7 times per week or 2–3 times per week after initial period.</td>
</tr>
<tr>
<td><strong>Children:</strong></td>
<td>20–40 mg/kg/day (max 1 gram) 5–7 days per week.</td>
</tr>
<tr>
<td></td>
<td>20–40 mg/kg/day (max 1 gram) 2–3 days per week after initial period daily.</td>
</tr>
<tr>
<td><strong>Renal failure/dialysis:</strong></td>
<td>12–15 mg/kg/dose 2–3 times weekly (not daily).</td>
</tr>
<tr>
<td><strong>Markedly obese individuals</strong></td>
<td>Should have an adjusted dose due to the decreased distribution of extracellular fluids in adipose tissues. Dosing based on actual weight will give supratherapeutic levels. The suggested adjusted weight is ideal body weight plus 40% of the excess weight.</td>
</tr>
<tr>
<td></td>
<td>Ideal Body Weight (Men): 50 kg plus 2.3 kg/inch over 5 ft</td>
</tr>
<tr>
<td></td>
<td>Ideal Body Weight (Women): 45 kg plus 2.3 kg/inch over 5 ft</td>
</tr>
<tr>
<td></td>
<td>Levels should be followed closely.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Route of Administration</strong></th>
<th>Intravenous or intramuscular (has been used intrathecally and intraperitoneally). Not absorbed orally.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th><strong>Preparation</strong></th>
<th>1 gram vial for injection.</th>
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</table>

<table>
<thead>
<tr>
<th><strong>Storage</strong></th>
<th>Store in the refrigerator.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th><strong>Pharmacokinetics</strong></th>
<th>For intravenous administration, infuse over 60 minutes for adults; 1–2 hours for children; intramuscular absorption is complete within 4 hours and peak levels are achieved at 1–2 hours. The intravenous peak is 30–60 minutes after the infusion is complete.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Peak levels</strong> for a 15 mg/kg dose are between 35 and 45 mcg/ml.</td>
<td></td>
</tr>
<tr>
<td><strong>Peak levels</strong> of 25–35 mcg/ml are acceptable if you anticipate using streptomycin for more than 6 months.</td>
<td></td>
</tr>
<tr>
<td><strong>Peak levels</strong> of 65–80 mcg/ml are obtained after a 25 mg/kg dose.</td>
<td></td>
</tr>
<tr>
<td>Trough levels should be &lt; 5 mcg/ml in patients with normal renal function.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Oral Absorption</strong></th>
<th>There is no significant oral absorption. Intramuscular absorption might be delayed if the same site is used consistently.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STREPTOMYCIN</strong> [CONTINUED]</td>
<td></td>
</tr>
<tr>
<td>-----------------------------</td>
<td></td>
</tr>
<tr>
<td><strong>CSF Penetration</strong></td>
<td>Penetrates inflamed meninges only.</td>
</tr>
</tbody>
</table>
| **Special Circumstances**    | **Use in pregnancy/breastfeeding:** Avoided in pregnancy due to documented cases of congenital deafness. Can be used while breastfeeding.  
**Use in renal disease:** Use with caution. Levels should be monitored for patients with impaired renal function. Interval adjustment is recommended for renal impairment or dialysis. See Dose – Renal Failure/Dialysis (previous page). The drug is not cleared by hemodialysis; see Chapter 5, Special Situations – Renal Failure.  
**Use in hepatic disease:** Drug levels not affected by hepatic disease (except a larger volume of distribution for alcoholic cirrhotic patients with ascites). Presumed to be safe in severe liver disease; however, use with caution—some patients with severe liver disease may progress rapidly to hepato-renal syndrome.  
**Diuretic use:** Coadministration of loop diuretics and aminoglycoside antibiotics carries an increased risk of ototoxicity. |
| **Adverse Reactions**        | Nephrotoxicity: Less nephrotoxic than amikacin.  
Ototoxicity: Increased with advanced age and prolonged use.  
Local pain with IM injections.  
Vestibular toxicity.  
Electrolyte abnormalities, including hypokalemia and hypomagnesemia. |
| **Contraindications**        | **Pregnancy** (congenital deafness seen with streptomycin and kanamycin use in pregnancy); **hypersensitivity to aminoglycosides**; caution with renal, vestibular, or auditory impairment. |
| **Monitoring**               | Monitor renal function by documenting creatinine at least monthly (more frequently if renal or hepatic impairment); document creatinine clearance if there is baseline renal impairment or any concerns; document baseline and monthly audiology exam.  
Question patient regularly about vestibular complaints and perform serial vestibular exams. Document peak and trough levels at baseline if there is any question about renal function. Some experts monitor aminoglycoside levels routinely, regardless of renal function. Monitor levels serially for patients with impaired renal function. |
| **2004 Wholesale Cost**     | $74 (TB clinic)  
$160 (community hospital) |
| **Patient Instructions**     | Store streptomycin in the refrigerator.  
**Call your doctor right away if you have:**  
- Problems with hearing, dizziness, or balance  
- Rash or swelling of your face  
- Trouble breathing  
- Decreased urination  
- Watery or bloody diarrhea  
- Swelling, pain, or redness at your IV site  
- Muscle twitching or weakness |
References


Extrapulmonary TB

There is scant information regarding extrapulmonary drug-resistant tuberculosis (TB) in the medical literature. Many of the series of multidrug-resistant TB (MDR-TB) cases in the literature describe a proportion of cases with extrapulmonary disease without specific mention of outcomes or treatment modifications.

Many of the series from New York in the 1990s reported large proportions of HIV-infected individuals who are known to have higher rates of extrapulmonary TB than normal hosts. More recently, several reports describe cases of MDR-TB meningitis and high mortality rates.

Treatment of drug-resistant extrapulmonary TB is complicated by several issues:

- **Several forms of extrapulmonary TB** (meningitis/pericarditis) are treated with adjunctive corticosteroid treatment in conjunction with an optimal anti-tuberculosis regimen. Use of corticosteroids for patients not receiving adequate anti-mycobacterial therapy could be problematic. Studies showing efficacy of corticosteroid therapy are reported for drug-susceptible cases. The indication for corticosteroids in patients with drug-resistant TB remains unclear.

- **Some forms of TB** (particularly scrofula and intrathoracic adenopathy) are known to worsen as the TB is being successfully treated. This is due to the immune reconstitution as the organism is being eliminated and is particularly common in HIV-infected individuals. This phenomenon is known as a “paradoxical reaction.” However, if the clinical worsening is actually due to microbiologic failure associated with unrecognized (or not yet diagnosed) drug resistance, it may inappropriately be attributed to a paradoxical reaction. In this case, the correct diagnosis (drug resistance and treatment failure) will be delayed.
Drug regimens and durations of treatment for drug-susceptible extrapulmonary TB are based on known penetration of first-line anti-tuberculosis drugs into tissues, years of experience, and some clinical trials. Unfortunately, much less is known regarding the penetration of second-line drugs into tissues. This is compounded by the increased rates of malabsorption and drug interactions experienced by individuals at risk for drug-resistant TB.

Serial cultures are often not available. Clinical and radiographic assessments should be used to determine duration of therapy. Computed tomography is often useful in following treatment progress in these patients.

ROLE OF SURGERY

Some forms of extrapulmonary TB might benefit from surgical debridement or resection in order to decrease the burden of disease. Surgery is not a replacement for full medical treatment of TB, but may offer a greater likelihood of success and may give the patient some symptomatic relief while the disease is being treated medically.

DRUG-RESISTANT CENTRAL NERVOUS SYSTEM TB

Several reports detail poor outcomes of drug-resistant TB meningitis. Most of the patients in these series were HIV-infected and many developed meningitis while already receiving treatment for MDR-TB. Any degree of drug resistance will hinder the treatment of TB meningitis or other central nervous system (CNS) TB because isoniazid (INH) is the most important drug in the treatment of TB meningitis. Interestingly, one series showed no increased risk of in-hospital mortality with INH resistance.

TB Drugs and Their CNS Penetration

INH is the most important drug in the treatment of TB meningitis. INH readily diffuses into the cerebrospinal fluid (CSF), independent of meningeal inflammation due to its small size and lipophilic nature. Levels approach those in serum.

Rifampin (RIF), rifabutin, ethambutol (EMB), para-aminosalicylate (PAS), and the aminoglycosides penetrate poorly into the CSF with non-inflamed meninges, but better with inflamed meninges. For RIF, 10–20% of the serum level reaches the CSF in the setting of inflamed meninges (still exceeding the minimum inhibitory concentration [MIC] of sensitive isolates).

Capreomycin does not penetrate into the CSF.

Pyrazinamide (PZA) crosses freely into the CSF. One pediatric trial detected a significantly improved outcome for short-course treatment of TB meningitis in children who received PZA vs. longer treatment in those who did not, suggesting a benefit of PZA in the regimen.

Ethionamide and cycloserine also have good CNS penetration, approaching that in serum, but a South African study evaluated CSF levels of ethionamide and concluded that doses of 20 mg/kg/day should be used in order to achieve useful levels in the CSF.
The **fluoroquinolones** have variable CSF penetration. Levofloxacin levels in the CSF are about 15–30% that of serum (level around 2 mcg/ml for a normal dose). Since higher doses are generally used to treat MDR-TB, CSF levels may be adequate to treat TB meningitis (MIC 0.5–1.0). Moxifloxacin and gatifloxacin have shown good CSF penetration in several animal studies (CSF levels approximately 50% of serum). Human data will be required to determine which fluoroquinolone will have best efficacy in the treatment of TB meningitis.

**Route of Administration**

If the patient is obtunded or severely ill, consideration should be given to use drugs that can be given parenterally: INH, RIF, fluoroquinolones, and aminoglycosides.

Two recent reports of treatment of MDR-TB meningitis in non-HIV-infected individuals describe the use of intrathecal aminoglycosides and fluoroquinolones with good success and tolerability. Since most of the reports of fatal MDR-TB meningitis were in HIV-infected individuals, it is hard to compare the outcomes of intrathecal vs. systemic administration of second-line anti-tuberculosis drugs. It is appealing, however, to consider this option for patients not responding quickly to systemic treatment.

**Summary - Extrapulmonary TB**

- Data regarding treatment of extrapulmonary drug-resistant TB are limited. A few cases are described within larger series of MDR-TB cases.
- Patients with extrapulmonary TB are at risk of treatment failure due to poor drug penetration to the affected tissue and the lack of accessibility of tissue for serial cultures.
- Surgical resection (scrofula) and drainage (empyema, abscesses, and arthritis) may decrease bacterial burden and improve outcome. Full medical treatment is still indicated.
- Drug-resistant TB meningitis is challenging to treat due to the incomplete CSF penetration of many second-line drugs. Intrathecal administration of medications and the use of newer fluoroquinolones may improve outcome and should be evaluated prospectively.
Patients with HIV/AIDS are at increased risk of developing active tuberculosis (TB) once infected compared to immunocompetent individuals. Additionally, TB increases HIV replication, promoting a vicious cycle of viral and mycobacterial proliferation. Patients with HIV are more likely to have atypical presentations of TB, such as extrapulmonary TB (including lymphadenopathy, miliary TB, and meningitis), sputum smear-negative TB, and sputum culture-positive TB in the absence of an abnormal chest radiograph. These individuals are less likely to have cavitary disease and more likely to have mid- and lower-lung disease than are individuals without HIV infection.

Factors that increase the risk for exposure to or development of drug-resistant TB in HIV-infected individuals include:

- Previous exposure to rifamycins
- Use of highly intermittent rifamycin treatment
- Malabsorption of drugs
- Drug-drug interactions
- Residence in congregate settings
- Co-morbid conditions, including mental health and substance abuse issues
- CD4 lymphocyte count below 100 cells/mm³

Unfortunately, HIV-infected individuals have higher mortality rates than non-infected multidrug-resistant TB (MDR-TB) patients when the TB is not treated early or aggressively or when the CD4 lymphocyte count is already very low. In the series describing the highest mortality with HIV and drug-resistant TB, the patients had advanced AIDS, and MDR-TB was not recognized initially—therefore, drug therapy was inadequate.

Treatment of drug-resistant TB in HIV-infected individuals is complicated by:

- Drug toxicity exacerbated by underlying conditions or toxicity from other drugs
- The sheer volume of medicines that must be taken for both conditions
- The fact that the immune system cannot always contribute to control of the TB disease
- Malabsorption of drugs
- Drug-drug interactions
- Paradoxical reactions where TB disease appears to worsen when immune reconstitution occurs
- Complex social, mental health, and substance abuse confounders
- Co-infection with hepatitis C or hepatitis B, which increases the risk of hepatotoxicity, especially when combined with some types of HIV therapy
Identify all HIV-infected patients by screening all patients with active TB for HIV.

To maximize care of HIV-infected patients:

- Identify all HIV-infected patients by screening all patients with active TB for HIV.
- Work closely with the patient’s HIV provider. If that provider does not have extensive HIV/TB expertise, consult such an expert throughout the course of therapy.
- Consider the best HIV regimen for immune reconstitution as well as the timing of initiation of highly active antiretroviral therapy (HAART) treatment for antiretroviral naive patients. Initiation of HAART therapy is associated with increased drug toxicity as well as the phenomenon of immune reconstitution. Immune reconstitution may exacerbate clinical symptoms of TB by stimulating an inflammatory response. In patients with CD4 lymphocyte counts over 200, it is reasonable to delay HAART therapy for several months. In patients with CD4 less than 100 (or patients with extrapulmonary TB and CD4 less than 200), it is advisable to begin HAART therapy as soon as TB therapy is well tolerated (usually within 1–2 months).
- Consider alternate drugs when interactions between TB and HIV drugs are present (e.g., rifabutin in place of rifampin).
  
  - **Rifamycins are inducers of cytochrome P-450 and interact with many drugs.** Rifampin (RIF) in particular leads to lower levels of protease inhibitors and non-nucleoside reverse transcriptase inhibitors (NNRTIs). Current recommendations about concomitant use of rifamycins and HAART therapy should be consulted.
  
  - **Didanosine products that contain an antacid should not be dosed in close proximity to fluoroquinolones.** As with all other milk- and divalent cation-containing products, dosing at least 2 hours apart from the fluoroquinolone dose is advised.
  
  - **The rifamycins and other TB drugs interact with a number of the anti-infectious agents that may be taken by HIV-infected patients, including the macrolide drugs, cidofovir, anti-fungal drugs, and others.**
  
- Intervene to avoid or treat symptomatic toxicity. Peripheral neuropathy, cutaneous reactions, gastrointestinal (GI) side effects, renal impairment, and neuropsychiatric effects may all be worse in HIV/TB patients.
- Use daily directly observed therapy (DOT).
- Closely monitor signs and symptoms of malabsorption: diarrhea, abnormal stools, abnormal nutritional studies, evidence of vitamin deficiencies, weight loss, etc.
- Consider therapeutic drug monitoring to detect malabsorption, drug-drug interactions for MDR-TB, or clinical suspicion of malabsorption.
- Involve a nutritionist and pay close attention to weight and nutrition. Consider use of appetite stimulants in situations of extreme malnutrition.
- Involve ancillary services such as social workers, substance abuse clinics, and mental health facilities.
- Involve the patient’s social support system, as appropriate.
Summary - HIV

**MDR-TB patients co-infected with HIV have higher mortality rates,** particularly when they are profoundly immunocompromised (CD4 lymphocyte count less than 100) and an optimal TB regimen is not initiated early in the course of disease.

**HIV-infected patients can be cured of their drug-resistant TB disease,** but require special monitoring and concurrent care of their HIV disease.

**Malabsorption and drug interactions increase risk of drug-resistant TB** as well as complicate its treatment.
Liver Disease

Many tuberculosis (TB) medications have the potential to cause hepatotoxicity and their use must be contemplated in the setting of severe liver dysfunction. Fortunately, the most important second-line anti-tuberculosis drugs used for treatment of resistant disease do not affect the liver. The following is a list of anti-tuberculosis medications and their effects on the liver:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect on Liver</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid (INH)</td>
<td>INH is most likely to cause hepatitis. In individuals with normal hepatic function, the hepatotoxic effects are usually reversible if the drug is stopped as soon as symptoms are evident. INH hepatotoxicity appears to be increased when rifampin (RIF) is used.</td>
</tr>
<tr>
<td>Rifampin (RIF)</td>
<td>RIF more commonly causes a cholestatic jaundice, but can potentiate the hepatocyte damage caused by INH.</td>
</tr>
<tr>
<td>Pyrazinamide (PZA)</td>
<td>PZA causes fewer episodes of hepatotoxicity than INH, but the events can be severe and prolonged, and worsen even after stopping therapy. PZA is thought to cause the most severe liver toxicity.</td>
</tr>
<tr>
<td>Ethionamide PAS</td>
<td>Ethionamide and para-aminosalicylate (PAS) have also been implicated in hepatotoxic drug reactions.</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Some of the fluoroquinolone drugs (ciprofloxacin, gatifloxacin, and moxifloxacin) have been associated with occasional cases of liver damage. Travafloxacin has been associated with severe liver toxicity in rare cases.</td>
</tr>
<tr>
<td>Levofloxacin Ethambutol (EMB) Aminoglycosides Cycloserine</td>
<td>Not commonly associated with liver dysfunction.</td>
</tr>
</tbody>
</table>
Treatment of drug-resistant TB in the setting of liver failure is complicated and depends on the degree of liver damage. At least 1 patient has successfully undergone liver transplantation for toxicity of multidrug-resistant TB (MDR-TB) treatment.

- **If the patient has end-stage liver disease and further worsening could be life-threatening** (transplant is challenging in the setting of active TB), **consider avoiding all hepatotoxic drugs.** The use of levofloxacin, EMB, an aminoglycoside, and cycloserine should be considered, if appropriate.
- **If the liver disease is not imminently life-threatening, the use of a rifamycin in the regimen is advised if the isolate is susceptible.**

**Summary - Liver Disease**

- INH and PZA are the anti-tuberculosis medications most often associated with hepatotoxicity.
- Second-line anti-tuberculosis medications are less commonly associated with hepatotoxicity.
Pediatrics

Treatment of drug-resistant tuberculosis (TB) in children can be easier—and more difficult—than treating the disease in adults.

<table>
<thead>
<tr>
<th>Easier Elements</th>
<th>More Difficult Elements</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Children with drug-resistant TB have almost always acquired it from a contagious teen or adult rather than evolving it over years of failed therapy. This means that their bodies tend to be strong and healthy when the treatment is started.</td>
<td>- Young children are more likely to develop TB meningitis.</td>
</tr>
<tr>
<td>- Children have few <em>M. tuberculosis</em> organisms in their diseased tissues compared to adolescents and adults, making amplification of resistance on treatment much less likely.</td>
<td>- It is difficult to obtain good clinical specimens for culture confirmation, susceptibility testing, and clinical monitoring.</td>
</tr>
<tr>
<td>- Some TB disease diagnosed in children is actually already being controlled by their own immune system.</td>
<td>- Anti-tuberculosis drugs are not sold in child-friendly formulations.</td>
</tr>
<tr>
<td>- Children tend to tolerate the second-line medications required for drug-resistant treatment better than do adults.</td>
<td>- It is more difficult to monitor children for drug toxicity.</td>
</tr>
<tr>
<td>- It is difficult to entice a child to take a few doses of medicines, much less 2 or more years of multiple, bad-tasting tablets crushed into sticky, sweet vehicles.</td>
<td>- Bronchoalveolar lavage (BAL) specimens have a slightly lower yield than gastric aspirate specimens. In sick children, especially those in whom the diagnosis of TB is not certain or in whom the concern for drug resistance is very high, a BAL is frequently useful.</td>
</tr>
</tbody>
</table>

An older child can be monitored during treatment with serial sputum specimens, but serial gastric aspirates are rarely valuable due to their low yield.

NOTE:

A negative culture never rules out tuberculosis.
Other specimens that can be analyzed (particularly for children suspected of having extrapulmonary TB):

- **Excisional biopsies of lymph node, bone, and other tissue are more likely to grow *M. tuberculosis* than are needle aspiration specimens.**
- **Cerebrospinal fluid should be collected if meningitis is suspected.** Larger volumes should be submitted in order to increase the yield of smears and cultures, and to submit specimens for polymerase chain reaction (PCR).
- **Blood and urine cultures for mycobacterial cultures are sometimes positive in children with disseminated TB disease** (contact your lab to obtain the proper bottles for processing the blood).

**TREATMENT**

There are no controlled trials for treatment of drug-resistant TB in children. Based on small series and experience in adult patients, the following regimens are recommended:

Isoniazid (INH) Mono-Resistant TB in Children

Six months of rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB). Longer treatment (9–12 months) is sometimes required if the patient has slow response to therapy.

PZA Mono-Resistant TB in Children

Frequently caused by *M. bovis*. *M. bovis* can be transmitted from a contagious adult, but more frequently is ingested in unpasteurized milk products. The spectrum of TB disease caused by *M. bovis* is the same as that caused by *M. tuberculosis*, but there is a disproportionate frequency of adenopathy (intra-abdominal and cervical in particular). The treatment for *M. bovis* TB is 2 months of INH, RIF, and EMB, followed by at least 7 months of INH and RIF (can be twice weekly by directly observed therapy [DOT]). Duration of therapy should be extended for *M. bovis* TB if the patient experiences a sluggish clinical response.

Multidrug-Resistant TB in Children

There are several series published, mostly from New York and South Africa. South African children were treated with 4–5 drugs (at least 2–3 drugs to which the presumed source case isolate was susceptible) for 9–12 months. No cases of disseminated disease were identified. All children were well after 30 months of follow-up. The authors from New York recommend 1 year of treatment for non-serious or non-life-threatening forms of TB and a minimum of 18 months for serious or life-threatening forms of TB. The long-term rates of TB reactivation are unknown for these children.

- **For multidrug-resistant TB (MDR-TB), multiple drugs to which the organism is susceptible should be employed**, including the fluoroquinolones and injectable agents.
- **At least 3 drugs to which the isolate is susceptible should be used for at least 18 months.**
- **In the case of symptomatic children or children with extensive radiographic disease, treatment should be continued at least 18 months after clinical or radiographic improvement begins.**

Given the paucity of clinical data and the inability to fully characterize children’s TB disease, the most prudent course to treat children with drug-resistant TB is:

Use the same principles as for adults and seek expert consultation.
TREATMENT REGIMENS

Drug-resistant TB in children should be treated by the most experienced clinician/clinic available. Consult with a pediatric TB expert throughout the course of care.

Drug Administration

Very few anti-tuberculosis drugs are available in liquid preparations or in small tablets appropriate for pediatric dosing. In general:

Approximate doses of medications are adequate. Exact doses of pill fragments and portions of capsules are impossible to attain. If the child's dose is 100 mg and the drug comes as a 250 mg tablet, 2 tablets will supply 5 doses. Any small discrepancy in dosing will even out over time.

Cut tablets into approximate fragments (freeze ethionamide in a small plastic bag before dividing into fragments); crush fragments for smaller children.

Jiggle capsules open and approximate fractions for serial doses.

Mix crushed tablets or capsule contents into a small amount of vehicle.

- Some powder will suspend into liquid well and can pass through a syringe. A dispenser with a bigger opening, such as a medicine dropper, is better than a syringe and will deliver a greater proportion of the drug without sticking in the syringe.
- If mixing the medicine in a vehicle before delivery, use a small amount of the vehicle. The child will not want to take many spoonfuls of the drug. Many children will prefer the crushed pills or granules delivered with a soft vehicle.
- Alternatively, a thin layer of soft vehicle can be placed on the spoon, the powder or pill fragment layered on top, followed by another layer of soft vehicle (making a medication sandwich and preventing drug taste in the vehicle itself).

Immediately after the medication is given, give good untainted food or drink to clear the palate.

Give lots of praise and incentives.

Some drugs can be mixed in a small amount of liquid and given to babies via a special medicine-dispensing pacifier or bottle. Some babies will reflexively suck the medication from a bottle while they sleep. Give water in a clean bottle afterwards to rinse the medicine out of the mouth.

Be flexible, but firm. The child should get a few choices, but not whether or not to take the medicine.

The method of delivery may need to be changed throughout the course of treatment.
SPECIFIC TB DRUGS
(See Tables 1–8, Pediatric Drug Dosing)

Ethambutol (EMB)
- Cautiously used in children because adults who were given high doses of EMB have developed optic toxicity. While it is challenging to monitor young children for signs of eye toxicity, there have not been well-documented cases of eye toxicity in children.
- EMB can and should be used to treat children with drug-resistant TB when the isolate is susceptible to EMB.
- Recommended dose of EMB for children: 15–25 mg/kg/day in a single daily dose. Since eye toxicity is dose-related in adults, many clinicians feel more comfortable keeping the dose closer to the 15 mg/kg dose. This is especially true when the drug is being used over the course of many months. Unfortunately, the drug is bactericidal only at the higher doses.
- Instruct families to watch for any evidence of eye problems: eye rubbing or excessive blinking, sitting closer to the television, or difficulty with accurate grasping. Monitor even young children by offering them Cheerios and watching their grasp. A child whose vision has changed will not be able to grasp the small objects as accurately as he/she had previously. Monitor older children with Snellen eye charts and color vision tools.
- EMB comes in 100 mg and 400 mg white tablets, which can be crushed fairly easily into liquid or food. It can be given independent of food intake.

Ethionamide
- Better tolerated by children than adults with fewer gastrointestinal (GI) side effects.
- Dose: 15–20 mg/kg/day in a single dose or divided doses (maximum 1 gram).
- To ensure tolerability, start with a small dose—around 5 mg/kg once a day and gradually increase the dose every 3–5 days. After a few weeks of full dose divided twice a day, the child could try the dose in a single daily dose with food.
- Ethionamide comes as a 250 mg coated tablet that is not scored. If the child needs a partial dose, the tablet can be frozen and then fractured in a small plastic bag. The fragments can be used over several doses in order to get an accurate dose in over the course of several doses.
- As with adults, children should be supplemented with additional pyridoxine when taking ethionamide, and thyroid function should be monitored.

Cycloserine
- Generally well tolerated in children, though there have been reports of central nervous system (CNS) side effects.
- Drug levels have not been as consistent as those seen in adults, but should still be monitored in order to minimize the risk of toxicity.
Fluoroquinolones have generally been avoided in children because arthropathy has been observed in animal models. Many thousands of children have received courses of fluoroquinolones (generally for short periods of time) and none have been found to have arthropathy or bone abnormalities. Selected patients have been monitored for fluoroquinolone toxicity by histopathologic examination, MRI, and ultrasound, without any detection of bone or joint damage. Case reports of at least 17 children treated with fluoroquinolones for more than 6 months have been reported without arthropathy. Rates of reversible arthralgia have been similar to those in adults.

National guidelines endorse the use of fluoroquinolones in the treatment of children with MDR-TB if the drug is vital to the regimen. Close observation by parents and care providers for musculoskeletal complaints is advised.

Levofloxacin has significantly better activity against TB than ciprofloxacin (which is licensed for treatment of urinary tract infection in children). Levofloxacin is currently being studied for otitis media and community-acquired pneumonia in children. Early pharmacokinetic data showed that doses of 5–7 mg/kg did not achieve levels comparable to adult therapeutic doses. Doses of 10 mg/kg in a single daily dose for children over 5 years of age, and 15–20 mg/kg/day, divided twice daily for less than 5 years of age, have been proposed based on early pharmacokinetic data in children and extrapolating from the drug-resistant TB experience in adults. There are no data establishing the safety or efficacy of the fluoroquinolones in treatment of TB in children. Levofloxacin comes as unscored 250 and 500 mg tablets. An oral suspension of 25 mg/ml is now available (approved based on bioequivalence data generated in adults).

Gatifloxacin has been studied in children for treatment of otitis media. A dose of 10 mg/kg/day in a single daily dose gives levels equivalent to a 400 mg dose in adults. Gatifloxacin is available as 200 and 400 mg coated tablets. An oral suspension may be available soon at 40 mg/ml.

Long-term use of fluoroquinolones may promote development of quinolone-resistant *Streptococcus pneumoniae* carriage. While children are not usually treated with fluoroquinolones for presumed pneumococcal disease, their older family members might be. Therefore, the possibility of fluoroquinolone-resistant pneumococcal disease must be considered.
Para-Aminosalicylate (PAS)

- PAS is marketed in a reasonably well-tolerated formulation of granules. The packets of granules contain 4 grams of PAS.
- Pediatric dose: 200–300 mg/kg/day in 2–4 divided doses (most children can tolerate the dose divided in only 2 daily doses). Maximum daily dose is 10 gm.
- Flatten out the packet of granules so that they are spread evenly in the packet. The packet can then be cut in order to approximate the dose needed—i.e., cut into 4 quadrants for 1 gram doses. The granules can be sprinkled on top of or mixed into a small amount of soft food and are best tolerated when taken with food. Some experts dose PAS with acidic food to enhance absorption.

Injectable Drugs

- A cornerstone in the treatment of MDR-TB in adults, injectable drugs should be included in the treatment of children with MDR-TB.
- While some adults will elect to receive the drugs intramuscularly, most children should very quickly have a more permanent intravascular catheter placed for long-term use. Percutaneously placed catheters will work for some children; younger children will usually require a surgically-placed Broviac-type catheter to last for many months of treatment.
- Children receiving aminoglycosides or capreomycin should be monitored, as are adults, with hearing and vestibular screens and renal function monitoring.
Tables 1–8. **PEDIATRIC DRUG DOSING**

The following tables are designed to help clinicians select pediatric doses based on fractions of tablets and capsules.

These are approximate doses. If a fraction of the tablet is given for one dose, and the remainder is given over subsequent doses, the exact dose will be given over a series of doses. It does not matter if each individual dose is exact; in fact, it will not be.

---

**Table 1. ISONIAZID**

<table>
<thead>
<tr>
<th>Child's weight</th>
<th>Daily isoniazid dose 10–15 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KILOGRAMS</strong></td>
<td><strong>POUNDS</strong></td>
</tr>
<tr>
<td>3–5</td>
<td>6.6–11</td>
</tr>
<tr>
<td>5–7.5</td>
<td>11–16.4</td>
</tr>
<tr>
<td>7.5–10</td>
<td>16.5–22</td>
</tr>
<tr>
<td>10–15</td>
<td>22–33</td>
</tr>
<tr>
<td>15–20</td>
<td>33–44</td>
</tr>
<tr>
<td>Over 20</td>
<td>Over 44</td>
</tr>
</tbody>
</table>

Maximum daily isoniazid dose is 300 mg

---

**Table 2. RIFAMPIN**

<table>
<thead>
<tr>
<th>Child's weight</th>
<th>Daily rifampin dose generally 12–17 mg/kg/dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KILOGRAMS</strong></td>
<td><strong>POUNDS</strong></td>
</tr>
<tr>
<td>4–7.5</td>
<td>9–16</td>
</tr>
<tr>
<td>7.5–12.5</td>
<td>17–27</td>
</tr>
<tr>
<td>12.5–17.5</td>
<td>28–38</td>
</tr>
<tr>
<td>17.5–25</td>
<td>39–55</td>
</tr>
<tr>
<td>25–35</td>
<td>55–77</td>
</tr>
<tr>
<td>Over 35</td>
<td>Over 77</td>
</tr>
</tbody>
</table>

Maximum daily rifampin dose is 600 mg
## PEDIATRIC DRUG DOSING

### Table 3. PYRAZINAMIDE

<table>
<thead>
<tr>
<th>Child's weight</th>
<th>Daily pyrazinamide dose 20–40 mg/kg/dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>KILOGRAMS</td>
<td>POUNDS</td>
</tr>
<tr>
<td>3–6.25</td>
<td>6.6–13</td>
</tr>
<tr>
<td>6.25–12.5</td>
<td>14–27</td>
</tr>
<tr>
<td>12.5–20</td>
<td>27–44</td>
</tr>
<tr>
<td>20–27</td>
<td>44–59</td>
</tr>
<tr>
<td>27–35</td>
<td>59–77</td>
</tr>
<tr>
<td>35–46</td>
<td>77–101</td>
</tr>
<tr>
<td>46–54</td>
<td>102–119</td>
</tr>
<tr>
<td>54–62</td>
<td>119–136</td>
</tr>
<tr>
<td>Over 62</td>
<td>Over 136</td>
</tr>
</tbody>
</table>

Dose obese children on lean body weight

**Maximum daily pyrazinamide dose is 2 grams**

### Table 4. ETHAMBUTOL

<table>
<thead>
<tr>
<th>Child's weight</th>
<th>Daily ethambutol dose 15–25 mg/kg/dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>KILOGRAMS</td>
<td>POUNDS</td>
</tr>
<tr>
<td>4–6</td>
<td>9–13</td>
</tr>
<tr>
<td>6–8</td>
<td>14–17</td>
</tr>
<tr>
<td>8–12.5</td>
<td>18–27</td>
</tr>
<tr>
<td>12.5–17.5</td>
<td>28–38</td>
</tr>
<tr>
<td>17.5–22.5</td>
<td>39–49</td>
</tr>
<tr>
<td>22.5–27.5</td>
<td>50–60</td>
</tr>
<tr>
<td>27.5–32.5</td>
<td>61–71</td>
</tr>
<tr>
<td>32.5–37.5</td>
<td>72–82</td>
</tr>
<tr>
<td>37.5–55</td>
<td>83–121</td>
</tr>
<tr>
<td>56–75</td>
<td>123–165</td>
</tr>
</tbody>
</table>

Dose obese children on lean body weight

**Maximum daily ethambutol dose is 2.5 grams**
## PEDIATRIC DRUG DOSING

### Table 5. CYCLOSERINE

<table>
<thead>
<tr>
<th>Child’s weight</th>
<th>Daily cycloserine dose</th>
<th>KILOGRAMS</th>
<th>POUNDS</th>
<th>MILLIGRAMS</th>
<th>250 mg CAP</th>
<th>10–20 mg/kg/day divided bid</th>
</tr>
</thead>
<tbody>
<tr>
<td>8–12</td>
<td>83 mg po bid</td>
<td>8–12</td>
<td>17–26</td>
<td>1/3 po bid</td>
<td>17–26</td>
<td></td>
</tr>
<tr>
<td>12–16</td>
<td>125 mg po bid</td>
<td>12–16</td>
<td>27–35</td>
<td>1/2 po bid</td>
<td>27–35</td>
<td></td>
</tr>
<tr>
<td>25–38</td>
<td>250 mg po bid</td>
<td>25–38</td>
<td>55–84</td>
<td>1 po bid</td>
<td>55–84</td>
<td></td>
</tr>
<tr>
<td>Over 38</td>
<td>Start with 1 capsule (250 mg) bid. If level less than 25 mcg/ml, consider total daily dose of 750 mg divided into 2 doses</td>
<td>Over 38</td>
<td>Over 73</td>
<td>1 po bid</td>
<td>Over 73</td>
<td></td>
</tr>
</tbody>
</table>

Maximum daily cycloserine dose is 1 gm

### Table 6. ETHIONAMIDE

<table>
<thead>
<tr>
<th>Child’s weight</th>
<th>Daily ethionamide dose</th>
<th>KILOGRAMS</th>
<th>POUNDS</th>
<th>INITIAL DOSE</th>
<th>DOSE SIZE</th>
<th>FINAL DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.4–11</td>
<td>82.5 mg po qhs</td>
<td>8.4–11</td>
<td>18.5–24</td>
<td>1/3 tablet</td>
<td>1 tablet</td>
<td>82.5 mg po bid</td>
</tr>
<tr>
<td>11.1–16.6</td>
<td>125 mg po qhs</td>
<td>11.1–16.6</td>
<td>24–36.5</td>
<td>1/2 tablet</td>
<td>1 tablet</td>
<td>125 mg po bid</td>
</tr>
<tr>
<td>16.7–20</td>
<td>165 mg po qhs</td>
<td>16.7–20</td>
<td>36.5–44</td>
<td>2/3 tablet</td>
<td>1 tablet</td>
<td>165 mg po bid</td>
</tr>
<tr>
<td>25–33.3</td>
<td>250 mg po qhs</td>
<td>25–33.3</td>
<td>55–73</td>
<td>1 tablet</td>
<td>1 tablet</td>
<td>250 mg po bid</td>
</tr>
<tr>
<td>Over 33.3</td>
<td>250 mg po qhs</td>
<td>Over 33.3</td>
<td>Over 73</td>
<td>1 tablet</td>
<td>1 tablet</td>
<td>250 mg po bid 500 mg po qhs</td>
</tr>
</tbody>
</table>

Maximum daily ethionamide dose is 1 gm

### Table 7. CAPREOMYCIN / AMIKACIN / KANAMYCIN / STREPTOMYCIN

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capreomycin/Amikacin/Kanamycin</td>
<td>15–30 mg/kg/day up to 1 gram IV or IM</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>20–40 mg/kg/day up to 1 gram IV or IM</td>
</tr>
</tbody>
</table>

Maximum daily dose is generally 1 gm, but a large muscular adolescent should be treated like an adult.
### PEDIATRIC DRUG DOSING

#### Table 8. PARA-AMINOSALICYLATE (PAS)

<table>
<thead>
<tr>
<th>Child’s weight</th>
<th>Daily PAS dose 200–300 mg/kg/day in divided doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>KILOGRAMS</td>
<td>POUNDS</td>
</tr>
<tr>
<td>8–10</td>
<td>17–22</td>
</tr>
<tr>
<td>10–15</td>
<td>22–34</td>
</tr>
<tr>
<td>15–20</td>
<td>35–44</td>
</tr>
<tr>
<td>20–30</td>
<td>45–66</td>
</tr>
<tr>
<td>30–40</td>
<td>67–88</td>
</tr>
<tr>
<td>Over 40</td>
<td>Over 89</td>
</tr>
</tbody>
</table>

Maximum daily PAS dose is 10 gm

---

### Summary - Pediatrics

- **Children with drug-resistant TB generally suffer fewer side effects with second-line anti-tuberculosis drugs than do adults.**
- **Dosing children with tablets and capsules requires patience and creativity.**
- **Fluoroquinolones should be used with care in young children.**
- **Children have a smaller bacillary load compared to adults.**
  
While some series report shorter courses of MDR-TB treatment, duration of treatment should generally approximate that of adults (at least 18 months).
Pregnancy

Treatment of drug-resistant tuberculosis (TB) during pregnancy is very challenging. All female patients of childbearing age with multidrug-resistant TB (MDR-TB) should strongly consider contraception/pregnancy avoidance. Some clinicians do monthly laboratory screening to detect pregnancy early.

Many of the medications used to treat drug-resistant TB are either teratogenic or their safety during pregnancy is unknown.

- **Consult with an MDR-TB expert throughout the course of pregnancy.**
- **Have serial discussions with the patient and concerned family members to discuss risks and benefits of various treatment options.**

For pan-susceptible TB during pregnancy, we generally avoid use of pyrazinamide (PZA) in the U.S. In the case of drug-resistant TB, PZA should be used when the isolate is susceptible. Treatment of mono-drug-resistant TB for pregnant women is the same as for non-pregnant individuals:

<table>
<thead>
<tr>
<th>Resistance</th>
<th>Mediations</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH monoresistance</td>
<td>RIF + EMB + PZA</td>
<td>At least 6 months</td>
</tr>
<tr>
<td>PZA monoresistance (M. bovis)</td>
<td>INH + RIF + EMB Followed by INH and RIF</td>
<td>2 months At least 7 more months</td>
</tr>
<tr>
<td>RIF monoresistance</td>
<td>INH + EMB + PZA</td>
<td>At least 18 months</td>
</tr>
</tbody>
</table>

*Consider addition of a fluoroquinolone or injectable drug after delivery to shorten course.*

**Several options face the pregnant MDR-TB patient and her team of health care providers:**

- Treatment of drug-resistant TB with the best possible, albeit frequently weak, MDR-TB regimen. The regimen can be strengthened after the baby delivers.
- Some experts continue treatment of MDR-TB in a pregnant woman with a “holding” regimen of first-line TB drugs. The rationale for this strategy is that even when in vitro data show that an isolate is resistant to isoniazid (INH) and rifampin (RIF), the population that are susceptible will respond, which allows some temporary improvement. Theoretically, such a regimen will not contribute to amplification of resistance (particularly if the isolate is already resistant to all the first-line drugs), but might allow the mother to deliver the baby safely without risk of worsening her TB disease. However, there is no proof as to the benefit of this strategy and the patient is exposed to costs and toxicity without guarantee of the proposed benefits.
- No treatment at all for very stable disease pending delivery of the baby.
- If the mother’s life is at risk without use of known teratogenic drugs, termination of the pregnancy is sometimes reluctantly considered.
TERATOGENICITY

- **Aminoglycosides** are the only TB drugs that have well-documented teratogenicity. Streptomycin and kanamycin have been implicated as the cause of mild to severe bilateral congenital deafness (eighth nerve toxicity) in up to 17% of pregnancies. For that reason, amikacin and capreomycin are also not recommended during pregnancy, but have been used safely in some reports.

- **Ethionamide** use has been associated with congenital defects in several children. In general there are not enough data to determine its safety during pregnancy.

- **Fluoroquinolones** are generally avoided during pregnancy due to the observation of arthropathy in puppy models and adverse events in monkeys receiving norfloxacin. **Levofloxacin** has not been found to be teratogenic in animals, but large doses have led to decreased fetal weight and increased fetal mortality in rats. One series reported 200 women exposed to fluoroquinolones in the first trimester and none of the babies suffered musculoskeletal abnormalities. Fluoroquinolone drugs have been used in the treatment of MDR-TB in pregnancy and have not been associated with identified teratogenicity.

- **PZA** is not included in the TB regimens of most pregnant U.S. women with drug-susceptible TB due to lack of controlled data during pregnancy. The World Health Organization (WHO) and the International Union Against TB and Lung Disease (IUATLD) do recommend routine use of PZA during pregnancy (as do some U.S. jurisdictions), and toxicity to the fetus has not been documented. For women with HIV co-infection or drug-resistant disease, PZA should be included in the TB regimen if the isolate is susceptible.

- **INH**, **RIF**, and ethambutol (EMB) have not been associated with teratogenic effects. Rifabutin, cycloserine, and para-aminosalicylate (PAS) have not been extensively studied, but animal models and anecdotal human reports have not shown toxicity.

INFECTION CONTROL

Infection control is particularly challenging during pregnancy and childbirth.

- Consult with experts in infection control and TB treatment to ensure that appropriate measures are in place in settings where these women will receive obstetrics (OB) care.

- If the patient is still contagious at the time of delivery, make plans for delivery well in advance. Arrange for a negative pressure birthing room and appropriately fit test personnel for N-95 or more efficient masks. It will not be realistic to expect that a laboring mother will be able to keep a mask on herself.

MANAGEMENT OF THE NEWBORN

Management of the infant born to a mother with active TB includes 2 major issues:

1. Is the baby already infected with TB (congenital TB)?
2. How can we prevent the baby from becoming infected with TB?

Breastfeeding

Most TB drugs cross into the breast milk at low levels. Mothers and their babies receiving INH, cycloserine, and ethionamide should be supplemented with vitamin B6 (pyridoxine). The doses of TB drugs that babies receive via breast milk are insufficient to treat or prevent TB in the infant. Small amounts of fluoroquinolones have been detected in human breast milk. Because of the risk of arthropathy in immature animal models, the American Thoracic Society (ATS) does not recommend use of fluoroquinolones during breastfeeding.
CONGENITAL TB

- Fortunately, congenital TB is exceedingly rare. It most commonly occurs when the mother has untreated (and often undetected) TB disease shortly after her primary infection, disseminated TB, or disease of the uterus or genital tract.

- Congenital TB is usually diagnosed in the first weeks to months of life and frequent findings include the following:
  - Fever
  - Irritability
  - Poor feeding
  - Skin lesions
  - Liver and/or spleen enlargement
  - Enlarged lymph nodes
  - Cough or increased work of breathing
  - Various chest radiographic abnormalities

- Routine evaluation of a baby whose mother has known or suspected active TB should include physical examination to evaluate for these findings as well as a chest radiograph.

- Examination of the placenta by a pathologist is sometimes helpful. Granulomata in the placenta increases the likelihood that the baby is infected. Fortunately, the placenta is an efficient organ and most babies born to mothers with granulomatous placenta will not themselves be infected.

- If the baby has physical findings or radiographic abnormalities to suggest congenital TB, the baby should immediately undergo gastric aspirate collection, a procedure that has a very high yield for both smear and culture (around 90% each) in cases of congenital TB. For a demonstration of gastric aspirate collection, refer to: http://www.nationaltbcenter.edu. For young babies, gastric aspirates can be collected after the baby is NPO after a long sleep several times in 1 day, and do not necessarily need to be collected in the early morning. Lumbar puncture for cell count, protein, glucose, bacterial and acid-fast bacilli (AFB) smear and culture, and TB polymerase chain reaction (PCR) should be performed for a child with suspected congenital TB. Mycobacterial culture of blood, skin lesions, and ear drainage are also sometimes helpful.

TREATMENT OF SUSPECTED CONGENITAL TB

If a newborn is suspected of having active or congenital TB, treatment for active TB should be initiated as soon as the aforementioned studies are collected (collect 2–3 gastric aspirates on the first day). Treatment should be based on the mother’s TB isolate susceptibility pattern in consultation with a pediatric TB expert.
PREVENTION OF INFECTION IN THE NEWBORN

- If the mother is still potentially contagious with drug-resistant TB, mother and baby should be separated until the mother is not contagious.
- If an infant whose mother has known contagious or suspected active TB is vigorous, afebrile, and has a completely normal physical exam and chest radiograph, consideration should be given to treating the infant prophylactically, in case the baby has been infected during the birth process and does not yet have active TB or to prevent post-natal acquisition of the organism. If the mother's isolate is sensitive to INH or RIF, that drug should be employed. If the mother has MDR-TB, the advice of a pediatric TB expert should be sought.
- If the baby is treated with INH and is breastfeeding, the baby should also receive 6.25 mg or one fourth of a 25 mg tablet of pyridoxine. If the mother is receiving INH, ethionamide, or cycloserine, the breastfed baby should also receive pyridoxine.
- **Because it is possible for an infant to have early, subclinical congenital TB, the infant should be followed closely (weekly) by an experienced pediatric provider and observed for development of the aforementioned findings.**
- If separation of the mother and infant is not possible and no practical prophylactic regimen is available, the bacille Calmette-Guérin (BCG) vaccine is sometimes administered. BCG does prevent cases of disseminated TB and TB deaths in infants. Unfortunately, BCG does not prevent TB infection, and it may make the interpretation of the tuberculin skin test (TST) challenging for the first year or two after administration.
- If the baby is asymptomatic and the mother has been receiving effective TB therapy and is deemed to be non-contagious, and there are no other potentially contagious source cases in the infant’s home, close monitoring without chest radiograph or prophylactic treatment is appropriate.

TST

The TST is rarely positive in newborns and contributes little to the early evaluation. The TST is not contraindicated in infants. Most experts recommend considering the skin test reliable between 6 and 12 months of life for immunocompetent children.

Summary - Pregnancy

Treatment of drug-resistant TB during pregnancy is challenging due to:
- Risk of teratogenicity of anti-tuberculosis drugs
- Infection control risks during OB care
- Risk of transmission to the infant

While PZA is avoided in drug-susceptible TB, it is recommended for use in drug-resistant TB during pregnancy.
Renal Failure

Patients with chronic renal failure undergoing hemodialysis are at 10- to 25-fold increased risk of developing active tuberculosis (TB) once infected, compared to the general population. Unfortunately, these patients are also at increased risk of development of drug resistance due to the difficulty of managing their TB disease. These patients require careful monitoring for treatment of TB and drug-resistant TB in particular.

Data regarding clearance of anti-tuberculosis drugs are best documented for patients with creatinine clearance less than 30 ml/minute or for those undergoing hemodialysis. For individuals with mild renal failure or undergoing peritoneal dialysis, the data are less clear. In addition to the effects on drug clearance, the diseases that cause renal failure and concomitant treatments can also impact drug levels (by altering absorption or drug interactions). Table 1 describes dosing changes for patients with renal insufficiency.

For TB drugs that are cleared by the kidney, the general strategy is:

- **To increase the interval between dosing rather than to decrease the dose.**
- **While there are some recommendations for giving large doses before dialysis and supplementary doses after dialysis, the easiest and most consistent method is to give the medications immediately following hemodialysis.** In most cases, the hemodialysis staff will administer both the parenteral and enteral therapy by directly observed therapy (DOT) and work closely with the provider and TB case manager. Their assistance is particularly helpful for monitoring toxicity and drug levels in these challenging patients.
SPECIFIC TB DRUGS

Ethambutol (EMB)
- Up to 80% cleared by the kidney.
- Incompletely dialyzed.
- Dose should be adjusted as per Table 1, but there may be an increased risk of accumulation of the drug and eye toxicity in the setting of renal failure.
- Drug levels may be helpful in cases where EMB is important for the regimen.
- In some circumstances (peritoneal dialysis, moderate renal failure without dialysis), the use of EMB should be considered carefully (and avoided, if appropriate).
- Little data are available regarding anti-tuberculosis drug dosing for patients on continuous ambulatory peritoneal dialysis (CAPD); however, a dose of 15 mg/kg/dose every 48 hours has been used successfully.
- Peak serum concentrations (2–3 hours post-dose) generally should be maintained within the normal range of 2–6 mcg/ml.
- The initial dose of EMB should be based on ideal body weight rather than total body weight if the patient is above his/her ideal body weight (see calculator at bottom of Table 1).
- Monitor carefully for red-green color discrimination and visual changes.

Aminoglycosides (Streptomycin, Kanamycin, Amikacin) and Capreomycin
- Cleared nearly entirely by the kidneys and only about 40% of the dose is removed by dialysis.
- There may be some accumulation of drug and this might increase the risk of ototoxicity. These patients should be monitored closely for ototoxicity (both hearing loss and vestibular dysfunction). Serum drug concentrations can be used to verify that adequate peak concentrations are achieved (for efficacy). Predialysis trough concentrations may be above the usual target ranges, since these patients will be unable to clear the drugs without the help of dialysis.
- The aminoglycosides have sometimes been instilled with peritoneal dialysate with careful serum concentration monitoring.
- The serum level of amikacin is most readily available in commercial labs. The aminoglycoside doses should be based on ideal body weight rather than total body weight if the patient is above his/her ideal body weight (see calculator at bottom of Table 1).

Fluoroquinolones (Variable Renal Clearance):

LEVOFLOXACIN
- Cleared more extensively by the kidney than is moxifloxacin.
- A dose of 750–1000 mg/dose 3 times weekly (not daily) is recommended for treatment of TB. The manufacturer’s literature for dosing levofloxacin for non-tuberculosis infections suggests using smaller doses that may not be adequate. Again, drug concentration monitoring might be beneficial and general toxicity monitoring is imperative.
MOXIFLOXACIN

- In one small study, moxifloxacin clearance was unaltered in the presence of renal insufficiency following single oral doses. No literature is available regarding its clearance with dialysis.

GATIFLOXACIN

- Excreted unchanged in the urine and so adjustment for renal impairment is necessary.
- Limited data are available for use in patients with renal impairment and TB.
- It may be appropriate to use a dose adjustment such as that used with levofloxacin (gatifloxacin 400 mg given 3 times weekly after dialysis).
- The manufacturer recommends:
  - Creatinine clearance > 40 ml/minute 400 mg daily
  - Creatinine clearance < 40 ml/minute 400 mg load and then 200 mg daily
  - Hemodialysis or CAPD 400 mg load and then 200 mg daily (dose after a hemodialysis session)

  This regimen may lead to levels that are too low to be effective in treatment of TB.

CYCLOSERINE

- Cleared by the kidney; toxicity appears to be closely related to elevated serum concentration.
- Peak serum concentrations (2 hours post-dose) generally should be maintained within the normal range of 20–35 mcg/ml.

PARA-AMINOSALICYLATE (PAS)

- Metabolized in the gastrointestinal (GI) tract and liver, but its inactive metabolite acetyl-PAS is eliminated renally. No specific toxicity of the metabolite is known. The manufacturer does not recommend its use in end-stage renal failure. However, in a well-performed study, clearance of the metabolite (and PAS) by dialysis was documented. In several case reports, PAS was used after dialysis.
- The American Thoracic Society (ATS) recommends using the usual daily dose and dosing after dialysis. There are few data regarding its use in patients with renal failure not yet on dialysis, but no clear evidence of toxicity.
Table 1.

**DOsing recommendations for adult patients with reduced renal function and for adult patients receiving hemodialysis**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Change in frequency?</th>
<th>Recommended dose and frequency for patients with creatinine clearance &lt; 30 ml/min or patients receiving hemodialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>No change</td>
<td>300 mg once daily, or 900 mg 3 times/week</td>
</tr>
<tr>
<td>Rifampin</td>
<td>No change</td>
<td>600 mg once daily, or 600 mg 3 times/week</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Yes</td>
<td>25–35 mg/kg/dose 3 times/week (not daily)</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Yes</td>
<td>15–25 mg/kg/dose 3 times/week (not daily)</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>Yes</td>
<td>750–1000 mg/dose 3 times/week (not daily)</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>Yes</td>
<td>250 mg once daily, or 500 mg/dose 3 times/week*</td>
</tr>
<tr>
<td>Ethionamide</td>
<td>No change</td>
<td>250–500 mg/dose daily</td>
</tr>
<tr>
<td>PAS</td>
<td>No change</td>
<td>4 gm/dose twice daily</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>Yes</td>
<td>12–15 mg/kg/dose 2–3 times/week (not daily)</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>Yes</td>
<td>12–15 mg/kg/dose 2–3 times/week (not daily)</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>Yes</td>
<td>12–15 mg/kg/dose 2–3 times/week (not daily)</td>
</tr>
<tr>
<td>Amikacin</td>
<td>Yes</td>
<td>12–15 mg/kg/dose 2–3 times/week (not daily)</td>
</tr>
</tbody>
</table>

- Standard doses are given unless there is intolerance.
- The medications should be given after hemodialysis on the day of hemodialysis.
- Monitoring of serum drug concentrations should be considered to ensure adequate drug absorption, without excessive accumulation, and to assist in avoiding toxicity.
- There should be careful monitoring for evidence of neurotoxicity.
- Data currently are not available for patients receiving peritoneal dialysis. Until data become available, begin with doses recommended for patients receiving hemodialysis and verify adequacy of dosing using serum concentration monitoring.
- Dose the aminoglycosides, pyrazinamide, and ethambutol by Ideal Body Weight for obese patients.

**Ideal Body Weight (Men):** 50 kg plus 2.3 kg/inch over 5 ft  
**Ideal Body Weight (Women):** 45 kg plus 2.3 kg/inch over 5 ft

**Estimated creatinine clearance calculations**

Men: Ideal Body Weight (kg) X (140 – age) / 72 X serum creatinine (mg/dl)  
Women: 0.85 X Ideal Body Weight (kg) X (140 – age) / 72 X serum creatinine (mg/dl)

Table adapted from the American Thoracic Society Treatment Guidelines.

* The appropriateness of the 250 mg daily dose has not been established.
Isoniazid (INH), rifampin (RIF), ethionamide, and PAS are not cleared by the kidney and their dosing does not require adjustment for renal failure. Most other anti-tuberculosis drugs require dose adjustment for significant renal insufficiency.

Dosing guidelines are well established for patients with creatinine clearance less than 30 ml/minute or undergoing hemodialysis. Adjustment for patients with more mild renal impairment or undergoing peritoneal dialysis is not as well described.

Therapeutic drug monitoring is always indicated for patients with impaired renal function receiving an injectable drug, EMB, or cycloserine for TB, and may be helpful for other medications as well.
REFERENCES

EXTRAPULMONARY TB


HIV


**LIVER DISEASE**


**PEDIATRICS**


**PREGNANCY**


RENAI FAILURE


The careful monitoring of patients with drug-resistant TB is essential to their safe and successful completion of therapy.

Initial Evaluation

The critical and exacting task of monitoring the patient with drug-resistant tuberculosis (TB) begins with a thorough and organized initial evaluation. This evaluation includes the same elements required for drug-susceptible TB patients:

- Demographic information (name, address, date of birth, race and ethnicity, etc.)
- Full TB history (including medications, surgeries, and complications)
- Past medical history (including medications, allergies, psychiatric history, HIV status, diabetes, and other complicating conditions)
- Social history (including substance use and housing)
- Source case and contact information (including incarceration history, previous residences, and household contacts)
- Review of systems
- Thorough physical exam
- Baseline laboratory evaluations (including HIV serology and pregnancy test)

Use a systematic approach to monitoring.
Documentation

During the intake process, use a standardized form to organize data regarding prior treatment, evaluation, and other notable events.

A DRUG-O-GRAM
- Documents previous and current drug treatment, weights, microbiology and radiology results, and other notable information in an easy-to-read, tabular form.
- See Monitoring Tool 1.

Another important document will assist all team members in monitoring a patient with drug-resistant disease:

A CARE PLAN
- Delineates the important monitoring events required at intervals through the course of care and after treatment is discontinued.
- Ensures that elements of care are not neglected and can be reviewed with patients so they can anticipate upcoming events.
- See Monitoring Tool 2 for a sample care plan that can be customized for individual patients.

Monitoring flow sheets can track progression of blood work; bacteriology results; and hearing, vision, and vestibular exams. See Monitoring Tools 3, 4, and 5 for examples of these flow sheets.

General Monitoring

General monitoring and relationship-building occur with each patient encounter:
- Hospitalized patients are monitored at least daily by physicians and other providers.
- Outpatients are monitored:
  - 5–7 days per week by staff dispensing directly observed therapy (DOT)
  - By physicians:
    - Every week or every other week early in the course
    - Monthly after things are going very well
    - Occasionally less frequently in the second year of treatment
  - By nursing staff, social workers, audiologists, etc., as needed

Direct and active monitoring includes culture collection, blood testing, radiographic imaging, audiology testing, and physical examination. Indirect monitoring involves observation of the patient’s affect, mentation, etc.
Specific Monitoring

**DRUG ADMINISTRATION**

Ideally, all TB treatment should be given by DOT, which includes watching patients swallow their medications. Treatment for multidrug-resistant TB (MDR-TB) should **always** be given by DOT (including pyridoxine supplementation). Weekend doses, drugs given more than once a day, and drugs tolerated only at bedtime will provide programmatic challenges. Every effort should be made to observe every dose of medication. This may require inpatient admission during the initial adjustment phase for some patients.

Routinely ask patients:

- “How did you take your medication?”
- “Did you take your medication around the same time as milk-based products, antacids, or vitamin products?”
  (These inhibit the absorption of fluoroquinolones.)
- “Did you throw up after taking your medicine?”

Serum drug levels and other laboratory tests (uric acid elevation in patients receiving pyrazinamide [PZA]) can be a clue as to accurate dosing.

**DRUG ABSORPTION AND DRUG INTERACTIONS**

HIV and other diarrheal and malabsorptive syndromes affect drug absorption and undermine TB treatment. Monitor patients at risk for poor absorption for diarrhea and other symptom changes.

Many drugs interfere with or contribute to toxicity with TB therapy. Monitor patients as to any new medication started. This should include over-the-counter therapy, such as diphenhydramine, vitamin supplements, antacids, and “alternative” or “herbal” supplements.
WEIGHT AND NUTRITION

Many patients with TB are poorly nourished. This is especially pronounced in patients who have developed drug-resistant disease over years of failed treatments. Weight and nutritional status are important markers for disease status. Addressing them is an important aspect of therapy.

- Monitor patients’ weight throughout the course of treatment.
- Maximize the nutrition of undernourished patients.
- Offer hospitalized patients flexible meals of their choice, have dietary consultation, and offer dietary supplementation.
- Some patients feel best and gain the most nutritional benefit from small, frequent meals throughout the day (mini-meals).
- Occasionally, tube feedings for supplementation are required, and rarely, parenteral nutrition is used (especially prior to surgery for best post-operative healing).
- Customize outpatient management to the nutritional status of the patient. Some patients will only need to have their weight monitored, and others will require food diaries, regular nutritional labs, and ongoing nutrition consultations.
- Some food supplements (such as Ensure) interfere with absorption of fluoroquinolones and should be offered more than 2 hours before or after the drug.

SUBSTANCE ABUSE AND MENTAL HEALTH

Some TB patients are at higher risk of substance abuse and mental health issues. Substance abuse treatment programs are important partners with TB clinics and providers. Similarly, treatment of mental health disease is paramount in keeping patients compliant with TB therapy.

- Closely monitor a patient’s success and/or relapse with substance abuse issues during TB treatment in order to anticipate toxicity (alcohol with isoniazid [INH] and cycloserine, methadone with rifamycins, etc.) and to avoid adherence complications.
- Closely monitor mental health symptoms—especially for patients receiving cycloserine. Cycloserine’s most common toxicities are depression, psychosis, and suicidal ideation.
- Even patients without underlying mental health issues will need significant mental health support and monitoring during the long and arduous treatment for drug-resistant TB. Situational depression will affect many and can be quite debilitating. Monitor patients for these symptoms and provide support as needed.

Ongoing TB education is essential…

Most people will only be able to process a small amount of information during the initial diagnosis and treatment period. Constant education and support will help patients and families to anticipate toxicities and tolerate inconveniences during the long course of treatment.
RESPIRATORY SYMPTOMS
- Routinely monitor the patient’s cough, respiratory status, and sputum production. Most TB patients’ respiratory symptoms improve in the first few weeks of effective treatment. Even most patients on appropriate MDR-TB treatment will improve symptomatically by 3–6 weeks on treatment.

Investigate failure to improve or return of respiratory symptoms after initial improvement. Consider all the following possibilities:

- Some patients will have another respiratory infection or process (malignancy among others).
- Some patients will be nonadherent with therapy or not achieving therapeutic levels.
- Some patients will be experiencing TB treatment failure:
  - Repeat cultures and susceptibilities.
  - Consider a regimen change (never add a single drug to a failing regimen).

Interpret respiratory symptoms in the context of the entire clinical picture: fever curve, weight gain, other systemic symptoms, intercurrent illness, microbiologic response to treatment, etc.

SYSTEMIC SYMPTOMS
- Monitor the following constitutional symptoms most commonly affected in TB patients:
  - Fever
  - Appetite
  - Energy

Other symptoms might be related to the specific site of TB disease and should be monitored based on baseline findings. For example, headache, vomiting, and neurologic changes are seen with central nervous system (CNS) disease.

- Screen for symptoms of co-morbid conditions, especially HIV.

While initial immune reconstitution may exacerbate TB disease, the long-term health of the patient and ability to cure TB disease relies on the successful treatment of HIV. The avoidance of, or at least recognition of, associated problems and other opportunistic infections will contribute to TB treatment success. In particular, gastrointestinal (GI) problems associated with HIV markedly contribute to poor drug absorption, treatment failure, and amplification of resistance.
**DRUG TOXICITY** (see Table 1)

- Warn **every** patient beginning any TB therapy to expect toxicity.
  - Even patients taking INH monotherapy frequently feel lousy in the first couple of weeks of therapy. If patients do not anticipate this reaction and are not reassured that it will improve, they will frequently stop the therapy.
  - Monitor patients for general toxicities and drug-specific toxicity at every health care visit (including during DOT encounters).
  - Patients with drug-resistant TB will experience much more toxicity than patients treated for drug-susceptible disease. Most of the second-line TB therapies give significant toxicity.

Help the patient to understand:

- They will feel worse before they feel better.
- The toxicity symptoms will improve.
- Steps can be taken to minimize the toxicity symptoms.
- In the long run, the treatments will cure the disease, save the patient’s life, and prevent transmission to loved ones.

- Take measures to minimize toxicity and to help patients tolerate the toxicity rather than losing the drug in the regimen. In many cases, there are no alternative drugs for replacement.
  - Change the timing of the dose to minimize toxicity.
  - Give the dose at bedtime.
  - Dose some medicines with food.
  - Serum drug levels are sometimes helpful. This is best documented in cycloserine. Keep the level below 35 mcg/ml to help avoid CNS side effects.
  - See Chapter 7, *Adverse Reactions*, for specific treatments for adverse events.

**Note:** While most drugs can be continued safely, in general, a patient who suffers vestibular toxicity from an aminoglycoside or capreomycin should not receive those drugs in the future.
Table 1.

COMMON SIDE EFFECTS OF ANTI-TUBERCULOSIS DRUGS

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gl side effects</td>
<td>Ethionamide, Quinolones, Para-aminosalicylate (PAS), Clofazimine, Rifabutin, Aminoglycosides</td>
</tr>
<tr>
<td>Headache</td>
<td>Quinolones, INH, Cycloserine, Ethambutol (EMB), Ethionamide</td>
</tr>
<tr>
<td>Skin problems</td>
<td>Clofazimine, Cycloserine, INH, Rifabutin, PAS, Ethionamide, Ethambutol (EMB)</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>Clofazimine, Quinolones</td>
</tr>
<tr>
<td>Hepatotoxicity (early symptoms are anorexia and malaise, then abdominal pain, vomiting, jaundice)</td>
<td>INH, Rifabutin, Ethionamide, Ethambutol (EMB), Ethionamide, PZA, Rifampin (RIF)</td>
</tr>
<tr>
<td>Behavioral changes</td>
<td>INH, Ethionamide, Cycloserine, Quinolones</td>
</tr>
<tr>
<td>Musculoskeletal / joint / tendons</td>
<td>Quinolones, PZA, Rifabutin, INH (positive antinuclear antibody [ANA])</td>
</tr>
<tr>
<td>Visual changes, eye pain, change in color vision</td>
<td>EMB, Rifabutin, Clofazimine, Linezolid</td>
</tr>
<tr>
<td>Hearing loss, ringing in the ears, vestibular toxicity</td>
<td>Aminoglycosides, Capreomycin</td>
</tr>
<tr>
<td>Dizziness</td>
<td>Cycloserine, Quinolones</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>INH, Ethionamide, Cycloserine</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Ethionamide, PAS</td>
</tr>
<tr>
<td>Hypokalemia / hypomagnesemia</td>
<td>Aminoglycosides, Capreomycin</td>
</tr>
</tbody>
</table>

Drugs in **boldface** most commonly cause this effect.

For specific drug toxicities, see Chapter 4, Medication Fact Sheets.
Routine toxicity monitoring for patients with MDR-TB frequently includes the following (see also Chapter 4, Medication Fact Sheets):

- Obtain complete blood counts at baseline and intermittently, as clinically indicated.
- Obtain creatinine twice monthly at least initially and at least monthly for patients receiving aminoglycosides or capreomycin. Interpret the creatinine carefully in patients with small body weight, over 50 years of age, and in those with diabetes (creatinine over 1.0 mg/dl is elevated in these patients). Baseline creatinine clearance should be documented in persons with serum creatinine greater than expected or if any concerns arise.
- Send liver function tests (LFTs) monthly (AST, ALT, Total Bilirubin).
- Monitor potassium, calcium, and magnesium monthly for patients on capreomycin and aminoglycosides.
- Test thyroid function (TSH) at baseline and every 3 months for patients on ethionamide or PAS. Monitor TSH sooner if symptoms of hypothyroidism develop or if baseline thyroid shows abnormalities. Use thyroid replacement if hypothyroidism is documented.
- Perform audiology and vestibular function monthly for patients receiving aminoglycosides or capreomycin (dizziness or ear ringing can also result from cycloserine/quinolones).
- Perform visual acuity and color discrimination screens monthly and watch for evidence of uveitis for patients on EMB, rifabutin, and clofazimine.

**MICROBIOLOGY**

Microbiologic response to TB treatment is essential in adult patients with pulmonary disease. *Even for drug-susceptible disease, the prompt conversion to culture-negative sputum is very reassuring and allows for the use of short-course TB therapy. For drug-resistant disease, monitoring of sputum for smear and culture positivity is even more important.*

Some experts base duration of drug therapy and use of injectable drugs on time to sterilization (18–24 months after culture conversion).

- Monitor serially in the early phases of treatment until the patient has 3 negative sputum smears.
- National guidelines suggest monthly monitoring (after smear conversion) of sputum for acid-fast bacilli (AFB) smear and culture throughout the entire duration of treatment of MDR-TB, at completion of therapy, and several times in the 2 years after treatment. Collecting 2 sputum specimens 8–24 hours apart will markedly reduce the chance of false-negative sputum culture results. In the second year of treatment, some programs feel comfortable with somewhat less frequent sputum collection.
- Most MDR-TB patients, whose disease will eventually be cured, convert their sputum cultures to negative within 3–4 months. Patients whose sputa are still culture-positive after 2–3 months of treatment should be reevaluated fully, including repeat susceptibility testing for the possibility of further development of resistance.
Whenever sputum is being collected, appropriate attention should be given to infection control. Sputum should be collected in a secure isolation area or an outdoor environment. **If the patient cannot spontaneously expectorate sputum, perform induction with hypertonic saline in an appropriately engineered environment.**

When smear or culture positivity persists or recurs, address and consider:

- **Adherence to therapy**
- **Accurate administration and dosing**
- **Drug absorption**
- **Adequacy of the drug regimen**
- **Development of new resistance**
- **Respiratory and constitutional symptoms**
- **Radiographic findings**
- **Possible poor penetration of drugs into a localized area;**
  - e.g., empyema, thick-walled cavity in poorly vascularized lung

Microbiologic monitoring of **extrapulmonary** disease is more difficult.

- Urine, blood, and even cerebrospinal fluid are easy and safe to obtain.
- Serial biopsies or aspirates are inconvenient, expensive, and carry a degree of risk. However, if the patient is not responding to therapy, or if there is any reason to suspect that the treatment is failing, strongly consider repeat specimen collection.

Serial culture collection in children is also difficult.

- Gastric aspirates are the primary source of AFB culture in children with pulmonary disease. These are only positive in 40% of children even before treatment begins.
- Consider repeat cultures in the context of clinical response to therapy vs. yield of the specimen.

**DRUG LEVELS**

There is little evidence that the use of therapeutic drug monitoring (TDM) contributes to successful outcomes of drug-resistant TB therapy. Despite this fact, many experts feel strongly about routine use of TDM. Experts who routinely use drug levels to manage their patients cite the following:

- Second- and third-line anti-tuberculosis therapies have much narrower therapeutic windows. The therapeutic serum level above the minimum inhibitory concentration (MIC) is very close to the level that causes toxicity.
- A drug dose can sometimes be increased if you see that the serum level is well below that which causes toxicity.
An elevated drug level can sometimes be noted before the patient suffers significant or discernible clinical toxicity—allowing the dose to be modified and avoiding dangerous toxicity.

In cases where few drugs are available, use of drug monitoring may allow you to maximize drug doses to avoid amplification of drug resistance and optimize chance of cure.

Situations in which drug levels are routinely used:

- Aminoglycoside levels in patients who have known renal dysfunction. The patient should have trough drug levels below the nephrotoxic level. With the once-daily dosing used for treatment of TB, this is seldom an issue for patients with reasonably normal renal function. Some experts routinely monitor aminoglycoside levels on all patients.
- Monitoring cycloserine levels can help the provider to predict and minimize CNS adverse reactions and prevent seizure activity.
- EMB levels may be useful for patients with reduced renal function.

See Chapter 4, Medication Fact Sheets, and Appendix 12, Therapeutic Drug Monitoring, for details about timing of blood draws, processing, and shipping of samples.

### RADIOGRAPHS

Radiographic response to TB treatment lags behind clinical and microbiologic response.

Obtain routine chest radiographs:

- **Every 3–6 months;**
- **At the end of therapy;** and
- **6, 12, and 24 months** after treatment is completed.

Additional radiographs are sometimes obtained when the patient has a clinical decompensation or intercurrent illness. CT scans and special views (lordotic) may be useful for individual cases.

In particular, CT scans should be obtained when a more accurate assessment of the extent of disease is needed for surgery, duration of treatment, or unexplained changes on the chest radiograph.

CT scans may be particularly useful for following lymph node and mediastinal disease, as well as extensive pleural and parenchymal changes. An end-of-treatment CT is often useful to obtain as a baseline for future follow-up in very complex cases. Radiographs (plain films, CT, or MRI) are particularly useful in monitoring response to treatment for patients whose disease cannot be followed microbiologically:

- **Intracranial lesions**
- **Abscesses**
- **Bone disease**
- **Pleural disease**
- **Deep lymph nodes**
Summary

The monitoring of patients with drug-resistant TB requires a systematic, organized approach. Helpful tools are the Drug-O-Gram and Care Plan, which should be developed and customized for each patient.

Elements that require monitoring include:

- Drug administration
- Weight and nutrition
- Drug absorption and drug interactions
- Substance abuse and mental health
- Respiratory and systemic symptoms
- Symptoms of drug toxicity
- Blood tests, visual screens, audiology and vestibular testing
- Bacteriology
- Therapeutic drug monitoring
- Radiology
## Monitoring Tool 1: **DRUG-O-GRAM**

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**Summary Date:**

**Name:**

**DOB:**

**Health Department:**

**Treating Physician:**

**File No.:**

**Treatment Regimen**

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**Bacteriology**

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**Susceptibility Results**

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*Adapted from LA County TB Control Program Drug-O-Gram*
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<td>Request/review old records</td>
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<td>CBC, LFTs, K+, Ca++, Mg++, Creat Clearance serially as indicated (see chapters 6&amp;7)</td>
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<td>HIV serology with pre/post test counseling</td>
<td>If HIV+ CD4 viral load</td>
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<td>Baseline TSH (cycloserine / ethionamide)</td>
<td>TSH q 3 mo - Synthroid if elevated TSH</td>
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<td>Review prior sputum results; Repeat sputum</td>
<td>Sputum x3 q1-2 weeks until smear-negative</td>
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<td>Review susceptibilities; request extended susceptibility tests</td>
<td>Follow-up pending susceptibilities</td>
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<tr>
<td>Infection control/isolation</td>
<td>Continue until culture-negative x3 (see chapter 8)</td>
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<td>Consider insertion of indwelling catheter</td>
<td>Aminoglycoside IV or Capreomycin in IV (MIS-2 days/wk)</td>
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<td>DOT initiated; pt educated</td>
<td>Educate as needed</td>
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<td>Pyridoxine 100-150 mg (or more)</td>
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<td>Baseline weight</td>
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<td>Nutritional assessment</td>
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<td>Audiology/vestibular screen</td>
<td>Continue monthly as long as aminoglycoside or capreomycin given</td>
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<td>Vision and color discrimination screens monthly while EMB, dapsone, or rifabutin used</td>
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** Substance abuse/psychosocial factors influencing compliance
** Education needs
** Complete contact eval (LHD)

* 24 hr. creatinine clearance if any elevation of creatinine or any question of renal compromise. Repeat if change in renal function.
** Some experts document drug levels for all patients. Adjust dose or interval and repeat as needed.

Adapted from Tuberculosis Resource and Education Center www.tsh.state.tx.us/tcid/TB-Education-Ctr.htm
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Adapted from Los Angeles County TB Control Program Lab Flow Sheet
Monitoring Tool 4: **BACTERIOLOGY FLOW SHEET**

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A more detailed bacteriology flow sheet is available at http://www.nationaltbcenter.edu
Monitoring Tool 5: **HEARING, VISION, & VESTIBULAR EXAM FLOW CHART**

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<td><strong>Vestibular Exam</strong></td>
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<td><strong>RHOMBERG</strong></td>
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Adapted from the Los Angeles County TB Program Eye/Ear Exam Flow Sheet
References


## Adverse Reactions

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<td>Hematologic Abnormalities</td>
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<td>Musculoskeletal Adverse Effects</td>
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Adverse reactions and toxicity accompany essentially all treatment courses for drug-resistant TB.

Introduction

Treatment of drug-resistant tuberculosis (TB) involves the use of multiple medications, and most patients will experience some difficulty tolerating them. The response of an individual patient, however, cannot be predicted. Medications should not be withheld because of fear of a reaction. Even some elderly or very ill patients will readily tolerate medications. By contrast, others may have serious problems tolerating relatively simple regimens.

Patients should be well-informed and recruited as partners in their therapy.

- Prior to initiating a treatment regimen, it is essential to discuss the benefits and risks of therapy. The patient should understand the need for treatment, the importance of each medication in the treatment regimen, and the possible side effects and toxicities.

- Assure patients that every possible attempt to make their treatment as easy as possible will be made, but stress that having enough effective drugs in the treatment is essential to achieving a cure. While side effects will be addressed and treated as aggressively as possible, patients should be mentally prepared for likely discomfort and should brace themselves for the long road ahead.

- Help patients realize that this may be their last opportunity for cure, and future treatment regimens could be more toxic and less effective.

- Breaks in therapy should be avoided whenever possible to maximize the effectiveness of treatment.

Pay close attention to the reported side effects of each patient. Most patients will be willing to continue medication despite symptoms when they understand the benefit of the medication, know that many of these symptoms improve after the first several weeks, and are assured that their providers are doing their best to evaluate and address their problems. Express appreciation for the patient’s efforts to cooperate. This recognition often helps a patient to continue therapy.

Do not stop a drug that leaves the patient at risk of relapse or treatment failure without consulting an expert in the management of drug-resistant TB. Likewise, a drug dose should not be reduced unless it can be done without compromising its activity in the regimen. In some cases, minor drug reactions and discomfort may persist and will have to be tolerated for the sake of the success of the regimen. In some instances, very serious adverse events will need to be considered.
as necessary in order to save a life. For example, some patients with extensive disease and extensive resistance may need an aminoglycoside to ensure cure. These patients should be informed that hearing loss may be inevitable in order to ensure the patient does not die of TB.

Gastrointestinal

The most difficult side effects at the initiation of treatment often relate to gastrointestinal (GI) upset. Nausea and vomiting are most often reported, but abdominal cramps and increased flatulence are equally troubling to some patients. Anorexia from nausea, vomiting, and/or the metallic taste caused by ethionamide can prevent weight gain or even cause worrisome weight loss. Pregnancy should be considered as the possible etiology of nausea and vomiting, especially if the symptoms occur after a period of initial tolerance. All female patients with multidrug-resistant TB (MDR-TB) should strongly consider contraception/pregnancy avoidance. Many providers do monthly laboratory screening to detect pregnancy early.

Causes of GI symptoms include:

- Gastritis
- Hepatitis or hepatotoxicity
- Biliary disease
- Pancreatitis
- Peptic ulcer disease
- Inflammatory bowel disease
- *Clostridium difficile* colitis
- Lactose intolerance
- Acute renal failure or nephrotoxicity
- GI TB if early in the course

**Nausea and Vomiting**

Treatment of Nausea and Vomiting:

- **First, ask the patient:** Patients may have strong ideas about which medication is causing them problems. Their opinions must be addressed and respected (even if no change can be made).

- Encourage the patient to continue to take the medication and assure them that for most patients many adverse reactions lessen over the first several weeks and may become tolerable or resolve entirely.
The following are specific interventions that can be attempted, depending on the drug:

- If the drug suspected of causing the symptoms is ethionamide or para-aminosalicylate (PAS), decrease the dose (ethionamide 250 mg, PAS 2–4 grams) to see if the lower dose is better tolerated. Advise the patient that this is a test to determine which drug is causing side effects and that the drug dose will be increased back to therapeutic dose in a manner that will be better tolerated. The dose of medication can be gradually increased over the next 2 weeks. Both medications can be given in 2 or 3 doses over the day, which may improve tolerance. Many patients tolerate the higher dose of ethionamide better in the evening (ethionamide 250 mg in a.m., 500 mg at bedtime; or may only tolerate 500 mg at bedtime). The goal should be to increase the ethionamide dose to at least 500 mg daily and the PAS dose to at least 8 grams daily.

- Administer antiemetics or antacids prior to medication or as needed. Note: Antacids cannot be given within 2 hours of fluoroquinolones.

The following are some specific options (adult doses):

- **Promethazine** (Phenergen) 12.5–25 mg PO, IV, or PR 30 minutes before the dose and every 6 hours as needed
- **Metoclopramide** (Reglan) 10–20 mg PO or IV every 4–6 hours as needed
- **Ondansetron** (Zofran) 8 mg PO 30 minutes before the dose and again 8 hours after the dose; for refractory nausea 24 mg 30 minutes before the dose can be tried

- Try to separate the responsible medication from other drugs by several hours or give it before bedtime to allow most of the adverse effects to occur during sleep. This is relatively easy if the patient is hospitalized, but in the outpatient setting, directly observed therapy (DOT) may only be available once daily. It may be necessary to allow the patient to self-administer the evening dose of medications or a dose later in the day. This can be problematic either way. If the medication is taken along with others and all medications are vomited, nothing is gained; alternatively, if the medication is essential to the regimen, even the most compliant patients may have difficulty taking a medication that predictably makes them feel bad.

- Give a light snack (crackers or toast, tea or soda) before medications.
- Space the medications out during the day to lessen the pill burden.
- Eliminate (or at least try to minimize) alcohol consumption to lessen GI irritation and the risk of hepatotoxicity.
- Treat gastritis or acid reflux. Proton pump inhibitors are very helpful in many patients; H2-receptor blockade may also be helpful. Use of a drug such as sucralfate interferes with absorption of fluoroquinolones if used within 2 hours of the dose.
- Minimize use of nonsteroidal anti-inflammatory drugs (NSAIDs). This may be difficult if the patient also has arthralgias and myalgias from medications. Try acetaminophen, although it has been reported to increase isoniazid (INH) hepatotoxicity.
- Diagnose and treat co-existing *Helicobacter pylori* infections.
- Encourage hydration. Sports drinks such as Gatorade or PowerAde may be helpful as they also replace electrolytes. However, the glucose content of these drinks would be unacceptable for most diabetics.
- If the odor of a medication is contributing, try concealing the odor by putting the drug into a gelatin capsule that can be purchased at a pharmacy.
- Electrolytes, BUN, and creatinine should be evaluated and corrected if significant vomiting or diarrhea occurs.

Evaluate the effects of the interventions you have used to decrease the nausea and vomiting. If the patient still has daily nausea that persists through much of the day and interferes with nutrition and hydration, despite employing strategies along with antiemetics, the medication may need to be stopped. This is an easier choice if an adequate regimen can be designed without the medication, but if it leaves the patient with a regimen likely to fail, some nausea and even vomiting may need to be tolerated at least in the initial period of treatment.

- Consider hospitalization with better access to antiemetic therapy, IV hydration, and spacing of medications, especially before a regimen is abandoned.
- In most instances, treatment with less than 4 active drugs to which the patient is susceptible should not be given.
- **Consultation with an expert is especially important in this situation.**
DIARRHEA

Diarrhea, along with increased flatus and cramping, can cause significant difficulty for patients, but very rarely does it lead to discontinuation of medication.

- PAS often causes diarrhea with the initiation of medication. Inform patients that diarrhea usually resolves or improves considerably after several weeks.

**Always start PAS at a low dose and then increase gradually over the next 2 weeks to minimize this problem as much as possible.**

See Figure 2 in Chapter 3, *Treatment.*

- Fluoroquinolones can also cause loose stools or diarrhea, along with increased flatulence. This can improve but may persist in part for the duration of therapy. Lactobacillus or foods such as yogurt (not given within 2 hours of the fluoroquinolone dose) with active cultures may improve symptoms by replacing normal flora. Loperamide (Imodium) 2–4 mg PO can be used initially and then 1–2 mg after each loose stool to a maximum of 8–16 mg/day for adults. Loperamide is approved for use in children over 2 years old. This may be used intermittently, especially when patients need to attend social functions or return to work. It should not be used daily. Encourage patients to tolerate some degree of loose stools and flatulence and remind them that the fluoroquinolone is a key drug in the treatment regimen.

If the diarrhea is severe, other etiologies may include:

- *C. difficile* colitis (especially if broad spectrum antibiotics used; e.g., fluoroquinolones)
- Other infectious diarrheas
- Parasitic disease
- Lactose intolerance, especially if patient is hospitalized and given foods not commonly part of their diet

Rarely, a drug may have to be discontinued if diarrhea is severe. Attempts to continue medication should be based on the importance of the drug in the treatment regimen and the availability of other substitute agents.
HEPATOTOXICITY

- Any GI complaint may represent hepatotoxicity. **If hepatotoxicity is suspected, hold all anti-tuberculosis medications that are potentially hepatotoxic until laboratory results are available.** The ALT or SGPT is the hepatocellular enzyme most directly associated with hepatocellular damage. If the enzymes are normal, continue medications using the strategies previously noted to lessen nausea and vomiting.

- If elevated liver function tests (LFTs) are detected, consider causes other than hepatotoxicity, such as gallstones, viral hepatitis, etc. These are potentially treatable causes that, if addressed, may make treatment of the TB easier.

- If the hepatocellular enzymes are less than 3 times the upper limit of normal, continue the medications using strategies for managing nausea and vomiting and observe carefully. If symptoms continue, repeat liver enzymes once more to exclude hepatotoxicity as a cause. If the bilirubin is increased, but the hepatocellular enzymes are only mildly elevated, evaluate for causes of direct and indirect hyperbilirubinemia and monitor the patient closely.

- If the enzymes are more than 3 times the upper limit of normal, hold all potentially hepatotoxic medications. If at least 3 medications remain in the treatment regimen that are not hepatotoxic (for example, ethambutol [EMB], the aminoglycosides, levofloxacin, and cycloserine), then these can be continued. If not, then all anti-tuberculosis medications should be held.
  - Monitor the LFTs weekly.
  - When liver enzymes fall to less than twice normal (some experts prefer to wait until the enzyme levels normalize or return to baseline), the remaining potentially hepatotoxic medications should be reintroduced one at a time. If other non-hepatotoxic medications were also held, they should be restarted along with the first possibly hepatotoxic drug. Carefully observe for clinical reactions and repeat liver enzymes twice weekly until the medication has been taken for at least a week and enzymes are stable. The next medication can then be added to the regimen and monitored. All remaining medications should be reintroduced in this manner.
  - If reintroduction of a medication leads to clinical symptoms of hepatotoxicity and enzymes increase, stop that medication and eliminate it from the regimen.
  - Even if a medication is identified as causing hepatotoxicity, reintroduce each additional medication one at a time because in some instances more than 1 medication may be responsible for the hepatotoxicity.

- Monitor liver enzymes at least monthly for the remainder of the treatment course.
Dermatologic and Hypersensitivity Reactions

MACULOPAPULAR RASH AND PRURITUS

Maculopapular rash and pruritus are common early side effects. These effects may resolve after the first several weeks of therapy without stopping medications. If the reaction is mild, continue treatment and treat the rash and pruritus symptomatically.

For minor dermatologic reactions, various agents may be helpful and allow continuation of the medication. They can be given prior to the anti-tuberculosis drug or as needed.

- **Diphenhydramine** (Benadryl) 25–50 mg PO, IV, or IM given before the medication, and then every 4–6 hours PRN may lessen skin irritation. If patients become drowsy, caution them not to drive or operate machinery.
- **Other antihistamines**: Chlorpheniramine (Chlor-trimeton) 4 mg PO before the medication and then every 4–6 hours as needed; hydroxyzine (Atarax) 25 mg PO or IM QID (can be increased to 50 mg QID); or loratadine (Claritin) 10 mg PO before the medication.
- **Hydrocortisone cream** can be used topically.
- **Low-dose prednisone** (10–20 mg/day) for several weeks can be tried if other measures are not helpful.

Drugs should not be continued if there are systemic symptoms, fever, urticaria, mucous membrane involvement, blistering of the skin, edema of the lips or eyes, or wheezing or compromise of the airway.

Evaluate other potential etiologies of rash and pruritus:

- Scabies and insect bites may masquerade as a drug rash.
- Contact dermatitis (question patient about use of new lotions, soaps, perfumes, etc.).
- Phototoxicity (may respond to sunscreens, but these may cause contact dermatitis).
- Other drugs, especially new agents, should be evaluated as possible etiologies.
- Other dermatologic causes; psoriasis, pityriasis, atopic dermatitis, etc.
- Dry skin, especially in diabetic patients, may be the cause of pruritus. Consider liberal use of lotions, such as petroleum jelly and lanolin (may be purchased in a feed supply store where it is less expensive). Dry skin is a serious problem with clofazimine.
- Hypothyroidism.
- Acneiform lesions may flare with the use of INH, ethionamide, and clofazimine. This will usually resolve after several months, often with improvement in the patient’s acne.
FLUSHING REACTIONS
Flushing and/or itching of the skin without a rash usually involve the face and scalp, and occur 2–3 hours after medications. Redness and watering of the eyes may also occur. This is usually due to rifampin (RIF) or pyrazinamide (PZA). It is usually mild and resolves in time without therapy. If it is bothersome to the patient, an antihistamine may be administered to treat or to prevent the reaction.

Patients taking INH may experience flushing and/or itching of the skin with or without a rash, plus possible hot flashes, palpitation, or headache 2–3 hours after consuming tyramine-containing foods (cheese, red wine) or certain fish (tuna). Advise patients not to ingest foods that precipitate the reaction while they are receiving INH.

PHOTOTOXICITY
Warn patients about the potential for phototoxicity if they are taking PZA, clofazimine, or fluoroquinolones. Caution them to limit sun exposure and to use sunscreens. This is especially important with clofazimine because sun exposure markedly increases the hyperpigmentation that occurs with this medication. Phototoxicity may occur for prolonged periods even after the causative drug is stopped.

Pseudojaundice (brownish discoloration of the skin) has been reported due to rifabutin. The sclera is clear and the bilirubin and other liver functions are normal.

LICHERNOID DRUG REACTIONS
Pruritic, flat-topped, violaceous papules may occur anywhere, but most commonly involve the wrists, shins, and back. Mucous membranes and the scalp may also be involved. Differentiation from lichen planus may be made by a biopsy showing eosinophilic infiltration. Lesions may resolve while medication continues. Topical hydrocortisone or antihistamines may be helpful to control pruritus. Medication should not be discontinued unless an equally effective drug is available for substitution. Identifying the medication responsible in a multidrug regimen may be difficult because lesions resolve slowly and EMB, INH, streptomycin, and cycloserine have all been identified as causing these lesions.

HIVES, URTICARIA
Hives and urticaria may be caused by nearly any drug in the regimen. They more commonly are due to INH, RIF, PZA, ethionamide, fluoroquinolones, and EMB.

All potentially responsible drugs should be stopped until the reaction resolves. If the initial reaction was not severe and there was NO evidence of anaphylaxis, angioedema, or airway compromise, try to identify the responsible drug by rechallenging (restarting) each drug one at a time. Usually the most important drug in a regimen should be started first unless there is strong suspicion that it is the cause of the reaction. In this situation, a desensitization attempt might be made. Tables 1 and 2, modified from the Philadelphia TB Control Program, present a possible way to rechallenge with various drugs. Following desensitization, medications should continue to be given 7 days a week for the remainder of therapy.
If a test dose of any drug causes a reaction, that drug should be discontinued, unless it is deemed essential to the regimen. If that is the case, desensitization can be considered.

If the initial reaction was severe, use 1/10th of the Day 1 dose listed in Table 1 and then increase carefully if tolerated. Give the drugs in a setting where a health care provider can respond to any reaction.

Table 1.
SUGGESTED DRUG RECHALLENGE DOSES*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose – Day 1</th>
<th>Dose – Day 2</th>
<th>Dose – Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>50 mg</td>
<td>300 mg</td>
<td>600 mg</td>
</tr>
<tr>
<td>Rifampin</td>
<td>75 mg</td>
<td>300 mg</td>
<td>600 mg</td>
</tr>
<tr>
<td>PZA</td>
<td>250 mg</td>
<td>1 gram</td>
<td>full dose</td>
</tr>
<tr>
<td>Ethionamide</td>
<td>125 mg</td>
<td>375 mg</td>
<td>500–750 mg</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>125 mg</td>
<td>250 mg</td>
<td>500–750 mg</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>100 mg</td>
<td>500 mg</td>
<td>full dose</td>
</tr>
<tr>
<td>PAS</td>
<td>1 gram</td>
<td>4 gram</td>
<td>6–8 grams</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>125 mg</td>
<td>500 mg</td>
<td>full dose</td>
</tr>
</tbody>
</table>

* Philadelphia TB Program 1998

Doses for the following drugs were not supplied by the Philadelphia program, but can be assumed to be the following, based on the doses given in Table 1:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose – Day 1</th>
<th>Dose – Day 2</th>
<th>Dose – Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>125 mg</td>
<td>500 mg</td>
<td>full dose</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>125 mg</td>
<td>500 mg</td>
<td>full dose</td>
</tr>
<tr>
<td>Fluoroquinolone</td>
<td>50 mg</td>
<td>200–250 mg</td>
<td>full dose</td>
</tr>
</tbody>
</table>
Implement these protocols only in a hospital or in a clinical area with the ability to monitor and respond to possible anaphylaxis, and when the drug is determined essential to success of therapy. Because isoniazid and rifampin are such important drugs, desensitization is most commonly attempted with these 2 medications.

Steroid therapy may be used with desensitization and then tapered over 2–3 weeks.

**Once desensitization has been successfully completed, it is essential that the patient take medication 7 days per week** for the remainder of treatment to avoid another possibly more severe reaction.

Do not attempt desensitization protocols if anaphylaxis occurred or the reaction was severe and involved significant systemic symptoms and/or mucous membranes as occurs with Stevens-Johnson syndrome or toxic epidermal necrolysis (TEN).

### Table 2. ORAL DESENSITIZATION FOR ISONIAZID, RIFAMPIN, & ETHAMBUTOL

<table>
<thead>
<tr>
<th>Time from start (hour:minute)</th>
<th>Dose of INH* (mg)</th>
<th>Dose of RIF** (mg)</th>
<th>Dose of EMB** (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0:00</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
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<tr>
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<td>1</td>
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<tr>
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<td>2</td>
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<td>1:00</td>
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<td>200</td>
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<tr>
<td>8:30</td>
<td>150</td>
<td>150</td>
<td>400</td>
</tr>
<tr>
<td>17:30</td>
<td>150</td>
<td>300</td>
<td>400</td>
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<tr>
<td>Early next a.m.</td>
<td>150 bid x 3 days</td>
<td>300 bid x 3 days</td>
<td>400 tid x 3 days</td>
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</table>

* Holland 1990

** Matz 1994
### Hematologic Abnormalities

Table 3 summarizes potential hematologic abnormalities associated with TB medications.

#### Table 3.

**HEMATOLOGIC ABNORMALITIES ASSOCIATED WITH ANTI-TUBERCULOSIS DRUGS**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Amikacin</th>
<th>Amox/Clav</th>
<th>Capreomycin</th>
<th>Clofazimine</th>
<th>Cycloserine</th>
<th>Ethambutol</th>
<th>Ethionamide</th>
<th>Gamma-interferon</th>
<th>Gatifloxacin</th>
<th>Imipenem</th>
<th>INH</th>
<th>Kanamycin</th>
<th>Levofloxacin</th>
<th>Linezolid</th>
<th>Moxifloxacin</th>
<th>PAS</th>
<th>Pyrazinamide</th>
<th>Rifabutin</th>
<th>Rifampin</th>
<th>Streptomycin</th>
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<tbody>
<tr>
<td>Aplastic anemia</td>
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<td>Eos</td>
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<tr>
<td>Hemolytic anemia</td>
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<td>X</td>
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<td>Red cell aplasia</td>
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<td>Hemolytic anemia</td>
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Other etiologies of hematologic abnormalities should be concurrently sought.
Severe Drug Reactions

Anaphylaxis is rare but can occur. Anaphylaxis presents within minutes of medication dosing. The patient classically has signs of airway compromise, such as stridor, wheezing, a feeling of the throat being closed, swelling of the tongue, and hoarseness. Additional symptoms include shock, urticaria, angioedema, confusion, and pruritus. Nausea, vomiting, cramping, and diarrhea may also occur. It is essential to identify the causative agent once the patient is stable. The use of a small challenge dose of medication may be needed and should be given in the hospital. Do not include drugs identified as causing anaphylaxis in the treatment regimen; do not try to desensitize to these agents.

Severe drug reactions may occur with any medication. Reactions associated with systemic toxicity, high fever, widely distributed urticaria, and bulla, along with mucous membrane involvement, is characteristic of Stevens-Johnson syndrome. When there is extensive sloughing of skin, toxic epidermal necrolysis (TEN) is likely. These should be distinguished from staphylococcal scalded syndrome, which requires antibiotic therapy. Each of these reactions needs immediate therapy, usually with systemic steroids and supportive care. A dermatology consultation and a skin biopsy should be requested if there is any question of the diagnosis. INH, RIF, EMB, streptomycin, ofloxacin, and cycloserine have been reported as causative agents. If a drug is identified as responsible for one of these reactions, it should never be used again.

RIFAMPIN HYPERSENSITIVITY REACTIONS

A variety of hypersensitivity reactions have been reported with RIF therapy. When any of these occur, treatment with RIF should be stopped. Do not try desensitization. Many patients require steroid therapy to control the reactions.

Reactions include:

- Cutaneous vasculitis
- Red cell aplasia
- Leukopenia and agranulocytosis
- Thrombocytopenia
- Disseminated intravascular coagulation
- Hemolytic anemia
- Pulmonary infiltrates
- Lupoid reactions
- Acute renal failure
Neurotoxicity

PERIPHERAL NEUROPATHY

Peripheral neuropathy is characterized by symmetrical polyneuropathy in nearly all cases. The first symptoms are tingling, prickling, and burning in the balls of the feet or tips of the toes. With further progression, sensory loss can occur. Ankle reflexes may be lost and weakness of dorsiflexion of the toes may be present. Symptoms may progress centripetally and also involve the fingers and hands. Unsteadiness of gait may develop due to proprioceptive loss. The diagnosis can usually be made clinically. The drugs most commonly implicated are INH, ethionamide, EMB, and cycloserine.

Neuropathy is more likely to occur in patients with diabetes, alcoholism, HIV infection, hypothyroidism, pregnancy, and with inadequate dietary intake of pyridoxine.

Pyridoxine prophylaxis (50 mg daily for patients with drug-susceptible TB under a standard treatment regimen) is usually adequate. If symptoms develop or progress, the dose can be increased to 100–150 mg daily.

Pyridoxine prophylaxis (100 mg daily) should be included for all patients (including a weight proportionate dose for children) receiving treatment for MDR-TB who take any of the above medications, but especially those taking ethionamide and/or cycloserine. Some experts prescribe 50 mg of pyridoxine for every 250 mg of cycloserine used. If symptoms develop or progress, doses of 150–200 mg may be tried. Caution should be exercised with individuals with end-stage renal disease, as pyridoxine may develop toxic levels in these cases and cause neurologic symptoms.

Additional interventions include:

- Correct vitamin and nutritional deficiencies.
- Address additional medical problems.
- Evaluate and correct electrolytes.
- Identify other potential medications that may cause peripheral neuropathy and change, if possible.
- Consider whether the dose of ethionamide or cycloserine can be reduced without compromising the regimen. Doses of aminoglycosides or fluoroquinolones should be reduced only if adequate serum levels will still be present. Monitor serum drug levels if doses are lowered.
- Physical therapy may be helpful but is often not available.
- Nonsteroidal anti-inflammatory agents or acetaminophen may be helpful.
- A tricyclic antidepressant (amitriptyline [Elavil] 25 mg PO at bedtime) can be tried in low dose if there are no contraindications. Linezolid cannot be given with tricyclic drugs or selective serotonin reuptake inhibitors (SSRIs) due to their mild MAO activity (risk of central nervous system [CNS] toxicity or serotonin syndrome). The dose of amitriptyline may be increased (to 150 mg maximum) if lower doses are not helpful.
- **Carbamazepine** (Tegretol), an anticonvulsant, at 100–400 mg PO BID can be tried. Blood dyscrasias and elevated liver function may complicate therapy, and a complete blood count (CBC) and liver function should be routinely monitored in patients on this medication.

- **Patients who fail to respond to a tricyclic may respond to gabapentin** (Neurontin). Adults should be treated initially with a single dose of 300 mg PO on Day 1, increased to 300 mg twice a day on Day 2, and 300 mg 3 times a day on Day 3. The dose may be titrated up to 1800 mg as needed for relief. Gabapentin is also associated with a wide range of adverse effects, including nausea and vomiting, as well as arthralgias and CNS symptoms. Decrease dosage with renal insufficiency.

- Rarely, medication may be discontinued, but only if an alternative drug is available or the regimen is not compromised.

### Central Nervous System Toxicity

A variety of mild effects may occur early in therapy, including drowsiness, headaches, concentration problems, irritability, mild mood changes, insomnia, and agitation. Caution patients to expect these effects and understand that they typically become less problematic after the initial weeks of therapy. **Tolerance develops towards most of these effects and the patient learns to cope with them.** These should not lead to the discontinuation of a medication unless unusual circumstances are present.

- Give medication at a time of day to minimize the effects. Consult the patient as to timing of drugs.
- Analgesics or NSAIDs may help headache.
- Limiting caffeine intake in the evenings may improve sleep disturbances.
- Supportive attempts from caregivers and family members and acceptance of the patient’s mood changes and irritability will make these side effects more tolerable.
- Exercise may also be effective.

### DEPRESSION

Depression can be relatively mild and managed with supportive attention from family and health care providers. Some level of situational depression is to be expected for most patients who deal with the difficulties of drug-resistant TB therapy.

- Assess and address underlying psycho/social issues.
- Assess patients for co-existing substance abuse and refer to counseling if appropriate.
- When depression is more significant, give a trial of antidepressant therapy. Consider psychiatric consultation. Tricyclic antidepressants and SSRIs should not be given to patients on linezolid.
- Question the patient regarding suicidal ideation any time depression is judged to be more than mild.
Cycloserine should not usually be part of an initial treatment regimen if significant depression is present.

[DEPRESSION CONTINUED]

- Reduce the dose of cycloserine and ethionamide to 500 mg daily to see if depression is lessened.
- If depression progresses or is not improved by a trial of antidepressant therapy, discontinue cycloserine and, possibly, ethionamide as well.
- Cycloserine should not usually be part of an initial treatment regimen if significant depression is present. When no alternative drugs are available and depression is controlled on therapy, some patients may tolerate cycloserine and ethionamide.

PSYCHOSIS

- If severe psychosis is present, hospitalize patient and put under 24-hour surveillance.
- Consider psychiatric consultation.
- Hold all medications that possibly contribute until the patient stabilizes.
- The most likely drugs to cause psychosis are cycloserine and fluoroquinolones. INH can occasionally be implicated.

- Pyridoxine (150 mg) should be given if not already part of the treatment.
- Start antipsychotic therapy (haloperidol [Haldol] PO, IV, or IM 0.5–5 mg) at the earliest sign of psychosis.
- When the patient has stabilized, all medications have been successfully restarted, and all symptoms have resolved, the antipsychotic drugs can be tapered with careful observation of the patient.
- Consider and address all other etiologies, especially illicit drugs, alcohol, and medical problems (meningitis, hypothyroidism, and depression).
- When symptoms resolve, the least likely medications that contributed to the symptoms should be reintroduced first, one at a time, with careful observation. If no alternative drug is available, cycloserine may be tried at low dose. Do not increase the dose to previous quantities without first checking a serum drug level. If any recurrence of psychotic behavior occurs, promptly and permanently discontinue cycloserine.
- Some patients may tolerate cycloserine with an antipsychotic drug if no other treatment options are available. These patients require special observation. Utilize this therapy only after consultation with an expert in the management of drug-resistant TB, and when the cycloserine is determined to be essential to the regimen and no alternative is available.

SUICIDAL IDEATION

- Hospitalize the patient and put under 24-hour surveillance.
- Discontinue cycloserine.
- Request psychiatric consultation.
- Initiate antidepressant therapy.
- Lower the dose of ethionamide to 500 mg daily until the patient is stable.
- Check the serum drug level of the fluoroquinolone and lower the dose if the serum level is high.
- Keep the patient in the hospital until the risk of suicide has passed.
SEIZURES

- Hospitalize patient.
- **Intravenous pyridoxine will stop seizures due to pyridoxine deficiency.**
- Hold cycloserine, fluoroquinolones, and INH and initiate anticonvulsant therapy (phenytoin, valproic acid).
- Increase pyridoxine to 150–200 mg daily.
- When seizures have resolved, restart medications one at a time.
- Continue anticonvulsant therapy during the remainder of therapy for drug-resistant TB.
- Evaluate for other etiologies of seizures.
- Check serum electrolytes, calcium, and magnesium.
- A history of prior seizures is not an absolute contraindication to the use of cycloserine, fluoroquinolones, and INH. Do not include cycloserine if an alternative drug is available.

Ototoxicity

**All of the aminoglycosides and capreomycin are toxic to the eighth cranial nerve and can cause both vestibular and auditory toxicity.** Streptomycin is much more likely to be associated with otic reactions. Transient giddiness and numbness, especially around the mouth, occur with streptomycin treatment. Medication can be continued. If the effects are particularly troublesome, consider a reduction in dose to alleviate the symptoms, if the treatment regimen is not compromised.

**VESTIBULAR TOXICITY**

- Observe the patient closely for tinnitus and unsteadiness.
- At least monthly, assess vestibular toxicity.

- Fullness in the ears and intermittent ringing in the ears are early symptoms of vestibular toxicity. When these are reported, it is sometimes possible to change the dosing to 2 or 3 times a week and continue the injectable agent for another month or more.

Watch the patient carefully. Toxicity is related to the total dose and is cumulative. It is impossible to predict for an individual patient what dose is tolerated.

- A degree of disequilibrium can be caused by cycloserine, fluoroquinolones, ethionamide, INH, or linezolid. Prior to stopping the injectable agent, evaluate whether these and/or other medications are causing the symptoms. Stopping the injectable should be done after carefully excluding other causes of the symptoms. Other drugs or all drugs can be held for several days to see if the symptoms improve. Symptoms of vestibular toxicity generally do not improve with holding medication.
If tinnitus and unsteadiness develop and these are attributed to vestibular toxicity, stop the injectable agent. This is one of the few adverse reactions that cause permanent intolerable toxicity and necessitate discontinuation of a class of agents. If the injectable agent is continued or an attempt is made to substitute one injectable for another, persistent vertigo, unsteadiness, tinnitus, and ataxia will develop. Drug-induced vestibular toxicity is not reversible.

**AUDITORY TOXICITY**

**Prevention and Monitoring**

Hearing loss is a direct effect of injectable medication toxicity to the eighth cranial nerve. Some degree of loss occurs in nearly all patients treated for drug-resistant TB. High-frequency loss usually occurs first. The effects are cumulative. Hearing loss may be reversible or permanent.

- Perform a baseline audiogram and repeat monthly. Monitor the ability of the patient to participate in normal conversation.
- Consider change of the injectable to 3 times a week, after 3–4 months, when the cultures are negative.
- Avoid loop diuretics because they increase eighth nerve toxicity.
- Streptomycin has less auditory toxicity, but has more vestibular toxicity.
- Resistance to streptomycin is common and should be excluded before substituting it for another injectable.

Some patients must tolerate significant hearing loss in order to achieve a cure of their drug-resistant TB. The decision to continue therapy with an injectable when significant hearing loss occurs should be discussed with an expert in the management of drug-resistant TB and also with the patient.

**OPHTHALMIC TOXICITY**

**PREVENTION AND MONITORING**

The most common drug causing toxicity to the optic nerve is EMB. Although there are case reports and small series of patients who have developed sudden severe, irreversible optic nerve toxicity, most experts feel that doses of 15 mg/kg given for less than 2 months are rarely associated with toxic changes to the optic nerve. Doses of EMB used to treat drug-resistant TB are frequently high (25 mg/kg), at least until culture conversion occurs, and EMB is continued for a period of up to 24 or more months. Ethionamide, linezolid, rifabutin, and clofazimine are rare causes of ocular toxicity.

Clofazimine toxicity produces a bull’s-eye pigmentary maculopathy and generalized retinal degeneration.

Linezolid produces a toxic optic neuropathy that is sometimes reversible.

Visual loss due to rifabutin is part of a pan-uveitis that is reversible.
When using any of these drugs:

- Conduct baseline visual assessment with acuity testing (Snellen chart) and testing of color discrimination (Ishihara tests) at the start of treatment.
- Conduct monthly testing of visual acuity and color discrimination during treatment.
- Educate patients to report any change in visual acuity or red-green color discrimination, scotomata, change in visual fields, erythema, or eye pain.
- Improve diabetic control.

- Avoid or adjust the EMB dose and dosing interval, and monitor levels when the creatinine clearance is less than 30 ml/minute.

- Correct nutritional deficiencies; consider a multi-vitamin for individuals with malnutrition along with TB therapy (wait until they are tolerating TB therapy before starting the multi-vitamin).

RETROBULBAR NEURITIS

- Stop EMB.
- Refer the patient to an ophthalmologist.
- Do not restart EMB unless another cause of the neuritis or vision problem is definitely identified.
- Rare cases of toxicity due to linezolid, ethionamide, and clofazimine have been reported. Stop their use when these drugs are implicated.

Gradual improvement in vision is noted in many patients after the offending medication is stopped. However, some series report fairly abrupt vision loss that is permanent. *Whenever a question about visual toxicity exists, immediately discontinue the offending medication.* Rifabutin is an exception to this rule and may often be continued, especially if the dose can be decreased. Evaluate potential nutritional deficiencies, especially of the B-complex vitamins and folate.

UVEITIS

Rifabutin, especially in higher doses (or given along with medications that decrease clearance, i.e., protease inhibitors), can cause pan-uveitis. Patients typically present with erythematous, painful eyes and blurring of vision.

- Hold rifabutin until symptoms have resolved and then reinstitute at a lower dose. A lower dose is needed if other drugs cause decreased clearance of the rifabutin, i.e., protease inhibitors.
- Consult an ophthalmologist.
- Consider other etiologies, especially in HIV-infected individuals; exclude bacterial and viral infection.
- Use topical steroid drops if ocular infection is ruled out.

Some patients may even improve with continued rifabutin therapy. If recurring uveitis is a problem, stop rifabutin.
Nephrotoxicity

PREVENTION AND MONITORING

All of the aminoglycosides and capreomycin can cause nephrotoxicity. Ongoing assessment of renal function is important.

- Perform a 24-hour creatinine clearance at baseline if there are any concerns about renal function abnormality and monitor the serum creatinine weekly for the first several weeks, and then at least monthly.
- Encourage adequate hydration.
- For adults over 59 years of age, decrease the dose of the injectable drugs to 10 mg/kg (max dose 750 mg).
- If baseline creatinine clearance is less than 70 ml/min, begin injectable therapy with a 3 times a week dosing regimen; if creatinine clearance is less than 50 ml/min, start twice weekly.
- Monitor serum drug levels and adjust the medication dose to achieve a peak level of 25–35 mcg 2 hours after an intramuscular injection or 1 hour after an IV infusion is complete. A trough level before the next dose should be less than 5 mcg/ml. Decreasing the dose to achieve levels of less than 20 mcg may not be effective.

For decreased renal function that develops during treatment:
- If there is a decrease in renal function, repeat a 24-hour creatinine clearance.
- Ensure adequate hydration.
- Hold the injectable agent for 1–2 weeks to allow renal function to stabilize.
- Check serum electrolytes and correct if needed.
- Evaluate other drugs the patient is taking and adjust dose and/or dosing interval if needed. If the clearance is less than 30 ml/minute, adjust the doses of EMB, PZA, some fluoroquinolones, cycloserine, all of the aminoglycosides, and capreomycin.
- For a creatinine clearance between 50 and 70 ml/min, the patient may tolerate 3 times per week aminoglycoside dosing at 12–15 mg/kg.
- For a creatinine clearance between 35 and 50 ml/min, twice weekly aminoglycoside dosing at 12 mg/kg should be tried.
- Monitor peak and trough drug levels. It is especially important that trough levels be less than the critical value before another dose of the drug is given.
- Follow renal function carefully.
ELECTROLYTE LOSS
All of the aminoglycosides and capreomycin can cause electrolyte disturbances due to renal tubular wasting of potassium, magnesium, and calcium salts. These effects are most pronounced with capreomycin. Chloride and hydrogen losses may also occur with resulting alkalosis. A defect in renal tubular resorption of chloride may be caused by these drugs. Nausea, vomiting, and diarrhea may also contribute to electrolyte abnormalities.

- Conduct baseline assessment and at least monthly follow-up of potassium, calcium, and magnesium during injectable drug treatment.
- Replace electrolytes as needed.
- Assess renal function when replacing electrolytes.
- If the potassium is low, also check the calcium and magnesium.
- Hypocalcemia is most commonly caused by hypoalbuminemia. If the calcium is low, check albumin and free calcium.
- Hypomagnesemia, if present, must be treated in order to correct hypocalcemia.

For severe electrolyte abnormalities, hospitalize and monitor the patient.

- Perform an electrocardiogram.
- Hold medications contributing to prolongation of the QT interval (fluoroquinolones).
- Hold medications (digoxin, tricyclic antidepressants) that may precipitate arrhythmias.
- Consider change of capreomycin to amikacin.

Musculoskeletal Adverse Effects

MYALGIAS AND ARTHRALGIAS
Pain and tenderness of the muscles and joints are relatively common side effects associated with a variety of drugs used to treat drug-resistant TB patients. One or more of the following drugs may be implicated: PZA, fluoroquinolones, rifabutin, INH, and ethionamide. Electrolyte disturbances associated with the aminoglycosides and capreomycin may also cause muscle pain and cramping. Hypothyroidism may also contribute.

- Do not discontinue medications.
- Nonsteroidal anti-inflammatory agents are usually helpful.
- If acute swelling, erythema, and warmth are present, evaluate for the presence of inflammatory diseases.
  - Aspirate joint for diagnosis if fluid is present.
  - Evaluate for infection, gout, or autoimmune disease.
  - Consider use of allopurinol if the patient is experiencing gout.
  - Consult with a rheumatologist.

- Evaluate for hypothyroidism or hyperthyroidism.
TENDONITIS AND TENDON RUPTURE
Tendon rupture has been reported with fluoroquinolone use and is more likely when new physical activities are undertaken and is more common in older patients and diabetics.

When significant inflammation of tendons or tendon sheaths occurs:

- Fluoroquinolones should generally be stopped.
- Administer nonsteroidal anti-inflammatory agents.
- Rest the joint.
- If the treatment regimen is likely to fail without the fluoroquinolone, inform the patient of the risk of tendon rupture and the risk of treatment failure. Carefully try to continue the fluoroquinolone.
  - Evaluate the fluoroquinolone dose and reduce if possible. Serum drug levels may help to direct therapy with the fluoroquinolone.
  - Rest the involved joint and avoid any strenuous activity.

When tendon inflammation is mild:

- Administer nonsteroidal anti-inflammatory agents and rest the joint.
- Evaluate the fluoroquinolone dose and reduce if possible. Serum drug levels may help to direct fluoroquinolone therapy.
- If symptoms progress, stop the fluoroquinolone therapy unless doing so is likely to cause treatment failure.

Miscellaneous Adverse Reactions

HYPOTHYROIDISM
Hypothyroidism may develop with either PAS or ethionamide; when both drugs are used, the incidence of hypothyroidism is greater.

- Assess baseline thyroid function prior to start of these medications and correct if needed. Assess thyroid function every 3 months unless clinical assessment indicates the need to evaluate sooner. Conduct monthly clinical assessments for hypothyroidism. Clinical assessments may be a better indicator of thyroid function than laboratory values.
- When thyroid stimulating hormone (TSH) begins to increase, evaluate for clinical evidence of hypothyroidism. Begin to monitor more frequently.
- When TSH rises to 1.5–2 times above upper limit of normal, begin thyroid hormone replacement. Most adults will require 100–150 mcg of synthroid daily.
  - Young healthy adults can be started on 75–100 mcg of synthroid daily.
  - Older patients should begin treatment with 50 mcg daily.
  - Patients with significant cardiovascular disease should start at 25 mcg daily.
- Repeat the TSH level after 1–2 months of treatment.
- Adjust thyroid hormone replacement until the patient’s TSH is within the normal range.

  - Increase thyroid hormone slowly in patients with significant cardiovascular disease.

  - When TB treatment is complete, stop thyroid hormone replacement; the thyroid gland will now be able to respond to endocrine stimulation with release of thyroid hormone.

**METALLIC TASTE**

Metallic taste is reported as an adverse reaction in patients taking ethionamide and clarithromycin. Fluoroquinolones may also cause changes in taste. Encourage the patient to tolerate this side effect. Sucking on lemon drops or other hard candy or chewing gum can be helpful. Normal taste returns when treatment is stopped.

**GYNECOMASTIA**

Breast enlargement can be a troublesome side effect of ethionamide therapy, especially for male patients. Galactorrhea has also been reported. Encourage patients to tolerate this side effect. Resolution occurs after treatment is stopped.

**ALOPECIA**

Hair loss can occur with either INH or ethionamide. In the first months of treatment, there can be significant thinning of the hair, but this is temporary and not progressive during treatment. Significant cosmetic change has not been reported.

**SUPERFICIAL FUNGAL INFECTION**

Vaginal or penile candidiasis may occur. This is most common with fluoroquinolone therapy and also is more likely to occur in diabetics. Cutaneous candidiasis in skin folds may also occur. Topical antifungal agents or short-course oral antifungal drugs are helpful. Exclude other diseases if response to treatment is not prompt.
Summary

Adverse reactions and toxicity accompany essentially all treatment courses for drug-resistant TB. Patients must be well informed so that they will know what to expect and can be partners in their therapy.

Close attention to toxicity and reports of discomfort are essential in maintaining the patient’s good will and cooperation with the regimen.

In many cases, some toxicity will have to be tolerated (although it should be treated and minimized). In many cases, offending drugs cannot be permanently discontinued; patients and staff need to understand that the treatment regimen would be compromised without the inclusion of many medications.

Common side effects include:

- **Gastrointestinal** (nausea, vomiting, diarrhea, abdominal pain, anorexia, taste perturbation, and hepatotoxicity)
- **Dermatologic reactions** (rashes, flushing, phototoxicity, alopecia, superficial fungal infections, and hypersensitivity)
- **Systemic hypersensitivity reactions**
- **Hematologic abnormalities** (leucopenia, thrombocytopenia, anemia, red cell aplasia, coagulation abnormalities, and eosinophilia)
- **Neurotoxicity** (peripheral neuropathy, CNS toxicity—depression, psychosis, seizures, and suicidal ideation)
- **Ototoxicity** (hearing loss and vestibular disturbance)
- **Ophthalmic toxicity** (visual loss, loss of color discrimination, uveitis, retrobulbar neuritis)
- **Nephrotoxicity** (renal impairment, electrolyte loss)
- **Musculoskeletal** (myalgias, arthralgias, tendonitis, and tendon rupture)
- **Endocrine** (hypothyroidism, gynecomastia)
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Case Management

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Case management is considered a critical component of effective TB control.

In the context of the tuberculosis (TB) program, case management refers to:

Assigning primary responsibility for coordination of patient care to ensure that the patient’s medical and psycho/social needs are met through appropriate utilization of resources.

Roles and Responsibilities

Case management of drug-resistant TB is demanding and complex, so assigning a case manager to the drug-resistant TB patient is highly recommended.

The case manager is the “team leader” of the case management team. The case manager coordinates the case management efforts of the treating physician and consultants, and other caregivers such as outreach workers, directly observed therapy (DOT) workers, social workers, correctional facility nurses, school nurses, and contact investigators.

The case manager has primary responsibility for ensuring that:

- The patient adheres to treatment through completion via DOT.
- The patient and significant others in his/her environment receive and understand education pertaining to drug-resistant TB disease, its transmission, and treatment.
- The patient follows through with all medical evaluations, including clinical and toxicity monitoring.
- Individuals in contact with the source case patient are identified, located, prioritized, evaluated, and treated as needed.
- Response to therapy is evaluated regularly, and if not in accordance with expected outcomes, is further evaluated.

Depending on the expertise, resources, and infrastructure of the clinic or medical provider managing the actual care of the patient, the case manager may have other roles and responsibilities. When primary clinical care is obtained through a private provider or when patients are hospitalized or incarcerated, the case manager may take on a liaison or coordination-of-care role. In addition to the above responsibilities, the case manager:

- Facilitates exchange of information between the family, medical providers, laboratories, pharmacies, insurance companies, and the public health infrastructure.
Builds relationships within all these systems to achieve the best results for the patient.
Ensures expert consultation has been sought and provides referral for consultation as needed.
Offers training, education, and resources to staff who will be providing patient care.

It is encouraging that model programs utilizing a case management approach in community-based care of drug-resistant TB patients have been showing very promising results. Unfortunately, in areas where TB control programs are small with fewer resources, and in which public health nurses deliver a wide range of public health services, 1 drug-resistant TB case can put a huge strain on the system.

This section highlights some of the challenges surrounding the care of drug-resistant TB patients in the U.S. and the role of case management in addressing them.

Ensuring Adherence to Treatment

The case manager must consider all potential barriers to adherence when structuring the plan of care for a patient’s treatment for drug-resistant TB. Anticipating and addressing potential barriers to adherence can not always prevent lapses in treatment or nonadherence; documentation of the interventions utilized will be important should legal orders need to be considered. A strong plan will include the following elements:

- Assessment of psycho/social and cultural needs
- Provision of education to the patient and patient’s family with the goal of obtaining commitment to the treatment plan
- Provision of treatment by DOT
- Use of incentives and enablers
- Use of culturally appropriate resources
- Use of legal orders

DIRECTLY OBSERVED THERAPY (DOT)

The consequences of treatment failure and further acquired drug resistance make DOT a high priority for cases of drug-resistant TB. Achieving this standard of care, however, requires far greater time and commitment in the treatment of drug-resistant TB than for drug-susceptible disease:

- Several of the second-line drugs used to treat drug-resistant TB are better tolerated when introduced gradually and may require twice or 3 times daily dosing.
- The use of injectable drugs requires a higher level of expertise, more time, and more technology than that required for observing the administration of oral drugs.
- Second-line agents require an extended treatment length and monitoring for adverse reactions.

DOT is so important to the treatment of drug-resistant TB that experts in the field of TB control around the world consider it a vital strategy.
The case manager must keep an open line of communication with the individual providing DOT and ensure that he/she can assess which signs and symptoms indicate potential medication toxicity. Any toxicity must be quickly identified, reported, and acted upon (see Chapter 6, Monitoring Patients, and Chapter 7, Adverse Reactions).

ADDRESSING PSYCHO/SOCIAL NEEDS

Be sure to assess the patient for strengths and barriers to adherence, and ensure that plans are in place for addressing issues such as mental illness, substance abuse, homelessness, and health insurance coverage. Costs associated with the treatment and management of patients with drug-resistant TB vary widely and are influenced by the amount and type of drug resistance as well as the extent of disease. For patients with limited or no health insurance coverage, charges associated with cost of drugs, diagnostic exams, and surgery may pose extreme financial burden on individuals and families.

Undocumented immigrant patients with drug-resistant TB may be eligible for Medicaid or Medicare if they are able to obtain legal status in the U.S. One avenue that might be explored is PRUCOL status (variably called Permanent Residence Under Color of Law, Persons Residing Under Color of Law, and Aliens Permanently Residing in the United States Under Color of Law). Organizations that provide pro bono immigration legal services can be very helpful in exploring options available to undocumented persons or low-income immigrants. Addressing these challenges early in the patient’s course of treatment will go a long way in establishing a foundation of confidence and trust.

Consider community services that can assist you in addressing these challenges:

- **Social services and programs for the medically indigent**
  - Medicaid and any other third-party payer eligibility.
  - In California, legal residents may be eligible for TB-MediCal, which may provide more outpatient benefits than other payer sources.
  - In some jurisdictions, all TB care can be provided free of charge in the public health setting.

- **Immigration law counsel—National Immigration Law Center:**
  - [http://www.nilc.org](http://www.nilc.org)

- **Drug and alcohol counseling**

- **Mental health programs**

- **Other community-based outreach services**

Your key to successfully assisting patients with these challenges is to develop a trusting relationship with the patient and to be familiar with resources in your community.
BRIDGING CULTURAL BARRIERS

Over three fourths of patients with MDR-TB in the U.S. are foreign-born, many of whom are recent arrivals.

Barriers to diagnosis and treatment may include:

- Cultural stigma about TB
- Fear of the cost of TB care and lack of eligibility for programs
- Concern that the illness might interfere with the immigration process
- Fear of deportation
- Hindered access to health care because of language or cultural barriers as well as the general difficulty of navigating complex health care systems in the U.S.
- Patient’s preference to seek traditional healing when ill
- Patient’s preference to seek out a physician from his/her own culture, who may not be familiar with diagnosis and treatment of drug-resistant TB
- Fear of loss of employment and financial stress
- For women: Loss of importance to family if she cannot continue usual activities or experiences disapproval of spouse

For patients with language or cultural barriers, explore local resources to help bridge the barriers and to facilitate communication and understanding:

- Bilingual health department staff
- Court interpreters, phone-accessed interpreters, university language departments
- Refugee health and social service programs
- Cultural health brokers
- Health care professionals from the patient’s culture
- Community leaders, community organizations
- Church-based services
- Traditional healers
- Other local health departments
- Legal resources

Few translated patient materials pertaining specifically to drug-resistant TB exist; however, there are a number of Internet sites offering general TB patient education material in various languages. Additional sites contain cultural information that may be helpful to the case manager in anticipating the patient’s cultural practices and needs (see Appendix 13, Multicultural Resources).

Engage the family in the patient’s care; encourage and praise their support. Do everything possible to get family members, especially spouses, to cooperate and support the treatment plan. An investment of time initially is well worth the benefits it often reaps.

Offer to evaluate family members for TB or latent tuberculosis infection (LTBI) and answer their questions.
PATIENT EDUCATION

The case manager can play a key role in coaching the patient through the various phases of treatment by assisting the patient to set achievable interim goals. The following phases may not fit the treatment course for all drug-resistant TB cases, but hopefully will provide a context for case managers to anticipate their patient’s educational capacity and needs.

1. Initial Phase

The initial phase is likely to be quite intensive as the patient may be very ill, in respiratory isolation, and facing a barrage of very toxic drugs.

- **Keep information simple** with a focus on the following: minimizing transmission; achieving commitment from the patient to comply with the treatment plan; and sharing information about contacts and legal requirements.

- If the case manager is not the individual actually providing the DOT, **regular contact with the DOT provider and weekly contact with the patient will be important during this phase** to ensure that the patient is tolerating the medication and that side effects are quickly addressed. While most patients will experience mild complaints that can be managed without a change in the drug regimen (e.g., initiating adjuvant therapy, changing dosing time), some warrant at least temporary discontinuation of the offending drug. Address all complaints, even if no change can be made. Make sure that the patient does not feel isolated during this phase.

- **If the patient is hospitalized, the case manager will need to provide support to the patient as well as the hospital staff.** Hospital staff who do not care for TB patients routinely will need to be reminded to observe each dose of medicine (not to leave the medicine at the bedside) and may need to be educated about many aspects of drug-resistant TB care. If the patient’s medical needs are not given careful attention during this initial phase, the patient is at higher risk for becoming demoralized and discouraged. Hospital staff should be encouraged to seek expert consultation when necessary.

- **Prepare the patient to expect some side effects** so that when they occur, the patient does not fear that the treatment is doing more harm than good. Close monitoring is needed to ensure side effects are responded to promptly, particularly when treatment is initiated in an outpatient setting.
2. Second Phase

This period begins once the patient is deemed non-infectious and continues until the injectable agent is discontinued. During this phase, the focus should be on helping the patient understand the disease and working together to identify barriers to achieving completion of treatment without interruption. Drug toxicity can occur at any phase in treatment and should continue to be closely monitored. If surgical intervention is indicated, it might occur during this phase.

- **Consider incentives and enablers that might aid adherence to treatment.** (See Use of Incentives and Enablers.)
- **Reevaluate the patient’s knowledge and understanding of the disease** and the potential serious side effects of treatment; reinforce information as needed.
- **Regularly assess for serious side effects** such as increasing depression, changes in vestibular function, etc. (See Chapter 6, Monitoring Patients, and Chapter 7, Adverse Reactions.)
- **Reinforce importance of monthly sputum collection, good nutrition, and physical activity as tolerated.**
- **Monitor monthly for signs of continued clinical improvement.**
- **Discuss management of injection site(s)** (care of IM/IV sites).
- **Review the patient’s plans concerning work, travel, or moving.**
- **Ensure that the patient understands that a non-infectious state is not equivalent to being cured.**

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**Information to reinforce during the initial phase:**

- **Simple infection control practices,** such as covering the mouth when coughing and disposing of tissues properly. Discuss the patient’s plans regarding work, travel, or moving.
- **Strategies for keeping the home well ventilated** with fresh air and adhering to visitor restrictions if isolated at home.
- **Expected side effects** and plan for addressing minor complaints should they occur.
- **Potential consequences of nonadherence to treatment** and respiratory isolation.
- **Maximizing nutritional intake.**
- **Sharing information** to assist in the identification and evaluation of contacts.
As appropriate, consider referral to programs such as CureTB or TBNet. Both programs are available at no cost to patients or clinicians. These programs can work with patients who are considering moving prior to completion of therapy.

- CureTB is a binational referral program based out of San Diego, California, for patients with TB who move between the U.S. and Mexico. Patients will be linked to care in Mexico and educated about the differences in services that can be expected. Note: Availability of second-line medications, acid-fast bacilli (AFB) cultures, and DOT is limited in many parts of Mexico. Telephone: 619-542-4013.
- TBNet is a comprehensive tracking and referral network within the Migrant Clinicians Network. TBNet helps provide continuity of care services for mobile populations with active TB or LTBI who move throughout the U.S. Telephone: 800-825-8205.

3. Third Phase

Provided continued clinical response is achieved, the third phase begins when the parenteral agent is discontinued and lasts until the end of treatment. While this may sound much like nearing the home stretch, it is really closer to passing the halfway point. The patient may well have to take oral medications for another year or more before reaching the finish line.

- Ensure vigilance in ensuring DOT and clinical response monitoring.
- Revisit the patient’s commitment to the treatment plan and the need to complete treatment to prevent relapse.
- Reassess the patient’s understanding of the consequences of nonadherence to treatment; reinforce information and address barriers as needed.
- Revisit the patient’s plans concerning work, travel, or moving.

4. Final Phase

The final phase begins once treatment is completed. The marathon is over, yet the patient will require clinical monitoring for the next several years to ensure that if a relapse occurs, it will be identified and acted upon quickly.

- Ensure that the patient is knowledgeable about signs and symptoms of TB and what to do should he/she experience them.
- Schedule follow-up appointments and arrange for reminder notification.
- Revisit the patient’s plans concerning work, travel, or moving.
USE OF INCENTIVES AND ENABLERS

Patient motivation commonly wanes once the patient begins to feel better and may affect the patient’s commitment to the treatment plan. The use of *incentives and enablers* is another strategy reported to be effective in assisting patients in maintaining adherence to treatment. Incentives are “small rewards” given to patients to encourage them through the lengthy treatment and monitoring period. Enablers refer to things that assist a patient to overcome a barrier, such as the provision of taxi or bus fare to attend a clinic appointment when a patient is without transportation means. The following resources address the use of incentives and enablers and give many examples for the case manager to consider:


USE OF LEGAL ORDERS

Legal measures are sometimes required when a patient with infectious, drug-resistant TB remains nonadherent despite interventions to overcome barriers and gain the patient’s cooperation. The case manager should be knowledgeable about the process for referring such patients and must ensure that documentation of all lesser restrictive measures employed has occurred. Local, regional, and/or state TB control programs can provide additional information on the state laws and regulations pertaining to TB when persistent nonadherence is occurring. See Chapter 9, *Ethical and Legal Issues.*
Clinical Response Monitoring

The case manager is responsible for ensuring that all necessary monitoring for both toxicity and clinical response occurs and that abnormal results are brought to the attention of the treating physician. (See Chapter 6, Monitoring Patients, and Chapter 7, Adverse Reactions.) To keep the confidence of the patient, health care providers, and DOT workers, the case manager must be detail-oriented, anticipate problems, and manage them as they occur. Helpful tools and strategies include:

- The Care Plan and the Drug-O-Gram, documents that can be customized for the case manager’s own needs and patient’s circumstances (see Chapter 6, Monitoring Patients, Monitoring Tools 1 and 2)
- Monitoring flow sheets to track progression of bacteriology results, blood work, audiograms, and vision/vestibular screening (see Chapter 6, Monitoring Patients, Monitoring Tools 3, 4, and 5)
- Real-time reminders on the computer or “Palm,” a tickler system, Post-it notes on the desk, highlighted messages on the desk calendar, a hanging file system, etc.

The case manager will be instrumental in assessing:

1. Conversion of sputum smear and culture
2. Resolution of symptoms
3. Weight gain and stabilization
4. The need to adjust medication as weight changes or as renal function changes
BACTERIOLOGY
- Obtain 3 sputa for AFB smear every 2 weeks until smears become negative.
- Collect 2–3 sputum samples monthly until cultures become negative.
- Once the culture has consistently converted to negative, obtain at least 1 specimen of sputum for AFB smear and culture monthly if clinically improving, and more frequently if indicated. Once the patient is no longer able to spontaneously produce sputum, you may need to arrange for sputum induction.
- Obtain sputum for AFB smear and culture at the end of treatment.
- A critical activity of the case manager is coordination of microbiologic evaluation for the patient’s cultures. Specimens should be of good quality and at least 5–10 ml in volume. Specimens need to be routed to the appropriate reference labs, specific susceptibility tests need to be requested, and results communicated as quickly as possible to the treating physician.

THERAPEUTIC DRUG MONITORING
- The case manager also frequently coordinates collection and transport of blood samples for therapeutic blood monitoring. Few reference labs perform these levels, and factors such as cost and a patient’s insurance status require the experience of the case manager. For details, see Appendix 12, Therapeutic Drug Monitoring.

SYMPTOMS
- Assess symptoms of TB monthly throughout treatment and document resolution of symptoms that were present at diagnosis. Monitor symptoms of drug toxicity.
- Conduct post-treatment symptom review during regularly scheduled follow-up appointments for 2 years after treatment completion.

WEIGHT
- Weight is a key marker for evaluating clinical improvement. Check weight monthly until stable, and then periodically (every 2–3 months) throughout the course of treatment and follow-up.
- When the patient has sustained substantial weight loss, or if the drug-resistant TB patient is an infant, monitor weight more frequently as a measure of clinical response to therapy and to ensure dose adjustments are made as weight increases.

A Word About Nutritional Supplements
Nutritional supplements such as Ensure and multi-vitamins are an important aspect of drug-resistant TB care, but they may impact the absorption of certain drugs commonly used in the treatment of drug-resistant TB (such as fluoroquinolones). Refer patients with co-morbidities impacted by nutritional intake (such as diabetes) for dietary consultation.
Continuity of Care

The role of the case manager becomes increasingly important when the drug-resistant TB patient is being treated in the private sector and/or changes providers during the course of his/her treatment. When the drug-resistant TB patient moves between facilities (such as a hospital or jail) and the community during the course of treatment, the case manager must ensure that appropriate treatment, monitoring, and education of the patient continues. This may require:

- Re-establishing relationships with a whole new group of staff.
- Providing training and/or information on drug-resistant TB to staff caring for the patient.
- Establishing processes for sharing information.

**INTERFACE WITH PRIVATE PROVIDERS**

If the patient is managed by a private provider:

- Make an appointment to meet the provider and the office staff as soon as possible.
- Make it clear through your actions and words that you are an ally and will be very helpful in the complicated management of the patient.
- Explain your legal responsibility to monitor the patient throughout the course of treatment.
- **Explain the regulations** in your state or jurisdiction regarding the provider’s responsibility to provide information to the health department.
- Explain the absolute **necessity of DOT** and that it is not in any way punitive.
- Relay the benefits of case management and DOT in the efficient treatment of drug-resistant TB.
- Explain the **infection control** practices required to keep office staff and other patients safe.
- Ensure that the office staff has been appropriately evaluated if unprotected exposure to the patient has occurred.
- Offer resources to help manage the patient’s co-morbid conditions, such as diabetes, malnutrition, and HIV.
- **Provide this Survival Guide and a list of consulting resources.** Stress the importance of an expert in drug-resistant TB being involved throughout the course of treatment. In some areas, ongoing consultation with the regional experts is routine (see Appendix 1, *List of Expert Resources for Drug-Resistant TB*).
- If the provider and staff have the infrastructure and resourcefulness to problem-solve for the patient (i.e., interfacing with insurance companies; seeking supplies of hard-to-get medications; making sure that the patient follows through on all monitoring; ordering and following through on susceptibility testing, blood levels, etc.), stay actively involved in order to ensure that **everything** gets done and is followed up on appropriately.
- Touch base with the office staff regularly. Continue to offer yourself as a resource, problem-solver, and advocate. Anticipate staff needs, such as an audiologist who takes the patient’s insurance or an interpreter who the patient trusts.
Infection Control

In order to halt the transmission of *M. tuberculosis*, the correct diagnosis must first be considered, the appropriate treatment must be initiated, and appropriate infection control measures must be instituted.

Safe infection control practices should always be followed when dealing with known infectious agents. When dealing with suspected or confirmed infectious drug-resistant TB, even greater emphasis should be placed on strict adherence to infection control standards, as there are limited options and scant data defining effective measures for preventing drug-resistant TB in exposed contacts.

**INFECTION CONTROL GUIDELINES**

- CDC’s *Guidelines for Preventing the Transmission of Mycobacterium tuberculosis in Health-Care Facilities* MMWR 1994; 43 (No. RR-13), available online at: http://www.cdc.gov/nchstp/tb/pubs/mmwrhtml/mmwr_infection.htm
- Francis J. Curry National Tuberculosis Center’s *Tuberculosis Exposure Control Plan: Template for the Clinic Setting* (Publication WPT-08), available online at: http://www.nationaltbcenter.edu

**DISCONTINUATION OF ISOLATION—RETURN TO CONGREGATE SETTINGS**

When is it safe to discontinue isolation for multidrug-resistant TB patients?

- Studies have shown that most transmission of TB occurs before drug treatment has been initiated and that smear-positive cases transmit more efficiently than smear-negative cases. A recent molecular epidemiology study concluded that 17% of secondary cases of TB in San Francisco was transmitted from smear-negative TB cases.
- For drug-susceptible TB, a patient receiving TB treatment is deemed to be non-contagious when he/she has produced 3 consecutive smear-negative sputa; has started an appropriate treatment regimen; and is clinically improved.
- Outbreaks of MDR-TB have been reported in hospitals, jails, and congregate settings. Transmission has been documented in households and in communities. The dramatic decline in MDR-TB cases in the U.S. since 1993 is attributable both to improved awareness and better drug regimens, but also to more aggressive infection control measures.
- MDR-TB takes a terrible toll on individuals and their families, and secondary cases should certainly be avoided whenever possible. Unfortunately, the aforementioned transmission studies primarily included drug-susceptible cases. The current guidelines reduce risk to contacts, but do not eliminate it. Patients with smear-negative, culture-positive sputum on treatment certainly could still transmit TB.
- Because the consequences of MDR-TB are so much more dire, and there are no proven regimens for window prophylaxis or treatment of LTBI, it is appropriate to be more cautious about returning MDR-TB patients back to their homes, schools, work sites, and congregate settings.

Nucleic acid amplification tests may be helpful in distinguishing NTM from *M. tuberculosis*, allowing for most efficient infection control efforts.
Particular care should be taken when considering if patients can return to settings where there are young children, immunocompromised individuals, and people who have not previously been exposed to the patient.

Some experts would consider MDR-TB patients potentially contagious as long as their sputum cultures remain positive. These experts recommend isolation while hospitalized and would not release MDR-TB patients to congregate settings until their sputum cultures become negative.

DISCONTINUATION OF ISOLATION—MANAGEMENT AT HOME

A number of factors should be taken into account when considering management at home:

- **Extent of disease, cavitation, and smear status** (reflect the bacillary load)
- **Extent of the drug resistance** (susceptibility to first-line drugs and fluoroquinolones increases likelihood of early sterilization)
- **Clinical and microbiologic response to treatment regimen**
- **Physical environment** (is the home very small and crowded with little air flow?)
- **Medical risks of household members** (young children, immunocompromised?)
- **Treatment status of household members** (on window prophylaxis or LTBI treatment?)
- **Stability of household** (relative likelihood that no new members will enter)
- **Anticipated adherence by case and contacts**
- **Safety and protection of service providers in the home**

While TB patients cannot be excluded from their families and homes indefinitely, every effort should be made to ensure the safety of contacts.

Decisions about home management should be made in consultation with the local health officer/TB controller and experts in drug-resistant TB.

Special precautions will be required if there are young children in the home, immunocompromised contacts, or a risk of persistent contagion.

Health care and other service providers entering the home to deliver DOT and/or other health care services (e.g., patient interviews) must comply with current infection control measures to prevent occupational exposure when caring for drug-resistant TB patients who are considered potentially infectious. Consultation with national (National Institute for Occupational Safety and Health [NIOSH]) and state occupational health and safety programs can provide information essential to consider when preparing for the care of infectious TB patients in the home setting.
TRANSPORTATION
Considerations for transporting the infectious drug-resistant TB patient:

- **Private car:** Have windows down, mask patient if possible, eat outdoors at stops.
- **By ambulance:** Identify an ambulance company that has negative pressure and high efficiency particulate air (HEPA) filtration. Patient should still wear surgical masks, and providers and drivers should wear N-95 masks.
- **By air:**
  - Air Specialists  877-227-8799
  - Angel Flight West  888-426-2643
  - Local Air Force base

Contact Investigation

One of the primary responsibilities of the case manager is to identify, locate, and evaluate contacts.

In general, the process of performing a TB contact investigation is the same whether a case is drug-resistant or not, and includes:

- Review of the index case’s medical history and history of present illness
- Interview of the case to identify contacts
- Performance of a field investigation
- Risk assessment for TB transmission
- Prioritization of contacts for evaluation
- Evaluation of contacts
- Provision of treatment for LTBI and essential follow-up of contacts
- Evaluation of contact investigation outcomes and decision of whether to expand the investigation

To determine whether the TB infection you find among contacts represents exposure to the recent drug-resistant TB case or exposure to a previous and possibly drug-sensitive case, consider:

- The transmission risk assessment findings
- The individual contact’s TB exposure history
TB TRANSMISSION RISK ASSESSMENT

The risk assessment focuses on the route of transmission, which in cases of TB is almost exclusively airborne. Assessing the risk of transmission helps determine which contacts should be given high priority for testing and evaluation.

The risk of TB transmission is contingent on 3 main factors:

1. **Infectiousness of the TB patient:**
   Symptoms, sputum smear status, site of TB, presence of cavitary disease

2. **Environment where transmission likely occurred:**
   Size of room, amount of ventilation, presence of air cleaning systems

3. **Characteristics of the contact’s exposure:**
   Frequency of contact and duration of the exposure

Indications of transmission include:

- High infection rate among contacts
- Infection in a young child
- Presence of converters*  
- Identification of a secondary case

**CONTACT TB EXPOSURE HISTORY**

A very thorough TB history of contacts with LTBI will help you to assess the likelihood of recent infection and to make treatment decisions.

Include these essential factors in your assessment:

- Prior tuberculin skin test (TST) history and baseline TST. Taking the time to look for prior TST history is time well spent in a drug-resistant TB investigation. Sources of this information include:
  - Employment or immigration health record
  - Primary care provider medical record
  - School/immunization health record
  - Other programs that the patient may have accessed, such as CureTB, TBNet, or programs such as foster care that have a health screening component on entry into the program
- History of previous exposure to TB—was it a pan-sensitive case? Was previous treatment for LTBI or active disease taken?
- Information on the contact’s country of birth, year of arrival (if foreign-born), and travel history is helpful and may give clues to prior exposure potential.
- History of incarceration (a situation in which TST is often performed).

*According to the American Thoracic Society (ATS), a skin test “converter” is someone who has an increase in reaction size of 10 mm or more within a period of 2 years.*
Drug Supply

**DRUG AVAILABILITY**
Second-line anti-tuberculosis drugs are sometimes hard to find. Creativity and perseverance will be required.

- If your local pharmacy does not carry the drug, ask them to order it and ask them how long it will take to get it.
- If the local pharmacy cannot obtain the drug in a timely fashion, call your local hospital or a neighboring TB clinic and ask if you can borrow a quantity of the drug.
- Try to identify a patient in the area who has recently been taking the drug and see how that person’s case manager obtained the drug.
- Contact the nurse consultant at the state health department (TB elimination section) or the state TB controller.

**DRUG SHORTAGES**
Some second-line drugs have pre-established production quotas that make access to the drug difficult when demand suddenly increases. If your state does not have a central pharmacy that stocks and distributes drugs used to treat drug-resistant TB, order and keep on hand a several-month supply of drugs to prevent treatment interruption due to supply shortages. If you are told a required drug is on back order, unavailable, or out of stock, report this immediately to your state TB control program. The Food and Drug Administration (FDA) is also a potential resource and can be contacted at: http://www.fda.gov/cder/drug/shortages; drugshortages@cder.fda.gov; telephone: 301-827-2350.

**DRUG STORAGE AND SAFETY**
Most of the drugs used to treat drug-resistant TB can be stored at room temperature (59–86°F; 15–30°C); however, some require refrigeration.

- Keep the following medications refrigerated:
  - Paser granules—store below 59°F (15°C); can also be stored in freezer
  - Streptomycin sulfate—store between 36–46°F (2–8°C)
- Work with the agency providing parenteral medications to make sure the suspended forms do not exceed their safe shelf-life.
- Ensure safety of needle handling and disposal.

See Chapter 4, *Medication Fact Sheets*, for more details about each drug.

“It costs 100 times more to cure MDR-TB than drug-susceptible TB.”
—World Health Organization
**PATIENT ASSISTANCE PROGRAMS (PAPs)**

The distribution of drugs used to treat drug-resistant TB varies throughout the country, with some states maintaining central purchasing and distribution. The cost of these drugs is also variable, but in general, they are expensive, particularly when you factor in the length of treatment. Patient assistance programs (PAPs) may be helpful in offsetting costs. Drugs used to treat drug-resistant TB that are known to be included in PAPs include:

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Generic name</th>
<th>Manufacturer</th>
<th>Eligibility criteria</th>
<th>PAP telephone</th>
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</thead>
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<tr>
<td>Trecator-SC</td>
<td>Ethionamide</td>
<td>Wyeth Pharmaceuticals</td>
<td>U.S. resident</td>
<td>800-568-9938</td>
</tr>
<tr>
<td>Floxin</td>
<td>Ofloxacin</td>
<td>Ortho-McNeil Pharmaceuticals</td>
<td>Without resources</td>
<td>800-577-3788</td>
</tr>
<tr>
<td>Levaquin</td>
<td>Levofloxacin</td>
<td>Ortho-McNeil Pharmaceuticals</td>
<td>Without resources</td>
<td>800-577-3788</td>
</tr>
<tr>
<td>Avelox</td>
<td>Moxifloxacin</td>
<td>Bayer Pharmaceuticals</td>
<td>Indicated use</td>
<td>800-998-9180</td>
</tr>
<tr>
<td>Zyvox</td>
<td>Linezolid</td>
<td>Pfizer</td>
<td>Without resources</td>
<td>888-327-7787</td>
</tr>
<tr>
<td>Augmentin</td>
<td>Amoxicillin/</td>
<td>GlaxoSmithKline</td>
<td>U.S. resident</td>
<td>866-PATIENT</td>
</tr>
<tr>
<td></td>
<td>clavulanate</td>
<td></td>
<td></td>
<td>866-728-4368</td>
</tr>
<tr>
<td>Lamprene</td>
<td>Clofazimine</td>
<td>Novartis</td>
<td>MDR-TB</td>
<td>301-827-2127</td>
</tr>
</tbody>
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Summary

The assignment of a case manager for cases of drug-resistant TB is highly recommended. The case manager coordinates activities of many team members and is responsible for ensuring that all details of treatment and monitoring are completed.

The case manager:

- Ensures adherence to treatment by coordinating DOT.
- Addresses psycho/social needs and facilitates treatment of substance abuse and mental health programs.
- Bridges cultural gaps by use of community resources and appropriate interpreters.
- Provides aggressive and ongoing education to patients, families, and other care providers.
- Coordinates clinic response and toxicity monitoring as well as communication of results to providers.
- Coordinates medical care given by private providers, medical consultants, and the TB clinic.
- Interfaces between families, providers, and institutions regarding infection control practices.
- Performs contact investigations and follows through with treatment of contacts.
- Works with providers, pharmacies, third party payers, and drug companies to ensure consistent drug supply.
References


## Ethical & Legal Issues

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**Note:** This chapter presents a general overview of the basic ethical and legal considerations that clinicians and health care organizations may face when managing cases of drug-resistant TB. Laws and procedures vary across jurisdictions. The individual clinician is advised to consult with local legal and public health authorities when faced with questions or concerns about specific cases.
Suboptimal ethical and legal attention to the issues surrounding drug-resistant TB has implications for both the patient and for the public.

For a number of reasons, the public health control of tuberculosis (TB) must be treated differently than other communicable diseases:

- TB is spread through the air, leading to the potential for more casual transmission than diseases that require sharing of body fluids or other intimate contact for transmission.
- An individual with active TB can be contagious for a long period of time and infect many other people.
- The consequence of transmission to others can be very dire, with significant morbidity to infected persons.
- Except for rare strains of multidrug-resistant TB (MDR-TB), and unlike some other deadly communicable diseases, TB can be cured and transmission can be prevented. Public health interventions are proven to be very successful both for the individual and for those sharing the air with that person.

Drug-resistant TB requires even more heightened medical and legal attention for at least 2 reasons:

1. It is more difficult to treat and cure, and therefore, any transmission of the infection to other individuals carries significant consequences.
2. Poor adherence to TB therapy can promote or amplify drug resistance and must be actively prevented.

All states have laws specific to the control of TB. Inherent in the use of public health authority is a struggle to balance 2 important principles: individual autonomy and protection of the public’s health. The exercise of powers granted by statute to control the behavior of persons with TB must always be tempered not just by the question “Is it legal?” but also “Is it ethical?”

**Conflict in Ethical Principles**

**INDIVIDUAL AUTONOMY**
- Rights to privacy
- Right to liberty and self-determination

**RISKS TO THE PUBLIC HEALTH**
- Transmission of TB
- Development and spread of drug-resistant TB
The Ethical Framework

The ethical context of public health differs from that of most of medicine. In medical ethics, one balances the risks to the individual patient of the proposed intervention with the benefit to that patient. In public health, however, while the risk, such as loss of privacy, is to the individual patient, the benefit is both to the patient and to society as a whole.

Examples of potential risks to the patient include:

**Loss of privacy**
- Reporting
- Contact identification

**Loss of liberty and self-determination**
- Court-ordered directly observed therapy (DOT)
- Long-term isolation, possibly even indefinite, in some cases of MDR-TB
- Detention

**Loss of legal rights**
- Unequal imposition of restrictions/interventions
- Lack of notice of legal consequences or opportunity to object to health orders
- Lack of legal counsel due to unwillingness of legal representatives to come into close proximity to an infectious patient, especially MDR-TB

Risks to the patient can be minimized if TB control interventions are provided in the context of an ethical framework in which interventions:

- Reduce morbidity or mortality.
- Are substantiated by individualized assessments based on science (sometimes lacking in the case of treatment and transmission of drug-resistant TB).
- Identify and minimize burdens to the patient through the use of least restrictive alternatives.
- Are implemented fairly and minimize social injustice or discrimination.
Legal Issues for Practitioners

TB control programs operate within a complex legal framework that balances the civil rights of individuals with society’s need for protection. A dialogue between medical and legal professionals is necessary to ensure that whatever steps are taken to isolate a sick person and cure the disease strike the appropriate balance with modern constitutional guarantees of privacy, liberty, and non-discrimination. These issues are the same whether a patient has drug-susceptible or drug-resistant TB. However, the consequences are more dire if a patient with drug-resistant TB remains contagious or his/her strain’s resistance is amplified. For this reason, all legal tools may be necessary when managing a case of drug-resistant TB.

LEGAL PRIORITIES

Priorities for TB control programs include ensuring that:

- Active cases of TB are identified, do not further transmit TB, and receive appropriate treatment.
- Persons at risk of having been infected due to recent exposure are identified, evaluated for the presence of infection, and receive treatment as needed.
- Persons at high risk of having TB infection or disease are appropriately screened and provided access to care.

Although there are variations among state TB control statutes, in general, laws specific to the control of TB deal with the first and second of these priorities. Among the legal powers usually delegated to public health authorities are reporting requirements, orders for persons to appear when and where directed, and orders for persons to remain isolated and/or detained for treatment.

REPORTING REQUIREMENTS

Examples of public health reporting requirements include the requirement for health care providers, institutions, and laboratories to:

- Report known or suspected cases of TB;
- Report when persons with TB self-stop the prescribed treatment (including being lost to follow-up);
- Provide clinical and treatment updates upon request; and
- Provide a treatment plan and obtain approval from the local TB controller prior to discharging or transferring a patient from a health care institution.

Health care providers caring for TB patients should be familiar with the reporting requirements in their jurisdictions. Reporting requirements are designed to provide the public health authorities with information necessary to ensure that persons with TB obtain timely, adequate, and appropriate treatment and are not lost to follow-up.
ORDERS TO APPEAR AND COMPLY

Public health authorities are granted legal power to “order” persons with or suspected of having TB to comply with directions. These “Health Officer Orders” often have the force of law in that violation of such an order is generally a misdemeanor and may lead to further legal action. Examples of Health Officer Orders include:

- Order to appear for examination to rule out active TB
- Order to complete treatment
  - Usually does not include the ability to force persons to take medications against their will
- Order to comply with DOT
- Order for admission into a health facility
  - Often for nonadherent patients with voluntary home isolation

ORDERS TO ISOLATE OR DETAIN

Perhaps the most intrusive power vested in local health authorities is the power to isolate or detain a nonadherent patient involuntarily if that individual is felt to represent a risk to the public’s health.

Two such types of orders are relatively commonplace in TB control:

- Order for an infectious patient to be isolated in his/her home or other facility as designated
- Order for a persistently nonadherent patient to be civilly detained at a health facility until the patient has completed a course of treatment

While involuntary detention of nonadherent persons with contagious TB has long been used, the increase of drug-resistant TB has added a new dimension to the issue of detention. Persons who are nonadherent with their anti-tuberculosis regimens, even after they are no longer contagious, may develop or amplify drug-resistant TB, leading to treatment failure and transmission of a difficult or even impossible-to-treat infection. The possibility for nonadherence, followed by the development of drug-resistant TB, has led to the institution of laws allowing the detention of patients until they are cured, rather than just until they are no longer contagious. For nonadherent patients with MDR-TB, this could lead to detention for many years.

Because of the degree of restriction of individual liberty inherent in the detention of nonadherent patients, every reasonable effort should be made to identify and address the patient’s barriers to adherence and to pursue the least restrictive alternatives that may allow the patient to achieve adherence to the treatment regimen. The decision to detain a patient must be made based on an individualized assessment of that patient.
Least restrictive alternatives that should be pursued prior to detention:

- **Education/counseling** (linguistically appropriate)
- **Removing cost as a barrier**
- **Voluntary DOT**
- **Use of incentives/enablers**
- **Provision of stable housing**
- **Referral to social services**
- **Alcohol and drug rehabilitation**
- **Health officer orders: isolation, DOT**

**Summary**

Many physicians are uncomfortable with discussions of the use of legal powers to “force” patients to adhere to treatment regimens.

MDR-TB patients may have more difficulty adhering to prolonged, complex TB regimens than do drug-susceptible patients.

TB patients, and drug-resistant patients in particular, present a risk to others in the community with whom they may come into contact.

While the physician’s primary focus is the individual patient, the public health department must also consider its legally mandated responsibility to protect the public’s health. Fortunately, the two are rarely in conflict.

Public health authorities rely heavily on health care providers to notify them of TB cases and to provide appropriate evaluation and treatment of persons with or exposed to TB.

Physicians often do not have the same resources as the health department to fully address a patient’s psycho/social needs and barriers to adherence to TB care. By working together, the physician and health department can meet the needs of most patients.

For those few patients who, for whatever reasons, continue to pose a risk to the public despite all efforts to address their barriers, ethical and legal options are needed to ensure that these patients do not continue to put others in the community at risk.
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The rise in TB resistance rates worldwide and outbreaks of MDR-TB have brought attention to the treatment of contacts to drug-resistant TB cases.

Challenges:
A Lack of Data and Consensus

In 1994, the Centers for Disease Control and Prevention (CDC) convened 31 experts who were unable to achieve consensus on treatment recommendations for contacts to multidrug-resistant tuberculosis (MDR-TB). Consequently, the CDC guidelines have not been updated since 1992. Unfortunately, the last decade has not provided more definitive data regarding the best approach to the identification, evaluation, and treatment of contacts to patients with MDR-TB.

THE IMPORTANCE OF TREATING LATENT TUBERCULOSIS INFECTION (LTBI)

- For the population as a whole, there is a 10% lifetime risk of developing tuberculosis (TB) disease following infection, half of the risk occurring within 1–2 years after infection.
- Treatment of LTBI is widely recommended for individuals at increased risk of developing active TB, including contacts of TB cases, HIV-infected and other immunocompromised hosts, children, and recent immigrants.
- Treatment with isoniazid (INH), rifampin (RIF), and the combination of pyrazinamide (PZA) and RIF have been shown to decrease the risk of progressing to active disease. (Note: The combination of RIF and PZA is not currently recommended for treatment of LTBI due to increased risk of hepatotoxicity.)
- Although some data suggest that MDR-TB may be less pathogenic than drug-sensitive TB, transmission of MDR-TB to health care workers, children, and immunocompromised persons and close contacts from exposure to MDR-TB is well documented, and full evaluation of all contacts should be aggressively pursued.
- Treatment of LTBI with drug-resistant TB or MDR-TB should be considered, given the high morbidity and mortality associated with active disease.
General Principles of Providing Care to Contacts & Selecting Treatment Regimens

- Evaluate exposed contacts expeditiously in order to identify any other active cases and to prevent further transmission.
- Rule out active disease prior to starting any treatment. Amplification of resistance by use of a suboptimal regimen must be avoided.
- Immunosuppressed contacts should be treated with a multidrug MDR-LTBI or window prophylaxis regimen rather than monotherapy.
- Efficacy of any regimen depends on adherence and completion of therapy.
- Educate patients on drug side effects, importance of compliance, and TB symptoms.
- Select the most effective, best tolerated regimen to which the isolate is likely to be sensitive.
- Window prophylaxis of very high-risk close contacts who are tuberculin skin test (TST)-negative should be considered when exposure is very intimate and prolonged, and transmission to other contacts has been documented.

Summary of Treatment Options

The range of treatment options for contacts to patients with MDR-TB includes:

- Treatment with 2 or more drugs to which the organism is sensitive
- Monotherapy with a fluoroquinolone (this option is employed by some experts and is not included in current national guidelines)
- Clinical monitoring for 2 years without medication if serial evaluation is feasible
- INH alone (for patients likely to have been infected before exposure to the drug-resistant case)

The recommended duration of treatment is generally 6–12 months.

Experts agree that, regardless of the decision to treat or the treatment option selected, it is important to: 1) follow those with presumed latent MDR-TB infection for a minimum of 2 years following exposure; and 2) educate patients about the signs and symptoms of TB in case they activate their disease.

While there are specific recommendations for the treatment of drug-resistant TB, these recommendations are also largely empirical, and all regimens must be individualized.

The use of bacille Calmette-Guérin (BCG) vaccine should be considered for infants and children with a negative TST who are continually exposed to a case of MDR-TB and who cannot be removed from this exposure.
Variables to Consider

When designing a protocol for treatment of contacts to drug-resistant TB, consider the following variables:

- Drug-susceptibility pattern of the *M. tuberculosis* isolate of the presumed source case
- Infectiousness of the source MDR-TB case, which can be evaluated by:
  - Smear and culture status
  - The presence or absence of cavitory disease
  - The site of TB involvement (pulmonary or laryngeal vs. other sites)
  - The evidence of transmission to other contacts
- Closeness and intensity of MDR-TB exposure, which can be evaluated by documenting hours of cumulative exposure and setting of exposure (i.e., indoor vs. outdoor, ventilation, etc.)
- Contact’s likelihood of prior exposure to drug-sensitive TB, which can be evaluated by:
  - TST history
  - Place of birth and history of foreign residence
  - History of prior exposures to active TB
- Likelihood that the contact will progress to active TB disease, including factors such as:
  - Immunosuppression (HIV, steroids)
  - Age (less than 5 years old, elderly)
  - Documented skin test conversion
  - Diabetes, renal failure, and certain other medical conditions
- Tolerability and toxicity of potential anti-tuberculosis drugs for treatment of LTBI
Drug-Resistant LTBI: Treatment Options

Treatment of contacts depends on the resistance pattern of the source case’s isolate. The following are suggestions for regimens that may be used in specific situations. The actual regimen chosen will depend on the individual case.

Table 1.

<table>
<thead>
<tr>
<th>Resistance pattern</th>
<th>LTBI treatment options</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH (rifampin-susceptible)</td>
<td>Adults: RIF 4 months *  Children: RIF 6 months</td>
</tr>
<tr>
<td>INH and RIF</td>
<td>PZA/Ethambutol (EMB) or Fluoroquinolone +/- EMB or PZA</td>
</tr>
<tr>
<td>INH, RIF, EMB</td>
<td>Fluoroquinolone +/- PZA</td>
</tr>
<tr>
<td>INH, RIF, PZA</td>
<td>Fluoroquinolone +/- EMB</td>
</tr>
<tr>
<td>INH, RIF, PZA, EMB</td>
<td>Fluoroquinolone +/- Ethionamide*</td>
</tr>
<tr>
<td>INH, RIF, PZA, EMB, injectable</td>
<td>Fluoroquinolone +/- Ethionamide*</td>
</tr>
<tr>
<td>INH, RIF, PZA, EMB, injectable, Ethionamide</td>
<td>Fluoroquinolone +/- Cycloserine</td>
</tr>
<tr>
<td>INH, RIF, PZA, EMB, and fluoroquinolone</td>
<td>Cycloserine/PAS or PAS/Ethionamide* or Ethionamide/Cycloserine</td>
</tr>
</tbody>
</table>

* Better tolerated in children than in adults.

Current national guidelines advise treatment of MDR-LTBI with 2 drugs to which the isolate is susceptible.

**DURATION OF THERAPY**

- National guidelines suggest treatment of MDR-LTBI for 6–12 months.
- HIV-infected, children, and other individuals with medical risks should receive 12 months of treatment (cases of active MDR-TB have been seen following 9 months of MDR-LTBI treatment in children).
- Lower-risk individuals should receive **at least** 6 months of treatment.
**MDR-LTBI TREATMENT OPTIONS**

Levofloxacin and a Second Drug (First-Line Agent Preferable) to Which Isolate Is Likely to Be Susceptible (e.g., PZA, EMB, Ethionamide, PAS)

- Follows CDC/American Thoracic Society (ATS) 1992 recommendations of using 2 drugs to which isolate is sensitive.
- Frequently poorly tolerated due to increased side effect profile.
- Side effects may deter patient from completing this regimen.
- Levofloxacin/EMB may be better tolerated than Levofloxacin/PZA.
- No data on efficacy in preventing progression to active disease.

Consider use in TST converters*, immunocompromised individuals, and those in whom recent transmission with MDR-TB is highly suspected.

Experience in Texas; New York City; and Orange County, California indicates high risk for hepatitis and intolerance to a fluoroquinolone and PZA.

Levofloxacin, Moxifloxacin, or Gatifloxacin Alone

- Better tolerated than 2-drug combination and therefore more likely to complete regimen.
- Demonstrated bactericidal activity against TB.
- No evidence of efficacy in preventing progression to active disease.
- Recommended by some TB experts because of the higher likelihood of completion and known *in vitro* anti-tuberculosis activity. This option is not included in current national guidelines.
- Some experts are reluctant to use fluoroquinolone monotherapy because of the possibility of developing resistance.
- Potential toxicity in children must be balanced against unproven benefits.

Consider use in TST converters* and those with newly documented positive TST, but who may have intermediate exposure to index case so that likelihood of exposure to MDR-TB is less certain.

---

* According to ATS, a skin test “converter” is someone who has an increase in reaction size of 10 mm or more within a period of 2 years.
INH Alone

- Proven to decrease likelihood of progression to active disease if infected with a drug-susceptible strain.
- Use for contacts with history of previously untreated LTBI.
- Use for contacts with lower likelihood of infection with MDR-TB.
- Consider for contacts to cases with low-level INH resistance. Can be used twice weekly by directly observed therapy (DOT) and/or with a second drug in these cases. Ask the lab what the level of INH resistance is (percent resistance with proportion method, minimum inhibitory concentration [MIC], or concentrations studied).

Other Possible Regimens Include:
- INH, Levofloxacin, and a third drug
- INH and Levofloxacin

No Treatment: Clinical Monitoring

- This is a reasonable alternative to treatment, given the lack of proven efficacy of treatment regimens in this situation and likely side effects of regimens.
- Evaluate with chest radiograph and symptom review every 3 to 6 months for 2 years.
- Educate contact about symptoms of active disease.

Consider especially when:
- Contact is not HIV-infected.
- Contact is over 5 years of age.
- Contact is not a documented converter or otherwise at risk for progression to active TB.
- An LTBI regimen is not tolerated despite best efforts.

ADHERENCE AND MONITORING

- Contacts to active TB cases should receive treatment by DOT if local resources permit, especially those at higher risk for progression and nonadherence.
- Individuals receiving treatment for drug-resistant LTBI should be monitored closely and supported through side effects.
- Side effects should be treated symptomatically and with great encouragement, as few alternate options are available.
Treatment of Children Exposed to Drug-Resistant TB

While good data are available for treatment of LTBI for drug-susceptible TB, scant data are available for treatment of drug-resistant LTBI:

- Children exposed to INH-resistant, RIF-susceptible TB should be treated with 6 months of RIF. A study of 157 adolescents receiving RIF for 6 months after exposure to INH-resistant active TB reported no cases of active TB (at least 56% protection).
- The 2-month regimen of RIF and PZA has not been studied in children, is associated with unacceptable hepatotoxicity in adults, and should not be used.
- In an unpublished series of MDR-LTBI in children, 14 children (age 4 months – 13 years) in New York City were treated with 2–3 drugs (without fluoroquinolones) and none developed active TB. Regimens included PZA, EMB, cycloserine, and ethionamide.
- In a South African series, 2 of 41 (5%) children who received 2–3 drug treatment (without fluoroquinolones) of MDR-LTBI developed active TB, compared to 13 of 64 (20%), who did not receive treatment.

**FLUOROQUINOLONE USE IN CHILDREN**

- Fluoroquinolones are used reluctantly in children due to the observation that puppies receiving fluoroquinolones have developed arthropathy and the reports of tendon rupture in adults.
- Thousands of children have received shorter courses of fluoroquinolones without report of arthropathy.
- Ciprofloxacin has recently been licensed for treatment of urinary tract infection in children. Liquid suspensions are available for ciprofloxacin and levofloxacin.
- Thirty-two children in the South African report received ofloxacin for treatment of MDR-TB for 6–12 months without development of arthropathy (age 7–36 months).

Young children with presumed MDR-LTBI should be treated with a 2–3 drug regimen for 12 months, including a fluoroquinolone if appropriate. If a fluoroquinolone is used, informed consent of the parents should be obtained. Families should be counseled regarding the puppy model risks and advised to watch closely for any joint pain, swelling, or decreased range of motion.
Window Prophylaxis

Window prophylaxis is the practice of treating TST-negative contacts to active TB cases with anti-tuberculosis therapy during the early phase when the TST may not yet have become positive.

- **Window prophylaxis prevents rapid progression to active TB soon after infection.**
- Individuals at very high risk of progressing to active TB if infected are targeted for window prophylaxis (very young children, immunocompromised contacts, close contacts to very contagious individuals).
- Contacts should be screened by history, physical exam, and chest radiograph to rule out early active TB before initiating window prophylaxis.
- Contacts are typically treated for 3 months from the end of risk of transmission, and then the TST is repeated. If the skin test has become positive, treatment for LTBI is completed. If the skin test remains negative, window prophylaxis is stopped, unless the contact is at risk for anergy (immunosuppressed or an infant younger than 6 months of age).
- Window prophylaxis typically consists of INH for INH-susceptible or RIF for INH-resistant/RIF-susceptible TB contacts.

- **Window prophylaxis for MDR-TB is problematic due to lack of efficacy data and toxicity of potential regimens.**
- Window prophylaxis for MDR-TB should be considered in consultation with TB experts for the following: very young children, and HIV-infected individuals with very intimate and prolonged contact with individuals likely to be contagious (smear-positive, cavitary disease, coughing source case, TST conversions among other contacts).

Follow-Up of MDR Contacts

- It is essential to carefully educate contacts who have not received treatment and those finishing MDR-LTBI treatment about the signs and symptoms of TB, stressing the need for prompt medical evaluation if symptoms occur.
- Patients who have not received treatment for MDR-LTBI should be screened with symptom review, physical examination, and chest radiograph every 3 to 6 months for 2 years.
- Given the lack of efficacy data on MDR-LTBI treatment, some experts recommend evaluation/symptom review, with or without chest radiographs, every 6 months for 2 years for high-risk contacts who have completed treatment (HIV and other immunocompromised individuals, children under age 5, TST converters).
Summary

While it is highly desirable to prevent MDR-TB cases by treatment of LTBI and use of window prophylaxis, there are limited efficacy data and lack of expert consensus to guide clinicians.

Treatment of LTBI should be considered particularly for patients at highest risk for progression to active TB.

Careful contact investigation is required to determine timing of infection. Patients who were previously TST positive were more likely infected with a susceptible strain and should be treated with INH.

Recommended treatment regimens include 2 drugs to which the source case isolate is susceptible for 6–12 months. Some experts now recommend monotherapy with a fluoroquinolone drug to which the isolate is susceptible for select cases.

Young children and patients who are immunocompromised should be treated with 2-drug regimens for at least 12 months.

For some patients, clinical monitoring without treatment can be considered.

All exposed patients should be monitored for symptoms and radiographically for at least 2 years for evidence of active TB.
REFERENCES MANA GING C ONTACTS

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Appendix 1: **LIST OF EXPERT RESOURCES FOR DRUG-RESISTANT TB**

### A.G. Holley Hospital/Florida State TB Control Program Hotline

**CONTACT**  
Florida TB Physicians Network

**PHONE**  
800-4TB-INFO (800-482-4636)

**E-MAIL**  
David_Ashkin@doh.state.fl.us

**ADDRESS**  
1199 West Lantana Road, Lantana, FL 33462

- **Types of consultation:** Telephone, e-mail, and in-person.
- All patients in Florida with disease caused by strains resistant to at least rifampin are reviewed and consultations are provided by members of the Florida TB Physicians Network (the medical/clinical arm of the Florida Bureau of TB).
- Can provide advice for patients not in jurisdiction.
- Sometimes, patients can be sent to our facility.
- **Comments:** Any Florida citizen being treated for TB has the availability of services from the staff of A.G. Holley Hospital (the state TB Hospital). There are no insurance requirements; it is a full-service program (e.g., surgery [at affiliated institution], behavioral medicine, social services, rehabilitation, research, etc.). Arrangements are being determined for the availability of providing both inpatient and outpatient (in-person) services for out-of-state patients. Consultation services are available through the hotline.
- Can provide ongoing consultation during drug-resistant treatment.

### California Department of Health Services

**TB Control Branch, Division of Communicable Disease Control**

**MDR-TB Service**

**CONTACT**  
Ann Raftery, RN, Coordinator

**PHONE**  
916-650-6882

**E-MAIL**  
araftery@dhs.ca.gov

**ADDRESS**  
2151 Berkeley Way, Room 506, Berkeley, CA 94704

- **Types of consultation:** Telephone and e-mail (for callers within California or other state agencies within the U.S.).
- Can provide on-site presentations related to MDR-TB.
- Can provide ongoing consultation during drug-resistant treatment.
Centers for Disease Control and Prevention
National Center for HIV, STD, and TB Prevention
Division of TB Elimination
International Research and Programs Branch
MDR-TB Team

CONTACT  Duty Officer of the Day
PHONE  404-639-8140
E-MAIL  tbinfo@cdc.gov
ADDRESS  CDC, Division of TB Elimination, Mailstop E-10
1600 Clifton Road, NE, Atlanta, GA  30333

- **Types of consultation:** Telephone, e-mail, and in-person (for outbreaks).

- In general, CDC/DTBE does not provide clinical consultation, though several staff members are physicians with clinical experience managing TB patients.

- Visit the CDC/DTBE website:  http://www.cdc.gov/nchstp/tb/
Chicago Department of Public Health TB Control Program

**CONTACT**  Susan Lippold, MD or William Clapp, MD
**PHONE**  312-746-5983
**E-MAIL**  lippold_susan@cdph.org  clapp_William@cdph.org
**ADDRESS**  2160 W. Ogden Ave., Chicago, IL  60612

- **Types of consultation:** Telephone, e-mail, and in-person.
- **Can provide advice for patients not in jurisdiction.**
- **Patients can be sent to our facility.**
- **Comments:** Insurance not needed for initial evaluation, further services available depending on needs and resources; TB medications available at no cost only to patients living in the City of Chicago.
- **Can provide ongoing consultation during drug-resistant treatment.**

Most of our MDR work is collaborative, utilizing the collective wisdom of recognized authorities (listed below).

<table>
<thead>
<tr>
<th>NAME OF AGENCY</th>
<th>CONTACT PERSON</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ADULT</strong></td>
<td></td>
</tr>
<tr>
<td>University of Illinois Hospitals and Clinics</td>
<td>Dr. Dean Schraufnagel</td>
</tr>
<tr>
<td>Department of Medicine</td>
<td>312-996-8039</td>
</tr>
<tr>
<td>Division of Pulmonary and Critical Care Medicine</td>
<td></td>
</tr>
<tr>
<td><strong>ADULT</strong></td>
<td></td>
</tr>
<tr>
<td>University of Illinois Hospitals and Clinics</td>
<td>Dr. James Cook</td>
</tr>
<tr>
<td>Department of Medicine</td>
<td>312-996-6732</td>
</tr>
<tr>
<td>Division of Infectious Diseases</td>
<td></td>
</tr>
<tr>
<td><strong>PEDIATRICS</strong></td>
<td></td>
</tr>
<tr>
<td>Rush-Presbyterian St. Lukes Hospital</td>
<td>Dr. James McAuley</td>
</tr>
<tr>
<td>Department of Pediatrics</td>
<td>312-942-6396</td>
</tr>
<tr>
<td>Division of Infectious Diseases</td>
<td></td>
</tr>
</tbody>
</table>
Francis J. Curry National Tuberculosis Center — TB Warmline

CONTACT Lakesha Franklin, Warmline Coordinator
PHONE 415-502-4700
E-MAIL tbcenter@nationaltbcenter.edu
ADDRESS 3180 18th Street, Suite 101, San Francisco, CA 94110

- Types of consultation: Telephone and e-mail.
- Can provide advice for patients not in jurisdiction.
- Patients can be sent to our facility—see *San Francisco Department of Public Health*.
- Can provide ongoing consultation during drug-resistant treatment.

Los Angeles County TB Control Program

CONTACT Jaimin Kim, PHN, MDR-TB Unit
PHONE 213-744-6160
ADDRESS 2615 S. Grand Avenue, Room 507, Los Angeles, CA 90025

- Types of consultation: Nursing and medical consultation for Los Angeles County cases.

National Jewish Mycobacterial Diseases Consult Line

CONTACT Carol Boyksvich, RN
PHONE 800-423-8891, ext 1353 or 303-398-1353
E-MAIL mycoconsults@njc.org
ADDRESS National Jewish Medical and Research Center
1400 Jackson Street, Denver, CO 80206

- Types of consultation: Telephone, e-mail, and in-person.
- Can provide advice for patients not in jurisdiction.
- Patients can be sent to our facility.
- Comments: Contact Ms. Boyksvich to discuss referral process or to ask for a clinical consultation (consultations provided by Michael Iseman, MD; Gwen Huit, MD; Charles Daley, MD; Scott Worthen, MD; Leonid Heifets, MD; and Charles Peloquin, PharmD).
- Our service provides comprehensive evaluation and treatment programs, including consideration of surgery. If indicated, surgery is performed at our sister institution, the University of Colorado Health Science Center.
New Jersey Medical School National Tuberculosis Center

**CONTACT**  Reynard J. McDonald, MD or Alfred Lardizabal, MD  
**PHONE**  800-4TB-DOCS or 973-972-3270  
**INTERNET**  http://www.umdnj.edu/NTBCweb  
**ADDRESS**  225 Warren Street, 2nd Floor, East Wing, Newark, NJ 07103

- **Types of consultation:** Telephone, e-mail, and in-person.  
- Consultants to the New Jersey DHSS for TB problems, including all cases of MDR-TB.  
- Center provides comprehensive diagnostic, treatment, and consultation services for TB patients in the state of New Jersey.  
- Can provide advice and consultation for patients not in jurisdiction.  
- MDR-TB work is collaborative, utilizing the collective wisdom of the following recognized authorities at the New Jersey Medical School National Tuberculosis Center:

<table>
<thead>
<tr>
<th>ADULTS</th>
<th>CHILDREN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr. Lee B. Reichman</td>
<td>Dr. George McSherry</td>
</tr>
<tr>
<td>Dr. Bonita Mangura</td>
<td>Dr. Helen Aguilla</td>
</tr>
<tr>
<td>Dr. Alfred Lardizabal</td>
<td></td>
</tr>
</tbody>
</table>

New York City Department of Health and Mental Hygiene

**CONTACT**  Diana Nilsen, MD  
**PHONE**  212-442-9737  
**E-MAIL**  dnilsen@health.nyc.gov  
**ADDRESS**  225 Broadway, 22nd Floor, New York, NY 10007

- **Type of consultation:** Telephone, e-mail, and in-person.  
- Can provide advice for patients not in jurisdiction.  
- Patients can be sent to our facility.  
- **Comments:** Free evaluation and treatment, including CXR, sputa, DOT, and meds in outpatient facilities.  
- Can provide ongoing consultation during drug-resistant treatment.
Partners In Health

CONTACT Jennifer J. Furin, MD, PhD
PHONE 617-525-7527
E-MAIL Jfurin@partners.org
ADDRESS 641 Huntington Ave., Boston, MA 02115

- **Type of consultation:** Telephone, e-mail, and in-person.
- Can provide advice for patients not in jurisdiction.
- **Comments:** We are a non-profit organization with more than 10 years of experience treating MDR-TB in resource-poor settings.
- Can provide ongoing consultation during drug-resistant treatment.

San Francisco Department of Public Health—TB Control Section

CONTACT Masae Kawamura, MD
PHONE 415-206-3387
E-MAIL masae.kawamura@sfdph.org
ADDRESS TB Clinic, San Francisco General Hospital, 1001 Potrero Ave., San Francisco, CA 94110

- **Types of consultation:** Telephone (in-person consultation for San Francisco patients only).
- Can provide advice for patients not in jurisdiction.
- Can provide ongoing consultation during drug-resistant treatment.

Texas Department of Health—TB Resource and Education Center

CONTACT Barbara J. Seaworth, MD
PHONE 210-534-8857, ext. 2489
E-MAIL Barbara.Seaworth@tdh.state.tx.us
ADDRESS 2203 SE Military Drive, San Antonio, TX 78218

- **Types of consultation:** Telephone, e-mail, and in-person (clinic).
- Can provide ongoing consultation during drug-resistant treatment.
- Provides consultations for all Texas cases of drug-resistant TB, contacts of drug-resistant TB, and use of fluoroquinolones, or other non-formulary drugs (linezolid).
- Can provide advice for patients not in jurisdiction.
- **Comments:** Some legislation has been passed to allow patients from other states to be sent to our facility, but it is still very difficult for non-Texas patients.
- We like to use a case management approach for all contacts to make sure treatment not only begins correctly but also continues on course, and that problems leading to toxicity and treatment failure are identified and corrected early.
## Appendix 2: Contact Information for Selected Organizations Working to Control and Prevent TB in the International Arena

<table>
<thead>
<tr>
<th>Organization</th>
<th>Contact Information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CureTB:</strong> Binational TB Referral Program</td>
<td><a href="http://www.curetb.org">http://www.curetb.org</a></td>
</tr>
<tr>
<td></td>
<td>619-542-4013</td>
</tr>
<tr>
<td><strong>Green Light Committee</strong></td>
<td><a href="http://www.who.int/gtb/policyrd/PDF/DOTSGLC.pdf">http://www.who.int/gtb/policyrd/PDF/DOTSGLC.pdf</a></td>
</tr>
<tr>
<td><strong>International Union Against Tuberculosis and Lung Disease (IUATLD)</strong></td>
<td><a href="http://www.iuatld.org">http://www.iuatld.org</a></td>
</tr>
<tr>
<td></td>
<td>(+33) 1-44-32-0360</td>
</tr>
<tr>
<td><strong>Médecins Sans Frontières</strong> (Doctors Without Borders)</td>
<td><a href="http://www.msf.org/">http://www.msf.org/</a></td>
</tr>
<tr>
<td></td>
<td>212-679-6800</td>
</tr>
<tr>
<td><strong>Partners In Health</strong></td>
<td><a href="http://www.pih.org/index.html">http://www.pih.org/index.html</a></td>
</tr>
<tr>
<td></td>
<td>617-432-5256</td>
</tr>
<tr>
<td><strong>Stop TB Partnership</strong></td>
<td><a href="http://www.stoptb.org/">http://www.stoptb.org/</a></td>
</tr>
<tr>
<td></td>
<td>+(41) 22-791-2708</td>
</tr>
<tr>
<td><strong>TBNet</strong> (Migrant Clinicians Network)</td>
<td><a href="http://www.migrantclinician.org/network/tbnet">http://www.migrantclinician.org/network/tbnet</a></td>
</tr>
<tr>
<td></td>
<td>800-825-8205</td>
</tr>
<tr>
<td><strong>Ten Against TB</strong></td>
<td><a href="http://www.r10.tdh.state.tx.us/obh/tatb.htm">http://www.r10.tdh.state.tx.us/obh/tatb.htm</a></td>
</tr>
<tr>
<td></td>
<td>915-834-7680</td>
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Appendix 3: **INTERNATIONAL RESOURCES FOR TB TREATMENT AND POLICIES**

The following websites are potential sources of information about the various TB protocols practiced in countries with high rates of immigration to the U.S.

<table>
<thead>
<tr>
<th>Country</th>
<th>Website Details</th>
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<tbody>
<tr>
<td><strong>Global</strong></td>
<td>The third report by the WHO/IUATLD Global Project on Anti-Tuberculosis Drug Resistance Surveillance presents data from 77 settings or countries: <a href="http://www.who.int/gtb/publications/drugresistance/2004/index.htm">http://www.who.int/gtb/publications/drugresistance/2004/index.htm</a></td>
</tr>
<tr>
<td></td>
<td>The WHO website provides links to, and contact information for, TB programs located throughout the world: <a href="http://www.who.int/topics/tuberculosis/en/">http://www.who.int/topics/tuberculosis/en/</a></td>
</tr>
<tr>
<td></td>
<td>The CDC Division of Global Migration and Quarantine is another source of information: <a href="http://www.cdc.gov/ncidod/dq/">http://www.cdc.gov/ncidod/dq/</a> E-mail: <a href="mailto:dqweb@cdc.gov">dqweb@cdc.gov</a></td>
</tr>
<tr>
<td><strong>Mexico</strong></td>
<td><a href="http://www.salud.gob.mx">http://www.salud.gob.mx</a></td>
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<tr>
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<td><a href="http://www.salud.gob.mx/unidades/cdi/nom/m006ssa23.html">http://www.salud.gob.mx/unidades/cdi/nom/m006ssa23.html</a></td>
</tr>
<tr>
<td><strong>India</strong></td>
<td><a href="http://www.tbcindia.org/documents.asp">http://www.tbcindia.org/documents.asp</a></td>
</tr>
<tr>
<td><strong>Philippines</strong></td>
<td><a href="http://www.doh.gov.ph/ncdpc/ncdpc.htm">http://www.doh.gov.ph/ncdpc/ncdpc.htm</a></td>
</tr>
</tbody>
</table>
Appendix 4: LABORATORY RESOURCES

The laboratory is the cornerstone of diagnosis and management of drug-resistant tuberculosis (TB) in the United States and other industrialized countries. While initial treatment regimens are designed empirically based on risk of resistance and prior use of antimicrobials, definitive regimens rely on accurate and timely susceptibility results.

There are several types of laboratories that culture mycobacteria:

- Hospital-based laboratories
- Local public health laboratories
- State public health laboratories
- Commercial laboratories

Each lab performs different services: different types of smears, culture methods, identification methods, rapid tests for early identification or species identification, and susceptibility testing and panels of drugs for susceptibility testing. Services and protocols may vary based on the source of the specimen (private provider vs. hospitalized patient), type of specimen (sputum vs. cerebrospinal fluid [CSF]), and third-party payer source.

Case managers and treating physicians should have an in-depth understanding of the laboratory practices of the facilities processing their patients’ specimens.

SPECIFIC ELEMENTS TO KNOW:

Will the lab perform nucleic acid amplification tests upon request? On any sputum requested or only smear-positive sputum?

Nucleic acid amplification tests (NAATs) rapidly identify mycobacterial DNA in clinical specimens. They are usually used to diagnose TB vs. nontuberculous mycobacteria (NTM) in smear-positive sputum in order to guide empiric treatment and infection control measures. They can be performed on smear-negative specimens as well, but negative results in such a case have a lower predictive value (higher probability of false-negative results) compared to smear-positive specimens. The test can be useful with various biopsy and autopsy specimens and various body fluids, especially with CSF when TB meningitis is suspected (these uses are less well studied). Contact individual laboratories regarding their policies and protocols for use of the NAAT tests.

Does the lab perform direct susceptibility tests upon request?

Direct susceptibility tests entail plating of clinical specimen directly onto drug-containing agar in order to fairly quickly determine drug resistance. This is not performed by all labs but can be useful, when available, for relatively rapid detection of drug resistance.

How and when will smear and culture results be reported to me?

Positive acid-fast bacilli (AFB) smears and *M. tuberculosis* cultures should be “automatically” reported to the local public health jurisdiction and the ordering physician or referring lab within 24 hours after the arrival of the specimen to the lab. Communication with the lab will ensure that the results reach the correct individuals immediately.
How can I keep track of serial cultures being performed at different laboratories?

It is advisable to submit serial cultures to the same laboratory, usually the local public health laboratory. Many public health departments and case managers can access their public health laboratories’ computerized results directly, making smear, culture, identification, and susceptibility status available as rapidly as possible. Additionally, most public health laboratories will automatically repeat susceptibilities for patients whose cultures remain positive after 3 months. Having all follow-up cultures at the same laboratory provides the greatest efficiency and optimal communication.

How can I ensure that adequate specimens are being submitted?

It is not possible to be sure of specimen adequacy. It is prudent to submit 2–3 specimens biweekly until the sputum is smear-negative. Two specimens (minimum volume 5–10 ml) should be collected at least monthly until the patient is consistently culture-negative. If there is any concern about quality of the specimen, arrange sputum induction for the patient, and always submit 2 specimens 8–24 hours apart.

Will drug susceptibility tests be performed immediately?

Some institutional contracts with mycobacteriology labs require an additional request from the ordering physician in order to perform susceptibility tests.

If the lab does not perform susceptibility tests on-site, where will the isolate be sent? Will it be sent automatically? How will that lab share results with me?

Contracts between payers and individual hospitals and labs determine where susceptibility testing is performed. The reference lab reports results to the referring lab.

What is the panel of drugs studied initially?

Many labs do not test for pyrazinamide (PZA) susceptibility and only test 1 concentration of each of the SIRE (streptomycin, isoniazid, rifampin, ethambutol) drugs.

Can I request that second-line susceptibility tests be performed as soon as growth is detected?

More extensive drug panels should be ordered if drug resistance is suspected. This saves several weeks of processing time in the case of high index of suspicion for drug resistance.

How can I arrange to receive results as soon as they are available?

Many labs perform confirmatory tests before releasing results. It is valuable to know that some AFB is growing even before identification is performed. It is helpful to know that the organism is \textit{M. tuberculosis} complex (frequently this is the extent of the speciation), even if the lab intends to fully speciate the isolate. The lab should know that you want to be informed of drug resistance detected by broth methods before confirmed at its reference lab or by an alternate method.

How can I arrange for a broader panel of drug susceptibility tests to be performed?

Many labs have a regional reference lab under contract to perform confirmatory tests or more extensive testing. In the case of many commercial labs and some public health labs, the list of second-line drugs tested may be quite limited. In the case of extensive drug resistance, many second- and third-line drugs may need to be tested in order to design a curative regimen for your patient. While unnecessary expense should be avoided, expeditious appropriate testing should be performed. Very comprehensive second- and third-line testing is only performed at a few reference laboratories.

An open dialogue with the laboratorian facilitates the prompt communication of results and the most efficient and comprehensive laboratory evaluation of the patient’s isolate.
Contact your state/local public health, hospital-based, or commercial laboratory for more information if it is not listed below.

### State Public Health Laboratories

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Tests performed</th>
<th>Requirements</th>
<th>Cost</th>
<th>Contact information</th>
</tr>
</thead>
<tbody>
<tr>
<td>California-DHS Microbial Disease Laboratory (MDL)</td>
<td>Indirect susceptibility testing: <strong>INH, RIF, PZA, EMB, SM</strong>, and levofloxacin</td>
<td>LJ Slants, Broth samples</td>
<td>None</td>
<td>Edward P. Desmond, PhD&lt;br&gt;Chief of Mycobacteriology &amp; Mycology Section&lt;br&gt;510-412-3700&lt;br&gt;FAX: 510-412-3706&lt;br&gt;Microbial Disease Laboratory c/o Specimen Receiving&lt;br&gt;California Department of Health Services&lt;br&gt;850 Marina Bay Parkway&lt;br&gt;Richmond, CA  94804&lt;br&gt;Most specimens come from county public health department labs&lt;br&gt;&lt;strong&gt;All&lt;/strong&gt; laboratories must submit all MDR-TB isolates from any CA resident</td>
</tr>
<tr>
<td></td>
<td>Rapid (molecular beacons) <strong>INH, RIF susceptibility testing</strong>: by request only – call Dr. Desmond or Grace Lin, 510-412-3929</td>
<td>Strongly smear-positive sputum LJ Slants, Broth samples</td>
<td>Full services available only to CA residents</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TB strain typing</td>
<td>LJ Slants, Broth samples</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The Florida Department of Health Central Laboratory Mycobacteriology Section</td>
<td>Smear and primary culture isolation; species ID; nucleic acid amplification of <em>M. tuberculosis</em> in raw specimens</td>
<td>Clinical specimens LJ Slants, Broth samples</td>
<td>None</td>
<td>Dr. David Beall, Director&lt;br&gt;904-791-1630&lt;br&gt;FAX: 904-791-1633&lt;br&gt;1217 Pearl St, Jacksonville, FL  32202&lt;br&gt;For detailed information see: <a href="http://www.doh.state.fl.us/lab/mycobacteriology1.htm">www.doh.state.fl.us/lab/mycobacteriology1.htm</a> <a href="http://www.doh.state.fl.us/lab/mycobacteriology2.htm">www.doh.state.fl.us/lab/mycobacteriology2.htm</a> <a href="http://www.doh.state.fl.us/lab/mycobacteriology3.htm">www.doh.state.fl.us/lab/mycobacteriology3.htm</a> <a href="http://www.doh.state.fl.us/lab/mycobacteriology4.htm">www.doh.state.fl.us/lab/mycobacteriology4.htm</a></td>
</tr>
</tbody>
</table>
# State Public Health Laboratories

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Tests performed</th>
<th>Requirements</th>
<th>Cost</th>
<th>Contact information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>New York State Department of Health Wadsworth Center</strong></td>
<td>Smear and primary culture; species ID using AccuProbe, deletion analysis (final ID within <em>M. tuberculosis</em> complex), DNA sequencing; nucleic acid amplification for NYS FAST TRACK specimens (if suspicion for MDR-TB, molecular assays are performed on strongly smear-positive specimens or upon growth in broth medium), other specimens by request. Several susceptibility testing methods available</td>
<td>Clinical specimens; can be sent as part of the NYS FAST TRACK program (Eligibility: newly diagnosed, AFB smear-positive, or high likelihood of TB and/or suspicion for drug resistance) Broth samples (at least 3 ml preferred) LJ Slants</td>
<td>Service free for all New York residents</td>
<td><strong>Max Salfinger, MD</strong>&lt;br&gt;Director, Clinical Mycobacteriology Laboratory&lt;br&gt;518-474-2196&lt;br&gt;FAX: 518-474-6964&lt;br&gt;P.O. Box 509, Albany, NY 12201&lt;br&gt;Street address:&lt;br&gt;120 New Scotland Avenue, Albany, NY 12208&lt;br&gt;E-mail: <a href="mailto:salfinger@wadsworth.org">salfinger@wadsworth.org</a>&lt;br&gt;Lab supervisor: 518-474-7043&lt;br&gt;www.wadsworth.org</td>
</tr>
</tbody>
</table>

Indirect susceptibility testing; first-line drugs: INH, RIF, PZA, EMB, SM; second-line drug susceptibility by agar proportion automatically upon detection of any first-line resistance: INH, RIF, EMB, SM, capreomycin, cycloserine, ethionamide, kanamycin, PAS, amikacin, ofloxacin

Molecular drug resistance assays for INH (*katG*), RIF (*rpoB*), PZA (*pncA*), EMB (*embB*)

TB strain typing
<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Tests performed</th>
<th>Requirements</th>
<th>Cost</th>
<th>Contact information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Texas Department of State Health Services</td>
<td>Smear and primary culture; species ID; HPLC for smear-positive specimens (MTB and common NTMs in smear-positive specimens); nucleic acid amplification performed weekly on HPLC inconclusive smear-positive specimens and upon request</td>
<td>Clinical specimens</td>
<td>Free for clients of the Texas TB Elimination program; other patients / hospitals will be billed</td>
<td>Denise Dunbar Mycobacteriology/Mycology Group Manager 512-458-7342 FAX 512-458-7167 <a href="mailto:Denise.dunbar@dshs.state.tx.us">Denise.dunbar@dshs.state.tx.us</a> Texas DSHS Mycobacteriology/Mycology Lab 1100 W. 49th, Austin, TX 79756 <a href="http://www.tdh.state.tx.us/lab/myco_home.htm">www.tdh.state.tx.us/lab/myco_home.htm</a> <a href="http://www.tdh.state.tx.us/lab/myco_clin-specs.htm">www.tdh.state.tx.us/lab/myco_clin-specs.htm</a></td>
</tr>
<tr>
<td>Mycobacteriology/Mycology Group</td>
<td>Indirect susceptibility testing: First-line INH, RIF, EMB. Second-line drugs upon detection of resistance or upon request: SM, PZA, ofloxacin, capreomycin, kanamycin, ethionamide, rifabutin</td>
<td>LJ Slants or Middlebrook agar slants</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Tests performed</th>
<th>Requirements</th>
<th>Cost</th>
<th>Contact information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centers for Disease Control and Prevention</td>
<td>Indirect susceptibility testing: INH, RIF, PZA, EMB, SM, ofloxacin, capreomycin, amikacin, kanamycin, ethionamide, PAS, rifabutin</td>
<td>LJ Slants preferred</td>
<td>None</td>
<td>Beverly Metchock, DrPH 404-639-2455 All specimens must come from state public health department labs</td>
</tr>
</tbody>
</table>
## Local Public Health Laboratories

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Tests performed</th>
<th>Requirements</th>
<th>Cost</th>
<th>Contact information</th>
</tr>
</thead>
</table>
| **Los Angeles County Public Health Laboratory** | Smear and primary culture; species ID; nucleic acid amplification for direct specimens by request | Clinical specimens LJ Slants | Free for LA County patients      | **Hector Rivas**  
Supervisor 1 for Mycobacteriology Section  
Anthony Gonzalez, PhD  
Technical Supervisor  
213-250-8619  
FAX: 213-481-2375  
313 N. Figueroa St., Room 1127  
Los Angeles, CA  90012  
www.lapublichealth.org/lab/labtb.htm  
www.lapublichealth.org/lab/tb-1.htm |
| **New York City Department of Health TB Laboratory** | Smear and primary culture; species ID; nucleic acid amplification for direct specimens by request; direct susceptibilities by request  
First-line drug indirect susceptibility testing by MGIT: INH, RIF, PZA, EMB; second-line drug susceptibility testing by agar proportion automatically if drug resistance detected: ethionamide, ciprofloxacin, PAS, capreomycin, kanamycin, cycloserine, and rifabutin | Clinical specimens LJ Slants Broth samples  
Confirmed speciation by the referring lab is greatly appreciated | MTD and drug susceptibilities free for New York City and 5 boroughs residents | **Dr. Adeleh Ebrahimzadeh**  
Lab Director and Research Scientist III  
212-447-6121  
FAX: 212-447-8283  
4355 1st Avenue, New York, New York  10016 |
## COMMERCIAL LABORATORIES

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Tests performed</th>
<th>Requirements</th>
<th>Cost</th>
<th>Contact information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Focus Technologies</strong></td>
<td>Smear and primary culture isolation; species ID; nucleic acid amplification or</td>
<td>Clinical specimens LJ Slants Broth</td>
<td>Contracted with each institution – see catalog for base price</td>
<td>Scientific Director of Microbiology&lt;br&gt;800-445-0185&lt;br&gt;FAX: 714-503-2093&lt;br&gt;Cypress, CA 90630&lt;br&gt;www.focustechnologies.com&lt;br&gt;www.focustechnologies.com/techsheets/MycobacterialTestingServices.pdf</td>
</tr>
<tr>
<td></td>
<td>HPLC of <em>M. tuberculosis</em> in raw specimens</td>
<td>samples Plates if safely packaged</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Direct and indirect susceptibility testing: <strong>INH, RIF, PZA, EMB, SM, rifabutin,</strong></td>
<td>LJ Slants Broth samples Plates if</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>ciprofloxacin, capreomycin, amikacin, ethionamide, PAS, cycloserine</strong></td>
<td>safely packaged</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Therapeutic drug levels: <strong>ciprofloxacin, capreomycin,</strong></td>
<td>Frozen serum</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td><strong>kanamycin, ethionamide, cycloserine,</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>INH, RIF, PZA, SM, rifabutin, ofloxacin</strong></td>
<td></td>
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<tr>
<td></td>
<td>Rifampin mutation analysis</td>
<td>Frozen smear-positive respiratory</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>AMPLICOR™ PCR on clinical specimens</strong></td>
<td>secretions or pure culture growth</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mayo Medical Laboratories</strong></td>
<td>Smear and primary culture; <em>M. tuberculosis</em> complex ID using AccuProbe or DNA</td>
<td>Clinical specimens LJ Slants Broth</td>
<td>Contracted with each institution – see catalog for base price</td>
<td>Nancy L. Wengenack, PhD&lt;br&gt;Director, Mycology/Mycobacteriology Laboratory&lt;br&gt;800-533-1710&lt;br&gt;FAX: 507-284-1759&lt;br&gt;e-mail: <a href="mailto:mml@mayo.edu">mml@mayo.edu</a>&lt;br&gt;200 First Street SW, Rochester, MN 55905&lt;br&gt;www.mayoreferenceservices.org/mml</td>
</tr>
<tr>
<td></td>
<td>sequencing; species ID upon request; nucleic acid amplification of <em>M. tuberculosis</em> from raw specimens</td>
<td>samples (sputum/CSF/tissue, etc.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Indirect susceptibility testing: <strong>INH, RIF, PZA, EMB</strong>; second-line: <strong>SM</strong></td>
<td></td>
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</tbody>
</table>
## Commercial Laboratories

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Tests performed</th>
<th>Requirements</th>
<th>Cost</th>
<th>Contact information</th>
</tr>
</thead>
</table>
| National Jewish Medical and Research Center   | Smear and primary culture isolation; species ID; nucleic acid amplification of *M. tuberculosis* in raw specimens; direct and indirect susceptibility testing; several susceptibility testing methods available | Clinical specimens    | For cost, download requisition from website                          | Leonid Heifets, MD, PhD, Director  
Mycobacteriology Reference Laboratory  
303-398-1339  
FAX: 303-398-1953  
To download a requisition for cultures or susceptibilities:  
www.nationaljewish.org/pdf/lab/mycobacteriology.pdf |
|                                               | INH, RIF, PZA, EMB, SM, rifabutin, ciprofloxacin, capreomycin, amikacin, kanamycin, ethionamide, cycloserine, imipenem, tobramycin, linezolid, PAS, and experimental drugs (all) | LJ Slants Broth samples | National Jewish will bill CO Medicaid, the patient's credit card, or the facility from which the specimen came | Charles Peloquin, PharmD, Director  
Infectious Diseases Pharmacokinetics Laboratory  
303-398-1427/main: 303-398-1422  
FAX: 303-270-2229  
To download a requisition for therapeutic drug levels:  
|                                               | Therapeutic drug levels: All                                                                                                                                                                                  | Frozen serum          |                                                                      | Customer service: 800-550-6227  
1400 Jackson St. Denver, CO 80206 |

The following websites give details for packaging, labeling, and shipping specimens and cultures:

- [http://www.njc.org/lab/tb_shipping.html](http://www.njc.org/lab/tb_shipping.html)
- [http://www.saftpak.com/650.htm](http://www.saftpak.com/650.htm)
Appendix 5: **DIRECT METHOD**

- The clinical specimen (usually acid-fast bacilli [AFB] smear-positive sputum) is digested, decontaminated, and diluted. The processed specimen is plated onto agar containing critical concentrations of anti-tuberculosis drugs and a control containing no drugs.
- Results are interpretable if appropriate growth (at least 50–150 colonies, identified as *M. tuberculosis*) is found on control agar (no drug). The number of colonies that grow on each drug-containing agar plate (or quadrant) is reported as a percent of the colonies that grow on the control plate. The isolate is resistant if more than 1% of the number of colonies on control agar grow on a given drug agar plate.
- The direct method takes 3–5 days longer than indirect method (from the time of plating).
- The direct method is problematic when specimen contains nontuberculous mycobacteria either in pure or mixed culture. The colonies should be scrutinized for the possibility of growth with nontuberculous mycobacteria.
- Currently, only agar methods are well studied; broth methods should not be used.
- Results from the direct method are usually confirmed using the indirect method, especially if the isolate is found to be drug-resistant.
- The direct method may more accurately represent the patient’s population of tuberculosis (TB) bacilli. Plates should be read each week for 3 weeks, giving time for slow-growing resistant colonies to be recognized.
- The direct method may be requested if drug-resistant TB is STRONGLY suspected, molecular assays are not available, and the sputum is AFB smear-positive.

**Figure 1.** Quad plate – Sputum containing AFB smear-positive organisms is plated onto each of the 4 quadrants. The top quadrant contains no antibiotic and has allowed growth of *M. tuberculosis* colonies. The other 3 quadrants contain antibiotic-containing discs. The antibiotic has diffused into the agar and suppressed growth of the *M. tuberculosis* in the 3 quadrants. This is a pan-susceptible TB isolate.
### Appendix 6: CRITICAL CONCENTRATIONS OF ANTIMYCOBACTERIAL AGENTS TO TEST AGAINST M. TUBERCULOSIS BY BROTH OR AGAR PROPORTION METHODS

<table>
<thead>
<tr>
<th>Antimicrobial agent</th>
<th>Typical MIC (µg/ml) for susceptible strains</th>
<th>Concentration in serum (µg/ml)</th>
<th>Medium and concentration (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>BD BACTEC 460TB</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>12B low/high</strong></td>
</tr>
<tr>
<td>Primary Agents</td>
<td></td>
<td></td>
<td><strong>0.1/0.4</strong></td>
</tr>
<tr>
<td>INH</td>
<td>0.05–0.2</td>
<td>7</td>
<td><strong>0.1/0.4</strong></td>
</tr>
<tr>
<td>RIF</td>
<td>0.5</td>
<td>10</td>
<td><strong>2/1</strong></td>
</tr>
<tr>
<td>PZA</td>
<td>20</td>
<td>45</td>
<td><strong>2.5/7.5</strong></td>
</tr>
<tr>
<td>EMB</td>
<td>1–5</td>
<td>2–5</td>
<td></td>
</tr>
<tr>
<td>Secondary Agents</td>
<td></td>
<td></td>
<td><strong>2/6</strong></td>
</tr>
<tr>
<td>SM</td>
<td>8</td>
<td>25–50</td>
<td><strong>2/6</strong></td>
</tr>
<tr>
<td>Capreomycin</td>
<td>1–50</td>
<td>30</td>
<td><strong>1.25</strong></td>
</tr>
<tr>
<td>Kanamycin</td>
<td>5</td>
<td>14–29</td>
<td><strong>5</strong></td>
</tr>
<tr>
<td>Cycloserine</td>
<td>5–20</td>
<td>20–40</td>
<td><strong>NR</strong></td>
</tr>
<tr>
<td>Ethionamide</td>
<td>0.6–2.5</td>
<td>2–20</td>
<td><strong>1.25</strong></td>
</tr>
<tr>
<td>PAS</td>
<td>1</td>
<td>7.5</td>
<td><strong>4</strong></td>
</tr>
<tr>
<td>Alternative Agents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifabutin</td>
<td>0.06–8</td>
<td>0.2–0.5</td>
<td><strong>0.5</strong></td>
</tr>
<tr>
<td>Amikacin</td>
<td>1</td>
<td>16–38</td>
<td><strong>1</strong></td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>0.5–2.5</td>
<td>3–11</td>
<td><strong>2</strong></td>
</tr>
</tbody>
</table>

The critical concentration is the level of drug that inhibits a wild-type TB strain (a strain which has not been exposed to TB drugs), but does not appreciably suppress the growth of a resistant strain.

* NR, no recommendation.


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Molecular methods are based on detection of specific mutations associated with drug resistance.

Ideal targets are genes whose mutations account for the vast majority of drug resistance; i.e., \textit{rpoB} for rifampin (RIF) resistance and \textit{pncA} for pyrazinamide (PZA) resistance. Several mutations that cause isoniazid (INH) resistance have been detected; however, 15–25% of INH-resistant isolates tested conventionally do not contain known mutations.

In the laboratory, DNA is released from the mycobacterial cells—either from clinical specimens (if sufficient mycobacteria are present) or from growth on solid medium or in broth.

Amplified products (amplicons) are detected by:

- DNA sequencing
- Gel analysis (traditional polymerase chain reaction [PCR])
- Enzyme-linked immunosorbent assay (ELISA)-based methods
- Fluorescent hybridization with probes or molecular beacons
- Other methods

Over 96% of resistance to RIF is associated with known mutations within an 81bp region of the \textit{rpoB} gene. Therefore, molecular testing of RIF resistance is highly reliable. Additionally, since RIF monoresistance is rare, detection of RIF resistance is usually diagnostic of MDR-TB.

A few reference laboratories are routinely using molecular methods to rapidly diagnose drug resistance, and others are studying the practicality of these methods. The methods require specialized instrumentation and expertise, but may become more practical as more applications are found for molecular methods and their use becomes more widespread.

Advantages include rapid turnaround times and the benefit of knowing the exact location of the point mutation.

Disadvantages of molecular assays include low sensitivity for some compounds, the potential for false-positive results due to amplicon contamination, and lack of standardization of the assays.
Appendix 8: **PROPORTION METHOD**

- Method of susceptibility testing using agar plates inoculated with either clinical specimen (direct method) or a suspension of mycobacterial growth (indirect method). See Appendix 9, *Indirect Method*.

- The proportion method is the gold standard method of drug susceptibility testing in the U.S. (Middlebrook 7H10 agar medium).

- Anti-tuberculosis drugs are added to the agar media in the form of stock solutions made from reference powders or drug-impregnated discs in order to achieve the critical concentration. Plates are either produced in-house or commercially purchased.

- The isolate is resistant if more than 1% of the number of colonies on the control agar grow on a given drug agar plate.

- Pyrazinamide is difficult to study using solid medium due to the requirements of achieving an acidic environment; therefore, the BD BACTEC 460TB is considered the gold standard.

*Figure 1. Quad plate – Inoculum of *M. tuberculosis* growth from broth has been plated into each of the 4 quadrants with the following results:*

**Control quadrant:**
- 90 colonies

**Isoniazid (INH) quad:**
- 30 colonies

**Rifampin (R) quad:**
- 23 colonies

**Streptomycin (S) quad:**
- 0 colonies

- Isoniazid 30/90 = 33% resistant
- Rifampin 23/90 = 25% resistant
- Streptomycin 0/90 = susceptible

This is an MDR-TB isolate.
The inoculum for indirect susceptibility testing is a suspension of mycobacteria that has already been cultivated on agar or an aliquot from the broth medium, rather than the clinical specimen itself, as for the direct testing.

Several colonies are picked from the solid medium in order to avoid a bias in testing.

Chocolate plates should be used to ensure that a pure strain is being studied rather than a mixture of different organisms. This is especially important if the source of the inoculum is from a broth system rather than from colonies on a solid medium.

Egg-based media, such as Löwenstein-Jensen, are not usually used in North America. The preferred agar is Middlebrook 7H10 agar media. If the drug-resistant strain does not grow sufficiently well on this media, 7H11 is sometimes successful (with adjusted critical concentrations of drugs).

Broth media (e.g., BD BACTEC 460TB or BD BACTEC MGIT 960, ESP culture system II, BacT/ALERT 3D) are used routinely for first-line TB drugs and occasionally for second-line TB drugs.

Figure 1. Quad plate – Inoculum of *M. tuberculosis* growth from broth has been plated into each of the 4 quadrants. The organism grows well in the control quadrant (top) and in the quadrant containing streptomycin (diffused into agar from the disc). The other 2 quadrants contain isoniazid (INH) and PAS, and the organism has not grown in these quadrants. The isolate is resistant to streptomycin and susceptible to INH and PAS.
Appendix 10: **BD BACTEC 460TB METHOD**

This method utilizes a broth system containing \( ^{14} \text{C} \)-labeled palmitic acid to grow the mycobacteria. If the organism grows in the broth, \( ^{14} \text{CO}_2 \) is released into the headspace in the vial and the machine detects the \( ^{14} \text{CO}_2 \), indicating growth.

- Drug-containing vials receive 100-fold more inoculum than the drug-free control vials for each strain (corresponding to the 1% resistance rate considered to be clinically significant).
- The method is faster than the proportion method using solid medium, but does not provide an estimate of percentage of resistant bacilli.
- Kits are available for testing the SIRE drugs (streptomycin, isoniazid, rifampin, and ethambutol), and pyrazinamide.
- Second-line drugs can be tested by adding stock solutions from reference powders of individual anti-tuberculosis drugs to the broth vial.
- Resistant strains should be confirmed by the agar proportion method or molecular assays.
- The results are interpreted based on the change in “growth index” in the drug-containing vials compared to the control vial (without drug). If the daily change in the control growth index exceeds that of the drug-containing vial, the isolate is susceptible.

![Figure 1. BD BACTEC bottles containing Middlebrook 7H12 media prior to inoculation.](image1)

![Figure 2. BD BACTEC machine.](image2)
Appendix 11: NEWER BROTH METHODS

- Newer broth methods are replacing the radiometric (\(^{14}\)C) system (in order to avoid use and disposal of radioactive materials) and are fully automated.

- Drug-containing vials receive 100-fold more inoculum than the drug-free control vials for each strain (corresponding to the 1% resistance rate considered to be clinically significant).

- These systems can detect and monitor growth for culture and can also be used to determine susceptibility to isoniazid, rifampin, ethambutol, pyrazinamide, and streptomycin. The organism is susceptible if there is less growth in the drug-containing tube compared to the control tube.

- The ESP Culture System II detects pressure changes due to gas production or consumption due to mycobacterial growth.

- The BD BACTEC MGIT 960 system (mycobacterial growth indicator tube) uses a fluorescence quenching-based oxygen sensor to detect mycobacterial growth. If mycobacteria are growing in the system, they consume oxygen and fluorescence is increased and detected by the system.

- The BacT/ALERT 3D system colorimetrically detects CO\(_2\) production in order to indicate mycobacterial growth.

*Figure 1. BD BACTEC MGIT (mycobacterial growth indicator tube) system – MGIT machine; upper right inset, MGIT tubes; lower right inset, antibiotics solutions for performing susceptibility testing in MGIT.*

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Appendix 12: THERAPEUTIC DRUG MONITORING

Therapeutic drug monitoring is routinely used for several circumstances:

- Aminoglycoside / capreomycin peak and trough levels in patients with renal impairment
- Cycloserine levels in order to minimize risk of CNS toxicity and safely use optimal dose
- Ethambutol levels in patients with significant renal impairment
- Known or suspected malabsorption

Some drug-resistant TB experts routinely monitor certain TB drug levels in anticipation of toxicity and to escalate a drug dose when possible.

Most hospital labs perform amikacin levels. Only a few laboratories perform drug levels for other TB drugs (National Jewish Medical Center and Focus Labs performing the most).

Table 1 details the time for blood collection after a drug dose.

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Hours after oral dose to “peak”</th>
<th>Hours after IV dose completed to “peak”</th>
<th>Hours after IM dose to “peak”</th>
<th>Time after dose for second level if desired*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td></td>
<td>1 hour</td>
<td>2 hours</td>
<td>trough</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>2–3 hours</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capreomycin</td>
<td></td>
<td>1 hour</td>
<td>2 hours</td>
<td>trough</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>2–3 hours</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clofazimine</td>
<td>2–3 hours</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cycloserine</td>
<td>2–3 hours</td>
<td></td>
<td></td>
<td>6 and/or 10 hours</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>2–3 hours</td>
<td></td>
<td></td>
<td>6 hours</td>
</tr>
<tr>
<td>Ethionamide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>2 hours</td>
<td>1 hour</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoniazid</td>
<td>1–2 hours</td>
<td>1 hour</td>
<td>4–6 hours</td>
<td></td>
</tr>
<tr>
<td>Kanamycin**</td>
<td>1 hour</td>
<td>2 hours</td>
<td></td>
<td>trough</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>2 hours</td>
<td></td>
<td></td>
<td>6–10 hours</td>
</tr>
<tr>
<td>Linezolid</td>
<td>2 hours</td>
<td>1 hour</td>
<td></td>
<td>trough</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>2 hours</td>
<td>1 hour</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>2 hours</td>
<td></td>
<td></td>
<td>6–10 hours</td>
</tr>
<tr>
<td>PAS</td>
<td>6 hours</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>2 hours</td>
<td></td>
<td></td>
<td>6 hours</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>3–4 hours</td>
<td></td>
<td></td>
<td>10 hours</td>
</tr>
<tr>
<td>Rifampin</td>
<td>2 hours</td>
<td></td>
<td></td>
<td>6 hours</td>
</tr>
<tr>
<td>Streptomycin</td>
<td></td>
<td>1 hour</td>
<td>2 hours</td>
<td>trough</td>
</tr>
</tbody>
</table>

* A second level may be obtained to limit toxicity (troughs with injectable drugs), to evaluate for delayed absorption, or to calculate a half-life in order to more accurately prescribe a drug dose and interval.

** Kanamycin is determined using a bioassay. All other antibiotics must be stopped at least 24 hours prior to sample collection for kanamycin.

Information excerpted from National Jewish Medical Center website (http://www.njc.org) and literature.
COLLECTING AND PROCESSING SAMPLES FOR THERAPEUTIC DRUG MONITORING

One milliliter of serum (about 2 ml of blood) is required per test. It is advisable to provide some excess serum in case there are technical problems.

- The patient should come to clinic with his/her medications.
- No doses of the medication to be tested should have been taken/given since the previously scheduled doses (12–24 hours prior).
- Observe the taking or injection of the medications and record the exact time and date.
- Collect the blood by direct venipuncture (timing as described by Table 1) and record the exact time of the blood collection.
  - For streptomycin, note if the patient is also receiving ampicillin.
  - Kanamycin is measured using a bioassay. Stop all other antibiotics for at least 24 hours prior to sampling.
- After the blood clots, centrifuge the samples, harvest the serum into labeled polypropylene (or polyethylene) tubes (allow room for expansion of sample inside tube), label, and freeze (-70°C is preferable, if available).
- Label the tubes with the patient’s name, date and time of collection, and the drug(s) to be assayed.
- The samples can be stored frozen until ready for shipping.
- Place the samples in a ziplock plastic bag and pack upright in a Styrofoam box (about 10 cubic inches in size) with 3 pounds of dry ice. Fill the empty air space with paper or Styrofoam “peanuts.”
- Complete the requisition and provide billing information. Place the requisition and billing page in a plastic bag and tape to the outside of the lid. The foam box is placed inside a cardboard box to prevent damage.
- Ship samples Monday through Thursday by an overnight delivery service that accepts dry ice packages.

Information excerpted from National Jewish Medical Center website (http://www.njc.org) and literature.
Appendix 13: MULTICULTURAL RESOURCES

Translated Patient Education TB Resources

AAPCHO
http://www.aapcho.org/display.pl?template=pp_topic#Tuberculosis

Canadian Lung Association
http://www.lung.ca/tb/notenglish/

EthnoMed
http://ethnomed.org/ethnomed/patient_ed/index.html#tuberculosis

Minnesota Department of Health

The 24 Languages Project
http://medstat.med.utah.edu/library/refdesk/24lang.html

New South Wales Health

General Interpreter Resources

CyraCom
http://www.cyracom.net/subpage.jsp?center_page=69
Customer Service Number: 1-800-481-3289

General Cultural Information Sites

EthnoMed
http://ethnomed.org/

The Cross Cultural Health Care Program
http://www.xculture.org/

Cultural Clues
http://depts.washington.edu/pfes/cultureclues.html

University of Michigan Patient Education: Cultural Competency
http://www.med.umich.edu/pteducation/cultcomm2.htm

Cultural Diversity—A Guide for Health Professionals
Appendix 14: FREQUENTLY ASKED QUESTIONS (FAQS)

General

1. **What is the optimal drug regimen for multidrug-resistant tuberculosis (MDR-TB)?**

   See Chapter 3, *Treatment*.

   The optimal drug regimen depends on the susceptibility pattern of the patient's tuberculosis (TB) isolate, the patient's previous TB treatment regimen, underlying health conditions, and other medications the patient currently takes. The patient should generally be initially treated with 4–6 drugs to which the isolate is susceptible. Depending on the susceptibility pattern of the isolate, the regimen should include all available first-line drugs, a fluoroquinolone, an aminoglycoside, and appropriate second-line oral drugs.

   In general, **avoid**:
   - Drugs the patient has taken previously (associated with a failing regimen)
   - Drugs that cause that individual undue toxicity
   - Drugs that cause unnecessary drug interactions

2. **How many drugs are necessary?**

   See Chapter 3, *Treatment*.

   The patient needs to complete therapy with **at least** 3 drugs to which the isolate is susceptible. In practice, this requires that the patient be initially treated with 4–6 drugs that he/she has not previously received. Using this strategy, the injectable drugs can be discontinued after a number of months if appropriate and other drugs that were very poorly tolerated can be trimmed away.

3. **How long post-culture conversion should a patient be treated: 18 months or 24 months?**

   See Chapter 3, *Treatment*.

   There are no randomized controlled studies that have determined optimal length of MDR-TB treatment. The American Thoracic Society (ATS) recommends 18–24 months of treatment for MDR-TB. Many experts prefer to choose the duration of therapy based on the time from culture conversion (sputa are consistently culture-negative). In general, the longer regimens are used for patients with more extensive disease and more extensive drug resistance pattern. Shorter regimens might be used for patients with more localized disease who responded promptly to therapy and whose resistance pattern allowed use of more bactericidal drugs in the regimen.

4. **The patient’s isolate is resistant to all first-line drugs and most second-line drugs. What options exist for treatment?**

   See Chapter 3, *Treatment*.

   Use as many/all drugs to which the organism is susceptible. This may include “third-line agents” such as linezolid, gamma-interferon, and β-lactam drugs (imipenem, amoxicillin/clavulanate). Consider use of higher doses of individual drugs (as tolerated by the patient and using therapeutic drug monitoring as appropriate). Consider prolonged use of an injectable drug if tolerated by the patient. Consider surgical intervention if the patient is an appropriate candidate.
5. Can a patient take split dose by self-administered therapy (SAT)?

See Chapter 8, Case Management.

Some drugs (cycloserine, ethionamide, and para-aminosalicylate [PAS] in particular) may not be tolerated in once-daily doses and must be given more than once a day (split doses). Ideally, all drug-resistant TB treatment will be given fully by directly observed therapy (DOT), even split doses. Patients who have difficulty taking their doses as once-daily doses (amenable to DOT) sometimes are well served by being hospitalized during the initial phase of treatment until they tolerate the regimen well enough at home.

6. Can weekend doses be given by SAT?

See Chapter 8, Case Management.

Ideally, all drug-resistant TB treatment will be given fully by DOT. Again, hospitalization in the early phase of treatment is sometimes necessary. After documented clinical and microbiologic improvement, some jurisdictions will treat patients with 5-days-per-week therapy by DOT or give SAT on the weekends when local resources do not permit monitored weekend administration.

Use of Specific Drugs

**FLUOROQUINOLONES**

1. Can I use fluoroquinolones in children? For active disease? For contacts to MDR-TB?

See Chapter 5, Special Situations – Pediatrics.

Fluoroquinolones are among the most important agents in MDR-TB treatment when the isolate is susceptible. Most experts feel that fluoroquinolones are indicated in children exposed to or infected with MDR-TB resistant to other first-line drugs.

Fluoroquinolones have been avoided in children because puppy models have suffered irreversible arthropathy. Irreversible joint destruction has not been seen in children who have received fluoroquinolones. Ciprofloxacin has been recently licensed for use in children for treatment of urinary tract infection. Levofloxacin and gatifloxacin have been studied for use in children. However, few children have received the very long courses of fluoroquinolones required for TB treatment. If a fluoroquinolone drug is very important for the treatment of an individual child, it can be employed after discussing risks and benefits with the parents and in consultation with a pediatric TB expert. The parents have to be aware of the potential risks and report to the provider and public health workers any signs or symptoms of joint problems (decreased mobility, pain, decreased range of motion, joint swelling, etc.). Additionally, all providers involved in the case should be actively screening for these processes. Finally, many experts avoid these drugs in children too young to show signs and symptoms of musculoskeletal complaints (children too young to sit up, crawl, etc.).
2. What is the optimal dose of levofloxacin for active disease? For latent tuberculosis infection (LTBI)?

See Chapter 3, Treatment.

A common strategy for levofloxacin is to initiate therapy at 500 mg daily. If tolerated, the dose can be elevated to 750 mg or even 1000 mg daily (sometimes in divided doses). If the patient weighs more than 100 pounds, a dose of at least 750 mg should be attempted. Fluoroquinolones should not be dosed in close proximity to milk-based products, antacids, or other divalent cations. Currently studied doses of the newer fluoroquinolones (gatifloxacin and moxifloxacin) are limited. At this time, doses should be limited to 400 mg daily to avoid the possibility of more drug-related toxicities. In the case of patients who are too sick to take enteral doses, the fluoroquinolones are available in IV forms.

AMINOGLYCOSIDES

1. What is the dose when one changes to thrice or twice weekly?

See Chapter 4, Medication Fact Sheets.

When aminoglycoside drugs are administered twice or 3 times weekly, the drugs are usually administered at the same dose as daily therapy for that individual (customized based on age, renal function, and sometimes drug levels). Some experts use higher doses and monitor levels closely.

2. What is the target blood level with intermittent dosing?

See Chapter 4, Medication Fact Sheets.

The target blood level depends on dose and planned duration of use.

3. How long do I need to use an aminoglycoside?

See Chapter 3, Treatment.

Expert opinions vary as there are no firm data to support a specific length of treatment. At a minimum, use the aminoglycosides for at least 6 months (longer if extensive disease, delayed culture conversion, or limited alternative medications). Some experts continue the aminoglycoside or capreomycin as long as absolutely possible (barring limiting side effects) and use doses to achieve somewhat lower peak levels to avoid toxicity.

4. What aminoglycoside is most frequently used?

See Chapter 4, Medication Fact Sheets.

The injectable drug chosen depends on several factors: susceptibility of the isolate, cost, route of administration, availability of therapeutic drug monitoring tests, and side effects. Many drug-resistant isolates are resistant to streptomycin; amikacin and kanamycin have cross-reactivity and therefore nearly identical resistance. Kanamycin and streptomycin are least expensive; amikacin levels are most readily available; streptomycin is less painful if used intramuscularly, but is associated with more vestibular toxicity.
5. A patient on aminoglycoside complains of slight tinnitus. How is this side effect monitored?

See Chapter 7, Adverse Reactions.

Patients receiving injectable agents should be monitored with hearing tests as well as vestibular monitoring. Patients who suffer tinnitus should be evaluated for the possibility that something other than the injectable agent is causing the problem. Sometimes patients who have isolated tinnitus can be monitored prospectively without change. If change is required, changing to intermittent therapy or lowering the dose of the injectable drug (while remaining in the appropriate therapeutic range) can sometimes lessen the symptoms. If the patient suffers unsteadiness or other vestibular signs or symptoms, the drug should be stopped. Vestibular toxicity is usually irreversible and is generally a contraindication to further use of these drugs.

Use of BCG

1. Is bacille Calmette-Guérin (BCG) indicated for a newborn exposed to a mother with a highly resistant strain of MDR-TB?

See Chapter 5, Special Situations – Pregnancy.

BCG should be administered to infants and young children who can not be separated from drug-resistant TB cases and for whom no practical prophylactic regimen is available. There are usually a number of other options before considering BCG use.

Side Effects

1. What do I do when a patient is nauseated but intolerant to compazine?

See Chapter 7, Adverse Reactions.

Other drug options include phenergen, metoclopramide, lorazepam, and ondansetron. Other options include dosing the drug with a snack, giving at a time of day away from other drugs, splitting the dose, etc.

2. A patient on cycloserine had a high depression score this week. What does this mean?

See Chapter 7, Adverse Reactions.

Extreme care should be exercised with patients receiving cycloserine and suffering mental health symptoms. Monitoring for suicidal ideation is crucial and the patient should be evaluated for the need for an antidepressant medication. A cycloserine therapeutic drug level should be collected and the dose held until toxicity can be ruled out as a cause.

3. What should be done for a teenage patient on fluoroquinolone with bilateral wrist pain?

See Chapter 7, Adverse Reactions.

For achiness without significant tendon inflammation, therapy can be continued with use of analgesics and rest. If significant tendon inflammation is present, the fluoroquinolone should be held and measures to reduce inflammation should be undertaken. The patient should not undertake unusual exertion to the area.
Infection Control

1. **Can I return a case patient to the home setting if his/her relative (non-immunocompromised) is tuberculin skin test (TST)-negative after several months of exposure to case?**

   See Chapter 8, *Case Management*.

   MDR-TB patients should be considered potentially infectious until they have 3 consecutive culture-negative sputum specimens. Decisions about management at home, and return to school and work, should be undertaken with local health officers and drug-resistant TB experts after considering many factors regarding the patient’s disease, treatment, and the household situation.

2. **A patient no longer has a productive cough. Are monthly induced sputa necessary?**

   See Chapter 6, *Monitoring Patients*.

   National guidelines suggest monthly sputum monitoring. Some experts collect 2 monthly sputa 8–24 hours apart to lessen the likelihood of false-negative results. If necessary, sputum induction is indicated both during and after treatment. MDR-TB patients have a higher risk of relapse and delayed sputum sterilization. Persistently positive cultures may be an early indicator for increasing drug resistance and may assist in determining length of treatment.

Payment (See Chapter 8, *Case Management*.)

1. **How can I pay for expensive drugs when a patient is uninsured?**

   Social workers and financial counselors should work with the family to investigate any third-party payer possible. If the patient is uninsurable, patient assistance programs (PAPs) sponsored by pharmaceutical companies can be explored. Some states and large jurisdictions have programs available to pay for drugs for all TB patients.

2. **How can I pay for hospitalization when a patient is uninsured?**

   Social workers and financial counselors should work with the family to investigate any third-party payer possible. Some states and large jurisdictions have programs available to pay for TB care or have specific TB inpatient facilities. Barring these options, the local “safety net” hospital that is funded to provide indigent care will have to admit the patient.

3. **Is an IV injectable agent more costly than IM preparation?**

   IV therapy is more expensive because in addition to drug costs, maintenance of the IV requires a home health agency, etc.
Press Release

1. **We are doing a highly visible contact investigation at a school. Do we need a press release?**

   A press release can be very helpful to update the media on results of testing and to educate the public. Some jurisdictions manage the contact investigation successfully without involving the media.

2. **Should we reveal in the press release that exposure was to an MDR strain? (If we did, it might create public angst and increase our workload.)**

   If the media is involved, it is better to be upfront about the nature of the isolate, but also state that medications are available for LTBI treatment. If this is not disclosed upfront, criticism will follow.

Laboratory

1. **When do I draw levels?**


   Draw cycloserine levels before increasing the dose from the initial regimen; draw aminoglycoside levels if appropriate after approximately 2 weeks of therapy.

2. **To which laboratory do I send for serum drug levels?**

   See Appendix 4, *Laboratory Resources*.

   In many cases, the patient’s insurance will mandate which lab will perform the therapeutic drug levels. Most large hospital labs will perform amikacin levels, and only a few reference labs perform many of the other TB drug levels.

3. **Are levels (therapeutic drug monitoring) useful? Necessary?**

   See Chapter 6, *Monitoring Patients*.

   There are no data to prove that patients monitored with drug levels have improved outcomes. In several circumstances, therapeutic drug monitoring is common: aminoglycoside levels in patients who have known renal dysfunction; cycloserine levels can help the provider predict and minimize central nervous system (CNS) adverse reactions and prevent seizure activity; and ethambutol (EMB) levels may be useful for patients with reduced renal function. Other therapeutic drug monitoring is used, depending on the patient’s other health issues, concomitant medications, number of drugs in the regimen, preference of the provider, etc.

4. **How do I interpret discordant sensitivities?**

   See Chapter 2, *Diagnosis*.

   Discuss results with the laboratorian, repeat the susceptibilities on a second sample, and send a sample to a reference laboratory for confirmation.
5. How do I clarify to my lab that we need a cycloserine blood serum level, not a cyclosporine?

Talk to the lab in advance, type or write the request very clearly, and if necessary, write in parentheses: (NOT CYCLOSPORINE). **Note:** Very few laboratories in the country perform cycloserine levels, while most large hospital labs perform cyclosporine levels. This may help you discuss this “send-out” test with your lab.

6. Molecular methods: How quick and accurate are the results?

As an example, “molecular beacons” is a real-time polymerase chain reaction (PCR) technology-based method performed by the California Department of Health Services Microbial Disease Laboratory. It uses PCR to rapidly detect gene mutations associated with drug resistance. If the specimen submitted is a smear-positive sputum or colony growth on solid media, the results are available within 24 hours of lab processing. If the specimen is submitted as growth in a broth medium, the lab must subculture the isolate on solid media before performing the beacons test. This may add up to 2 weeks to the process. The sensitivity of the test is 83% for isoniazid (INH) and 97% for rifampin (RIF). Discuss the results with the laboratory and a drug-resistant TB expert before implementing management plans based on the results.

7. How do I ship/package specimens to send to National Jewish since it’s out of state?


8. What type of courier do I use to send specimens out of state?


9. When sending specimens to the State of California Microbial Disease Laboratory (MDL) for isolate identification, are susceptibilities automatically performed or is an additional request necessary?

Specific requests are necessary. Susceptibility testing is not automatically performed. Of note, at the time of printing, MDL is performing susceptibility testing in broth media only, and the only second-line susceptibility testing being performed is levofloxacin. Check with the laboratory (contact information in Appendix 4, *Laboratory Resources*) for current testing capabilities.

When dealing with any laboratory performing TB culture, identification, and susceptibilities, you should determine whether susceptibilities will automatically be performed and under which circumstances second-line susceptibilities will be performed. Many commercial laboratories have contracts defining these details for individual clients and third-party payers. Lengthy delays will occur if these details are not defined early on. Sometimes, the physician who ordered the initial culture will need to order first- and second-line susceptibility tests.

10. Why does pyrazinamide (PZA) susceptibility testing take longer? Is there a quicker method?

PZA susceptibilities are technically difficult in agar because of the low pH required. Many laboratories do not perform them at all. BD BACTEC 460TB is considered the gold standard.
Treatment and Evaluation of Contacts

1. **How do I treat contacts?**

   See Chapter 10, *Managing Contacts*.

   Each contact is managed on an individual basis. Determinants include extent and intimacy of contact with the source case, susceptibility pattern of the source case isolate, evidence of transmission from the source case, prior TST results, risks for progression to active TB, etc. If treatment of drug-resistant LTBI is desired, the regimen is generally based on the susceptibility pattern of the source case.

2. **For contacts to an MDR case with positive TST and who refuse treatment, how often should a symptom review or chest radiograph be done?**

   See Chapter 10, *Managing Contacts*.

   Untreated contacts should be monitored every 3–6 months for at least 2 years.

3. **Can a single drug be used to treat MDR-TB infection?**

   See Chapter 10, *Managing Contacts*.

   Lower-risk contacts are sometimes treated with fluoroquinolone monotherapy based on *in vitro* drug activity data. No controlled data are available regarding treatment of drug-resistant TB contacts, and current national guidelines recommend 2-drug MDR-LTBI treatment.

4. **When should LTBI treatment with levofloxacin be discontinued for ambiguous side effects?**

   See Chapter 7, *Adverse Reactions*.

   Every effort should be made to safely continue the patient on therapy, including use of rest and analgesics. Significant inflammation of the tendon should be treated with at least temporary cessation of the fluoroquinolone.

5. **Can moxifloxacin be used to treat MDR-LTBI?**

   While programs have less experience with moxifloxacin use, it has excellent *in vitro* activity against many drug-resistant TB strains and has been used in some patients with good success.
CASE EXAMPLE 1

Olga, a 41-year-old female from the Ukraine, is experiencing her second episode of tuberculosis (TB).

1986

Olga was first diagnosed with TB in the Ukraine and treated with isoniazid (INH)/rifampin (RIF)/ethambutol (EMB) for 6 months and streptomycin (SM) daily for 6–8 months. Olga was hospitalized during her treatment and claims she was very adherent. After her discharge, she took INH for 2 additional years for “prophylaxis.” Drug susceptibilities of this episode are unknown.

What else would you like to know about this episode?

- Does she have any written documentation or copies of radiographs?
- Was she hospitalized the entire time (i.e., all doses observed)?
- Were there any interruptions in any of the medications due to drug supply or tolerance?
- How extensive was her disease and what kind of clinical and radiographic improvement did she have?
- Why did she receive 2 additional years of INH? Had her radiograph not improved; did she still have significant symptoms?

1994

Olga arrives in the U.S.

3/01

Olga develops a cough, intermittent fever/night sweats, scant blood-tinged yellow sputum, and shortness of breath.

4/14/01

Olga presents to the TB clinic with those symptoms and opacification of the left lung with an air-fluid level. On initial exam, she is a thin, well-appearing female with decreased breath sounds at the left base and bronchial breath sounds at the left apex.

4/17/01

Treatment is started with INH, RIF, pyrazinamide (PZA), EMB, levofloxacin, and capreomycin. Four out of four sputa return culture-positive for *M. tuberculosis*, with 2 out of 4 smear-positive.

*Because she does not have documentation of completely observed therapy and a previously susceptible isolate, Olga is treated with an empiric “expanded” regimen including 3 drugs that she had not previously received.*

5/19/01

BACTEC susceptibilities show resistance to all first-line agents, including SM.
Conventional solid agar susceptibilities show borderline resistance to EMB and SM, and full resistance to INH, RIF, and PZA. Second-line drug susceptibilities show additional resistance to capreomycin and ethionamide but susceptibility to amikacin, clarithromycin, linezolid, clofazimine, and levofloxacin.

A 5-French percutaneously-inserted central catheter is placed for IV imipenem and amikacin.

Because of her extent of disease and extended resistance pattern, Olga receives 7 drugs to which the isolate is susceptible. Unfortunately, 2 of the drugs are “third-line” drugs with limited track records of clinical efficacy in treatment of MDR-TB.

Olga’s revised regimen is as follows: (weight ~110 lbs/50 kg)

- Levofloxacin 750 mg qd
- Cycloserine 500 mg qd
- PAS granules 4 grams bid
- Imipenem 1 gram IV bid
- Amikacin 750 mg qd
- Clarithromycin 500 mg bid
- Clofazimine 100 mg qd

 Clinically, the patient is doing remarkably well despite the weaknesses of her initial regimen; sputum culture conversion occurs within a month of treatment initiation.

Olga is tolerating a dose of levofloxacin that is common in treatment of MDR-TB (750 mg daily). Some patients will even tolerate 1000 mg per day.

Negative cultures (final results) are obtained. Monthly sputum smears and cultures are negative. Olga’s cough and symptoms have resolved, and from her appearance, one would never guess she has a destroyed left lung and MDR-TB.

A toxic cycloserine level of 40 µg/ml is measured on June 16. A repeat level (29.1 µg/ml) is drawn on July 1 and found to be within therapeutic range of 20–35 µg/ml. Olga has not shown any signs of emotional or mental instability.

Screening audiology exam shows significant hearing loss in the right ear compared to baseline.

Many patients experience hearing loss on long-term aminoglycosides. Olga’s loss is unilateral and not yet noticeable to her. Since she had already received more than 2 months of daily amikacin, her providers change her to 3 times weekly amikacin and are able to stabilize her hearing loss.
Follow-up chest radiograph shows minimal change. Given Olga’s destroyed left lung, she is referred to National Jewish Hospital for surgical and treatment evaluation to improve the chance of a lasting cure.

**Contact investigation:** Olga has been unemployed for 2 years. She is married and a mother of 2 children (12 and 7 years old). Her husband had a history of a positive TST prior to meeting the patient. Her older daughter was born in the Ukraine and has a history of BCG vaccination and positive TST (11 mm) in 1994. Olga’s younger son remains TST negative. Both children are healthy, asymptomatic, and have had recent chest radiographs that are normal. There is no evidence of household transmission from either TB episode to date.

**Lessons Learned**

- Drug-resistant TB should be suspected in patients from countries with high incidence of drug resistance.
- MDR-TB patients with little or no improvement in chest radiograph after completing treatment are at high risk for reactivation.
- Patients with risk for harboring a drug-resistant TB isolate (incomplete documentation of prior susceptibilities, treatment, and response to treatment) should be considered for an empiric expanded regimen with at least 3 drugs that the patient has not previously received. An aminoglycoside or injectable drug other than SM should be included in the regimen.
- Careful monitoring for toxicities can limit their impact on the viability of the regimen and prevent serious adverse events for the patient.
- Surgical intervention is sometimes considered for patients with localized disease, especially those with extensive resistance patterns or disease that is unlikely to be cured because of significant lung destruction.
**Case Example 2**

Eva is a 25-year-old Peruvian woman who emigrated to the U.S. to join her American husband. She is healthy and has no symptoms of TB.

**6/4/86**

Eva has a tuberculin skin test (TST) placed for pre-employment screening before employment in a hospital. The TST results in 20 mm induration, and chest radiograph shows right-sided pleural fluid in the right base, which layers on decubitus views. The radiographs show no infiltrates or adenopathy. The pleural fluid is aspirated and pathology shows that the fluid is an effusion only. No malignant cells are seen and cultures grow no bacteria, acid-fast bacilli (AFB), or fungus.

*TB can cause a pleural effusion due to hypersensitivity reaction to a pleural-based TB lesion. In this case, a pleural biopsy is required to see the granulomatous changes and to grow the AFB. Pleural fluid grows *M. tuberculosis* in the event of a pleural-based lesion eroding into the pleural space and causing an empyema with purulent pleural fluid. The diagnosis of pleural TB is often missed because of the failure to obtain a pleural biopsy. In addition, sputum culture can be helpful and is often forgotten when focusing on the effusion. Pulmonary disease may be masked by an effusion or be too subtle to be seen on the radiograph.*

**7/30/86**

When the AFB cultures are negative at 6 weeks, the employee health provider at Eva’s hospital concludes that she has latent tuberculosis infection (LTBI) and treats her with INH.

*Monotherapy with INH should never be initiated until the possibility of active TB is ruled out. This practice promotes the development of resistance.*

**10/20/86**

Eva experiences fever and some shortness of breath, which she attributes to a viral process.

**12/15/86**

Eva reports the symptoms to the employee health provider when she can no longer perform her duties in the hospital. Her provider obtains a chest radiograph that shows enlargement of the pleural fluid and development of extensive infiltrates.

*Patients being treated with INH for LTBI should be screened monthly for toxicity, adherence to therapy, and symptoms of active TB. Eva’s symptoms of active TB should have been uncovered during active screening.*

**12/20/86**

Eva’s provider concludes that she has active TB and adds RIF and PZA to her regimen. No sputum is collected.

Extensive contact investigation is performed in the hospital and several co-workers have documented skin test conversion. Because Eva does not have direct patient care responsibilities and because transmission is apparently limited, further contact investigation is not performed.
After initial clinical improvement, Eva reports clinical worsening. Repeat chest radiograph shows continued worsening. Eva’s provider calls the county TB controller for advice. The TB controller is quite agitated about the fact that the case was not reported when Eva was considered a TB suspect, and a pleural biopsy and sputum were not obtained for culture and susceptibility testing.

_Pulmonary and extrapulmonary TB are reportable diseases in all 50 states. TB should be reported within 1 working day of clinical suspicion of the disease. Reporting should not be delayed while providers are waiting for smear and culture results. Specimens for smear and cultures should be obtained from all practical sources._

Sputum is collected and is smear-positive and eventually grows multidrug-resistant TB (MDR-TB) (resistant to INH and RIF).

_Eva should have been presumed to have INH-resistant TB when her disease blossomed on INH alone. A TB expert, who would have treated her with 4-drug therapy, should have been involved. INH-resistant TB is treated with at least RIF, PZA, and EMB, as PZA alone does not “protect” the rifampin from development of resistance._

Lessons Learned

- Pleural TB requires a pleural biopsy for histologic and culture diagnosis unless _purulent_ fluid is drained by thoracentesis.
- Monotherapy with INH should not be initiated until active TB is ruled out.
- Individuals inexperienced in TB care should refer the patient to an experienced provider _and_ all providers should notify the public health department within 1 working day if they are treating a patient that they suspect has TB.
- Cultures should be collected from all practical sites.
- When INH resistance is considered, initiate _at least_ RIF, PZA, and EMB.
CASE EXAMPLE 3

Sam is a 29-year-old injection drug user serving time in U.S. federal prison.

5/10/99  Sam converts his TST during an incarceration at a county jail. His chest radiograph is normal and he has no symptoms of active TB. He is diagnosed as having LTBI and completes 9 months of INH by DOT at another facility.

6/30/01  Sam complains of an increasing cough that is not improved by antibiotics. The possibility of TB is entertained, but Sam relays to the providers that he has already received 9 months of INH.

While INH treatment for LTBI reduces the risk of progression to active TB for susceptible isolates by 85–90%, it has no impact on high-level INH resistance. Additionally, some patients who report prior completion of LTBI in fact have not been completely adherent; other patients have been reinfected by another strain. Patients with signs and symptoms of TB should be evaluated by chest radiography and sputum collection if indicated.

10/1/01  Sam’s cough is treated for several months as reactive airways disease and on his third visit to the clinic, he begins to cough up blood. The prison nurse calls for records regarding Sam’s prior TB treatment and 1 month later, receives information that: 1) Sam did receive a full course of INH; and 2) after Sam’s release from the first jail, an MDR-TB case and a number of conversions attributable to that case were identified. Investigations show that Sam and the MDR case had been housed in areas of “shared air” and that the source case was symptomatic in the months before Sam converted his skin test.

11/3/01  Sputum is collected, the local health department is notified of the case, and Sam is treated with an expanded regimen based on the 1999 source case susceptibilities (PZA, amikacin, levofloxacin, ethionamide, and cycloserine).

If the epidemiologic link between Sam and the MDR case had not been strong, an empiric regimen using first-line drugs and at least 3 drugs to which the suspected source case was susceptible could have been employed. This allows a strong regimen in case this is a pan-susceptible isolate or an MDR isolate.

11/20/01  Sam is transferred to the county hospital for isolation and is later diagnosed with TB resistant to INH, RIF, EMB, and SM.

Comparison of drug susceptibility patterns can assist in linking cases epidemiologically. Alternatively, molecular fingerprinting methods can be used if both isolates are still available.
The case manager meets with the county hospital staff to ensure that they are informed about the care required for drug-resistant TB (DOT of all medication, required monitoring, respiratory isolation requirements, etc.) and to establish a process for coordination of TB care.

The local health officer is notified that although Sam is still smear-positive, he is being transferred back to the prison to serve out his sentence because his condition is stable, he is tolerating the expanded regimen, and the prison has a room where he can continue respiratory isolation. The health department case manager contacts the prison nurse and provides information about the drug-resistant TB treatment and care required for Sam.

As a measure of quality assurance, the case manager asks to review Sam’s health and treatment records. Through much perseverance, the case manager discovers that Sam has stopped receiving his cycloserine dose because the prison had run out of the drug, and it was improperly recorded as taken. The case manager assists with obtaining the cycloserine, provides ongoing education and instruction on required toxicity monitoring, and promptly addresses lapses in Sam’s care during the several months he is in the prison.

Lessons Learned

- TST converters should be treated for LTBI once TB disease has been ruled out. In addition, inmates with positive TSTs and risk factors for progression to active TB (such as injection drug use) should be treated for LTBI. If the source case has drug-resistant TB, the LTBI regimen should be tailored to the source case susceptibility results.
- Patients who have completed LTBI treatment can still develop TB for various reasons: drug resistance, poor adherence, exogenous reinfection, or bad luck.
- Not all patients with MDR-TB are foreign-born or have previously received treatment for active TB.
- Contact investigations should prioritize activities to those with the highest level of exposure and higher risk of progression to active TB. Contacts should be sought who interfaced with the source case beginning 3–6 months before symptoms began.
- When a hospital notifies the health department about an active TB case, the case manager assigned to the case should meet with hospital staff to ensure that the hospital staff is informed about appropriate TB care.
- TB training is essential for correctional staff, and correctional facilities should have a TB protocol in place to be able to house inmates with active TB.
CASE EXAMPLE 4

Anna is a 57-year-old diabetic Filipino woman.

7/10/98  Anna entered the U.S. with B-notification, Class B2 status (pulmonary TB suspect) and was not considered clinically active. Sputa were not collected overseas.

7/17/98  Anna is screened at the TB clinic.

Past history: Treated for TB in the Philippines from 1993 to 1996 with "pills and some injections," followed by irregular use of Rifater (combination of INH, RIF, and PZA) until the time of the exam.

Symptoms: Chronic cough with white sputum, fatigue, anorexia, and fever for months. Anna's immigration chest radiograph (February 17, 1998) reveals extensive pathology with a right upper lobe cavitory infiltrate with volume loss and fibro-nodular infiltrates of the right lower lobe and left mid-lung field. Her repeat chest radiograph in clinic shows no significant change.

7/17/98– 7/20/98 Two out of three sputum samples collected are AFB smear-positive and all 3 specimens eventually grow M. tuberculosis.

7/21/98  Anna is treated with INH, RIF, PZA, and EMB by DOT.

Serious consideration should have been given to initiation of an expanded regimen. The irregular nature of Anna's prior treatment and immigration from an area of high levels of resistance put her at great risk. Additionally, her cavitory disease and high bacillary load put her at risk for amplification of resistance if the wrong regimen is chosen. Delay in correct treatment also prolongs risk of transmission to contacts.

8/30/98  Anna's M. tuberculosis is found to be resistant to INH, RIF, and EMB by broth methods and the laboratory sets up confirmatory tests using the agar proportion method.

9/20/98  Anna's case manager inquires as to the susceptibility results and is only now told of the "preliminary" susceptibility results. Anna has not appreciably improved clinically or microbiologically.

Laboratories should notify the provider and public health department of "preliminary" results unless they have strong reasons to consider them inaccurate. In this case, Anna's risk of resistance is so high, the laboratory could have been asked to perform direct susceptibility tests, which could have hastened the results, and first- and second-line susceptibilities could have been ordered as soon as growth of M. tuberculosis was detected.

Anna's provider and case manager should have been suspicious when the susceptibility results were not sent several weeks after the initial growth of M. tuberculosis was reported.
Drug susceptibilities confirm resistance to INH, RIF, and EMB (the laboratory does not perform PZA susceptibility tests). Anna’s isolate is sent to a reference lab for second-line susceptibility testing, and a new sputum is sent immediately for first- and second-line susceptibility testing to determine whether amplification of resistance had occurred.

Cycloserine, SM, and levofloxacin are added; INH, RIF, and EMB are discontinued.

Sputum culture becomes negative 2 months after institution of an appropriate regimen. Anna has resolution of cough, fever, fatigue, and anorexia. Her weight has increased by 10 pounds.

**Lessons Learned**

- Overseas immigration screening is not always reliable. Do not allow overseas tests and evaluations to drive an immigrant’s evaluation upon arrival in the U.S. A chest radiograph consistent with active disease, including cavitory lesions, requires sputum collection before immigration. Immigrants with positive sputum smears are barred from U.S. entry until they become smear-negative. Notify CDC’s Division of Quarantine whenever a newly arriving “classified” immigrant is smear-positive on initial evaluation. Any immigrant with a chest radiograph consistent with active TB, whether symptomatic or not, should have TB ruled out using appropriate laboratory and clinical evaluations.

- Drug resistance should be suspected in someone with prior TB treatment, especially with irregular drug administration and limited treatment documentation.

- Once suspicious of drug resistance, utilize the resources of the lab by asking for direct susceptibilities from smear-positive sputum and ordering first- and second-line drug susceptibility testing as soon as growth is detected. If available, seek rapid susceptibility information with molecular techniques from smear-positive sputum, growth in broth, or colonies on agar.

- Strongly consider an expanded empiric regimen in a patient with such an irregular history of previous TB treatment and risk of resistance amplification. An initial regimen with at least 3 drugs to which the isolate is susceptible will hasten clinical improvement, lessen risk of amplification of resistance, and prevent transmission to contacts.
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