

CURRY  
INTERNATIONAL  
TUBERCULOSIS  
CENTER

# Drug-Resistant Tuberculosis

A SURVIVAL GUIDE FOR CLINICIANS

3RD EDITION



Edmund G. Brown Jr, *Governor*  
STATE OF CALIFORNIA

Diana S. Dooley, *Secretary*  
CALIFORNIA HEALTH &  
HUMAN SERVICES AGENCY



Karen Smith, MD, MPH, *Director*  
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**Supplemental materials are available online:**

<http://www.currytbcenter.ucsf.edu/products/drug-resistant-tuberculosis-survival-guide-clinicians-3rd-edition>

# Introduction to this *Survival Guide*

## The need for expertise

At the time of completion of this third edition of the *Survival Guide*, the World Health Organization (WHO) announced that tuberculosis (TB) now ranks alongside HIV as the leading cause of death from infectious disease worldwide. Although global efforts have begun to decrease the overall incidence of TB, there is a significant task ahead to reach elimination, particularly with the rising threat of drug resistance. As noted in the *National Action Plan for Combating Multidrug-Resistant Tuberculosis* (released by the White House, December 2015), of the estimated global burden of 480,000 cases of multidrug-resistant tuberculosis (MDR-TB), only 10% are being cured each year. Whether a provider practices in a high- or low-burden country for TB, the need for expert knowledge on how to appropriately care for drug-resistant TB remains vital.

Given the steady decline of TB cases in the United States (and even lower incidence of drug-resistant TB disease), health care providers—especially in low-incidence areas of the United States—may lack the knowledge and experience needed to successfully diagnose and treat TB, much less to manage the complications posed by drug resistance. In recognition of these challenges, national guidelines call for treatment of drug-resistant TB to be provided by or in close consultation with experts. The Tuberculosis Control Branch of the California Department of Public Health (CDPH) has provided such expert consultation services for the past 12 years to systematically address the care of drug-resistant TB cases in California. The original CDPH model was based on the shared expertise of two successful programs: the Texas Department of State Health Services and the Los Angeles County MDR-TB Unit, which utilize a multidisciplinary team approach to provide longitudinal oversight and case management advice throughout the entire course of complex treatment.

To complement its service, CDPH collaborated with the Curry International Tuberculosis Center (CITC) to develop the first edition (2004) of *Drug-Resistant Tuberculosis: A Survival Guide for Clinicians* as a practical reference for providers. A second edition was released in 2008 and reprinted in 2011. Recognizing the national need for such a resource, CDPH and CITC have disseminated the *Guide* to jurisdictions and providers across the country. In preparation for the third edition, the editors conducted an extensive needs assessment, including a national survey of TB controllers, public health and private sector clinicians, and other users of the *Guide*. In-depth key informant interviews with TB experts and practitioners were also conducted to ensure that the third edition content best reflects the evolving dynamics of diagnosing and treating drug-resistant TB. A group of 16 authors representing experts from public health and academia contributed to the writing, and a national panel of 34 peer reviewers provided commentary. This third edition of the *Guide* presents the best practice strategies available in late 2015.



## What's new in the third edition of the *Guide*

- Updated epidemiology of TB and MDR-TB is featured in **Chapter 1, *Epidemiology and Background***.

---

- Find updated information about diagnosing TB disease and drug-resistance, including the use of rapid molecular testing, in **Chapter 2, *Diagnosis***.

---

- **Chapter 3, *Laboratory***, is a new chapter presenting information about the laboratory tests used to confirm TB disease and drug resistance, including detailed discussions on understanding critical concentrations and minimum inhibitory concentration (MIC), advanced molecular detection methods, and the genes and mutations associated with drug resistance .

---

- **Chapter 4, *Treatment***, includes information based on current evidence and expert consensus for the treatment of drug-resistant TB, including information on the use of new drugs and therapeutic drug monitoring.

---

- Updated information about 23 medications used to treat tuberculosis is found in **Chapter 5, *Medication Facts Sheets***, including 5 new fact sheets not included in the second edition of the *Guide*: bedaquiline, clarithromycin, delamanid, meropenem, and rifapentine. Also new in Chapter 5 is a diagram illustrating “New anti-TB drugs in the pipeline.”

---

- Expanded information about diagnosing and treating drug-resistant TB disease and LTBI in children is now devoted to its own chapter—**Chapter 6, *Pediatrics***.

---

- New sections on “TB and Diabetes” and “Solid Organ Transplant” have been added to **Chapter 7, *Co-Morbidities and Special Situations***.

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- Two previous chapters were reconfigured into an expanded single **Chapter 8, *Monitoring and Case Management***.

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- **Chapter 9, *Adverse Reactions***, and **Chapter 10, *Contacts***, contain the latest information and best practice recommendations.

---

- Streamlined **Appendices** offer updated lists of resources and contact information.

## Description of the *Guide* and target audience

The *Guide* contains information and user-friendly tools and templates for use by any U.S.-based 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 healthcare providers in the fight against drug-resistant TB and should serve as an useful adjunct to expert consultative services. The 10 chapters cover major topics pertaining to epidemiology, diagnosis, laboratory issues, treatment, TB medications, pediatric TB, co-morbidities and special situations, monitoring and case management, adverse reactions, and management 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 5, Medication Fact Sheets**, to find the properties and details of individual drugs. When a patient is experiencing a potential side effect, the clinician can turn to **Chapter 9, Adverse Reactions**, for a review of appropriate management of toxicity, or to **Chapter 5** for the individual fact sheets about the medications the patient is receiving.

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.

### A lack of data

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 Food and Drug Administration (FDA)- licensed for these indications. Examples include amikacin, all of the fluoroquinolones, linezolid, and rifabutin. Much-needed research is currently underway to more thoroughly document the clinical efficacies of various treatment regimens for drug-resistant TB. In many cases, the information presented in this *Guide* is based on expert opinion, given the paucity of randomized controlled trials in this area.

At the time of publication for the third edition of the *Guide*, the first set of U.S. national guidelines for the care and management of drug-resistant TB are under development and will serve as a new key reference with additional best practice guidance for providers.

### Areas of practice variation

In recognition of the complexity of care and the gaps in evidence-based guidance, it is important for providers to appreciate key areas of practice variation. The following are a few examples of elements of drug-resistant TB care that vary among experts and existing guidelines (there are no randomized controlled trials to support any of these preferences):

- **Total duration of injectable drug therapy:** Current WHO guidelines recommend 8 months of injectable therapy. More common practice in the United States is to use culture conversion as a benchmark and administer the injectable drug for at least 6 months after culture conversion. Some experts use these drugs up to 12 months, especially if there are fewer than 3-4 oral drugs to complete therapy.

- **Total duration of therapy:** Some experts recommend 18-24 months of therapy total, and some treat 18-24 months from the time of culture conversion. International guidelines (WHO) recommend at least 20 months total duration. Recommendations based on expert consensus in this version of the *Survival Guide* recommend a total duration of at least 18 months beyond culture conversion. Pediatric series have used shorter durations of therapy.
- **Number of drugs in the regimen:** Newer series suggest that better outcomes are associated with more drugs. Expert opinion varies: some experts begin with 4 to 6 drugs to which the isolate is susceptible with the goal of using 3 to 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.
- **Duration of daily aminoglycoside/capreomycin therapy:** Assuming good clinical and microbiologic response, some experts feel comfortable using daily injectable therapy for as little as 1-2 months before changing to 3-times-weekly therapy. Others use 6 months of daily therapy (barring toxicity or renal impairment) before changing to intermittent therapy.
- **Dose of aminoglycoside/capreomycin:** The standard daily/intermittent dose for the aminoglycosides is 15 mg/kg/dose. Some authors use up to 25 mg/kg/dose for intermittent therapy and tolerate peak levels up to 65 to 80 mcg/ml. Experts who treat with longer courses of injectable drugs are comfortable with peak levels as low as 20 to 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.
- **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 central nervous system [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 diarrheal processes). Some experts use TDM routinely and serially, especially for monitoring the levels of injectable drugs.
- **Treatment of MDR-LTBI and use of window prophylaxis for MDR-TB contacts:** Some providers use fluoroquinolone monotherapy for MDR-LTBI, and some use 2-drug therapy. Some experts and jurisdictions use window prophylaxis for contacts to MDR-TB, typically with 2 drugs to which the isolate is susceptible.

Each case presents specific complexities. The need for individualization of care ultimately determines management decisions. While use of this *Guide* should serve as a useful supplement during care, consultation with experts remains an essential component of successful treatment and should be encouraged throughout the care of all drug-resistant cases. Contact information for expert resources can be found in **Appendix 1**.

# Acronyms and Abbreviations

<b>AFB</b>	acid-fast bacilli	<b>CXR</b>	chest x-ray
<b>AIDS</b>	acquired immunodeficiency syndrome	<b>DLM</b>	delamanid
<b>AK</b>	amikacin	<b>DM</b>	diabetes mellitus
<b>ALT</b>	alanine aminotransferase	<b>DOT</b>	directly observed therapy
<b>ANA</b>	antinuclear antibodies	<b>DST</b>	drug-susceptibility testing
<b>AMX/CLV</b>	Amoxicillin/clavulanate	<b>EMB</b>	ethambutol
<b>ART</b>	antiretroviral therapy	<b>ETA</b>	ethionamide
<b>AST</b>	aspartate aminotransferase	<b>FDA</b>	Food and Drug Administration
<b>ATS</b>	American Thoracic Society	<b>FQN</b>	fluoroquinolone
<b>BAL</b>	bronchoalveolar lavage	<b>GI</b>	gastrointestinal
<b>BCG</b>	bacille Calmette-Guérin	<b>HEPA</b>	high efficiency particulate air
<b>BDQ</b>	bedaquiline fumarate	<b>HIV</b>	human immunodeficiency virus
<b>BID</b>	twice a day	<b>IDSA</b>	Infectious Diseases Society of America
<b>BMI</b>	body mass index	<b>IGRA</b>	interferon gamma release assay
<b>BUN</b>	blood urea nitrogen	<b>IM</b>	intramuscular
<b>CAPD</b>	continuous ambulatory peritoneal dialysis	<b>IMP/CLN</b>	imipenem/cilastatin
<b>CBC</b>	complete blood count	<b>INH</b>	isoniazid
<b>CDC</b>	Centers for Disease Control and Prevention	<b>IRIS</b>	immune reconstitution inflammatory syndrome
<b>CDPH</b>	California Department of Public Health	<b>IUATLD</b>	International Union Against Tuberculosis and Lung Disease
<b>CFZ</b>	clofazimine	<b>IV</b>	intravenous
<b>CITC</b>	Curry International Tuberculosis Center	<b>KM</b>	kanamycin
<b>CLR</b>	clarithromycin	<b>LFT</b>	liver function test
<b>CM</b>	capreomycin	<b>LFX</b>	levofloxacin
<b>CNS</b>	central nervous system	<b>LPA</b>	line probe assay
<b>CS</b>	cycloserine	<b>LTBI</b>	latent tuberculosis infection
<b>CSF</b>	cerebrospinal fluid	<b>LZD</b>	linezolid

<b>MAC</b>	<i>Mycobacterium avium</i> complex
<b>MAO</b>	monoamine oxidase
<b>M. bovis</b>	<i>Mycobacterium bovis</i>
<b>MDDR</b>	<i>Molecular detection of drug resistance</i>
<b>MDR-TB</b>	multidrug-resistant tuberculosis (resistant to at least isoniazid and rifampin)
<b>MXF</b>	moxifloxacin
<b>MIC</b>	minimum inhibitory concentration
<b>MIRU</b>	mycobacterial interspersed repetitive units
<b>MPM</b>	meropenem
<b>M. tb complex</b>	<i>Mycobacterium tuberculosis</i> complex
<b>M. tuberculosis</b>	<i>Mycobacterium tuberculosis</i>
<b>NAAT</b>	nucleic acid amplification test
<b>NIOSH</b>	National Institute for Occupational Safety and Health
<b>NNRTI</b>	non-nucleoside reverse transcriptase inhibitor
<b>NPO</b>	nothing by mouth
<b>NSAID</b>	nonsteroidal anti-inflammatory drug
<b>NTM</b>	nontuberculous mycobacteria
<b>OFX</b>	ofloxacin
<b>PA</b>	posteroanterior
<b>PAP</b>	patient assistance program
<b>PAS</b>	para-aminosalicylate
<b>PCR</b>	polymerase chain reaction
<b>PO</b>	by mouth
<b>PPD</b>	purified protein derivative
<b>PSQ</b>	pyrosequencing

<b>PZA</b>	pyrazinamide
<b>qam</b>	every morning
<b>qd</b>	once a day
<b>qhs</b>	every evening
<b>qid</b>	four times a day
<b>QFT-G</b>	QuantiFERON®-TB Gold
<b>QFT-GIT</b>	QuantiFERON®-TB Gold In Tube
<b>QT</b>	the interval from the beginning of the QRS complex to the end of the T wave on an electrocardiogram
<b>RFB</b>	rifabutin
<b>RFLP</b>	restriction fragment length polymorphism
<b>RIF</b>	rifampin
<b>RPT</b>	rifapentine
<b>SGPT</b>	serum glutamic-pyruvic transaminase
<b>SM</b>	streptomycin
<b>SOT</b>	solid organ transplant
<b>SSRI</b>	selective serotonin reuptake inhibitor
<b>TB</b>	tuberculosis
<b>TID</b>	three times a day
<b>TSH</b>	thyroid stimulating hormone
<b>TST</b>	tuberculin skin test
<b>WBC</b>	white blood cell
<b>WHO</b>	World Health Organization
<b>XDR-TB</b>	extensively drug-resistant tuberculosis



# Epidemiology & Background

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# Efforts to control TB throughout the world have been challenged in recent decades by the emergence of drug-resistant TB.

Drug-resistant tuberculosis (TB) is a deadly communicable disease that poses a serious global health threat. It impacts not only individual patients and their families, but also imposes tremendous burdens on overextended public health systems that may lack the resources needed to contain it.

## DEFINITIONS

- **Multidrug-resistant (MDR)** refers to TB caused by *Mycobacterium tuberculosis* (*M. tuberculosis*) that is **resistant to at least isoniazid (INH) and rifampin (RIF)**.
- **Pre-extensively drug-resistant (Pre-XDR)** refers to MDR-TB that is **also resistant to either a fluoroquinolone or a second-line injectable anti-TB drug (kanamycin, capreomycin, or amikacin), but not both**.
- **Extensively drug-resistant (XDR)** refers to MDR-TB that is **also resistant to both a fluoroquinolone and a second-line injectable anti-TB drug**.

## Drug-resistant TB across the globe

In 2014, an estimated **480,000 people developed MDR-TB and 190,000 people died from MDR-TB**. **By 2015, 105 countries had reported at least one case of XDR-TB**. An estimated **21% of MDR-TB cases worldwide have additional resistance to a fluoroquinolone, and 9.7% have XDR-TB**. According to the World Health Organization (WHO), more than half of the global burden of MDR-TB is currently in three countries: India, China, and the Russian Federation.

Worldwide and in most countries with a high burden of MDR-TB, WHO estimates that **in 2014 only 41% of those with MDR-TB were actually diagnosed by laboratory testing**.

Fortunately, there are new and vigorous efforts for control of TB and for early diagnosis and treatment of drug-susceptible and drug-resistant TB worldwide. Large-scale implementation of rapid molecular tests for early detection of both the presence of TB and, at

a minimum, rifamycin resistance has occurred in many high-burden countries. *The Patients' Charter for Tuberculosis Care*, developed by the World Care Council, promotes a “patient-centered” approach to tuberculosis care. The updated *International Standards for Tuberculosis Care (ISTC)* presents a set of widely accepted, evidence-based standards describing a level of care that all practitioners, public and private, should seek to achieve in managing patients with, or suspected of having, TB.

WHO reported improvements in detection and treatment of MDR-TB in 2014: 111,000 people with MDR-TB were started on second-line treatment, equivalent to 90% of the 123,000 newly-detected cases that were reported and eligible for treatment globally. **However, treatment coverage gaps for detected cases were much larger in some countries**, notably the high-burden countries of China (49%), Myanmar (44%), and Nigeria (53%).

Finally, improvements in early identification and enrollment into treatment must also be followed by quality of care measures that ensure treatment success. Only three high-burden countries reported a treatment success rate for MDR-TB of 75% or higher. **On average, only 50% of MDR-TB patients in the 2012 cohort of detected cases were treated successfully.** Many countries lack the resources needed to provide sufficient quality of care. These disparities must be addressed to prevent further transmission of disease and more extensive resistance.

In many high-burden countries, a standardized MDR-TB regimen is used due to the lack of routine access to second-line drug-susceptibility testing (DST). The success or failure of treatment of these cases overseas can impact the presentation of drug resistance in the United States (U.S.) through immigration. It is important for U.S. clinicians to understand the diversity of global practices.

A milestone for improved MDR-TB care occurred in 2012 when **bedaquiline (BDQ) fumarate** (Sirturo, Janssen) became the first TB drug in a novel class to be approved in 40 years. In October 2013, the U.S. Centers for Disease Control and Prevention (CDC) issued provisional guidance for its use in the treatment of MDR-TB. A second new drug, **delamanid** (Delyba, Otsuka), also gained provisional approval for use in the European Union in 2014, and additional drugs are in the development pipeline.

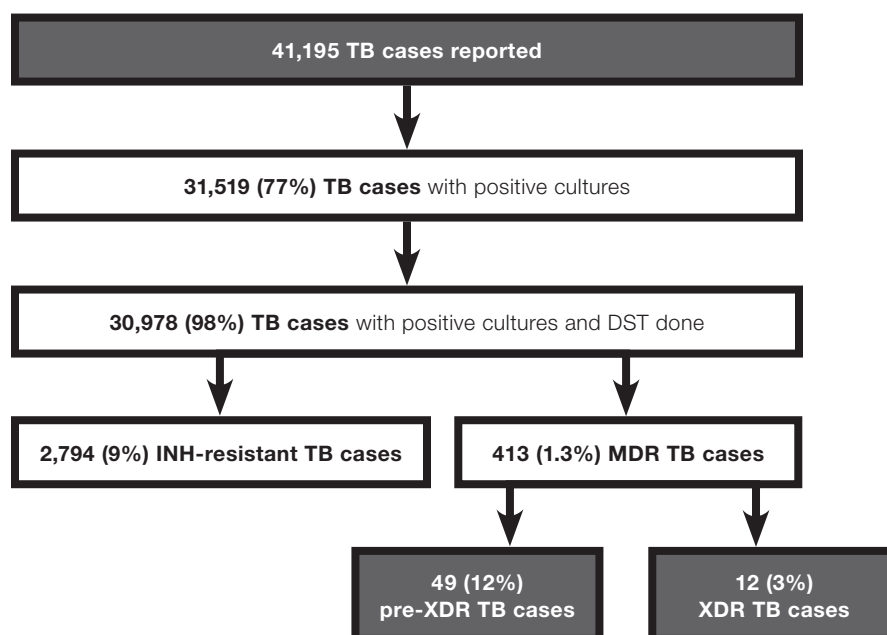
## Drug-resistant TB in the United States

In the United States in 2010-2013:

- 413 TB patients had MDR-TB based on initial DST. Of these, 49 patients had pre-XDR-TB, and 12 patients had XDR-TB. In other words, 15% of U.S. MDR-TB patients had pre-XDR or XDR.
- Thirty-eight states plus the District of Columbia reported at least 1 MDR-TB case; 19 states reported at least 1 pre-XDR-TB case; and 8 states reported at least 1 XDR-TB case. See Figure 1.

FIGURE 1.

### Drug-resistant TB in United States, 2010-2013



Although the number of drug-resistant cases of TB in the United States declined as the number of total reported TB cases decreased, there has been little change in the percentage (1.0–1.6%) of TB patients with MDR-TB during 2000–2013. On the other hand, the percentage of patients with INH resistance has increased from 7.9% in 2000 to 9.2% in 2013. The increase in INH-resistant TB is troubling because it is one mutation away from becoming MDR-TB.

In recent years, the percentage of patients with pyrazinamide (PZA)-resistant TB has also increased (from 2.0% to 3.3% during 1999–2009). TB patients with PZA resistance include those with TB infections caused by *M. bovis* (a member of the *M. tuberculosis* complex that is intrinsically resistant to PZA) and *M. tuberculosis*. *M. bovis* accounted for an average of 1.7% of culture proven cases from 2008–2013.

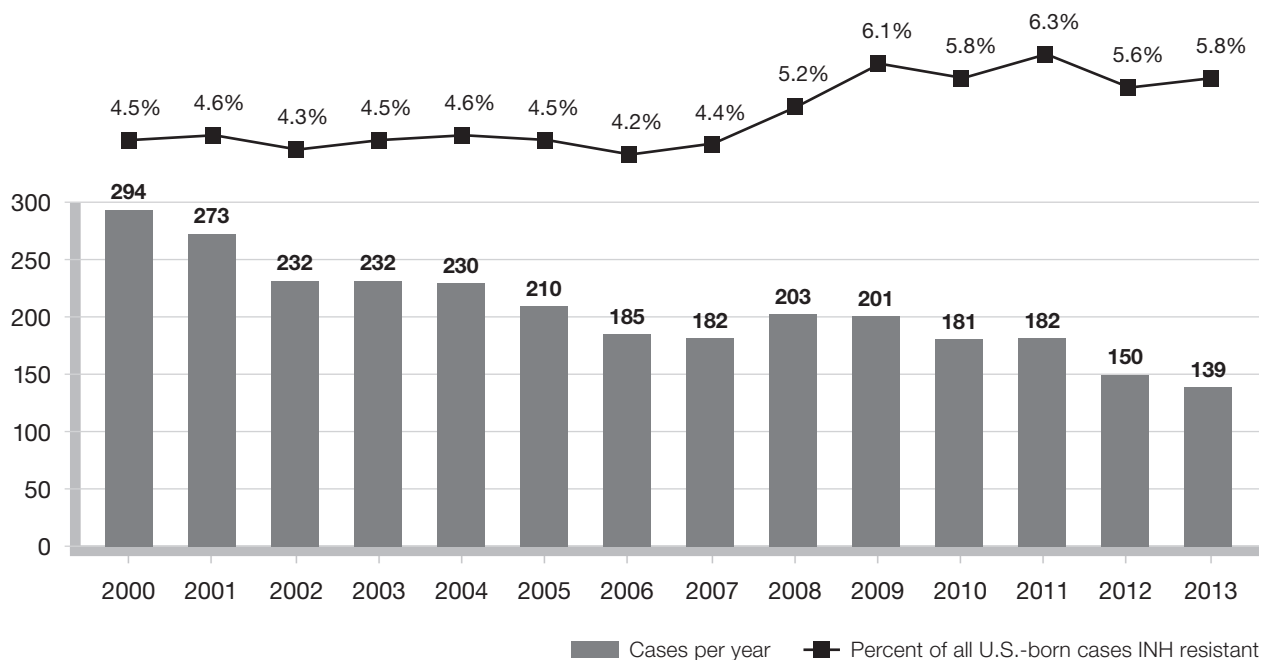
In the United States, drug resistance in foreign-born persons with TB is much more common than in U.S.-born persons with TB, corresponding to the higher rates of drug resistance in the countries of origin.

- In 2013, 90% of MDR-TB cases in the United States were among foreign-born persons.
- Among foreign-born patients who arrived in the United States within 2 years of TB diagnosis (recent arrivers), 3.2% had MDR-TB, compared to 1.4% of those diagnosed with TB more than 2 years after they arrived (remote arrivers).

Figure 2 shows that the percentage of U.S.-born TB patients with INH resistance increased from 4.5% to 5.8% from 2000 to 2013. Among foreign-born TB patients over the same time period, the percentage of INH-resistant TB remained the same, at about 11% in both recent and remote arrivers.

FIGURE 2.

### U.S.-born INH resistant TB cases and percentages, 2000-2013



The small percentage of U.S.-born TB patients with MDR-TB slightly declined from 2000 (0.6%, N=42) to 2013 (0.4%, N=9), while the percentage of foreign-born recent (3%, N=33) and remote (1.4%, N=47) arrivers with MDR-TB remained stable over the same time period.

Overall, drug-resistant TB is also more common among TB patients who were born in countries with an estimated high prevalence of drug resistance. Discordance between WHO and U.S. estimates of MDR-TB by country-of-origin was documented in a recent study that demonstrated that the U.S. National TB Surveillance system (NTSS) better predicted the prevalence of drug resistance in foreign-born U.S. residents with TB than the WHO/International Union Against Tuberculosis and Lung Diseases (IUATLD) Global Project on Anti-Tuberculosis Drug Resistance Surveillance (Global DRS). Of the 413 foreign-born patients diagnosed with MDR-TB in the United States from 2010 to 2013, 75% were born in only 15 countries. Table 1 shows the drug resistance pattern for the top 15 countries of origin for cases of drug-resistant TB in the United States.

*INH-resistant TB among U.S.-born patients slightly increased from 2000-2013. Rates of INH-resistant and MDR-TB among all groups have otherwise remained stable during this period.*



TABLE 1.

**Drug resistance among foreign-born TB patients in the United States, 2010-2013 (Top 15 countries)**

Country of origin	Total TB cases*	MDR		Any resistance**		INH resistance	
		No.	%	No.	%	No.	%
India	2,122	40	1.9	258	12.2	166	7.8
Philippines	3,068	39	1.3	484	15.8	386	12.6
Mexico	5,542	37	0.7	652	11.8	324	5.8
Vietnam	2,002	32	1.6	365	18.2	293	14.6
China	1,478	23	1.6	162	11.0	133	9.0
Peru	373	14	3.8	51	13.7	38	10.2
Laos	284	12	4.2	49	17.3	36	12.7
Ukraine	93	12	12.9	21	22.6	17	18.3
Haiti	753	11	1.5	58	7.7	53	7.0
Republic of Korea	461	11	2.4	56	12.1	54	11.7
Burma / Myanmar	426	9	2.1	60	14.1	47	11.0
Dominican Republic	296	8	2.7	31	10.5	27	9.1
Ecuador	307	8	2.6	31	10.1	26	8.5
Guatemala	777	8	1.0	61	7.9	49	6.3
Ethiopia	635	7	1.1	60	9.4	58	9.1

\*Total cases with positive cultures and initial susceptibilities performed

\*\*TB isolates with any first-line drug resistance (INH, RIF, ethambutol [EMB], PZA)

Source: Robert H. Pratt, National Tuberculosis Surveillance System, Division of Tuberculosis Elimination, Centers for Disease Control and Prevention (email communication, November 14, 2014).

**Drug resistance is also more common in TB patients who reported having had previous TB.** In the United States in 2013, 4.2% of all patients who reported previous TB had MDR-TB, whereas only 1.2% of patients who did not report previous TB had MDR-TB. These differences in percentages with MDR-TB were evident among both U.S.-born patients (2.2% with previous TB vs. 0.3% without previous TB) and foreign-born patients (5.1% with previous TB vs. 1.7% foreign-born patients without previous TB).

## MDR-TB: A staggering cost for a small percentage of TB cases

A 2014 study by Marks, et al., of MDR-TB patients in the United States in 2005-2007 determined that the direct costs to treat drug-resistant TB averaged \$134,000 per MDR-TB patient and \$430,000 per XDR-TB patient. In contrast, the estimated cost per non-MDR-TB patient was \$17,000.

## Sources of drug-resistant TB in the United States

There are 4 primary sources that explain the epidemiology of drug-resistant TB in the United States:

- **Resistance acquired during treatment in the United States**
- **Recent transmission of drug-resistant *M. tuberculosis***
- **Reactivation of latent drug-resistant TB infection**
- **Entry of patients into the United States with active drug-resistant *M. tuberculosis* disease**

A cross-sectional study of 92 MDR-TB cases reported in the United States 2007-2009 determined that:

- 5% of patients had a documented **previous episode of TB in the United States and likely relapsed with acquired drug-resistant disease.**
- 22% of MDR-TB cases were the result of **recent transmission.**
- 41% had **reactivation disease** (one-third of those with reactivation disease had a previous episode of TB in another country, indicating possible acquired resistance outside of the United States).
- Another 22% occurred in **patients originating from another country who entered the United States with active TB disease.**
- 10% could not be classified because there were insufficient data.

MDR-TB transmission has been documented across the world, with a 2010 report of half of MDR-TB cases occurring within individuals with newly-identified TB (rather than previously-treated TB), in 30 countries.

# How is drug resistance generated?

Drug resistance is generated at the molecular level when genes responsible for the specific form of drug resistance (e.g., *rpoB* for rifampin) of *M. tuberculosis* develop a **spontaneous mutation**. The prevalence of resistant mutants associated with each first-line drug used to treat TB has been estimated, and resistance to new drugs (e.g., bedaquiline) has already been identified. **A typical pulmonary cavity will contain an estimated 10<sup>7</sup> to 10<sup>9</sup> organisms**, therefore making it likely that some organisms in these cases may exhibit a spontaneous mutation for resistance. See Table 2.

TABLE 2.

## Select anti-tuberculosis drugs and prevalence of resistant mutants

Drug	Year introduced	Prevalence of resistant mutants within a wild-type population of <i>M. tuberculosis</i> bacteria
Streptomycin	1945	3.8 x 10 <sup>-6</sup>
Isoniazid	1952	3.5 x 10 <sup>-6</sup>
Pyrazinamide	1952	1.0 x 10 <sup>-5</sup>
Ethambutol	1962	3.1 x 10 <sup>-5</sup>
Rifampin	1967	1.2 x 10 <sup>-8</sup>
Bedaquiline	2013	?

Within wild-type populations, resistance to more than one TB drug is even rarer as resistance to the various drugs is not linked genetically. Inherent resistance to more than one TB drug is the product of the prevalence of resistance to the individual drugs.

- INH and RIF: 3.5 x 10<sup>-6</sup> x 1.2 x 10<sup>-8</sup> equals 4.2 x 10<sup>-14</sup>

Mutations conferring drug resistance to *M. tuberculosis* become important for the TB patient when amplified by health care system-related factors and/or patient behaviors. Contributors to the development of acquired resistance during treatment for TB include: inadequate clinical management, poor adherence, drug malabsorption, and unstable drug supply. Enhancers of transmission of MDR-TB include factors that extend the infectious period; e.g., delayed diagnosis and/or delayed treatment initiation with an appropriate regimen, and delayed bacteriological conversion of sputum. Inadequate infection control can also contribute to transmission of MDR-TB.

In a **patient with active TB disease**, 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 in the diagnosis**
  - **Disbelief in the efficacy or necessity of the treatment**
  - **Chaotic lifestyle; substance abuse**
  - **Cultural issues**
  - **Pregnancy**
  - **Neuropsychiatric disease**
- There may be a dispensing or administration error regarding the correct dose.
- The patient may not be prescribed the appropriate dose.
- The patient may not absorb the full dose of medication and/or have disease in areas where the penetration of one 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 one 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 disease, 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 (rifabutin in an HIV patient for *Mycobacterium avium* complex [MAC] prophylaxis; a fluoroquinolone for community-acquired pneumonia).
- The patient may take TB medicines without a prescription (sometimes available over-the-counter outside the United States, or if taking medications belonging to someone else).
- 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 directly observed therapy (DOT): either the patient takes 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 to 3 months of administration of an inadequate drug regimen**.

## Summary

- Globally in 2014, an estimated 480,000 people developed MDR-TB and 190,000 people died from MDR-TB. By 2015, 105 countries had reported at least one case of XDR-TB. More than half of the global burden of MDR-TB is currently in three countries: India, China, and the Russian Federation.

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- Despite recent improvements in early identification and enrollment into treatment, high-burden countries often lack the resources needed to ensure quality of care for treatment success.

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- Ninety percent of MDR-TB cases in the United States occur among the foreign-born.

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- Fifteen percent of MDR-TB patients in the United States had pre-XDR or XDR-TB.

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- Risk factors for INH-resistant and MDR-TB in the United States include country-of-origin, recent arrival (within 2 years) in the United States, previous TB, and exposure to an individual with INH-resistant or MDR-TB during the infectious period.

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- The percentage of TB patients with MDR-TB is not increasing in the United States, but the percentage of U.S.-born TB patients with INH resistance, and PZA resistance overall, is increasing in the United States.

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- The increase in INH-resistant TB is troubling because it is one mutation away from becoming MDR-TB.

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- It is essential to implement strategies to assure DOT and completion of an adequate regimen in order to reduce development or amplification of drug resistance.

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# Diagnosis

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# The first steps in diagnosing drug-resistant TB are to recognize that the patient is at risk and to expedite the laboratory diagnosis.

## Introduction

The diagnosis of tuberculosis (TB) frequently requires a high index of suspicion, especially in low-prevalence areas. The index of suspicion should be based on consideration of clinical and epidemiological risk factors, symptoms, physical examination findings (e.g., enlarged lymph nodes or other findings suggestive of possible extra-pulmonary involvement), and radiographic findings. Once TB is considered, sputum or other specimens are collected for TB nucleic acid amplification test (NAAT), acid-fast bacilli (AFB) smear, growth detection, and drug-susceptibility testing (DST). **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 conventional DST results return weeks to months later can result in inadequate drug regimens, amplification of drug resistance, and additional disease transmission.

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

- Treat the patient with the most appropriate regimen
- Minimize transmission
- Prevent acquisition of further drug resistance
- Offer appropriate care to contacts
- Provide the best chance of cure

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

# Risk assessment for drug resistance

## The most important predictors of drug-resistant TB are:

- **Previous episode(s)** of TB treatment
- **Worsening clinical and/or radiographic findings** while on TB therapy
- **Origin** from, history of residence in, or frequent travel to a **region or country with a high prevalence of drug-resistant TB**
- **Exposure to an individual with known (or highly suspected) infectious drug-resistant TB**, or exposure to individuals in congregate settings where drug resistance has been documented

## Risk factors in persons with a history of prior TB

**Suspicion for drug-resistant TB should be high** and rapid molecular testing for drug resistance should be performed if the patient has 1 or more of the following characteristics on current or prior treatment:

- Lack of conversion of cultures to negative during the first 3 months of therapy
- Lack of improvement or only partial improvement in TB symptoms
- Worsening of TB symptoms or radiograph findings despite TB treatment
- Non-adherence or intermittent or erratic ingestion of prescribed anti-TB regimen
- Lack of directly observed therapy (DOT) or poorly supervised therapy
- Documented treatment failure or relapse: the risk for suspected acquired resistance in relapse cases is significantly lower if use of high-quality DOT with an appropriate regimen can be verified, but a rapid molecular test should still be obtained
- History of an inappropriate treatment regimen, including:
  - Administration of single-drug therapy
  - Too few effective drugs
  - Inadequate drug dosing

## Risk factors in persons without prior TB history

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

- Exposure to a person with documented drug-resistant TB
- Exposure to an individual highly suspected of having drug-resistant TB, including those who have received more than one course of TB treatment, prolonged treatment or who had a delayed response to treatment
- Residence in or travel to a region with a high prevalence of drug-resistant TB (See **Chapter 1, Epidemiology**, for a list of the top 15 countries of origin for multidrug-resistant [MDR] TB patients in the United States, and **Resources** at the end of this chapter)

- Among foreign-born persons with TB, arrival in the United States within the previous two years (per 2010-2013 U.S. national surveillance data)
- 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 a history of previous TB treatment requires a great deal of patience and attention to detail. In a confidential setting, allow plenty of time, use 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 nonjudgmental 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 or antibiotics for many months for a lung problem?

If your patient answers **“yes”** to any question(s) that indicate he or she may have been treated previously for TB, the following types of questions should be asked to obtain more information regarding previous treatment:

- Where were you treated?
- What medicines did you receive?
- How many different medicines? How many pills each day? What sizes and colors were the pills/capsules?
- Did you receive injections?
- How long were you on treatment?
- Were you told you were cured? Did your TB ever come back?
- How many times were you treated for TB?
- When did you start?
- When did you stop? Why did you stop (completed treatment, bad reaction to the medicine)?
- It's hard to remember to take medicine every day. Did you take medications daily? Every pill?
- TB medicine can be expensive. Were you ever without medication?
- Did you miss medication sometimes? How often?
- Did healthcare workers watch you taking your medications?
- Did your urine turn orange?
- Did you feel better?
- Did you ever have a sputum collected for testing? What was the result?
- If positive, did your sputum test get better on treatment (change from positive 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 to repeat treatment for TB? That you had TB that was drug resistant?
- Did your TB symptoms return after finishing treatment?

**TB treatment outside of the United States:** If the patient was previously treated for TB in the United States, records detailing his/her treatment should be obtained directly from the appropriate state and/or local jurisdiction. Past treatment outside the United States may be available through CureTB (Mexico/Latin America) or TB Net (see **Appendix 2, Selected Organizations Working to Control and Prevent TB in the International Arena**). If the patient was treated in Western Europe, Canada, or by a private provider in a high-resource country, records should be available and can be sought directly through the appropriate national/regional program. Immigration health records (e.g., class B1 records) may also be informative and should be obtained.

Many resource-limited countries, particularly those documented as among the highest TB burdened countries, use standardized World Health Organization (WHO) TB regimens and diagnostic algorithms that may differ from recommended U.S.-based practices. **Appendix 3, International Resources for TB Treatment and Policies**, lists key WHO reference documents and other websites that may be helpful in understanding and identifying TB policies in selected countries.

If your patient answers “no” to the questions that indicate he or she may have been treated previously for TB, the following types of questions should be asked to evaluate if the patient has been exposed to drug-resistant TB:

- Have you been exposed to or had contact with anyone with TB (or who may be sick with a chronic cough)?
- If yes, when was that? Where were you exposed? For how long you were exposed?
- What is that patient’s name and age? Where was he/she treated? How long was he/she treated? Was he/she cured?
- Did you have a skin or blood test for TB? 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 healthcare worker observed you take the pills, or did a healthcare 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?

**Whenever possible, obtain records regarding treatment of a presumed source case.**



## Testing for TB infection

Suspicion of or evaluation for TB sometimes begins with the use of an interferon gamma release assay (IGRA) such as QuantiFERON-TB Gold (QFT-G) or T-SPOT.TB, or the tuberculin skin test (TST). None of these tests have perfect accuracy for diagnosis of TB infection or TB disease.

Studies suggest that the IGRA and TST may be negative in up to 40% of newly diagnosed, culture-positive TB cases. **A negative IGRA test or TST does not rule out TB disease, and a positive IGRA test or TST does not distinguish between TB infection and TB disease. When a clinical suspicion for active TB disease exists, further testing for TB disease should continue regardless of IGRA or TST result.**

For more information about testing for TB infection, see **Chapter 10, Contacts**.

## Testing for TB disease

- All patients in whom a **clinical suspicion for active pulmonary TB disease** exists should at a minimum have **one sputum specimen examined by NAAT and three sputum specimens**, collected at least 8 hours apart, **examined by AFB smear microscopy and mycobacterial culture**.
- Culture remains the gold standard for the diagnosis of TB—it is the most sensitive test and enables comprehensive drug susceptibility testing. Sputum specimens should be submitted for culture regardless of whether or not NAAT is ordered.
- All patients in whom a clinical **suspicion for active drug-resistant pulmonary TB disease** exists should have a **sputum specimen submitted for rapid molecular testing for drug resistance**. For more information, see section: **Testing for drug resistance**, and **Chapter 3, Laboratory**.
- Patients in whom **extrapulmonary disease** is suspected should also have specimens from the site of disease examined by AFB smear, culture, and histopathology (when applicable). Rapid molecular tests may be performed on some non-respiratory specimens in laboratories capable of validating the assay. Specialized reference laboratories have the capacity to attempt molecular diagnosis through DNA extraction when formalin-fixed tissue is the only available specimen. For more information regarding molecular tests for extrapulmonary specimens, refer to **Chapter 3, Laboratory**.
- **Patients in whom suspicion of active TB disease is high should be started on an appropriate treatment regimen empirically** because culture often takes up to 2-6 weeks before a positive result is obtained. For more information on choosing an appropriate treatment regimen, refer to **Chapter 4, Treatment**.

## Molecular assays for identification of *Mycobacterium (M.) tuberculosis* complex

NAATs are molecular assays that have been available since 1995, but initially had limited uptake due to cost and availability. Fortunately, with improved access, molecular assays are having a significant impact on TB care. The Centers for Disease Control and Prevention (CDC) 2009 recommendations **promote the use of NAATs in all patients for whom a diagnosis of TB is being considered** if the results would influence clinical or public health decision-making. When feasible, NAATs should also be considered for all

patients being evaluated for TB to prevent delays in diagnosis and treatment initiation. The type of NAAT used will vary based on local availability, but most commonly it will be a polymerase chain reaction (PCR)-based method.

- NAATs are more sensitive than sputum smear microscopy but a negative NAAT does not rule-out active TB disease. If clinical suspicion for TB is high, NAAT testing should be repeated on a second specimen to increase sensitivity for diagnosing TB. When NAAT results are negative, decisions regarding empiric anti-TB treatment should be based on clinical suspicion of TB, risk of adverse outcomes, and public health considerations.
- NAATs have high specificity and positive predictive value for identifying TB.

Although different NAATs are available, increased implementation of the semi-automated Xpert MTB/RIF assay is anticipated and is worth mentioning within its global context.

- The Xpert MTB/RIF assay was approved by the U.S. Food and Drug Administration (FDA) in 2013 and can rapidly identify the presence of *M. tuberculosis* complex. The assay also rapidly identifies mutations in the *rpoB* gene that confer rifampin (RIF) resistance. See section: **Molecular assays for identification of drug resistance.**
- The Xpert MTB/RIF assay can be performed on raw sputum specimens, requires minimal sample preparation, provides results within 2 hours and is highly accurate for detecting *M. tuberculosis* complex.
- However, **false-negative results** do occur, particularly when sputum smears are negative or scanty-positive. **False-positive** results for identifying *M. tuberculosis* complex are less common, but do occur particularly when a patient has had a previous episode of TB disease.

Since Xpert MTB/RIF was first endorsed by WHO in 2010, there has been rapid uptake in many high-burden countries. In 2013, WHO updated its prior endorsement to recommend the use of Xpert MTB/RIF as the initial diagnostic test, when feasible, for **all patients** being evaluated for pulmonary TB and for some forms of extrapulmonary TB.

## Testing for drug resistance

Definitive diagnosis of drug-resistant TB requires that *M. tuberculosis* complex be isolated and drug-susceptibility results be completed and conveyed to the clinician. State and/or local TB control officials should be notified promptly when drug resistance is either strongly suspected or confirmed.

Different techniques of **conventional, growth-based DST** may be used and are outlined in more detail in **Chapter 3, Laboratory**. With all techniques, growth detection and identification of *M. tuberculosis* complex may take a few weeks, and DST requires an additional 1 to 3 weeks. Slow growth of some mycobacterial strains (a common characteristic noted in many MDR-TB strains) further lengthens the time to identification and DST. Delays in reporting of culture confirmation and/or drug-susceptibility results to the treating provider can further delay the diagnosis of drug-resistant TB and initiation of appropriate treatment, resulting in ongoing transmission risk.

- In interpretation of *M. tuberculosis* complex drug-susceptibility results, clinical trials have ascertained that when tested on solid media, if more than 1% of organisms within a population are resistant to a given drug, clinical success with that drug is less likely.

- The interpretation of growth-based DST 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 process: 1) mycobacteria may reside within or outside of human cells; 2) mycobacteria have a long replication time and may exist in a continuum between dormant and active states; and 3) mycobacteria can live in a variety of tissue types for which drugs may have different penetration levels.
- The concentration that constitutes the breakpoint 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 that has not been exposed to TB drugs) *M. tuberculosis* complex strain, but does not appreciably suppress the growth of a resistant strain.** The critical concentration may be different depending on the medium used for the assay.
- **If, on solid media, more than 1% of the strain’s population grows at the critical concentration of the drug for that particular medium, the isolate is considered to be resistant to that drug and other drugs must be used in the regimen.** Be aware that isoniazid [INH], streptomycin [SM], and fluoroquinolones may be tested at both low and high concentrations and it may be possible to still consider use of drugs that display low-level resistance only.

More detailed discussions regarding critical concentrations, use of high- and low-level testing of selected drugs, and interpretation of MICs can be found in **Chapter 3, Laboratory**.

## Molecular assays for identification of drug resistance

**Molecular assays for identification of drug resistance** can hasten the time from weeks to 1-2 days to identify the presence of drug resistance. All molecular assays detect mutations in mycobacterial DNA that are known to cause resistance to a specific anti-TB drug. Because resistance mechanisms at the molecular level are not fully understood, current molecular assays cannot detect all drug resistance. Growth-based DST should be performed when isolates are available.

Current assays include:

- **Xpert MTB/RIF assay:** In addition to detecting *M. tuberculosis* complex, Xpert MTB/RIF also detects mutations in the *rpoB* gene that confer RIF resistance and is currently the only non-sequencing molecular test for drug resistance approved by the FDA. The detection of RIF resistance is predictive of MDR-TB because RIF mono-resistance is relatively uncommon. Although accuracy is high, false-positive results can occur. **Positive results that are unexpected for the clinical circumstance (e.g., positive result for RIF resistance in a patient without risk factors for drug resistance) need closer review; consider consultation with experts.** Further consultation with the laboratory can help determine whether the result is likely to be false-positive; e.g., if cycle threshold values are high and end-point fluorescence values are low, or when RIF resistance is detected by multiple probes suggesting the presence of nontuberculous mycobacteria (NTM). In this situation, confirmation using a sequence-based test should be done. For more details regarding test performance of the Xpert MTB/RIF assay, refer to **Chapter 3, Laboratory**.

- **Line-probe assays (LPAs):** LPAs are currently performed primarily outside of the United States, but are available at some U.S. reference laboratories for rapid identification of INH and RIF (MTBDRplus, Hain Lifesciences) or fluoroquinolones, ethambutol (EMB), and injectable agents (MTBDRs/, Hain Lifesciences).
- **Sequencing-based assays:** Molecular assays that use a sequencing technique (e.g., Sanger sequencing, pyrosequencing or testing through the CDC Molecular Detection of Drug Resistance [MDDR] service) have the advantage of reporting on the actual mutations, which can be useful in interpretation.

**When drug resistance has been identified by non-sequencing molecular assays (e.g., Xpert MTB/RIF or others) in low-incidence settings, confirmation by a sequence-based method is recommended** because non-sequencing assays can report silent mutations as drug resistant.

For more details regarding different types of molecular assays for drug resistance identification and the genes and mutations associated with drug resistance, see **Chapter 3, Laboratory**.

## When to use rapid molecular tests for drug resistance

**Rapid molecular tests for drug resistance should be requested in all cases identified as at risk for drug-resistant TB (Table 1).** Rapid identification of drug resistance is also indicated in circumstances where earlier identification of resistance confers a significant medical or public health advantage or in specific situations where molecular methods may have an advantage over conventional laboratory testing.

TABLE 1.

### Indications for molecular resistance testing

<b>Increased risk for drug resistance</b>	<ul style="list-style-type: none"> <li>• Patients born in or who have spent significant time (e.g., more than 1 month) in countries with high prevalence of drug resistance</li> <li>• Known contact to a drug-resistant TB case (or case with features highly suspicious for drug resistance)</li> <li>• Patients not responding to the current regimen</li> <li>• Patients who were treated previously and have relapsed</li> </ul>
<b>Increased consequences of drug resistance</b>	<ul style="list-style-type: none"> <li>• Case in a congregate or other setting with large numbers of contacts (e.g., correctional facilities, healthcare facilities, schools)</li> <li>• Patients in whom unidentified drug resistance may have significant consequences because of young age (less than 5 years old) or immunocompromised status</li> <li>• Case has contacts with risks for rapid progression of TB disease and in whom effective preventive “window” treatment is needed (such as young children under age 5, or immunocompromised persons)</li> </ul>
<b>Laboratory issues</b>	<ul style="list-style-type: none"> <li>• Cultures are mixed with other bacteria (conventional DST would be delayed or not possible to perform at all)</li> <li>• AFB smear-positive but culture negative (molecular tests can provide drug-susceptibility results despite lack of growth)</li> <li>• Pathology specimens not initially sent to mycobacteriology lab</li> </ul>
<b>Program priorities</b>	<ul style="list-style-type: none"> <li>• Universal MDR-TB screening via rapid molecular testing for all NAAT- or smear-positive TB patients may be available in some jurisdictions to identify drug-resistant TB cases earlier</li> </ul>

Although there are significant advantages offered by the addition of rapid molecular assays, **growth-based susceptibility testing remains an integral diagnostic test to confirm molecular results** and to investigate susceptibility to drugs for which molecular detection of resistance is not yet possible.

# Communication with the TB laboratory

**If drug resistance is strongly suspected based on the patient's prior treatment history or exposure to drug-resistant TB, discuss concerns immediately with your TB laboratory.**

- Timely and frequent communication with the laboratory is essential.
- Some laboratories do not perform DST unless a specific and/or separate order for DST has been submitted. Clarify the process if the laboratory's protocols are not well known to you.
- If the laboratory that provides mycobacterial culture services has limited capacity for DST, the provider should arrange for the isolate to be sent to a reference laboratory immediately. Consult with the laboratory about which second-line drug DSTs are performed and which reference laboratory is being used.
- If necessary, 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. The CDC MDDR service offers molecular sequencing services for rapid detection of drug resistance, as do other reference laboratories. In some jurisdictions, molecular methods are also available locally.
- The clinician should know the name, telephone number, and contact person for each laboratory that will process and perform DST on isolates for patients with suspected drug resistance.
- The clinician should expect traditional DST results within 1-3 weeks of TB identification on culture and should contact the laboratory if reports are not received in this time period. For a list of expected turn-around times for mycobacteriology laboratory services, see **Chapter 3, Laboratory, Table 1**.

## When to order second-line drug testing

- **When resistance to RIF or more than one first-line drug** (INH, RIF, pyrazinamide [PZA], or EMB) is found, **DST should be requested for the full spectrum of second-line agents**. Amikacin, capreomycin, a fluoroquinolone (levofloxacin or moxifloxacin), and ethionamide are the minimum second-line drugs for which to test. Fewer laboratories perform testing for cycloserine, para-aminosalicylic acid, rifabutin, linezolid, clofazimine, and other agents, but these too may be important in some clinical situations.
- **When co-morbidities warrant a non-standardized regimen.**



## False-positive results

False-positive results for culture or DST may be suspected when:

- The patient's clinical manifestations do not seem to be compatible with the laboratory findings, particularly when associated with the following:
  - *M. tuberculosis* is cultured from a sample processed together with another patient's sample that is smear-positive.
  - Only one culture is positive among several specimens collected.
- Unusual drug resistance patterns are found in unrelated patients suggesting possible errors in inoculation or mislabeling of specimens.

The suspicion of a false positive result is greater when more than one of these conditions is met.

**Cross-contamination** can cause false-positive results for isolation of *M. tuberculosis* complex or detection of drug resistance. Cross-contamination occurs when aerosols produced during the processing of specimens containing *M. tuberculosis* inoculate other specimens processed on the same day or reagents used for the decontamination of specimens. **When there is a question regarding laboratory results, it is important to discuss the situation with the laboratory.**

### Other potential causes for false-positive results

- **Errors at the specimen collection site:**
  - Mislabeling of specimens or mistakes in entry of demographic data at the clinical site of collection
  - Contamination of medical devices used for collecting specimens, such as inadequate cleaning of bronchoscopy tubing
- **Errors in the laboratory:**
  - Mislabeling of specimens or media:
    - when transferring a specimen from the original container to a centrifuge tube
    - when inoculating media with specimen
    - when working up a positive culture for identification or DST
  - Malfunctioning biosafety cabinet
  - Malfunction of laboratory test systems (e.g., releasing results when controls failed)
  - Cross-contamination due to poor technique or using a common vessel to add reagents to all specimens
  - Failure to check for contamination with non-AFB microorganisms
  - Failure to check for mixed infection with NTM; if present, the NTM may be the source of the drug resistance pattern
  - Data entry errors or errors in electronic reporting

**Rapid molecular tests for drug resistance** may report RIF resistant results that are false-positive due to the presence of **silent mutations**. These are mutations identified within a gene associated with drug resistance that do not confer *in vitro* resistance. For example, rapid molecular testing with Xpert MTB/RIF may report RIF resistance for an isolate later found to be RIF sensitive by growth-based (phenotypic) DST. Further investi-

gation using DNA sequencing can help to identify the responsible mutation as a known silent mutation, and thus confirm that the molecular test result should be considered a false-positive. For more discussion on silent mutations and causes for discordant results, see **Chapter 3, Laboratory**.

**When investigating results of questionable validity**, check all possible sources of errors.

- If possible, collect another specimen or test another isolate from the same patient.
- Repeat testing from the original sample (if still available).
- Repeat DST by using another method or another laboratory.
- Request genotyping to help identify false positive culture results due to cross-contamination, such as when the strain under investigation matches the isolate from another case diagnosed in the same laboratory and there is no epidemiologic link between the two cases.
- Consult with laboratory experts. It may take a team effort, with candid communication between the healthcare provider and laboratory personnel, to find a solution.

While gathering additional information from the laboratory or waiting for repeat DST results, **decisions regarding the prescribed drug regimen should be based on patient and public health factors**. Empiric expansion of the drug regimen can be considered for patients who have not responded well to standard therapy, or who have extensive disease or risk factors for poor outcomes. When the risk of transmission is high (e.g., residence in a congregate setting), empiric expansion of the drug regimen may be considered to reduce the risk of extended isolation if the drug resistance is confirmed. On the other hand, when individual patient or public health risk is low, standard or current therapy can be continued.

## Discordant results

**Discordant test results** can occur between different laboratories.

- Although new methods are validated against the standard method, perfect agreement cannot always be achieved. Discrepancies in results due to differences in methodology, medium, and critical concentrations are inevitable.
- Some strains of *M. tuberculosis* complex have MICs that are close to the critical concentration tested. Experience over time has shown that the reproducibility for testing of these strains can be suboptimal.
- Tests at the different laboratories may not have been performed using the same specimen.
- Errors can occur during DST, including:
  - Failure to use a standardized, well homogenized inoculum
  - Failure to add a drug to the broth medium
  - Adding the wrong drug or concentration
  - Inoculation errors
  - Failure to recognize a **mixed infection** (*M. tuberculosis* complex and an NTM) which is more difficult to detect in broth systems
  - Failure to recognize **contamination with a non-AFB microorganism**, which is more difficult to recognize in broth systems

- Changes in the performance of DST or support of mycobacterial metabolism can occur when a new lot of culture media is made or received, and when a new lot of drug solutions is prepared or a new drug kit is received. Laboratories should perform proper quality control to ensure that DST performs as expected.
- If a subculture has to be made for DST, the microbiologist must take growth from various parts of a slant or a plate to assure that the organisms tested are diverse enough to be representative of the initial population.
- In the case of possible **emerging resistance**, testing different populations may result in different resistance patterns. If emerging resistance is suspected due to known risks for acquired resistance or inadequate regimen, a change in regimen may be indicated. See **Chapter 4, Treatment**.

**Discordant results may also be encountered when different methods for testing drug resistance are used.** Early results from molecular tests for drug resistance may on occasion be discordant with results reported later from the conventional growth-based (phenotypic) DST, which is currently considered the gold standard.

- In a 2014 evaluation comparing results of isolates tested through the CDC MDDR molecular service with matching results using growth-based (phenotypic) DST from public health laboratories, overall concordance for resistance was 93.9% for RIF and 90% for INH.
- Current molecular methods for detecting INH resistance test primarily for *inhA* and *katG* mutations, which identify approximately 85% of resistant strains. Testing for less common mutations is not routinely performed, and the mutations associated with resistance are unknown in 10-15% of remaining cases.
- For RIF resistance, the discordance between molecular and growth-based DST can be complex. Emerging evidence suggests that sequence-based testing may prove to be a better reference standard for determining resistance. The identification and implications of silent and disputed mutations that may be the source of test discordance are areas of continued investigation. For more details, see **Chapter 3, Laboratory**.

**What to do if discordant test results are found:**

- Assess whether results fit the clinical and epidemiological picture.
- Talk to the laboratory director and discuss reasons for conflicting results.
- Ask how the laboratory ruled out mixed infection with NTM or contamination with non-AFB microorganisms.
- If in doubt, your public health laboratory or a reference laboratory should repeat the test using the most recent isolate available.
- Discordance between rapid molecular tests and the growth-based (phenotypic) DST results should be investigated further with a sequence-based method.
- When the clinical level of suspicion for resistance is strongly at odds with the initial rapid molecular test (Xpert MTB/RIF or line-probe assay) results, confirmation using a sequence-based method is recommended.
- For more detailed discussions, see sections: ***Molecular tests for drug resistance*** and ***Difficulties interpreting results from molecular tests*** in **Chapter 3, Laboratory**.

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

# Use of strain typing

Genotyping of *M. tuberculosis* complex can be useful in:

- Detecting unrecognized outbreaks or confirming outbreaks under investigation
- Investigating or identifying false-positive results (i.e., laboratory cross-contamination)
- Distinguishing between relapse or reinfection (if a previous isolate was genotyped or is still available for genotyping)
- Documenting the progression of acquired drug-resistant TB versus reinfection with a drug-resistant strain
  - TB due to a specific strain may initially be susceptible to a panel of drugs, but with inappropriate or inadequate treatment, a sub-population of drug-resistant TB organisms will flourish. In such instances, the resistant and susceptible populations are part of the same strain and therefore, have the same genotype. However, the drug-resistant bacteria will have acquired mutations that confer drug resistance. Reinfection with a resistant strain is likely to demonstrate a different genotype.

## 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 known or high risk for drug-resistant TB
  - Are failing TB treatment
- Each TB patient should be assessed for risk of drug resistance.
- Rapid molecular testing for drug resistance should be performed when risks for drug-resistant TB are identified.
- Communication to the laboratory that drug resistance is suspected is essential for rapid susceptibility testing and optimal patient care.
- Proper control of TB transmission requires timely performance of all required laboratory tests.
- Drug-resistant TB should be confirmed by a public health laboratory or reference laboratory.
- If a patient is suspected or confirmed to have MDR/XDR-TB, consultation with an expert in TB for further management and treatment is recommended.

## Resources

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### WHO map of global MDR-TB notification.

<http://www.who.int/tb/challenges/mdr/en/>

Accessibility verified November 5, 2015.

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### The Online TST/IGRA Interpreter.

An online tool that estimates the risk of active TB for an individual with a TST reaction of  $\geq 5$ mm, based on his/her clinical profile.

<http://www.tstin3d.com>

Accessibility verified November 1, 2015.

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### The BCG World Atlas.

An interactive website providing detailed information on current and past BCG policies and practices for over 180 countries.

<http://www.bcgatlas.org>

Accessibility verified November 5, 2015.

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# Laboratory

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# The role of the laboratory is critical in the diagnosis of TB, and even more so for drug-resistant TB.

Definitive diagnosis of drug-resistant tuberculosis (TB) requires that *Mycobacterium (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, infection control, and public health management of drug-resistant TB.

**Molecular technology** is enabling much more rapid diagnosis of drug resistance. It is important to note that new technologies generate new questions, and the best way to interpret molecular resistance results is still evolving. Despite the expanding knowledge and experience with molecular methods, **conventional growth-based drug-susceptibility testing (DST) remains the gold standard.** However, growth-based DST is complex and various methods are used. Discrepant results may be generated due to differences in methodology, critical concentrations, and inoculum preparation and render the interpretation of growth-based DST results very challenging. These challenging laboratory results can have significant implications for treatment and often necessitate expert consultation.

## General information on TB laboratory work

Several types of laboratories perform diagnostic mycobacteriology testing, including hospital-based laboratories, local and state public health laboratories, and commercial laboratories. Laboratories may choose to provide different levels of services and different methods for the services they offer. Refer to **Table 1** for a list of mycobacteriology laboratory services. Services and protocols may vary based on the setting where the specimen is collected (e.g., outpatient vs. hospital), type of specimen (e.g., sputum vs. cerebrospinal fluid [CSF]), and third-party payer source. A single specimen can pass through several different laboratories in order to complete testing.

Case managers and treating physicians should have an understanding of the laboratory practices of the facilities processing their patients' specimens.

TABLE 1.

**Mycobacteriology laboratory services**

<b>Test</b>	<b>Expected turnaround time (from specimen receipt at laboratory)</b>	<b>Comments</b>
<b>AFB smear</b>	1 day	Fluorochrome staining is more sensitive than carbol-fuchsin acid fast staining (Ziehl-Neelsen or Kinyoun methods).
<b>Nucleic acid amplification testing (NAAT)</b> For identification of <i>M. tb</i> complex	1-2 days	Commercial, FDA-cleared tests and laboratory developed tests available. Excellent sensitivity and specificity for testing smear-positive sediments. Testing smear-negative sediments usually has reduced sensitivity and specificity.
<b>Molecular detection of drug resistance</b> (may also include identification of <i>M. tb</i> complex)	1-3 days	Becoming more widely available, particularly for rifampin testing. See Table 5 for more information. New technologies are emerging.
<b>Mycobacterial culture and identification</b>	Positive cultures: average of 2-3 weeks incubation. Smear-negative specimens may take >4 weeks to turn positive. 6-8 weeks to report negative.	When a culture takes 5-6 weeks to turn positive, consider investigation for possible cross-contamination.
<b>Identification of positive cultures</b>	1 day to 1 week for identification of <i>M. tb</i> complex, MAC, <i>M. kansasii</i> , and <i>M. goodii</i> by DNA probes. Identification of other non-TB mycobacteria may take days or months depending on method used.	Laboratories may batch tests; testing time by DNA probes or MALDI-TOF is less than 2 hours.
<b>Growth-based DST</b>	Liquid broth systems: 1-2 weeks after setting up DST. (4 weeks or longer from specimen receipt at laboratory.) Solid media (agar proportion method): 3-4 weeks.	DST cannot be performed on mixed or contaminated cultures. Laboratories usually perform DST in batches.
<b>Genotyping</b>	MIRU: 2 weeks Spoligotype: 1 month	MIRU is performed at the Michigan TB laboratory. Spoligotyping is performed at CDC. Expedited genotyping may be requested for investigation of outbreaks or cross-contamination.
<b>Interferon gamma release assays (IGRA)</b>	1-2 days (longer if batched)	Usually performed by clinical laboratory (not mycobacteriology laboratory).

## Communication between clinician and laboratory

The optimal laboratory diagnosis of TB begins with a close relationship and open dialogue between the healthcare provider, TB control, and the TB laboratory.

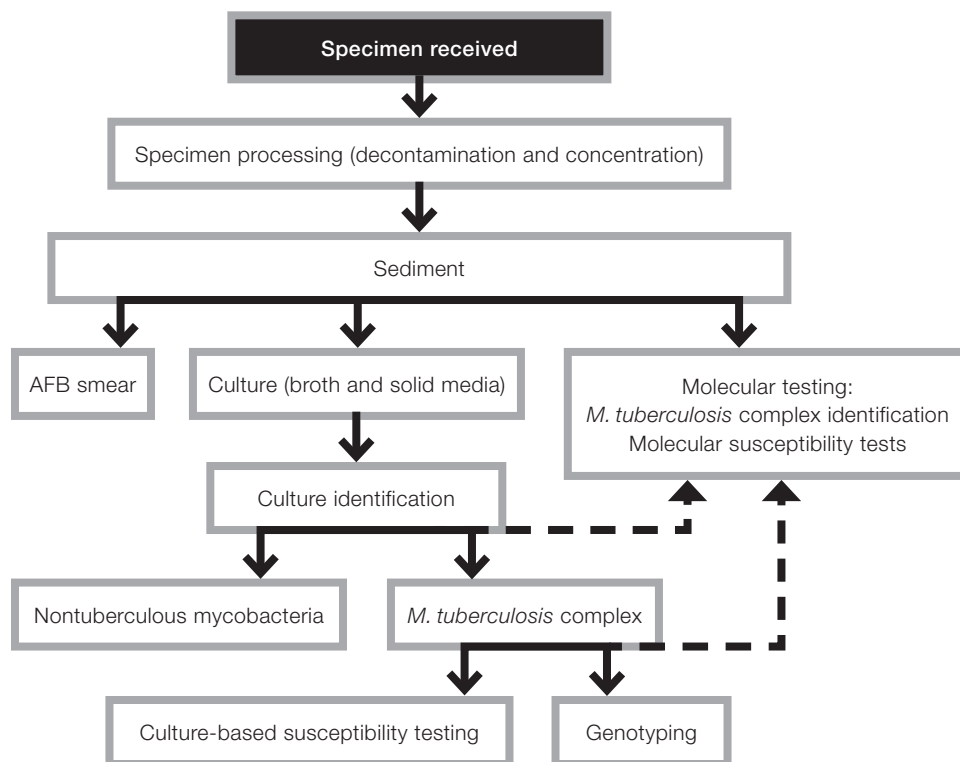
Include the following information with the laboratory request in order to maximize the laboratory's contribution:

- **Diagnostic versus follow-up specimen**
- **Date when anti-TB treatment was started and drug regimen**
- **Is drug resistance suspected?**

The laboratory should inform submitting providers about test availability and requirements for optimum testing, such as sample volume requirements, transit conditions, and test performance and limitations. Such information promotes proper utilization of the test by clinicians, and laboratories benefit from having optimal samples to test for better testing outcomes. As laboratory technologies advance, laboratories may need to inform clinicians about new tests that are available for implementation. As clinical practices evolve, clinicians may need to inform laboratories about tests that are no longer necessary to perform and about tests they hope laboratories can offer. Additionally, clinicians and laboratories may wish to work together on diagnostic algorithms. One example is the use of nucleic acid amplification tests (NAAT) for rapid identification of *M. tuberculosis* complex and molecular testing for drug resistance. Such communications can optimize scarce resources and maximize the laboratory's contribution to patient care.

FIGURE 1.

### Mycobacteriology laboratory workflow



## How should specimens be collected for smear and culture?

### FOR ALL SPECIMENS:

- Contact your laboratory for specific instructions
- Collect into sterile container
- Do not use preservatives
- Follow proper collection procedures and obtain an adequate volume to enhance recovery of organisms
- Process within 24 hours if possible
- Keep refrigerated until processed to reduce overgrowth of other microorganisms, especially for non-sterile specimens

### RESPIRATORY SPECIMENS:

**Preferably three specimens collected at least 8 hours apart and at least one of which is an early morning expectorated specimen or induced (some programs prefer all specimens to be induced)**

- **Note:** Centers for Disease Control and Prevention (CDC) and World Health Organization (WHO) guidelines differ; internationally, two specimens are recommended. Incremental benefit of the third specimen is relatively small and may be even less if NAAT is used.

#### Expectorated sputum

- Preferably early morning (before brushing teeth), consider rinsing mouth with sterile or bottled water to reduce risk of contamination with non-tuberculous mycobacteria.
- Volume of 5-10mL ideal; should be >2mL.

#### Sputum induced with nebulized hypertonic (3-10%) saline

- Note on the requisition form and label specimen as induced because these are more likely to be watery in appearance and could be mistakenly considered unacceptable by the laboratory.

#### Bronchoscopy: lavage, brushings, biopsies

- Induced sputum have equivalent or better yield for diagnosis compared to bronchoscopy specimens.
- Bronchoscopy can target specific areas of the lung.
- Can obtain specimens from persons unable to produce sputum specimen by other methods.
- Post-bronchoscopy sputum collection may have higher yield than sputum collected at other times.

**Gastric aspirate** (for more information on how to perform gastric aspirate, see **Chapter 6, Pediatrics**)

- Used for diagnosing pulmonary TB in young children.
- Yield highest in the youngest children.
- Early morning collection after nothing by mouth (NPO) overnight.
- Mycobacteria die rapidly in gastric lavage fluid, which needs to be neutralized with sodium carbonate to pH of 7.0, especially if specimen will not be processed immediately.
  - Add 100 mg of sodium carbonate to 5-10 mL specimen.

### EXTRAPULMONARY SPECIMENS:

#### Urine

- Collect 3-5 early morning midstream specimens (not a 24-hour urine collection).
- 10-40 mL specimens.
- Do not pool specimens or use preservatives.

#### Stool

- Not routinely performed, contact your laboratory if needed.
- Recovery of acid-fast bacilli (AFB) is not high due to overgrowth of other bacteria.
- Collect at least 1 gram.
- No transport media needed.
- Refrigerate if transport time >1 hour; do not freeze.

#### Pleural fluid, peritoneal fluid, pericardial fluid, joint aspirate

- At least 10 mL specimen preferable.
- No swabs.
- Bloody specimens can be put in sodium polyanethol sulfonate (SPS) yellow-top tube.

#### Blood

- Collect in patients with suspected mycobacteremia (e.g., sepsis, immunocompromised).
- Special blood culture media for AFB are commercially available.
- If blood has to be transported before inoculation of the SPS, heparin or citrate may be used as anticoagulant.
- Blood collected in EDTA or in conventional blood culture bottles and coagulated blood are not acceptable.

#### Cerebrospinal fluid

- Minimum of 2-3mL, but 5-10mL preferable.

#### Tissue biopsy

- Any tissue specimen, not formalin-fixed, can be cultured for mycobacteria.
- Placement in formalin or other fixative eliminates ability to culture and perform growth-based DST. (Occasionally it is possible to extract nucleic acid from formalin-fixed specimens for molecular testing but this requires specialized methods and is only available in select laboratories—see section: **Molecular methods on fixed specimens**.) Careful communication with operating room staff will increase the likelihood that a specimen will be submitted in a sterile cup without formalin.

Adapted from: *A Clinician's Guide to the TB Laboratory*, Heartland National Tuberculosis Center.



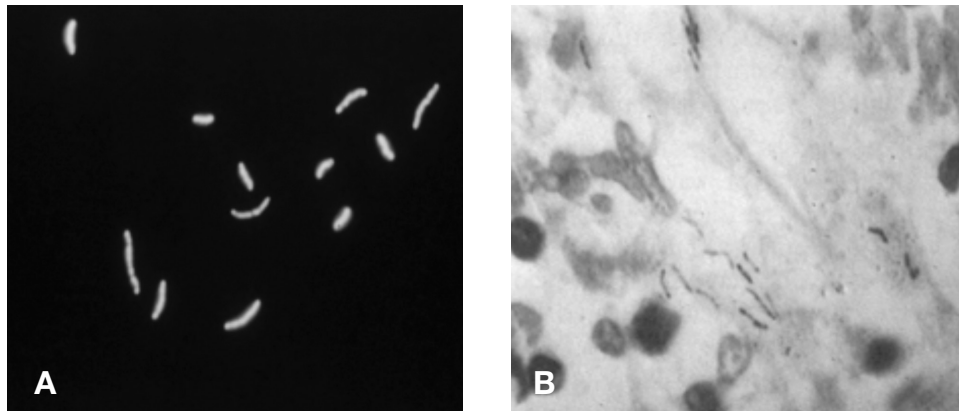
# Microscopy, culture identification, and growth-based testing

## AFB smear

CDC recommends using fluorochrome staining methods for acid-fast bacilli (AFB) smear microscopy. It is more sensitive than the Ziehl-Neelsen staining method. Stains are typically done on concentrated specimens digested and decontaminated with N-acetyl-L-cysteine-sodium hydroxide (NALC-NaOH). AFB smear results should be reported within 24 hours of receipt of specimens. Varied semi-quantitative reporting systems are in use: Rare, few, moderate, numerous; 1+ to 3+ (WHO); and 1+ to 4+ (CDC). It is estimated that the detection limit for smear positivity is 5,000 to 10,000 AFB per mL of sputum. AFB smear is not *M. tuberculosis* complex -specific; nontuberculous mycobacteria (NTM) are stained positive as well. *Nocardia*, *Rhodococcus*, *Legionella*, *Cryptosporidium*, *Isospora*, *Cyclospora*, *Actinomyces* and *Microsporidia* may also show various degrees of acid-fastness.

Figure 2 presents photographs containing the typical appearance of AFB in microscopic examinations.

FIGURE 2.



**A:** Fluorochrome (auramine-rhodamine) stained AFB are seen as golden-orange rods when viewed under a fluorescent microscope.

Source: California Department of Public Health Microbial Diseases Laboratory

**B:** Carbol-fuchsin stained (Ziehl-Neelsen method) AFB are seen as red rods when viewed under a light microscope.

Source: Centers for Disease Control and Prevention

## Culture identification

Once AFB are grown in culture, culture identification is often done by DNA probes. Accu-Probe (Hologic [previously Gen-Probe, Inc], San Diego, CA) Mycobacterial Culture Identification kits are the most commonly used commercial kits and they can identify *M. tuberculosis* complex, as well as some NTM including *M. avium* complex (MAC), *M. kansasii* and *M. goodii*. Species other than these can be identified by MALDI-TOF (Matrix Assisted Laser Desorption Ionization Time-of-Flight), high performance liquid chromatography (HPLC), DNA sequencing, or laboratory developed PCR assays. Additional studies



using growth rates, pigmentation and selected biochemical tests may assist further identification.

**If a mixed culture (*M. tuberculosis* complex and NTM) is suspected**, rapid identification of *M. tuberculosis* complex and detection of drug resistance by molecular methods should be pursued. If *M. tuberculosis* complex is identified, a pure culture should be obtained for growth-based DST (see **Confirmation of results** section).

In the United States, 99% of isolates identified as *M. tuberculosis* complex are *M. tuberculosis*. Because *M. bovis* including BCG is naturally pyrazinamide- (PZA-) resistant, speciation within *M. tuberculosis* complex can be important particularly in regions where the prevalence of *M. bovis* is high or when mono-PZA-resistance is detected.

## Conventional growth-based drug susceptibility testing (DST)

Conventional growth-based DST is also referred to as phenotypic, conventional, or culture-based drug susceptibility testing. Unlike molecular resistance testing, a pure culture must be obtained before setting up growth-based DST.

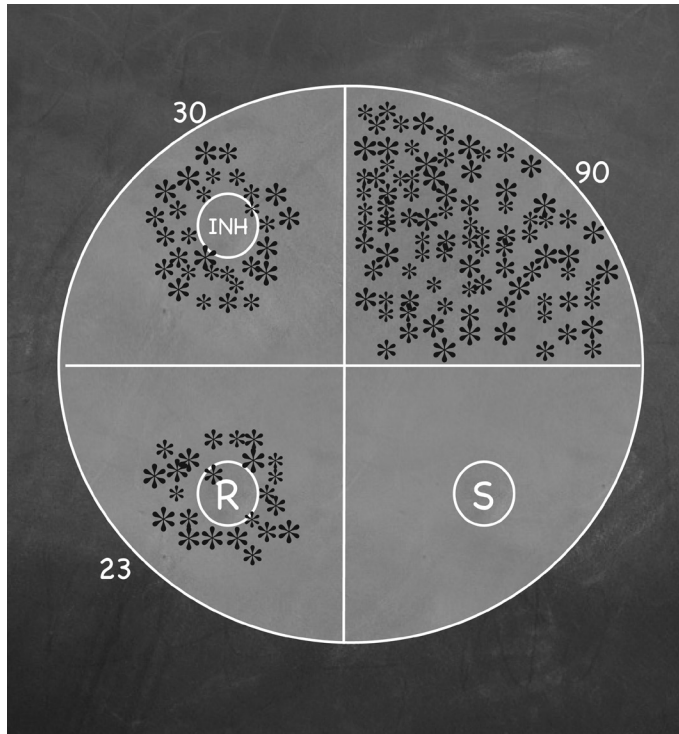
Many methods for performing growth-based DST have been developed and are in use. In general these methods have good concordance. However, in the course of managing drug-resistant TB cases, clinicians are likely to encounter growth-based DST results from multiple methods and laboratories. Various DST methods are validated to yield “equivalent” results, but discordant results may occur and they are challenging to interpret. The two most common methods used in the United States are performed in solid media by the agar proportion method or liquid broth systems. They are outlined below, along with features of each test that are important for clinicians to know.

### Solid media—agar proportion method

- The agar proportion method using Middlebrook 7H10 or 7H11 agar is the reference standard for DST in the United States.
- A standardized cell suspension is prepared from a pure isolate and inoculated onto each quadrant of an agar plate. Each quadrant contains a specific drug at its critical concentration or no drug as a control. Plates are incubated for 21 days before colony counts are taken.
- The isolate is considered resistant if the number of colonies in the drug quadrant is equal to or more than 1% of that in the control quadrant. An example of determining the results using the agar-proportion method is demonstrated in Figure 3.
- PZA is difficult to study using solid medium due to the requirements of testing at an acidic pH, causing many isolates to fail to grow. PZA growth-based DST typically is performed using liquid media.
- The critical concentrations used with 7H10 and 7H11 may be different.
- The Lowenstein-Jensen (LJ) proportion method is not used in the United States because it is more prone to contamination, but it is inexpensive and frequently used in low-resource settings.

Indirect DST refers to testing on positive culture growth, while direct DST is done on AFB smear-positive sediments. The direct DST has an advantage of more rapid results, but it may be more likely to become contaminated, and yield uninterpretable results.

FIGURE 3.

**Agar proportion method for drug-susceptibility testing.**

Quadrant plate—Inoculum of *M. tuberculosis* growth from liquid media has been inoculated 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.*

**Liquid media**

MGIT 960 (Becton Dickinson, Sparks, MD)

- MGIT 960 is a modified proportion method and the most frequently used method in the United States.
- Food and Drug Administration (FDA) approved for testing first-line drugs (rifampin [RIF], isoniazid [INH], ethambutol [EMB], PZA) and streptomycin [SM].
- Results are available in about 1 week (4-14 days) after the test is set up.

- Second-line drugs can also be tested with result accuracy comparable to that of the agar proportion method with the exception of cycloserine (CS).
- The method is based on the fluorescence produced from reduced oxygen in the MGIT medium due to microbial growth. The fluorescence generated is then converted to “growth units” (GU). In general, more GU indicates more growth.
- When the growth control generates GU to 400 within 4-14 days, the DST is valid for interpretation. If a drug-containing MGIT tube yields GU < 100, the organism is interpreted as being susceptible; if GU is  $\geq 100$ , the organism is considered resistant.

VersaTREK (Trek Diagnostics System, Thermo Fisher Scientific, Oakwood Village, OH)

- FDA approved for testing first-line drugs (RIF, INH, EMB, PZA).
- Results are available in about 1 week after test set-up (3-13 days). Resistant results may be reported faster (minimum of 3 days) than susceptible results (minimum of 6 days).
- The method is based on detection of pressure changes (oxygen consumption due to microbial growth) within the headspace above the broth medium in a sealed bottle.

Sensititre (Trek Diagnostics System, Thermo Fisher Scientific, Oakwood Village, OH)

- The method uses a 96-well microbroth dilution plate to test both first- and second-line drugs, but it does not include PZA or capreomycin (CM). It provides MIC results for each of the 12 drugs tested (see **Table 2**).
- Test must be set up from colonies obtained from solid media, which may delay DST set-up due to slower growth on solid media. Results are available within 10-21 days after the test is set up.
- *M. tuberculosis* complex has been traditionally tested using a single critical concentration of a drug. The usefulness of MIC results for clinical management of TB patients requires further investigation. See section: **MIC—when to order and how to interpret.**

MODS (microscopic observation drug susceptibility) assay (Hardy Diagnostics, Santa Maria, CA)

- The MODS assay is considered a rapid growth-based (7H9 broth) test for detection of *M. tuberculosis* complex and drug resistance to INH and RIF on NALC-NaOH processed sputum specimens.
- The median turnaround time is 7 days. Valid reports may be generated between 5-21 days after inoculation of drug plates (24-well format).
- The test is based on visualization of the cording morphology of *M. tuberculosis* complex in liquid medium which is recognizable using an inverted microscope.

## Confirmation of results

When growth-based DST results are available, drug-resistant results must be verified to rule out contamination with other non-AFB bacteria or mixed culture with NTM; this is especially important when liquid media is used.

- For drug-resistant results obtained by a liquid system, a contaminated drug-containing tube is likely to show homogeneous turbidity. Examining a smear made from the drug-containing tube or bottle should demonstrate presence of AFB with morphology compatible with *M. tuberculosis* complex and absence of non-AFB bacteria

or NTM. Sub-culturing from DST media onto a 7H10 plate and observing microscopic colonial morphology in a few days can be helpful in ruling out the presence of NTM.

- Performing growth-based DST from a pure culture evidenced by no growth on non-selective media (e.g., blood agar plate) is not sufficient to rule out contamination, which may be introduced when DST is being set up.
- If the original culture is not pure, use of molecular methods to detect drug resistance mutations is recommended.
- When the patient does not have risk factors for drug resistance, the treating physician should communicate with the public health program and the laboratory to confirm resistance results, ensure that the risk of contamination or a mixed culture has been ruled out, and to discuss any other sources of a possibly erroneous result.

#### Clinical scenario:

A U.S.-born patient with a first episode of culture-positive TB is reported to have resistance to INH, RIF, and PZA. The physician is surprised by this result and confirms lack of risk factors for drug resistance. The patient has clinically improved after 4 weeks of first-line TB treatment. The physician calls the laboratory to confirm the results. A smear of the growth from the drug-containing MGIT reveals mixed morphology. Molecular testing shows *M. tuberculosis* complex but no mutations indicating drug resistance. Further testing indicates presence of NTM and *M. tuberculosis* complex in the DST cultures. The patient continues to do well on first-line TB treatment.

#### Reliability of growth-based DST results

- Reliability of growth-based DST by drug
  - Reliable: INH, RIF, fluoroquinolones, amikacin (AK), CM, kanamycin (KM)
  - Less reliable or no data: EMB (more often tests susceptible by MGIT 960 compared to agar proportion), PZA (more often falsely resistant), SM, oral second-line drugs, third-line drugs
  - Critical concentrations of third-line drugs and certain second-line drugs have not been fully established

# Critical concentration, minimum inhibitory concentration (MIC), and what they mean

## Critical concentrations

Drug-susceptibility testing in the mycobacteriology laboratory is usually performed using a single drug concentration—the **critical concentration**, which provides categorical interpretation (susceptible or resistant).

- The **critical concentration** is the level of drug that inhibits 95% of wild-type TB strains that have not been exposed to the drug, but does not appreciably suppress the growth of strains that are resistant to the drug (based on clinical treatment failure).

A **critical concentration is not a minimum inhibitory concentration** (MIC); however, the MIC of microorganisms susceptible at a critical concentration should have an MIC < critical concentration and those resistant should have MIC > critical concentration. See section: **MIC—when to order and how to interpret**.

- The critical concentration used for an individual drug may differ based on the method of growth-based DST (see Table 2). Although critical concentrations are chosen to provide equivalent results across methods, it is difficult to achieve 100% equivalency and some discordance may be seen.
- Discordance can also be encountered within the same method, especially when the MIC of a strain is close to the critical concentration. The reproducibility of testing in these strains tends to be poor.
- High and low level resistance
  - Some drugs, such as INH, are routinely tested at more than one concentration. Some experts use these results to select a higher dose of the drug when it tests resistant at the lower concentration and susceptible at the higher concentration. The higher dose may achieve *in vivo* concentrations sufficiently high to overcome resistance at the lower concentration.
- **Table 2** shows the critical concentrations for commonly-used methods for growth-based DST. It also shows the normal peak concentration in serum for standard doses of anti-mycobacterial drugs. The clinical relevance of the relationship between *in vitro* susceptibility at a given critical concentration and the normal peak concentration can involve complex pharmacodynamics including the mechanism of action of the drug, the penetration of drug to the site of infection, whether mycobacteria are in an active or dormant state, and the patient's metabolism of the drug.

TABLE 2.

### Critical concentrations of antimycobacterial agents by broth systems or agar proportion methods

Drug	Normal peak concentration in serum with standard doses* (mcg/mL)	MGIT 960 low/high	VersaTREK low/high	Agar 7H10 low/high	Agar 7H11 low/high	Sensititre (range of concentrations tested)
<b>First-line drugs</b>						
• Isoniazid	3-6	0.1 / 0.4	0.1 / 0.4	0.2 / 1	0.2 / 1	0.03-4
• Rifampin	8-24	1	1	1	1	0.12-16
• Pyrazinamide	20-60	100	300	NR	NR	NA
• Ethambutol	2-6	5	5 / 8	5 / 10	7.5	0.5-32
<b>Injectable agents</b>						
• Streptomycin	35-45	1 / 4	NA	2 / 10	2 / 10	0.25-32
• Capreomycin	35-45	2.5 or 3	NA	10	10	NA
• Amikacin	35-45	1 or 1.5	NA	4	NA	0.12-16
• Kanamycin	35-45	2.5	NA	5	6	0.6-8
<b>Fluoroquinolones</b>						
• Levofloxacin	8-12	1.5	NA	1	NA	NA
• Moxifloxacin	3-5	0.25	NA	0.5	0.5	0.06-8
• Ofloxacin		2	NA	2	2	0.25-32
<b>Second-line oral agents</b>						
• Cycloserine	20-35	NR	NR		60**	2-256
• Ethionamide	1-5	5	NA	5	10	0.3-40
• Para-aminosalicylate	20-60	NA	NA	2	8	0.5-64
<b>Other agents</b>						
• Rifabutin	0.3-0.9	0.5	NA	0.5	0.5	0.12-16
• Linezolid	12-26	1	NA	NA	NA	NA
• Clofazimine	0.5-2.0	NA	NA	NA	0.25**	NA
• Bedaquiline***		NA	NA	0.008-2	0.008-2	NA

\* Serum drug concentrations are provided in this table for comparison with the critical concentration. This information is not a substitute for therapeutic drug monitoring.

\*\* Source: Personal communication with National Jewish Health.

\*\*\* Bedaquiline MIC testing available at CDC.

NR: not recommended. NA: not available. MGIT is a trademark of Becton, Dickinson and Company. VersaTREK and Sensititre are trademarks of TREK Diagnostic Systems.

## MIC—when to order and how to interpret

Minimum inhibitory concentration (MIC) testing differs from testing using a critical concentration in that the organism is tested at a series of drug concentrations, usually a series of two-fold dilutions, and the result is the lowest concentration that inhibits growth of the bacteria. Although in most cases testing using the critical concentration is sufficient, there are situations described below with certain drugs where MIC can be helpful in guiding management of difficult cases. However, no categorical interpretations (susceptible or resistant) for MIC results for *M. tuberculosis* complex have been recommended by the Clinical and Laboratory Standards Institute (CLSI).

Situations when MICs may be useful for clinical management:

- **Resistance to fluoroquinolone**

When fluoroquinolone resistance is found by critical concentration or by molecular testing, an MIC—usually for MFX—can help inform whether an increase in dose may benefit the patient. Although there is minimal published evidence to support this approach, **some MDR-TB experts use “high-dose” MFX at 600mg or 800mg daily for patients with MFX MIC of 1 or 2 mcg/mL.**

- **Resistance to injectables**

In cases with extensive resistance, obtaining an MIC to an injectable medication to which there is resistance at the critical concentration may help determine whether an increased dose is likely to benefit the patient. **High peak levels can be achieved with high intermittent dosing (e.g. 25 mg/kg 2-3x per week) and some MDR-TB experts would use this dosing regimen if it could achieve a peak that is 5–8 times higher than the MIC.**

- **Bedaquiline (BDQ)**

BDQ is tested by determining an MIC. Testing is available at CDC through submission of isolates to state public health laboratories.

### Clinical scenario:

A patient with presumed MDR-TB is being treated with an empiric MDR-TB regimen of PZA, AK, moxifloxacin (MFX), CS, and ethionamide (ETA). The patient’s isolate subsequently tests resistant to INH, RIF, EMB, and MFX at standard critical concentrations for these drugs. MFX is increased to 600mg daily and MIC testing for MFX is requested to determine whether MFX should be continued at this higher dose or should be discontinued. The MIC for MFX returns as 1.0 mcg/mL (within the range that some experts would use high-dose MFX). MFX is continued at 600mg.



# Molecular methods for detection of *M. tuberculosis* complex DNA and drug resistance mutations

Molecular assays able to be performed directly on clinical specimens without the requirement for growth in culture have significantly shortened turnaround time for detection of *M. tuberculosis* complex and drug resistance. These tests are **recommended by CDC for routine use in patients for whom a diagnosis of TB is being considered**. Use of these tests can dramatically shorten time to diagnosis of TB and MDR-TB from weeks to hours.

It is important for clinicians who are interpreting molecular tests of drug resistance to know the advantages and limitations of the tests. There are **two major types of molecular tests described below: sequencing and nonsequencing (or probe-based) tests**. The chief distinction is that probe-based tests can only determine that there is a mutation present in the gene; they generally cannot identify specific mutations (for some exceptions, see section: ***Line-probe assay***). In contrast, tests that employ sequencing do identify specific mutations and results of these tests reveal more information and can be more predictive of drug resistance. For this reason, in the United States **CDC and the Association of Public Health Laboratories (APHL) recommend confirming a resistant result from a nonspecific probe-based test with a sequencing test**.

Indication for use of molecular assays for drug resistance is found in **Chapter 2, *Diagnosis***.

## Molecular detection of *M. tuberculosis* complex

The amplified *M. tuberculosis* direct test (MTD; Hologic [formerly Gen-Probe], San Diego, CA) was the first molecular assay approved by FDA (1995) for testing concentrated specimens to identify *M. tuberculosis* complex. It is still available in some laboratories and can be used for testing smear-positive and smear-negative specimens. However, it cannot identify drug resistance. Its sensitivity and specificity for smear-positive specimens are 96.9% and 100% respectively, and those for smear-negative specimens are 72% and 99.3% respectively.

**GeneXpert MTB/RIF assay** was the second assay approved by FDA (2013) for testing raw or concentrated sputum specimens, either smear-positive or smear-negative, to detect *M. tuberculosis*. The assay detects *M. tuberculosis* complex and resistance to RIF by real-time PCR with five molecular beacon probes (A-E) that cover the RIF-resistance determining region of *rpoB*. The assay does not have a specific probe for *M. tuberculosis* identification; rather, the detection of *M. tuberculosis* is based on the fluorescent signal production from at least two of the five probes. Recent data from the United States reported in the *MMWR* (2/27/15) shows sensitivity for detection of *M. tuberculosis* complex on smear-positive specimens by a single Xpert MTB/RIF Assay is approximately 97%, and that for testing smear-negative specimens is 55%.

For more information regarding Xpert MTB/RIF assay for identifying drug resistance, see section: ***Molecular Tests for Drug Resistance***.

**Non-FDA-approved methods.** There are laboratory developed tests for detection of *M. tuberculosis* complex by real-time PCR performed at commercial laboratories or public health laboratories. Clinicians may request laboratories to provide the performance data for assessing the results from those tests.

## Genes associated with drug resistance

Table 3 provides a summary of genes associated with drug resistance and the predominant mutations found in clinical isolates.

- Although major genes associated with drug resistance have been identified, the understanding of drug resistance at the genetic level remains variable and incomplete. Therefore, 100% sensitivity for detecting all drug resistance is not currently achievable.
- Furthermore, there are mutations that do not confer *in vitro* resistance or are associated with unpredictable susceptibility by growth-based methods. Specificity for resistance detection by molecular methods for certain drugs is not 100% (using growth-based testing as the gold standard).

TABLE 3.

### Genes and mutations associated with drug resistance in *M. tuberculosis*

Antimicrobial agent	Gene	Sensitivity	Specificity	Selected mutations* and comments	
Isoniazid (INH)	<i>katG</i>	86.0	99.1	315Thr(ACC)	Most frequent mutation, associated with high-level INH resistance. Some other mutations in codon 315: Thr(ACA), Asn(AAC), Ile(ATC), Thr(ACT), Gly(GGC)
	<i>inhA</i> promoter			-15T	Often associated with low-level INH resistance and ethionamide (ETA) resistance. Some other mutations: -8C, -8A, -8G, -9T, -16G, -17T
	<i>fabG1</i>			203 Leu(CTA)	Acts with its adjacent region as a promoter to upregulate the expression of <i>inhA</i> .
	<i>ahpC</i> promoter	4.5	100	-54A	Associated with INH resistance. Some other mutations: -48T, -51T, -52A, -52T
Rifampin (RIF)	<i>rpoB</i>	97.1	97.4	531 Leu(TTG)	Most frequent mutation seen with MDR TB. Associated with RIF and RFB resistance. Detectable by HAIN, mutation identified Detectable by Probe E of Xpert MTB/RIF, mutation <b>not identified</b> **
				526Tyr(TAC) 526 Asp(GAC)	Associated with RIF and RFB resistance. Detectable by HAIN, mutation identified Detectable by Probe D of Xpert MTB/RIF, mutation <b>not identified</b> **
				516 Val(GTC)	Often associated with RIF resistance but retains RFB susceptibility Detectable by HAIN, mutation identified Detectable by Probe B of Xpert MTB/RIF, mutation <b>not identified</b> **
				Silent mutation: 514 Phe(TTT)	Most frequent silent mutation. Not associated with RIF resistance Detectable by HAIN, missing WT3, mutation <b>not identified</b> ** Detectable by Probe B of Xpert MTB/RIF, mutation <b>not identified</b> ** Incorrectly reported as “RIF resistance detected”
				“Disputed” mutations***	511 Pro(CCG), 516 Tyr(TAC), 526 Asn(AAC), 526 Leu(CTC), 526 Ser(AGC), 533 Pro(CCG), 572 Phe(TTC)
Ethambutol (EMB)	<i>embB</i>	78.8	94.3	306Val(GTG)	Most frequent mutation associated with EMB resistance. Detectable by HAIN, mutation identified. Some other mutations in codon 306: Leu(CTG), Ile(ATA), Thr(ACG), Ile(ATT), Ile(ATC), Leu(TTG). Not all mutations in <i>embB</i> are associated with EMB resistance.

#### Table footnotes:

\* See Figure 4 for information on understanding reporting of mutations.

\*\* Identified or not identified refers to whether the assay will include the specific mutation in the reported result. For more information, see section: **Probe-based tests**.

\*\*\* “Disputed” mutations are mutations in the *rpoB* gene that are associated with variable susceptibility results in growth-based assays but have been reported in the literature to have clinical significance. MIC testing may be warranted. For further explanation, see section: **Difficulties interpreting results of molecular tests**.

Antimicrobial agent	Gene	Sensitivity	Specificity	Selected mutations* and comments	
<b>Pyrazinamide (PZA)</b>	<i>pncA</i>	86.0	95.9	No predominant mutations	Widely distributed throughout the gene and the promoter. Not all mutations are associated with PZA resistance.
Fluoroquinolones <b>Moxifloxacin (MXF)</b> <b>Levofloxacin (LFX)</b> <b>Oflxacin (OFLX)</b>	<i>gyrA</i>	79.0	99.6	94 Gly(GGC)	Most frequent mutation, usually MFX MIC > 1. MFX may still contribute to therapy, if MIC ≤ 2 µg/mL; may need to increase MFX dosage.  Detectable by HAIN, mutation identified  Some other mutations in codon 94: Tyr(TAC), His(CAC), GCC(Ala), AAC(Asn)  Some other mutations: 91 Pro(CCG); 88 Ala(GCC), 88 Cys(TGC)
				90 Val(GTG)	A frequent mutation. Usually MFX MIC ≤ 1. MFX may still contribute to therapy.  Detectable by HAIN, mutation identified
<b>Amikacin (AK)</b>	<i>rrs</i>	90.9	98.4	1401G	Most common mutation; associated with AK-resistance. Detectable by HAIN, mutation identified
				1402T	Usually <b>not</b> associated with AK-resistance.
				1484T	Associated with AK-resistance Detectable by HAIN, mutation identified
<b>Capreomycin (CM)</b>	<i>rrs</i>	55.2	91.0	1401G	Most common mutation; usually associated with CM-resistance. Detectable by HAIN, mutation identified
				1402T	Associated with CM-resistance.
				1484T	Associated with CM-resistance. Detectable by HAIN, mutation identified
	<i>tlyA</i>			No predominant mutations  Mutations are widely distributed throughout the gene. Some mutations are highly associated with CM resistance: GGG196GAG, GC insertion at nucleotide 202, GT insertion at nucleotide 755	
<b>Kanamycin (KM)</b>	<i>rrs</i>	86.7	99.6	1401G	Most common mutation; associated with KM resistance. Detectable by HAIN, mutation identified
				1402T	Associated with KM-resistance.
				1484T	Associated with KM-resistance. Detectable by HAIN, mutation identified
	<i>eis</i> promoter			-10A  Highly associated with KM-resistance. Some other mutations: -14T, -37T	
<b>Bedaquiline (BDQ)</b>	<i>atpE</i>				Mutations in C ring of the ATP synthase may be associated with BDQ resistance. Only observed in laboratory-induced resistant strains thus far.

Table adapted with modification from: Lin SY, Desmond EP. Molecular diagnosis of tuberculosis and drug resistance. *Clin Lab Med.* 2014;34(2):297-314. Sensitivity and specificity data from: <http://www.cdc.gov/tb/topic/Laboratory/MDDRUUsersGuide.pdf> and Lin, et al. Pyrosequencing for rapid detection of extensively drug-resistant Mycobacterium tuberculosis in clinical isolates and clinical specimens. *J Clin Microbiol.* 2014;52(2):475-482.

## Molecular tests for drug resistance

There are several types of molecular tests for drug resistance. These tests have varying methods, advantages, and availability. See Table 4 for comparison of current molecular tests and more detail in the text that follows.

TABLE 4.

### Current molecular methods for detection of drug resistance in *M. tuberculosis*

	<b>Cepheid Xpert MTB/RIF</b>	<b>HAIN MTBDR<sub>plus</sub> &amp; MTBDR<sub>sl</sub></b>	<b>Pyrosequencing<sup>a</sup></b> (Laboratory-developed, non-commercial tests)	<b>Sanger sequencing<sup>a</sup></b> (Laboratory-developed, non-commercial tests)
<b>Methodology</b>	Real-time PCR Molecular beacon probes	PCR Line probes	PCR Pyrosequencing	PCR Sanger sequencing
<b>Specimen types</b>	<ul style="list-style-type: none"> <li>Clinical specimen</li> <li>Concentrated specimen<sup>b</sup></li> </ul>	<ul style="list-style-type: none"> <li>Concentrated specimen<sup>b</sup></li> <li>Culture</li> </ul>	<ul style="list-style-type: none"> <li>Concentrated specimen<sup>b</sup></li> <li>Culture</li> </ul>	<ul style="list-style-type: none"> <li>Concentrated specimen<sup>b</sup></li> <li>Culture</li> </ul>
<b>Testing time</b>	2.5 h	6-7 h	5-6 h	1-2 days
<b>Drugs tested</b>	RIF	INH, RIF (MDRTB <sub>plus</sub> ) EMB, FQ, AK, CM, KM (MTBDR <sub>sl</sub> )	INH, RIF, EMB, FQ, AK, CM, KM Other drugs possible	INH, RIF, EMB, FQ, AK, CM, KM, PZA Other drugs possible
<b>Results</b>	<ul style="list-style-type: none"> <li>Mutation detected or not detected</li> <li>No sequences provided</li> </ul>	<ul style="list-style-type: none"> <li>Mutation detected or not detected</li> <li>Sequences of a few frequent mutations are provided</li> </ul>	Sequences provided	Sequences provided
<b>Methodology limitations</b>	<ul style="list-style-type: none"> <li>Difficult to detect mixed susceptible and resistant population</li> <li>Silent mutations and mutations not conferring resistance lead to false resistance interpretation</li> </ul>	<ul style="list-style-type: none"> <li>Difficult to detect mixed susceptible and resistant population</li> <li>Silent mutations and mutations not conferring resistance lead to false resistance interpretation</li> </ul>	<ul style="list-style-type: none"> <li>Mixed population can be detected, but the sensitivity has not been well characterized</li> <li>Not suitable for detecting mutations spread throughout a gene (e.g., <i>pncA</i>)</li> </ul>	<ul style="list-style-type: none"> <li>Mixed population can be detected, but the sensitivity has not been well characterized</li> </ul>
<b>Advantages</b>	<ul style="list-style-type: none"> <li>Little hands-on time</li> <li>Easy to perform</li> <li>Easy to implement</li> <li>Point-of-care capability</li> </ul>	Low equipment costs	<ul style="list-style-type: none"> <li>Users may evaluate association of a mutation with resistance</li> <li>Fairly wide applicability</li> <li>Possible to detect mixed population</li> </ul>	<ul style="list-style-type: none"> <li>Users may evaluate association of a mutation with resistance</li> <li>Wide applicability</li> <li>Possible to detect mixed population</li> </ul>
<b>Availability</b>	FDA cleared; widely available in clinical and public health laboratories	Not FDA cleared for use in the U.S. Available internationally and in select U.S. reference laboratories.	Laboratory-developed test at several public health laboratories including California (requires approval: grace.lin@cdph.ca.gov or ed.desmond@cdph.ca.gov) New York state (limited to NY; tlab@wadsworth.org), and others.	Available through CDC Molecular Detection of Drug Resistance (MDDR) service (also uses pyrosequencing.) Requires approval: TBLab@cdc.gov

a. Assays using pyrosequencing or Sanger sequencing technologies are laboratory-developed tests. The performance characteristics may vary. Laboratories may validate their own assays for testing specimens from nonrespiratory specimens. Check with your laboratory.

b. Clinical specimens concentrated by NALC-NaOH are suitable. Smear-negative specimens may be tested, but the sensitivity is lower than that for smear-positive specimens.

Table adapted with modification from Lin SY, Desmond EP. Molecular diagnosis of tuberculosis and drug resistance. *Clin Lab Med.* 2014;34(2):297-314.

## Probe-based tests

### **Molecular beacon assay**

- **Xpert MTB/RIF** (Cepheid, Sunnyvale, CA) detects *M. tuberculosis* complex and resistance to RIF by real-time PCR with five molecular beacon probes (A-E) that cover the RIF-resistance determining region of *rpoB* (see Figure 3).
  - FDA-approved for testing smear-positive or negative sputum specimens. The system is easy to operate and results are available within approximately 2.5 hours.
  - Sensitivity/specificity of detecting RIF resistance are 95% and 98% respectively (from a 2014 meta-analysis by Steingart, et al., the majority of data from low- or middle-income countries).
  - The Xpert MTB/RIF assay detects the presence or absence of mutations within the 81 base pair core region of *rpoB*. When mutations are detected, the assay issues reports stating “RIF resistance detected.” Certain mutations in the *rpoB* gene do not confer *in vitro* RIF resistance (silent or neutral mutations). CDC and APHL recommend confirmation of *rpoB* mutations with a sequence-based method.
    - A frequently encountered silent mutation, 514Phe(TTT), is detectable by probe B. Although the prevalence of this silent mutation has not been fully investigated, data from the California Department of Public Health show a frequency of 16.9% (26 of 154). [From a total of 1,538 specimens sequenced, of the 154 containing *rpoB* mutations, 26 had this silent mutation (unpublished data)]. These data suggest a lower positive predictive value of *rpoB* mutations detected by Xpert and other nonsequence-based assays for RIF resistance in an area with low prevalence of RIF resistance.
  - Especially for patients in whom TB or drug-resistant TB is not suspected, clinicians may wish to discuss Xpert MTB/RIF results with the performing laboratory to get more information. A resistant result involving Probe B might indicate a silent mutation (some resistance conferring mutations are also detectable by Probe B). High cycle threshold (Ct) values, corresponding to smaller quantities of mycobacterial DNA or mutations detected by multiple probes (which are rare), should be interpreted with caution.

For further information, see section: ***Difficulties interpreting results from molecular tests.***





TABLE 5.

### Interpretation of line-probe assay

Line-probe band pattern	Interpretation/comments
All wild-type bands are present with absence of all mutant bands.	<ul style="list-style-type: none"> <li>No mutations are present within the targeted DNA segment; this suggests susceptibility to the drug.</li> </ul>
Missing at least one wild-type band and presence of one of the mutant bands.	<ul style="list-style-type: none"> <li>A specific mutation is present and its sequence is identified. Drug resistance is predicted.</li> </ul>
Missing at least one wild-type band but none of the mutant bands are present.	<ul style="list-style-type: none"> <li>A mutation is present but not one of the frequent mutations; the identity of the mutation is not given.</li> <li>It is likely to be associated with drug resistance, but one cannot rule out silent mutations or other mutations not conferring resistance.</li> </ul>
All wild-type bands are present and one of the mutant bands is also present.	<ul style="list-style-type: none"> <li>Possibly a mixed population or a mixed infection with two different strains, a wild-type strain and a drug-resistant strain.</li> <li>The variable intensity of the band may add difficulties in interpretation for this scenario. It is advisable to repeat the test or to confirm by a sequence-based method, or to defer the interpretation to culture-based drug susceptibility testing results.</li> </ul>

(Table adapted with modification from Lin SY, Desmond EP. Molecular diagnosis of tuberculosis and drug resistance. *Clin Lab Med.* 2014;34(2):297-314.)

### Sequence-based tests

A sequence-based test not only detects presence or absence of mutations, but also provides the identity of a mutation. This allows a user to identify if a mutation confers *in vitro* resistance. Furthermore, specific mutations may be used to predict a range of MICs.

- Pyrosequencing (PSQ)** is a real-time sequencing method that sequences a short stretch of nucleotides and is capable of detecting any mutation within the targeted length with the mutation identity provided. It is not suitable for detecting mutations which are widely spread throughout the gene, such as PZA-resistance associated *pncA* mutations. A well-designed PSQ assay is sensitive enough to detect mutations from concentrated specimens.
- Sanger sequencing** is the gold standard of sequencing, using the dye-terminator technology. It is capable of sequencing hundreds of nucleotides. CDC's MDDR service provides sequencing that detects mutations associated with resistance to EMB, PZA, AK, CM, KM, and fluoroquinolones by Sanger sequencing and to INH, RIF by PSQ. The service has a short turnaround time (1-2 days).

- **Next generation sequencing** can be used to perform partial genome or **whole genome sequencing** and can provide the same information as PSQ and Sanger sequencing in addition to information on many other genes; however, it is not yet widely available in clinical laboratories. It requires sophisticated software to handle enormous amounts of data and has a longer turnaround time. At present, it requires higher concentrations of DNA extracted from cultures, so it is not yet sensitive enough for testing direct specimens.

### Choice of molecular tests

- If a sequence-based method is available locally, it is the method of choice.
- If Xpert MTB/RIF is readily available, it can be used for detection of *M. tuberculosis* complex and RIF-resistance. When a mutation is detected, confirmation by a sequence-based method is recommended.
- If INH-resistance is suspected, use a method which can at least detect the most common INH-associated mutations, *katG* and *inhA*.
- If RIF-resistance is detected, MDR-TB is likely and the specimen should be tested for mutations associated with resistance to other drugs.

### Difficulties interpreting results from molecular tests

Molecular testing is enabling much more rapid diagnosis of likely drug resistance, yet with new technologies come new questions. Difficulties interpreting results may arise from the way tests are reported, clinicians' lack of familiarity with molecular terminology, and—most importantly—from evolving knowledge regarding the clinical implications of specific mutations. Among the most challenging situations for the clinician is when molecular and growth-based test results are discordant.

- **Discordance between molecular and growth-based test results** may occur and can be confusing. Examples of this are isolates with certain mutations in the *rpoB* gene that may test susceptible for rifampin by growth-based methods. These mutations have been referred to as “**disputed mutations.**” Most laboratories performing sequence-based assays should be able to identify these mutations in test reports. However, reporting parameters and language may vary by laboratory.

Several clinical case series have been published reporting **poor treatment outcomes for patients with these disputed mutations** when treated with standard first-line therapy. In a 2013 study evaluating samples from two countries with a high burden of drug-resistant TB, disputed *rpoB* mutations were responsible for over 10% of rifampin resistance among first-line failure and relapse cases.

The best clinical approach to managing patients with strains possessing disputed mutations is not known and may depend on the presence of other factors such as additional drug resistance, the extent of disease, comorbidities (diabetes, HIV status and treatment, etc.), serum drug concentration, patient adherence, and nutritional status. Expert clinical and laboratory consultation for patients with a disputed *rpoB* mutation may be helpful.

**Silent and neutral mutations** (defined in *Types of mutations*) are additional causes for discordance between molecular and growth-based test results and can be identified through sequencing as sources of false-positive molecular resistance results.

## Types of mutations

**Silent mutations:** alteration in DNA sequence but no resulting amino acid change, and thus, not associated with drug resistance. Also called synonymous mutations.

- 514 TTT(Phe) mutation in *rpoB* is the most common silent mutation. Information regarding this silent mutation contributing to false-positive rifampicin resistance results when using Xpert MTB/RIF can be found in the section: **Probe-based assays**.

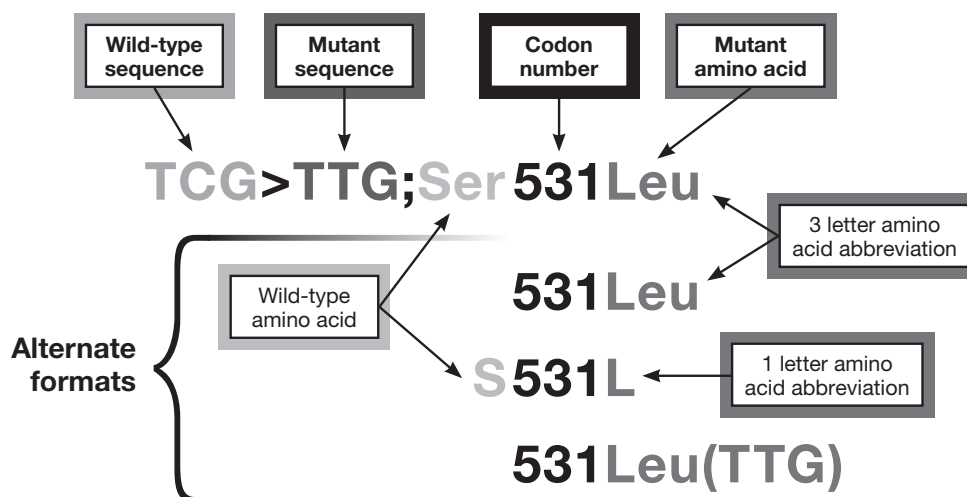
**Missense mutations:** alteration in DNA sequence results in change in amino acid sequence. Also called nonsynonymous mutations.

- May confer different levels of resistance or no resistance.
- A missense mutation that has no effect on growth-based test results is also called a **neutral mutation**. Neutral mutations can be present in both drug susceptible and drug resistant strains. This term is used on the CDC's MDDR report.

- **Understanding sequence-based molecular test reports** can be challenging. Results can be reported using various formats, abbreviations and numbering systems. Figure 5 shows variations of reporting formats based on the example of an *rpoB* mutation using the format of CDC MDDR results. All reports should indicate the location (codon number or nucleotide number) and the mutant sequence or amino acid detected. This information can be used to make additional conclusions about the likelihood and extent of resistance (see **Table 3: Genes and mutations associated with drug resistance**).

FIGURE 5.

**Guide to understanding sequence-based molecular test reports based on the example of an *rpoB* mutation using the format of CDC's MDDR Service results.**



- **Both growth-based susceptibility testing and molecular testing are important in constructing treatment regimens.** Growth-based testing still plays an integral role in providing crucial additional information and testing drugs for which molecular tests are not yet available.

#### Clinical scenario:

Long-term elderly resident of the United States who was born in Mexico presents with 3 months of cough and cavitory lesion on chest radiograph. He has not been treated for TB before and has no known contact with an MDR-TB case. Xpert MTB/RIF assay performed on AFB smear-positive sputum is reported as “MTB detected, RIF resistance detected.”

Confirmatory sequence-based testing is requested prior to starting an MDR-TB regimen because likelihood of MDR-TB is low given the patient’s history. **Sequencing assay reveals mutation at 514TTT(Phe), a silent mutation. Growth-based susceptibility testing confirms RIF susceptibility.** The patient does well on standard first-line treatment.

### Molecular tests on extrapulmonary specimens

Molecular tests for drug resistance can also be performed on non-respiratory specimens. However, no molecular assay is FDA cleared for use on non-respiratory specimens, and assays therefore must be validated by individual laboratories. Many laboratories do not have the capability to validate or run molecular tests on extrapulmonary specimens. *Xpert MTB/RIF* performance for testing extrapulmonary specimens has been published (See Table 7).

TABLE 6.

**Meta-analysis of the sensitivity and specificity of Xpert MTB/RIF in diagnosing extrapulmonary TB and rifampicin resistance in adults and children compared against culture as a reference standard, by type of extrapulmonary specimen**

Specimen type	No. of studies, No. of samples	Median (%) pooled sensitivity (pooled 95% CrI*)	Median (%) pooled specificity (pooled 95% CrI*)
Lymph node tissue and aspirate	14 studies 849 samples	84.9 (72–92)	92.5 (80–97)
Cerebrospinal fluid	16 studies 709 samples	79.5 (62–90)	98.6 (96–100)
Pleural fluid	17 studies 1385 samples	43.7 (25–65)	98.1 (95–99)
Gastric lavage and aspirate	12 studies 1258 samples	83.8 (66–93)	98.1 (92–100)
Other tissue samples	12 studies 699 samples	81.2 (68–90)	98.1 (87–100)

\*CrI: credible interval; the CrI is the Bayesian equivalent of the confidence interval

Adapted from WHO, 2013: Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF system. Policy statement.

WHO 2013 guidelines recommend Xpert MTB/RIF as the preferred initial diagnostic test for CSF for patients suspected to have TB meningitis, given the urgency of rapid diagnosis.

### Molecular tests on formalin-fixed specimens

Rarely, only fixed specimens are obtained and no other specimens are available to confirm TB when AFB or other pathologic findings consistent with TB are seen. When laboratory confirmation of the diagnosis is important for patient care, specialized laboratories are able to extract DNA from fixed specimens for analysis. Extracted DNA can also sometimes be used to perform molecular tests for drug susceptibility.

- **CDC Infectious Diseases Pathology Branch** offers this service in addition to a wide range of testing for identifying other microbes. Requests should come primarily through public health laboratories; CDC approval is required before submission of specimens. (<http://www.cdc.gov/ncezid/dhcpp/idpb/specimen-submission/index.html>) email: Pathology@cdc.gov
- **National Jewish Health Mycobacteriology Laboratory** offers *M. tuberculosis* complex, speciation within *M. tuberculosis* complex, and MDR-TB/XDR-TB testing

on formalin-fixed specimens, available 7 days a week. ([http://www.nationaljewish.org/getattachment/professionals/clinical-services/diagnostics/adx/ordering-tests/requisitions/myco\\_rec\\_web.pdf.aspx](http://www.nationaljewish.org/getattachment/professionals/clinical-services/diagnostics/adx/ordering-tests/requisitions/myco_rec_web.pdf.aspx)) email: [salfingerm@njhealth.org](mailto:salfingerm@njhealth.org)

- **University of Washington Medical Center Molecular Diagnosis Section** offers identification of *M. tuberculosis* complex and NTM from tissue specimens including fixed specimens. (<http://depts.washington.edu/molmicdx/mdx/tests/afbpcr.shtml>) email: [molmicdx@uw.edu](mailto:molmicdx@uw.edu)

## Therapeutic drug monitoring (TDM)

### When to order TDM

Therapeutic drug monitoring is routinely used for several circumstances:

- **Aminoglycoside/CM** serum concentrations especially in patients with **renal impairment**
- **CS** concentrations in order to minimize risk of **CNS toxicity** and to safely use optimal dose
- Known or suspected **malabsorption** (e.g., diabetes, gastrointestinal disorders)
- **Lack of expected clinical response** or **relapse** while on appropriate drugs and doses, administered by directly observed therapy (DOT)
- Patients with **few effective drugs** in their regimen, in order to optimize the effect of available drugs
- Patients with potentially significant **drug-drug interactions** such as rifamycins and antiretrovirals
- **EMB** concentrations in patients with significant **renal impairment**

Many drug-resistant TB experts routinely monitor certain TB drug concentrations in anticipation of toxicity and to escalate a drug dose when possible.

### Where to send a specimen for TDM

Most hospital and commercial laboratories perform AK serum concentrations. Only a few laboratories perform drug concentrations for other TB drugs.

#### ***Drugs tested for first- and second-line therapeutic drug monitoring tests:***

Capreomycin	Ethionamide	p-Aminosalicylic Acid
Ciprofloxacin	Isoniazid	Pyrazinamide
Clarithromycin	Levofloxacin	Rifabutin
Clofazimine	Linezolid	Rifampin
Cycloserine	Moxifloxacin	Rifapentine
Ethambutol	Ofloxacin	Streptomycin

**Laboratories and contact information:**

University of Florida  
 idpl.pharmacy.ufl.edu/  
 peloquinlab@cop.ufl.edu  
 352- 273-6710

National Jewish Health  
 njlabs.org  
 salfingerm@njhealth.org  
 303-398-1422

**How to send a specimen for TDM****Collecting and processing samples for TDM**

- 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.
- Specimens should be collected after at least 4-5 half-lives have elapsed since the initiation of the drug. In practice, approximately 1 week works well in most cases. A shorter time can be used for adjustments of dose or schedule.
- Random samples generally are not informative.
- The patient should come to clinic with his/her medications and should plan to be at the clinic for at least 2 hours.
- See Table 7 for timing of specimen collection. On the day of blood draws only, rifabutin (RFB) can be given 1 hour before the other TB drugs so that only 2 venipunctures are required.
- 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 7) and record the exact time of the blood collection.
- For SM, note if the patient is also receiving ampicillin.
- Label the tubes with the patient's name, date and time of collection, and the drug(s) to be assayed.
- The specimen should be stored frozen until ready for shipping;  $-70$  degrees C is preferable, but at a minimum  $-20$  degrees C.
- For detailed instructions for processing and submitting specimens for TDM, see:  
 University of Florida: [idpl.pharmacy.ufl.edu](http://idpl.pharmacy.ufl.edu)  
 National Jewish Health: [njlabs.org](http://njlabs.org)

**How to interpret results of TDM**

For information about how to interpret results of TDM, see **Chapter 4, Treatment**.



TABLE 7.

**Suggested time for blood collection after an oral dose.**

<b>Drug name</b>	<b>Hours after oral dose to “peak”</b>	<b>Time after dose for additional concentration if desired*</b>
Clarithromycin	2-3 hours	
Clofazimine	2-3 hours	
Cycloserine	2 hours	6 hours
Ethambutol	2-3 hours	6 hours
Ethionamide	2 hours	6 hours
Isoniazid	1-2 hours	4-6 hours
Levofloxacin	2 hours	6 hours
Linezolid	2 hours	6 hours
Moxifloxacin	2 hours	6 hours
PAS	6 hours	
Pyrazinamide	2 hours	6 hours
Rifabutin	3-4 hours	7 hours
Rifampin	2 hours	6 hours
<b>Drug name</b>	<b>Hours after completion of infusion/injection to “peak”</b>	<b>Time after dose for additional concentration if desired*</b>
Amikacin	1.5-2 hours (IV)	6 hours (IV or IM)
Capreomycin	2 hours (IM)	
Kanamycin		
Streptomycin		

\*An additional concentration may be obtained to evaluate for delayed absorption or to calculate a half-life in order to more accurately prescribe a drug dose and interval.

# National TB genotyping service

The Michigan Department of Community Health is under contract with CDC to provide genotyping services to TB programs in the United States. **TB programs, through their state or county public health laboratories, should submit the initial isolate from each culture-positive TB patient to the genotyping laboratory.**

The genotyping laboratory uses the following genotyping methods:

- **Spoligotyping** (performed at CDC)
- **Mycobacterial interspersed repetitive units (MIRU)** analysis (performed at Michigan)
- IS6110-based **restriction fragment length polymorphism (RFLP)** analysis (special request)
- **Whole genome sequencing (WGS)**

Spoligotyping and MIRU analysis are PCR-based genotyping methods. The genotyping laboratories will analyze all the submitted isolates by both PCR-based genotyping tests. Under certain circumstances and upon the request of the TB program, isolates that have matching genotypes by both spoligotyping and MIRU analysis can be further typed by RFLP. Whole genome sequencing, having greater discriminatory power, is used to further type strains having the same genotypes by spoligotyping and MIRU but no epidemiology links by the conventional contact investigation.

The CDC-supported genotyping services are offered at no cost to TB programs.

The **objectives of universal TB genotyping** are:

1. To determine the extent and dynamics of ongoing transmission in order to focus program interventions in specific areas and populations
2. To assess TB transmission in outbreaks and to refine contact investigations
3. To identify nosocomial transmission not identified by conventional methods
4. To investigate possible false-positive culture results so that clinicians can be notified of diagnostic errors quickly, allowing for termination of unnecessary TB treatment

These objectives are of particular importance in the care and investigation of drug-resistance cases, and all programs are encouraged to support these efforts toward universal genotyping.

## Summary

- Two-way communication between clinician and laboratory is crucial to ensure appropriate testing and optimal turnaround time.

---

- Appropriate and adequate specimen collection and handling ensures the most clinically useful laboratory results.

---

- Both conventional growth-based and molecular tests have important roles in diagnosis of tuberculosis and drug resistance.

---

- A critical concentration is not a minimum inhibitory concentration (MIC). Requesting an MIC determination can be helpful in some situations.

---

- Some mutations do not confer resistance, but may reflect silent or missense mutations. To maximize the information obtained from molecular testing, results from probe-based molecular tests for drug resistance showing resistance should be confirmed by sequence-based tests.

---

- Discordance in susceptibility test results can occur across test types and laboratories. Discordance can have multiple possible causes and can be clinically confusing.

---

- Molecular assays may be performed on extrapulmonary specimens and on fixed specimens at certain laboratories.

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- Therapeutic drug monitoring (TDM) can play an important role in managing patients with drug resistance, but requires care in specimen collection, handling, documentation, and interpretation.

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# Treatment

3rd edition contributor: **CHARLES L. DALEY, MD**

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Management of drug-resistant TB is often complicated. Even under the best circumstances, successful treatment outcomes can be difficult to achieve compared to drug-susceptible disease.

## Consultation with experts

Treatment of tuberculosis (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 inappropriate management of a drug-resistant case can have life-threatening consequences.

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 empiric 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 in the decision to pursue rapid drug resistance testing in a patient with risk factors.
- 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.

Providers caring for a known or potential case with drug-resistant TB should:

- Consult with a local or regional expert in the treatment of drug-resistant TB. Ideally, written communication will be shared for clarity of recommendations after the discussion.
- 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 an expert before making changes in the treatment regimen.
- Consult an expert for help in addressing slow response and managing adverse reactions.

See **Appendix 1, Expert Resources for Drug-Resistant TB.**



# Classification of anti-tuberculosis drugs

Anti-tuberculosis drugs have classically been categorized into first-, second-, and third-line drugs, which is the primary system used in U.S. guidelines and in this *Survival Guide*.

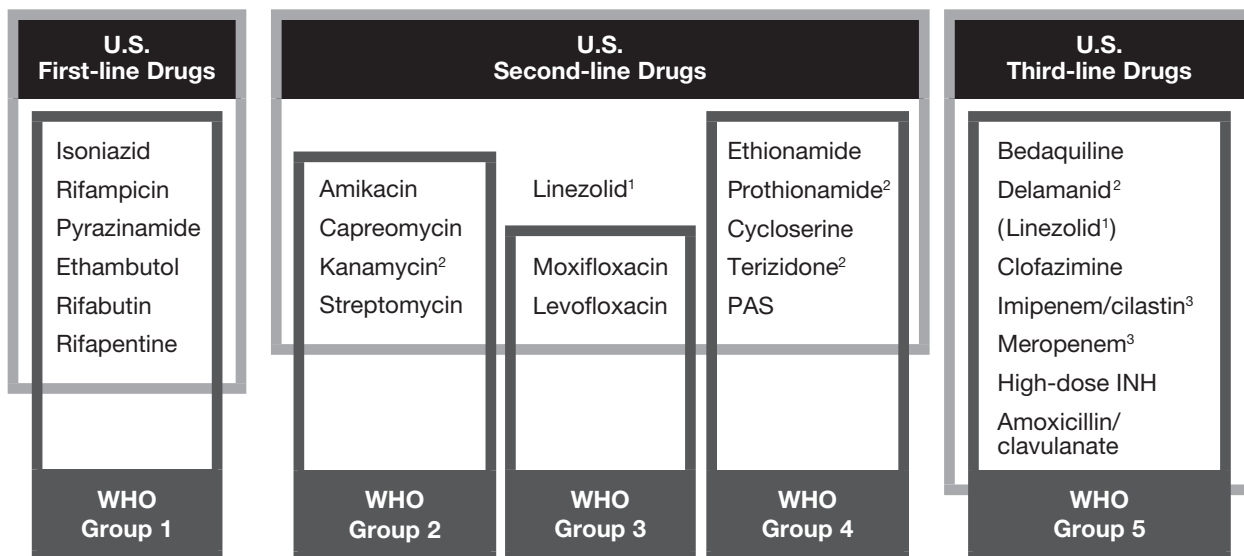
First-line drugs are traditionally those drugs that are used as the core drugs in the treatment of drug-susceptible TB. Second-line drugs include the fluoroquinolones, aminoglycosides/polypeptides, and other drugs that are used to treat multidrug-resistant (MDR-) TB. Third-line drugs are also used to treat drug-resistant TB but typically have less activity, more adverse reactions, and less evidence supporting their use than first- and second-line drugs.

*Proper treatment with a second-line regimen often represents the patient's best hope for cure. Seek expert consultation when considering treatment initiation for drug-resistant TB.*

The classification system adopted by the World Health Organization (WHO) further divides the drugs into 5 groups. The 5-group system is based on efficacy, experience of use, safety, and drug class. Where new drugs fall within these systems has not been determined. The relationship between these two classification systems, and the primary anti-tuberculosis drugs currently in use globally, are shown in Figure 1.

FIGURE 1.

## Comparison between standard U.S.-based classification and the WHO classification system for anti-tuberculosis drugs



1. Linezolid: Traditionally classified as third-line drug, but now often used as a second-line agent in the United States (but considered WHO Group 5)

2. Kanamycin, prothionamide, terizidone, and delamanid: Not currently available in the United States

3. Clavulanate (available as amoxicillin/clavulanate): Recommended as an adjunctive agent to imipenem/cilastatin and meropenem

# Starting an expanded empiric treatment regimen

Molecular diagnostics have greatly decreased the time to obtain results from drug susceptibility tests (DST), allowing earlier initiation of an appropriate treatment regimen while awaiting additional phenotypic results. For many drugs, however, accurate molecular tests are not available and the risk of drug resistance must be anticipated. **Treatment for drug-resistant TB may need to be initiated even before susceptibility results (molecular or growth-based) are available.**

The decision to start an expanded empiric regimen (inclusion of second-line drugs), prior to DST results, will be determined by the level of suspicion for drug-resistant TB and the severity of illness. When suspicion for drug-resistant TB is high (e.g., concern for treatment failure or previous treatment, especially if self-administered), then an expanded empiric treatment regimen may be warranted. An expanded regimen is especially important in cases with life-threatening TB.

## Who to consider for an expanded empiric MDR-TB regimen

- Patients in whom TB treatment is failing (i.e., who remain culture positive after 4 months of treatment)
- 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

**There are situations in which it may be more appropriate to initiate a 4-drug (first-line) regimen or to 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.
- Deferring treatment until drug-susceptibility results are available is an appropriate option only if the patient is not severely ill and can be isolated to prevent infection of contacts.
- Initiation with an empiric 4-drug (first-line) regimen may be appropriate if prior first-line treatment for pan-sensitive disease was completed under well-documented directly observed therapy (DOT) conditions, and primary suspicion is relapse due to the original strain.

*Given the importance of having drug-susceptibility results, every effort should be made to obtain high-quality specimens for culture and DST.*

## Expanded empiric treatment regimen

An expanded empiric regimen usually consists of the 4 first-line drugs (isoniazid [INH], rifampin [RIF], ethambutol [EMB], pyrazinamide [PZA]) and 2 or more additional drugs. Additional drugs to consider include:

- A later generation fluoroquinolone
- An injectable agent, other than streptomycin (SM); because of the frequency of SM resistance in the world, better alternatives would be amikacin (AK) or capreomycin (CM)
- Consider use of linezolid (LZD), ethionamide (ETA), cycloserine (CS), or para-aminosalicylate (PAS)

The use of the standard 4 first-line drugs with the addition of a single drug (a fluoroquinolone or an injectable agent) is not a sufficient expanded empiric regimen for MDR-TB. When extensive disease or resistance is suspected, do not limit the empiric regimen to just 6 drugs.

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 the patient's region of origin

**The treatment regimen can be changed once the DST results are available.**

## Individualized treatment regimens

Once drug resistance has been documented, the following individualized treatment regimens are recommended:

### **Mono-resistant *Mycobacterium (M.) tuberculosis*** **Isolated resistance to INH**

INH mono-resistance is one of the most common forms of drug resistance. WHO, American Thoracic Society (ATS), and Infectious Diseases Society of America (IDSA) recommend **RIF, EMB, and PZA ± a later generation fluoroquinolone for 6-9 months**. The optimum regimen for the treatment of INH mono-resistant tuberculosis is unknown; however, effective treatment regimens are readily available.

- A 2009 systematic review/meta-analysis by Menzies, et al., found that among patients with INH mono-resistant TB, outcomes were improved with longer duration of RIF and PZA, use of daily treatment (not intermittent treatment) and with greater numbers of effective drugs.
- Studies in the United States have reported relapse rates of 2 to 5% using 3- to 4-drug regimens administered for 6 or more months. However, a large proportion (26-59%) of patients had treatment discontinued or the duration of treatment extended because of drug-related adverse reactions, usually associated with PZA.
- Treatment outcomes do not differ based on whether the isolate has low- or high-level INH resistance *in vitro*.

- Addition of a fluoroquinolone was associated with improved outcomes in studies from Taiwan and the Republic of Korea.
- In the RIFAQUIN trial, a 6-month regimen that included daily RIF, EMB, PZA and moxifloxacin (MXF) (400 mg) for 2 months followed by once-weekly doses of both MXF and high-dose rifapentine (RPT) (1200 mg) for 4 months, was reported to be as effective as a standard 6-month regimen in drug-susceptible TB. Therefore, the 6-month regimen should be effective for INH mono-resistant TB as long as the isolate is susceptible to the fluoroquinolones.

**Conclusion:** Based on current evidence, there are at least 3 options for treatment of patients with INH-resistant disease.

---

**OPTION 1: Daily RIF, EMB, and PZA (± fluoroquinolone), all given for 6 to 9 months depending on the microbiologic, clinical, and radiographic response to treatment**

- 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.
- Continuation of INH in the setting of documented isolated resistance to INH is not necessary, given the high cure rate with this regimen.
- A fluoroquinolone may be added to the regimen, especially in patients with extensive and/or cavitary disease. (Confirm fluoroquinolone susceptibility.)

---

**OPTION 2: If the patient does not tolerate PZA, a regimen consisting of RIF, EMB and a later-generation fluoroquinolone for 9-12 months could be used**

- Confirm fluoroquinolone susceptibility.

---

**OPTION 3: Daily RIF, EMB, PZA and MXF (400 mg) for 2 months followed by once-weekly doses of both MXF and high-dose RPT (1200 mg) for 4 months**

- Confirm fluoroquinolone susceptibility.

### Isolated resistance to RIF

RIF mono-resistance is uncommon but increasing in some areas of the world. 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 (RFB) and RPT**. In approximately 80% of strains where RIF resistance is documented, the strain is also resistant to RFB. Therefore, use RFB only when *in vitro* or molecular susceptibility is documented. Some experts may use RFB under these conditions, but not consider it a fully reliable drug in the regimen.
- Using molecular testing to identify the particular mutation associated with RIF resistance may help to rapidly identify isolates that retain susceptibility to RFB (see **Chapter 3, Laboratory**). This is also important as various labs use different cut points to test RFB susceptibility, and the molecular test is likely a better indicator.
- Resistance to RPT is universal in RIF-resistant isolates.

WHO recommends that patients with rifamycin mono-resistance be treated with a full MDR-TB regimen including INH until DST results to INH are available and appropriate adjustments can be made. However, in settings such as the United States where MDR-TB is relatively uncommon and reliable DST is readily available, other options are preferable:

---

**OPTION 1 (preferred): INH, EMB, and a fluoroquinolone daily for 12 to 18 months, supplemented with PZA for at least 2 months during the intensive phase**

---

**OPTION 2: INH, EMB, PZA daily for 18 months**

**For both options 1 and 2:**

- In patients with extensive cavitory disease, or to shorten the duration of therapy (e.g., 12 months), addition of an injectable agent for at least the first 2 months is recommended.
  - Most experts would consider **Option 1** the preferred regimen.
- 

**OPTION 3: INH, PZA, SM daily for 9 months**

- This option is generally not preferred, and susceptibility to SM must be documented.

### Isolated resistance to EMB, PZA, or 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.
- Most PZA mono-resistant isolates are due to *M. bovis*.

### Poly-resistant *M. tuberculosis*

TB due to organisms that demonstrate *in vitro* drug resistance to more than 1 anti-TB drug (but not INH and RIF) is referred to as poly-resistant TB. Any number of combinations of resistance can occur, but the outcome of treatment is usually good.

- Treatment should include the use of as many first-line agents as possible plus a fluoroquinolone, and in some cases, an injectable drug.

Table 1 presents recommended regimens for the treatment of non-MDR drug-resistant TB.

TABLE 1.

## Treatment regimens for the management of mono-resistant and poly-resistant TB

Pattern of drug resistance	Suggested regimen	Minimum duration of treatment (months)	Comments
INH (± SM)	RIF, PZA, and EMB (± fluoroquinolone)	6–9 months	A fluoroquinolone may strengthen the regimen for patients with extensive disease. For additional options, see section: <b>Isolated resistance to INH.</b>
INH and EMB	RIF, PZA, and fluoroquinolone	6–9 months	A longer duration of treatment should be used for patients with extensive disease.
INH and PZA	RIF, EMB, and fluoroquinolone	9–12 months	A longer duration of treatment should be used for patients with extensive disease.
INH, EMB, PZA (± SM)	RIF, fluoroquinolone, plus an oral second-line agent, plus an injectable agent for the first 2–3 months	9–12 months	A longer course (6 months) of the injectable may strengthen the regimen for patients with extensive disease.
RIF	INH, EMB, fluoroquinolone, plus at least 2 months of PZA	12–18 months	An injectable drug may strengthen the regimen for patients with extensive disease. For additional options, see section: <b>Isolated resistance to RIF.</b>
RIF and EMB (± SM)	INH, PZA, fluoroquinolone, plus an injectable agent for at least the first 2–3 months	12–18 months	A longer course (6 months) of the injectable may strengthen the regimen for patients with extensive disease.
RIF and PZA (± SM)	INH, EMB, fluoroquinolone, plus an injectable agent for at least the first 2–3 months	18 months	A longer course (6 months) of the injectable may strengthen the regimen for patients with extensive disease.
PZA	INH, RIF	9 months	Most commonly seen in <i>M. bovis</i> infections.

## Multidrug-resistant *M. tuberculosis* (MDR-TB)

Treatment of MDR-TB, defined as resistance to at least INH and RIF, requires a prolonged multidrug regimen. **The optimal number of drugs, combination of drugs, and duration of therapy has not been established.**

### Number of drugs and stepwise approach to choosing

Recent reports of the outcomes of treatment for MDR-TB describe better outcomes in terms of lower rates of mortality, treatment failure, and recurrent TB, and faster rates of sputum conversion in those who received at least 5 likely effective drugs compared with 4 likely effective drugs. Taking into consideration current evidence and U.S. expert opinion, this *Survival Guide* **recommends 4-6 likely effective drugs (and optimally at least 5) for the treatment of MDR-TB.** Four drugs may be sufficient in some cases with limited disease and/or limited extent of resistance (e.g., a patient with lymph node disease and resistant only to INH and RIF).

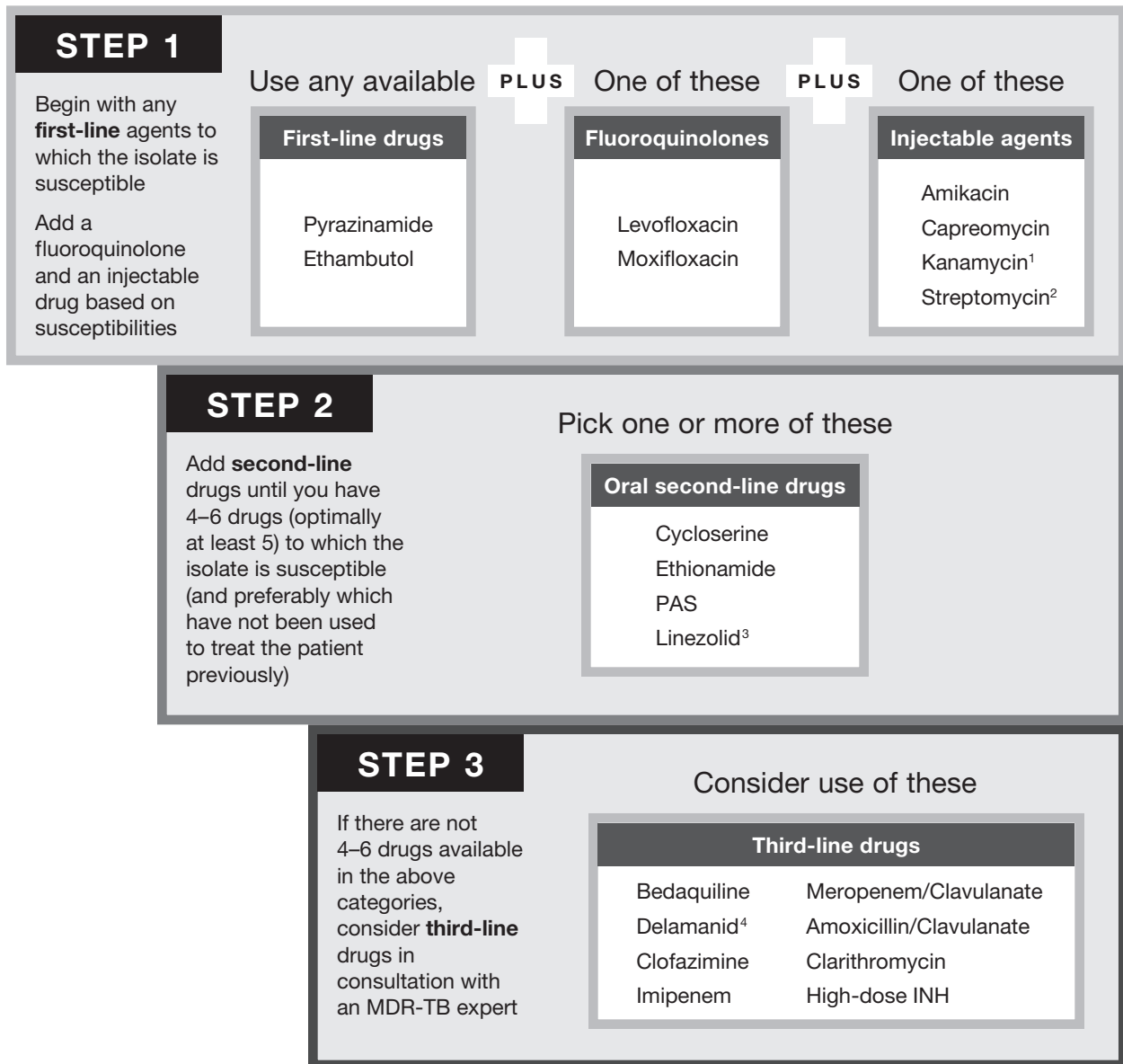
Data from another individual data meta-analysis reported treatment success was highest if at least 6 drugs were used in the intensive phase and 4 in the continuation phase in the treatment of XDR-TB.

Figure 2 describes a step-wise approach to building an individualized MDR-TB regimen.



FIGURE 2.

## Building a Treatment Regimen for MDR-TB



1 Not available in U.S.

2 SM: use only if not previously used and if documented susceptibility

3 Although traditionally considered a third-line drug, many experts now use LZD as a second-line drug option

4 Awaiting FDA approval

## Duration of therapy

The optimal duration of therapy is not known. Based on expert opinion, the 2003 ATS/IDSA/CDC guidelines recommended 18-24 months of therapy depending on the extent of disease and resistance pattern. Earlier editions of this *Survival Guide* expanded upon these recommendations to suggest minimum treatment durations for MDR-TB of 18-24 months beyond culture conversion, again based on expert opinion. New U.S. guidelines that specifically address treatment for drug-resistant TB are under development, as are updates to the 2011 recommendations by WHO.

- The only study that has attempted to define the optimum duration of therapy was the individual patient meta-analysis used by WHO to formulate the 2011 treatment recommendations.

### WHO 2011 treatment recommendations for MDR-TB

*WHO recommendations were based on the results of a systematic review and individual patient meta-analysis that included 32 studies and over 9,000 patients (XDR-TB patients were excluded) reported by Ahuja, et al., in 2012. Based on this review:*

- WHO recommends that patients with MDR-TB be treated with at least 4 likely effective drugs as well as PZA during the intensive phase, defined as the time that the injectable is being given.
- Drugs likely to be effective are those that have not been taken previously by the patient and/or to which *in vitro* drug susceptibility has been documented.
- Regimens should include an injectable (AK, CM, KM), a higher-generation fluoroquinolone, ETA, and either CS or PAS (if CS cannot be used), and PZA.
- In patients with highly-resistant organisms, Group 5 drugs may be needed. These should be chosen in consultation with someone who has experience using these drugs to treat MDR-TB.

#### **WHO recommendations for duration of therapy:**

- Intensive phase should be at least 8 months in duration.
- Total duration of therapy should be at least 20 months in those who have never been previously treated for MDR-TB, and at least 24 months in those previously treated for MDR-TB.

Concerns exist regarding the applicability of the WHO individual patient meta-analysis to U.S.-based care of drug-resistant TB. More evidence for practice guidance on optimum treatment duration using an individualized approach (based on phenotypic and genotypic DST) is needed. With the capacity for earlier diagnosis using rapid molecular methods, successful and safer application of LZD, and strong overall treatment success rates, U.S. expert consensus continues to support utilization of culture conversion as the primary guide for minimum treatment duration within the practice conditions of a high-resource setting. On an individual basis, the extent of disease, resistance pattern, and clinical response to treatment will influence final regimen choices and treatment duration.

## Recommended duration of therapy, based on current U.S. expert opinion and practice

As with drug-susceptible TB, the treatment is typically divided into two periods: **intensive phase** and **continuation phase**. The intensive phase is the initial period during which the injectable agent is administered. The period of treatment after the injectable agent is removed is referred to as the continuation phase. Newer regimens under investigation may not include two distinct phases.

- **Intensive phase:** recommend *at least 6 months beyond culture conversion* for the use of injectable agent.
- **Total duration treatment:** recommend *at least 18 months beyond culture conversion*.

There may be patients in whom a shorter duration of therapy would be sufficient, as good treatment outcomes with 9–12 months of therapy have been reported (see section: **Short-course regimens**). Some experts would use shorter treatment durations in patients with **minimal radiographic disease, low bacillary burden**, and **children**. Studies have shown that, in patients who have converted cultures to negative within 2–3 months, treatment success is highly likely to be achieved.

As newer and more effective drugs become available, the strength of the regimen and treatment response may be the most important factors in determining treatment duration.

### Short-course regimens

Recent studies have reported excellent treatment outcomes using shorter durations of therapy than typically used for the treatment of MDR-TB.

- As reported in 2010 by Van Duen, et al., a 9-month regimen consisting of clofazimine (CFZ), high-dose gatifloxacin (GFX), EMB, and PZA throughout the course of treatment, supplemented by prothionamide, KM, and high-dose INH for a minimum of 4 months was associated with a relapse-free cure of 88% among 206 patients with MDR-TB in Bangladesh.
- In a 2014 follow-up report including 515 consecutive patients, the 4-month intensive phase was extended until culture conversion. Of the 515 patients enrolled into the observational study, 84.4% had a bacteriologically successful outcome. Due to extensive disease, only half of the patients completed treatment within 9 months but 95% did so within 12 months. The strongest predictor for a bacteriologically unfavorable outcome was high-level fluoroquinolone resistance, particularly when compounded by initial PZA resistance.
- In Niger, 75 patients with MDR-TB were prospectively followed and treated with a standardized 12-month regimen similar to the aforementioned studies. Cure was achieved in 58 (89.2%) of patients.
- Among 150 MDR-TB patients in Cameroon, 89% successfully completed treatment with a 12-month standardized regimen.

**Conclusion:** There is growing evidence that optimizing the use of currently available drugs can shorten treatment duration for MDR-TB to 9-12 months. These results must be confirmed in a randomized clinical trial before becoming the standard of care.

## Selection and dosing of individual drugs: Additional considerations when building an MDR-TB regimen

Design of the treatment regimen can be difficult and must take into account several factors.

When building the treatment regimen, consider:

- *In vitro* susceptibility results of the drugs
- Cross-resistance
- Whether the patient has taken the drug before
- Potential overlapping drug toxicity or tolerability issues

### Cross-resistance

Providers must be aware of the potential for cross-resistance when using DST results to guide the building of an individualized regimen. While mutations associated with resistance to specific drugs and those that confer risk for cross-resistance are clearly described for some anti-TB drugs, it is important to note that for many of the drugs currently in use, neither the mutations nor mechanisms for resistance are known.

**Be aware of potential cross-resistance that can occur between certain drug classes (Table 2).**

### Avoid drugs used previously to treat the patient's TB

Data from National Jewish Health 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. Some experts may choose not to count previously used drugs as one of the target 4-6 likely effective drugs.

### Consider side effects when choosing drugs

For example, in someone with depression, it may be desirable to avoid **CS**. When possible, try to avoid using drugs that have similar toxicity profiles. For example, the combination of **PAS** and **ETA** increases the risk of hypothyroidism and gastrointestinal toxicity. On the other hand, in some patients there is no choice because these may be the only drugs

TABLE 2.

**Cross-resistance for anti-tuberculosis drugs**

Drug	Cross-Resistance	Comments
Isoniazid	Ethionamide	Cross-resistance to ethionamide is very common (up to 70%) when there is low-level resistance to isoniazid due to a mutation in <i>inhA</i> or the promoter region.
Rifampin	Rifamycins	Cross-resistance among the rifamycin class of drugs is typical. In <20% of strains that are resistant to rifampin, rifabutin may retain susceptibility <i>in vitro</i> . The clinical significance of this is unknown.
Ethambutol	None	
Pyrazinamide	None	
Streptomycin	Kanamycin	Rarely may be cross-resistant to kanamycin.
Amikacin	Kanamycin	High likelihood of cross-resistance because it is associated with the same mutations ( <i>rrs</i> ).
Kanamycin	Amikacin	High likelihood of cross-resistance because it is associated with the same mutations ( <i>rrs</i> ). However, there are some kanamycin mutations ( <i>eis</i> ) that do not cause amikacin resistance.
Capreomycin	Amikacin/Kanamycin	Variable frequency of cross-resistance has been reported.
Fluoroquinolones	Other fluoroquinolones	In general, there is a complete class effect cross-resistance among fluoroquinolones <i>in vitro</i> . However, data suggest that moxifloxacin may continue to demonstrate some activity despite <i>in vitro</i> resistance to ofloxacin. For details, see <b>Chapter 3, Laboratory</b> , Table 3.
Cycloserine	None	
PAS	None	
Ethionamide	Isoniazid	Low-level cross-resistance to isoniazid may occur due to mutation in <i>inhA</i> or the promoter region.
Clofazimine	Bedaquiline	Cross-resistance has been demonstrated in both directions through efflux-based resistance.
Linezolid	None	
Bedaquiline	Clofazimine	Cross-resistance has been demonstrated in both directions through efflux-based resistance.
Delamanid	None	Evidence for cross-resistance to Investigational drug PA-824.

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 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, should be stopped prior to completion of therapy. Therefore, the patient should receive a sufficient number of drugs from the beginning of therapy, i.e. 4 to 6 likely effective drugs (and optimally at least 5), to make sure that there are at least 3 to 5 oral drugs remaining after the injectable is discontinued.

*Ultimately, the safest and most effective drugs to complete the treatment regimen should be chosen.*

- It is important to note that intolerance to 1 agent does not necessarily mean the patient will be intolerant to another agent in the same classification group.
- Given the limited number of drug options, every effort should be made to manage side effects to maintain an adequate and effective regimen. See **Chapter 9, Adverse Reactions**, for details on management of side effects.

## Individual regimens for specific MDR-TB resistance patterns

### Resistance to INH and RIF

A regimen consisting of an injectable agent during the intensive phase (for at least 6 months beyond culture conversion), and PZA, EMB, and a newer-generation fluoroquinolone (MFX or high-dose levofloxacin [LFX, 750-1000 mg] and 1 additional oral agent (LZD, ETA, CS or PAS) given for at least 18 months beyond culture conversion is recommended. In patients with extensive or cavitary disease, a longer duration for the injectable agent may be considered, as well as an additional oral drug. The use of more than 1 additional oral drug should be considered if there has been prior use of PZA or EMB.

### Resistance to INH, RIF, and EMB

A regimen consisting of an injectable agent during the intensive phase (for at least 6 months beyond culture conversion), and PZA, a newer-generation fluoroquinolone (MFX or high-dose LFX [750-1000 mg]), and 2 additional oral agents (LZD, ETA, CS, or PAS) for at least 18 months beyond culture conversion is recommended. In patients with extensive or cavitary disease, a longer duration for the injectable agent may be considered, as well as an additional oral drug.

### Resistance to INH, RIF, and PZA

A regimen consisting of an injectable agent during the intensive phase (for at least 6 months beyond culture conversion), and EMB, a newer-generation fluoroquinolone (MFX or high-dose LFX [750-1000 mg]), and 2 additional oral agents (LZD, ETA, CS, or PAS) for at least 18 months beyond culture conversion is recommended. In patients with extensive or cavitary disease, a longer duration for the injectable agent may be considered, as well as an additional oral drug.

### Resistance to INH, RIF, PZA, and EMB

A regimen consisting of an injectable agent during the intensive phase (for at least 6 months beyond culture conversion), and a newer-generation fluoroquinolone (MFX or high-dose LFX [750-1000 mg]), and 3-4 oral agents (LZD, ETA, CS, PAS or additional third-line agents if needed) should be given for at least 18 months beyond culture conversion. In patients with extensive or cavitary disease, a longer duration for the injectable agent may be considered.

### Resistance to all first-line drugs and fluoroquinolones (Pre-XDR-TB)

In this setting, a regimen containing an injectable agent such as an aminoglycoside or polypeptide (e.g., CM) is critical. Consider extended use of an injectable agent for at least 12 months if tolerated. Additionally, 4–5 second- and third-line oral drugs (WHO Groups 4 and 5) should be used. LZD, bedaquiline (BDQ) or delamanid (DLM) (if available) should be used when possible. However, caution should be used if BDQ and DLM are given together as there are currently no safety data available for co-administration of these drugs. High-dose MFX can be considered unless there is documented *in vitro* resistance to high concentrations of the drug (MIC  $\geq 3$ ). See **Chapter 3, Laboratory**. Treat the patient for at least 24 months. Therapeutic drug monitoring (TDM) may be useful in this situation. Consider surgery if there is focal cavitary disease.

- Consider extending treatment for at least 24 months beyond culture conversion.

### Resistance to all first-line drugs and injectables (Pre-XDR-TB)

MFX (or high-dose LFX [750-1000 mg]) plus at least 4-5 second-line oral drugs (WHO Groups 4 and 5) should be used. LZD, BDQ or DLM (if available) should be used when possible. However, caution should be used if BDQ and DLM are given together as there are currently no safety data available for co-administration of these drugs. Treat the patient for at least 24 months. TDM may be useful in this situation. Consider surgery if there is focal cavitary disease.

- Consider extending treatment for at least 24 months beyond culture conversion.

*Treatment must be more aggressive in situations where the patient has extensive resistance, extensive disease, or multiple previous failed treatment efforts. The duration of therapy will depend on the anti-tuberculosis drugs used, the extent of the disease, and treatment response.*

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



## Extensively drug-resistant *M. tuberculosis* (XDR-TB)

**XDR-TB is defined as resistance to at least INH, RIF, a fluoroquinolone, and 1 of 3 second-line injectable agents (AK, KM, or CM).** Treatment of patients with XDR-TB is challenging because of the lack of potent anti-TB drugs, frequency of adverse reactions, and poor treatment outcomes. However, the approach to designing a treatment regimen is the same as with MDR-TB (Figure 2). Surgery should be a consideration in patients with XDR-TB.

- In a 2010 systematic review and meta-analysis by Jacobson, et al., evaluating 13 observational studies including 560 patients, the pooled treatment success rate was 43.7% with a mortality of 20.8%.
  - Patients who received a later-generation fluoroquinolone reported a higher proportion of favorable treatment outcomes ( $p = 0.012$ ) despite documented *in vitro* resistance to earlier generation fluoroquinolones.
- Results from the 2013 individual data meta-analysis by Falzon, et al., reported treatment success was highest if at least 6 drugs were used in the intensive phase and 4 in the continuation phase. New drugs such as BDQ and DLM were not included in this analysis.
- Treatment success has varied with worsening outcomes as additional resistance occurred. Treatment success for MDR only, MDR + injectable, MDR + fluoroquinolone, XDR was 64%, 56%, 48%, 40%, respectively.
- Among XDR-TB patients, the odds of treatment success are lower in those with isolates resistant to all second-line injectables.

### Conclusion:

- Based on these studies, XDR-TB patients should be treated with **at least 6 likely effective drugs**, if possible.
  - Repurposed or new drugs such as LZD, BDQ, and DLM (if available) should be strongly considered.
  - High-dose MFX (600-800 mg daily) should be used unless there is documented *in vitro* resistance to high concentrations of the drug.
  - Consider high-dose INH treatment if only low-level resistance is documented.
  - Use PZA and/or EMB if organism remains susceptible.
  - Consider CFZ.
  - Meropenem (MPM) or imipenem (IMP) are additional choices.
- When resistance to AK has been documented or in the setting of an empiric regimen for suspected XDR-TB, CM is the injectable of choice. If the injectable agent is a key component necessary for an effective regimen, duration should be at least 12 months (or potentially longer if tolerated).
- **Duration of treatment for XDR-TB should be at least 24 months beyond culture conversion.**
- Expert consultation should be obtained to assist management throughout the treatment duration.

**Table 3 presents recommended regimens for the treatment of MDR/XDR-TB.**

TABLE 3.

### Treatment regimens for the management of patients with MDR/XDR-TB

Pattern of drug resistance	Suggested regimen	Minimum duration of treatment	Comments
INH and RIF (± SM)	PZA, EMB, newer-generation fluoroquinolone (MFX or high-dose LFX), and injectable agent during the intensive phase (for at least 6 months beyond culture conversion), and 1 additional oral agent (LZD, ETA, CS or PAS).	18 months beyond culture conversion	In patients with extensive or cavitary disease, a longer duration for the injectable agent may be considered, as well as an additional oral drug. Consider using more than 1 additional oral drug if there has been prior use of PZA or EMB.
INH, RIF (± SM), and EMB or PZA	EMB or PZA (if available), a newer-generation fluoroquinolone (MFX or high-dose LFX), injectable agent during the intensive phase (for at least 6 months beyond culture conversion), and 2 additional oral agents (LZD, ETA, CS, or PAS).	18 months beyond culture conversion	In patients with extensive or cavitary disease, a longer duration for the injectable agent may be considered, as well as an additional oral drug.
INH, RIF, EMB, PZA (± SM)	Injectable agent during the intensive phase (for at least 6 months beyond culture conversion), and a newer-generation fluoroquinolone (MFX or high-dose LFX), and 3-4 oral agents (LZD, ETA, CS, PAS or additional second- or third- line agents if needed).	18 months beyond culture conversion	In patients with extensive or cavitary disease, a longer duration for the injectable agent may be considered.
INH, RIF, EMB, PZA, fluoroquinolone (Pre-XDR)	4-5 second- or third-line drugs (include LZD, BDQ, or DLM) and an injectable agent.	24 months beyond culture conversion	Duration of injectables should be at least 12 months if tolerated. Consider high-dose MFX. Consider surgery. TDM may be useful.
INH, RIF, EMB, PZA, injectables (Pre-XDR)	MFX (or high-dose LFX) plus at least 4-5 second- or third-line oral drugs. Include LZD, BDQ, or DLM, if available. Include an injectable drug if there is 1 available to which the isolate is susceptible.	24 months beyond culture conversion	Consider surgery. TDM may be useful.
INH, RIF, fluoroquinolone, injectable (XDR)	5-6 second- and third-line agents. LZD, BDQ, or DLM should be used; high-dose MFX can be added (unless documented resistance). Use PZA and/or EMB if remains susceptible. Include an injectable drug if there is 1 available to which the isolate is susceptible.	24 months beyond culture conversion	Consider high-dose INH treatment if low-level resistance is documented. Consider surgery. TDM may be useful. For more recommendations, see section: <b>XDR-TB</b> .

# Specific drugs

## First-line (WHO Group 1)

### PZA

PZA is an essential first-line drug that allows shortening of an INH- and RIF-based regimen to 6 months. Its role in the treatment of MDR-TB has been uncertain because of limited availability, reliability, and reproducibility of phenotypic DST.

WHO recommends that PZA be included in all treatment regimens for MDR/XDR-TB. This recommendation is based on a systematic review and meta-analysis that reported a small benefit in treatment outcomes when PZA was included in MDR-TB regimens.

- In a 2012 retrospective analysis of the outcomes of MDR-TB in Hong Kong by Chang, et al., 194 patients were stratified by PZA use and drug susceptibility. PZA users with documented PZA susceptibility were more likely to demonstrate early culture conversion and treatment success than non-PZA users and PZA users with PZA-resistant organisms.
- In a 2015 retrospective study by Franke, et al., of 668 patients with MDR-TB in Peru, the mortality rate for a regimen of 5 likely effective drugs, including likely effective PZA (usually based on DST results), was similar to that for regimens of 5 likely effective drugs without PZA. There was no demonstrated benefit of PZA when the drug was considered unlikely to be effective.

**Conclusion:** Based on the studies noted, PZA should be included if deemed likely to be effective (drug susceptible and/or never used). In situations in which PZA resistance is documented, the drug may be discontinued.

### Rifamycin

The rifamycins (RIF, RFB, RPT) are essential first-line drugs for the treatment of drug-susceptible TB. Loss of RIF from the treatment regimen results in the need to prolong the duration of therapy to 12-18 months. By definition, MDR- and XDR-TB are resistant to RIF *in vitro* or by molecular assays documenting mutations in the *rpoB* region of the genome.

- RIF-resistant strains may be susceptible to RFB in <20% of strains tested by various DST methods. Susceptibility to RFB and resistance to RIF is strongly associated with a specific mutation Asp-516-Val which can be identified by line-probe assays or sequencing.
- RPT should not be used to treat MDR- or XDR-TB because cross-resistance with RIF is 100%.

**Conclusion:** RFB should be considered for addition to the MDR-TB treatment regimen when *in vitro* susceptibility has been documented in a reliable laboratory and especially if molecular assays document the Asp-516-Val mutation. Under these conditions, most experts would consider RFB as an adjunct to a regimen containing 4-6 likely effective drugs.

## Second-line: Injectable agents (WHO Group 2)

The aminoglycosides (KM and AK) and polypeptide (CM) are active *in vitro* against *M. tuberculosis* and represent a critical component in treatment regimens during the initial phase of therapy. They can be given either intramuscularly (IM) or intravenously (IV). SM is relatively well tolerated, but resistance to this drug is common. Many experts avoid the use of SM, even if testing shows susceptibility, if the drug has been used before. There have been no clinical trials comparing the effectiveness of the different injectables. When choosing an aminoglycoside or polypeptide agent, weigh toxicity profiles, cost, and likelihood of cross-resistance of the different drugs.

- In the WHO sponsored meta-analysis, no second-line parenteral agent was found to be superior (except that CM was more effective if the case was resistant to kanamycin [KM]).
- All of the injectable agents have potential for renal toxicity and electrolyte disorders.
- **AK** has excellent *in vitro* activity against *M. tuberculosis* and is widely available in the United States. It is easier to obtain AK serum concentrations than CM concentrations. Ototoxicity and vestibular toxicity are more common with AK than CM. The volume of injection for AK IM is larger than for the comparable dose of CM.
- **CM** has less ototoxicity and vestibular toxicity than AK and is more expensive, but the drug has been well tolerated when given for long periods of time.
- Significant electrolyte disturbances can occur with **CM** (as well as with the aminoglycosides), so close monitoring is required. There are case reports of safe use of CM in pregnancy and during breast-feeding. See **Chapter 7, Co-Morbidities and Special Situations**, section on Pregnancy.
- **SM** should be considered in patients with XDR-TB in whom the drug is likely to be effective (*in vitro* susceptible and no history of prior use). SM may be less painful than AK when given IM.
- **KM** is no longer available in the United States.

### Cross-resistance among injectables

Resistance to the aminoglycosides and polypeptides is most commonly conferred through a mutation in the *rrs* gene. Studies have reported variable rates of cross-resistance among these drugs, but in general:

- **AK**-resistant isolates are resistant to KM and occasionally CM.
- **KM**-resistant isolates are usually resistant to AK and possibly CM.
- **CM**-resistant isolates are variably resistant to KM and AK.
- **SM**-resistant isolates are usually susceptible to **other injectables** unless the other drugs have been used previously.

**Conclusion:** **AK** is usually the first choice for an injectable, because of the ease of procurement, administration, and of obtaining serum levels. **CM** should be reserved for situations in which there is demonstrated resistance to **AK** and in patients with XDR-TB, and possibly if there is pre-existing hearing loss. **CM** may also have a role in pregnant MDR-TB patients.

## Second-line: Fluoroquinolones (WHO Group 3)

The fluoroquinolones have potent *in vitro* and *in vivo* activity against *M. tuberculosis* and the loss of a fluoroquinolone from an MDR treatment regimen is associated with poor treatment outcomes. Data from *in vitro*, murine, and human studies have demonstrated that later generation fluoroquinolones (LFX, MFX, GFX) are more active than ciprofloxacin or ofloxacin (OFX) and in a murine model; MFX had superior efficacy compared with LFX.

- WHO recommends that all patients with MDR-TB receive a later generation fluoroquinolone (and specifically avoid the use of ciprofloxacin). In the individual patient meta-analysis used to formulate WHO recommendations, use of the fluoroquinolones was associated with cure and this association was strongest with later generation fluoroquinolones.
- In two retrospective studies, LFX (500-1000 mg/day) and MFX (400 mg/day) showed similar treatment success in MDR-TB patients.
- In a 2012 randomized open label trial by Koh, et al., LFX (750 mg/day) and MFX (400 mg/day) were shown to have similar culture conversion rates at 3 months.

Resistance to the fluoroquinolones is conferred by mutations in gyrase A and B. Cross-resistance among the fluoroquinolones is common but not universal. Recent studies report that approximately 30% of OFX-resistant strains are still susceptible to MFX. Several recent studies have evaluated the significance of this retained susceptibility.

- *In vitro* data and murine models have demonstrated better treatment outcomes with use of later generation fluoroquinolones in the setting of OFX resistance.
- A 2010 systematic review/meta-analysis by Jacobson, et al., reported that use of a later generation fluoroquinolone in the setting of XDR-TB was associated with better treatment outcomes.
- In a 2014 retrospective study from the Republic of Korea by Jo, et al., MDR-TB patients with OFX-resistant disease had significantly better treatment outcomes when the isolate was MFX-susceptible (treatment success in 73% vs. 42%).

Potential side effect profiles may influence choice of fluoroquinolones. Some general considerations include:

- LFX has less effect on the QT interval compared with MFX; therefore, LFX may be warranted in some cases where this is a concern such as in cases receiving CFZ and BDQ. LFX requires dose-adjustment with renal impairment (if creatinine clearance <50 mL/min), but is presumed to be safe to use with liver disease.
- MFX does not require dose adjustment in renal failure, but is infrequently associated with hepatotoxicity and thus should be used with caution in cases of liver impairment.
- For more details see **Chapter 5, Medication Fact Sheets**.

**Conclusion:** MFX or high-dose LFX (750-1000 mg) should be used in the treatment of all cases of MDR- and XDR-TB except in the setting of documented *in vitro* resistance to high concentrations of MFX. Recent studies suggest no clinical advantage between MFX or LFX for MDR-TB. When fluoroquinolone resistance is found by critical concentration or by molecular testing, an MIC—usually for MFX—can help inform whether an increase in dose may benefit the patient. Although there is minimal published evidence to support this approach, some MDR-TB experts use “high-dose” MFX at 600mg or 800mg daily for patients with MFX MIC of 1 or 2 mcg/mL. Potential side effect profiles may influence the

choice between these two agents. For further information on use of MICs or on mutations for fluoroquinolone resistance, see **Chapter 3, Laboratory**.

## Second-line: Other oral agents (WHO Group 4)

### LZD

LZD has traditionally been considered a third-line agent, but many experts now utilize this drug as a second-line drug, and in some circumstances, as a preferred agent over other second-line and third-line drugs when building a regimen. LZD exhibits variable activity *in vitro*, modest activity in murine models, and limited early bactericidal activity at 600 mg once or twice daily. Despite the limited activity in these settings, there are case reports, observational reports, and two randomized studies that suggest excellent activity in humans, although the drug is associated with a high frequency of adverse events.

- In a systematic review (11 studies, 148 patients) the pooled success rate was 68% with no significant difference in success with  $\leq 600$  mg vs  $> 600$  mg per day. Pooled estimate of any adverse event was 62%, with 36% discontinuing LZD due to adverse events.
- In 2 randomized studies, XDR-TB patients treated with LZD had higher culture conversion and treatment success than those in control arms.
  - However, in both studies, 82% of the patients had clinically significant adverse events; of these patients, 93% had events that were possibly or probably related to LZD. A 300 mg dose was associated with a lower rate of adverse reactions, but there was a trend towards acquired resistance at the lower dose.
- Early experience with LZD documented high rates of myelosuppression and neurologic toxicity (with peripheral and optic neuropathy often not reversible). Reduction in the dose from 600 mg twice daily to once daily was associated with reduced hematologic toxicity but neurotoxicity remained high with discontinuation rates as high as 70%.
- Administration of LZD concurrently with serotonergic agents, i.e. antidepressants such as selective serotonin reuptake inhibitors (SSRI), can lead to serious (sometimes fatal) reactions such as serotonin syndrome or neuroleptic malignant syndrome-like reactions.
- Using 300 mg per day, Koh, et al., in the Republic of Korea reported good treatment outcomes in XDR-TB patients, but still reported discontinuation of LZD in 27% of the patients due to peripheral neuropathy and optic neuritis.

**Conclusion:** LZD is an active drug and should be considered for all MDR- and XDR-TB regimens. In order to avoid hematologic toxicity, LZD should be given once daily at 600 mg per day. Patients should be monitored closely for development of neurologic or hematologic toxicity, and the dose reduced to 300 mg per day in selected patients who develop toxicity.

### ETA, CS, PAS

The drugs ETA, CS, and PAS are generally bacteriostatic (ETA may be weakly bactericidal at higher doses). There are few data supporting one drug over the other in terms of efficacy. In an individual data meta-analysis used to formulate current WHO recommendations, the association with cure was higher with ETA than CS, which was higher than PAS.

The decision of which drug(s) to use is often based on the side effect profile of the drug, the presence of low level cross-resistance, and the ability to measure drug serum concentrations (in the case of CS).

- Both PAS and ETA can have gastrointestinal side effects, and the combination of the two is likely to cause hypothyroidism.
- Mutations in the *inhA* region of *M. tuberculosis* can confer resistance to ETA as well as to INH at low concentrations. In this situation, ETA may not be the best choice of a second-line drug unless the organism has been shown to be susceptible with *in vitro* testing and/or no *inhA* mutation is detected.
- CS may be associated with significant neuropsychiatric adverse reactions, so serum drug concentrations should be measured. Use with caution in patients with pre-existing depression or other mental health issues. As the drug does not have significant gastrointestinal adverse reactions, it is a good companion drug with either ETA or PAS.

**Conclusion:** When choosing an oral second-line drug, **ETA** would be the first choice except in the setting of low-level INH resistance and/or the presence of an *inhA* mutation. The combination of ETA and PAS is associated with high rates of gastrointestinal intolerance and hypothyroidism.

## Third-line (WHO Group 5)

### CFZ

**CFZ** is approved for treatment of multibacillary *M. leprae*, but has been used also to treat drug-resistant TB and nontuberculous mycobacterial infections for which it has excellent activity *in vitro* and in murine models. Synergy has been demonstrated between CFZ and EMB or MFX *in vitro*. In November 2004, the manufacturer, Novartis, discontinued drug distribution in the United States. CFZ is now available through an investigational new drug (IND) application to the U.S. Food and Drug Administration (FDA). See **Chapter 5, Medication Fact Sheets** for procurement information.

- There have been three systematic reviews examining the use of CFZ for the treatment of MDR-TB. CFZ appears to be well tolerated (despite associated skin discoloration and photosensitivity).
  - Pooled severe adverse drug reactions were 0.1%, requiring withdrawal of CFZ.
  - Treatment success ranged from 17% to 88% with pooled proportion of 62% to 65%.
- CFZ-containing regimens have been associated with a higher percentage of culture conversion (40% vs 29%) and an independent predictor of conversion and survival in patients with XDR-TB.
- In a small randomized controlled trial, sputum culture conversion and cavity closure occurred earlier in patients in the CFZ-containing regimen, and treatment success was higher (74% vs. 54%).

**Conclusion:** CFZ appears to be a well-tolerated drug and likely contributes activity to a multidrug regimen.



## Carbapenems

$\beta$ -lactam antibiotics undergo rapid hydrolysis by beta lactam enzymes in *M. tuberculosis* rendering them inactive. However, the combination of amoxicillin plus a  $\beta$ -lactamase inhibitor was shown to be active *in vitro* against *M. tuberculosis* and in an early bactericidal study in humans. Although the carbapenem antibiotics are poor substrates for  $\beta$ -lactam enzymes, they have variable *in vitro* and *in vivo* activity against *M. tuberculosis*. The combination of carbapenems with the  $\beta$ -lactamase inhibitor clavulanate has been shown to improve the MIC of MPM and is bactericidal in murine tuberculosis. Clinical experience with carbapenems for the treatment of MDR/XDR-TB is limited and the duration of treatment is generally restricted to the intensive phase.

- Eight of ten patients treated with intravenous **IMP** as part of a multidrug regimen converted sputum cultures to negative, and 7 remained culture negative after treatment.
- Five of six patients with severe XDR-TB converted cultures to negative with a regimen containing **MPM plus amoxicillin/clavulanate** (included as a source for clavulanate which is not available as a free-standing drug).

**Conclusion:** Based on these studies, it appears that a **carbapenem plus clavulanate** can be used as an active component of an MDR/XDR-TB regimen.

## High-dose INH

Resistance to INH is most commonly conferred through mutations in *katG* or *inhA*. Resistance to *katG* results in inhibition of catalase activity and the development of high-level resistance (resistance at 1.0 mg/mL on solid media) to INH whereas mutations in *inhA* or the promoter region result in lower levels of resistance (resistance at 0.2 mg/mL). Theoretically, **it may be possible to overcome the resistance in the setting of low-level resistance by increasing the dose of INH.**

- Use of INH (standard dose) 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 INH.
- In a double-blind randomized controlled trial of high-dose INH (16-18 mg/kg) vs placebo in addition to second-line drugs, those who received high-dose INH were 2.38 times more likely to convert cultures to negative than those on placebo and they had a 2.37 times higher rate of being culture negative at 6 months. There was a higher frequency of peripheral neuropathy in the high-dose INH arm (but pyridoxine was not provided).

**Conclusion:** High-dose INH should be considered in patients whose isolate has low-level resistance *in vitro* and evidence of an *inhA* mutation with no evidence of a *katG* mutation.

## New drugs

### Bedaquiline (BDQ)

BDQ is a diarylquinoline drug with significant *in vitro* and *in vivo* activity against *M. tuberculosis*. Both WHO and the CDC have issued guidelines for the use of BDQ in the treatment of MDR- and XDR-TB based on the following studies:

- Efficacy of the drug has been assessed in 3 Phase IIb studies, 2 of which were randomized placebo-controlled trials and the other a noncomparative single-arm open-label trial.

- Sputum culture conversion at 8 weeks and 24 weeks was higher in the BDQ arm compared with placebo.
- A higher mortality was noted in the BDQ (12.6%) compared with the control arm (4.9%) in the 2014 Phase IIb studies by Diacon, et al. Seven patients died during the trial at a median of 386 days after the last dose. No common cause for the excess mortality was identified, but follow-up observational studies have not reported a high mortality rate.
- A total of 35 patients with MDR-TB, including 19 with XDR-TB, were treated with BDQ in a compassionate use protocol in France, reported by Guglielmetti, et al. At 6 months of treatment, culture conversion was achieved in 97%. Seven patients (20%) experienced a  $\geq 60$  milliseconds increase in QT interval leading to discontinuation in 2 (6%).
- CDC recommends that BDQ be used for 24 weeks of treatment in adults with laboratory-confirmed pulmonary MDR-TB when an effective treatment regimen cannot be provided without it. BDQ may be used on a case-by-case basis in children, HIV-positive persons, pregnant women, extrapulmonary MDR-TB, and patients with co-morbid conditions. It may be used on a case-by-case basis for longer than 24 weeks. EKG monitoring at baseline and 2, 12, and 24 weeks of treatment is advised.
- WHO recommends that BDQ may be added to a WHO-recommended regimen in adult MDR-TB patients when an effective treatment regimen containing 4 second-line drugs in addition to PZA cannot be designed, and when there is documented evidence of resistance to any fluoroquinolone in addition to multidrug resistance.
- Use of BDQ as a replacement for the injectable agent in MDR-TB is currently under investigation.
- Unfortunately, acquired resistance to BDQ has been reported.

**Conclusion:** BDQ is recommended for the treatment of MDR- and XDR-TB as part of a combination therapy (minimum 4-drug therapy) administered by DOT when an effective treatment regimen cannot be otherwise provided. There are currently no safety data on the concurrent use of DLM and BDQ.

### Delamanid (DLM)

DLM is a nitro-dihydro-imidazooxazole derivative which was approved for the treatment of MDR-TB by the European Medicines Agency (EMA), but has not yet received FDA approval. Although data regarding the use of DLM in the treatment of MDR-TB are limited, WHO has issued recommendations for the use of DLM.

- In a 2012 randomized controlled trial published by Gler, et al., 481 patients were randomized to receive DLM 100 mg twice daily, 200 mg twice daily, or placebo for 2 months in combination with a WHO-recommended regimen. Sputum culture conversion in liquid broth occurred in 45.4% of the patients taking DLM at 2 months compared with 29.6% on the placebo regimen. QT prolongation was more common, but there were no clinical events related to QT prolongation.
- In an open label study by Skripconoka, et al., reported in 2013, mortality was reduced to 1% among those who received DLM for 6 months vs 8.3% in those who received  $\leq 2$  months in a combined analysis of 3 studies.

**Conclusion:** DLM appears to be an active agent in a multidrug regimen which should be considered for treatment of MDR/XDR-TB once the drug becomes available through FDA approval (or when obtained through a compassionate use program). There are currently no safety data on the concurrent use of DLM and BDQ.

# Administration of the treatment regimen

**Case management and appropriate DOT are key activities that contribute to quality care and successful outcomes in the treatment of drug-resistant TB.**

For detailed information on monitoring and case management best practice, see **Chapter 8, *Monitoring and Case Management***.

Outcomes of treatment are 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 utilizing strong case management, DOT, and in consultation with experts in the treatment of resistant disease.**

MDR-TB can be treated primarily in the outpatient setting.

1. DOT can be delivered in the field or clinic (or through newer video technology).
2. Dosing of oral medications for MDR/XDR-TB should always be daily, not intermittent.
3. Although 7-days-per-week DOT is optimal, this may not be programmatically feasible. If 7-days-per-week is not possible, 5-days-per-week DOT can be used for patients who are not hospitalized or institutionalized, with medications self-administered on weekends.
4. Injectable agents are typically given 5 days per week for at least 2-3 months (and until culture conversion is documented); after which, 3-days-per-week dosing can be used for the remaining duration of injectable use, normally through at least 6 months beyond culture conversion.
5. In patients who are severely ill, treatment should be administered 7 days per week (including the injectable drugs).

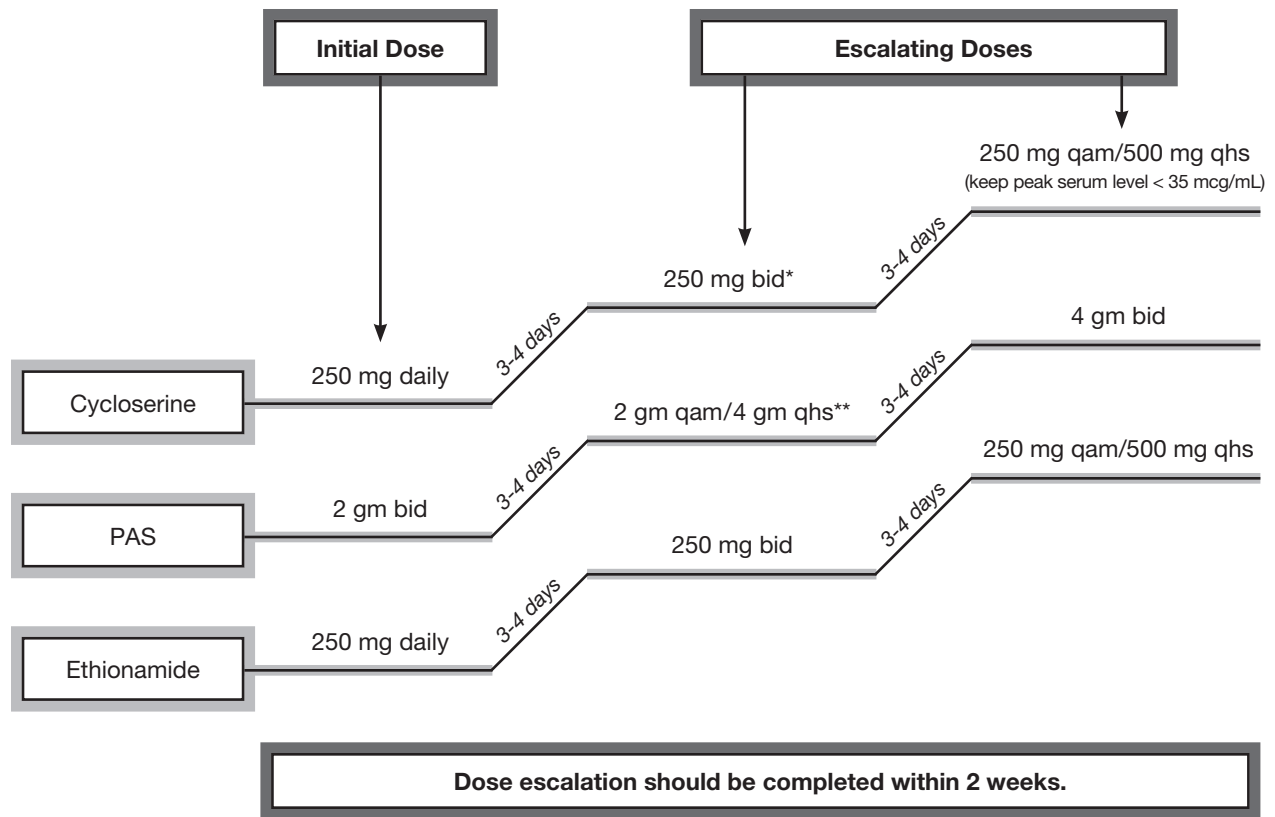
*Treat all forms of drug-resistant TB utilizing strong case management, DOT, and in consultation with experts in the treatment of resistant disease.*

## Escalation of dosages (drug ramping)

Most drugs should be started at full dose except **CS**, **ETA**, and **PAS**, in which case the dose of the drug can be increased over a 1-2-week period. Beginning with a low dose and gradually increasing the dose leads to greater tolerability and allows the clinician time to manage drug-related adverse effects. This approach of slowly escalating drug dosage is referred to as “drug ramping.” Obtain serum drug levels (especially for CS) 1-2 weeks after the goal dose has been reached. See examples of drug ramping in Figure 3.

FIGURE 3.

## Dose escalation (drug ramping)



The patient is begun on a low starting dose and the dose is increased every few days until the targeted dose is reached. The dose escalation should be completed within 2 weeks. Some patients will tolerate consolidation of all three drugs to once daily dosing which can enhance adherence.

\* For some patients, daily dose of cycloserine 500 mg may achieve goal serum concentration.

\*\*Goal of PAS 6 gm daily may be appropriate for smaller patients.

## Therapeutic drug monitoring (TDM)

### When to order TDM

TDM is routinely used for several circumstances:

- **Aminoglycoside/CM** serum concentrations, especially in patients with renal impairment
- **CS** concentrations in order to minimize risk of central nervous system (**CNS**) **toxicity** and to safely use optimal dose
- Known or suspected **malabsorption** (e.g., diabetes, gastrointestinal disorders)
- **Lack of expected clinical response** or **relapse** while on appropriate drugs and doses, administered by DOT
- Patients with **few effective drugs** in their regimen, in order to optimize the effect of available drugs

- Patients with potentially significant **drug-drug interactions** such as rifamycins and antiretrovirals
- **EMB** concentrations in patients with significant **renal impairment**

Many drug-resistant TB experts routinely monitor certain TB drug concentrations in anticipation of toxicity and to escalate a drug dose when possible.

## How to interpret results of TDM

Interpret drug levels in the context of several factors:

- Timing of blood draw relative to administration
- Evidence for poor response to treatment or side effects
- Known factors likely to increase or decrease clearance of drug (e.g., renal dysfunction, liver dysfunction, drug interactions)

Serum concentrations answer the question, “Does my patient have adequate drug exposure?”

- Published normal ranges, under most circumstances, represent safe and effective drug exposures.
- Like other tests, serum concentrations cannot by themselves predict failures or relapses. They can indicate if the patient has lower than expected drug exposure for a given dose of a given drug, and that problem is readily correctable with concentration-guided dose escalation.
- If a reported drug concentration is not consistent with the clinical scenario, consider repeating the test prior to dose adjustment.

**Maximum concentration ( $C_{max}$ ) and half-life ( $t_{1/2}$ ):** Two concentrations separated by several hours (usually 4 hours) can be used by a pharmacist to calculate a maximum concentration ( $C_{max}$ ) and a half-life ( $t_{1/2}$ ). These concentrations can also detect delayed absorption and malabsorption. Generally, the 2-hour sample is higher than the 6-hour sample. When there is delayed absorption, 6-hour values are higher than 2-hour values, and the 6-hour level may approach the therapeutic range. In cases of malabsorption, both values are low. Calculation of  $C_{max}$  and  $t_{1/2}$  is not appropriate when 6-hour values are higher than 2-hour values.

- **If drug concentration is higher than planned,** consider reducing dose of the drug especially if signs of toxicity are present (e.g., agitation or depression with a high CS level, or hearing loss with AK).
- **If drug concentration is lower than planned,** consider increasing dose of the drug to achieve a concentration in the planned range. Typical “maximum” doses of drugs can be exceeded when serum concentrations are low, but this should be done with caution and monitoring.

For information on where to obtain TDM tests, instructions on timing of blood collected for specific anti-TB drugs, and processing of specimens, see **Chapter 3, Laboratory**.

# Role of surgery in the treatment of drug-resistant TB

Surgery is sometimes necessary to cure patients with MDR- or XDR-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.

Two systematic reviews/meta-analyses and an extensive review have evaluated the impact of surgery and its associated risks:

- Estimated pooled treatment success rate of pulmonary resection for patients with MDR-TB of 84%, with 92% achieving early success (30 days post-operative) and 87% long-term success. Patients who had surgical resection were twice as likely to have a favorable outcome as those who received chemotherapy alone and they were less likely to die.
- Predictors of good outcomes across the studies included surgical resection, body mass index (BMI)  $\geq 18.5$ , and use of  $\geq 4$  effective drugs in the treatment of MDR/XDR-TB.
- Perioperative morbidity and mortality has ranged between 0-39% (median 23%) and 0-5% (median 1.3%), respectively.
- In a subgroup analysis of 5 studies reporting outcomes of 422 XDR-TB patients, there was an even larger treatment effect related to surgery.

## Surgery should be considered:

- When cultures continue to be positive beyond 4 to 6 months of treatment for MDR/XDR-TB; and/or
- When extensive patterns of drug resistance exist that are unlikely to be cured with chemotherapy alone; and/or
- When patients develop complications such as massive hemoptysis or persistent bronchopleural fistula.

## To maximize the potential success of surgery:

- 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 smear conversion has occurred, and ideally after culture conversion.
- Even after successful lung resection, the patient should complete a full course of treatment. If there are no positive cultures after surgery, the date of surgery can be considered the date of culture conversion.

# Outcomes of treatment

Treatment outcomes for MDR-TB vary depending on a number of factors, including the drug-resistance pattern and the drugs used in the treatment regimen. Two systematic reviews including 36 observational studies reported pooled treatment success rates of 62% (range: 36% to 79%). None of the studies included in the systematic reviews included new drugs such as BDQ and DLM.

Factors associated with **treatment success** include:

- Treatment duration of at least 18 months
- DOT throughout treatment
- Surgical resection
- Fluoroquinolone use
- No previous treatment

Factors associated with **unfavorable outcomes** include:

- Male gender
- Alcohol abuse
- Low BMI (lack of weight gain)
- Smear positivity at diagnosis
- Fluoroquinolone resistance
- Presence of XDR resistance pattern

As described in a 2014 paper by Marks, et al., treatment outcomes in the United States are more favorable. Among 134 patients with MDR/XDR-TB who were alive at diagnosis and followed for treatment outcomes in the United States between 2005-2007, 78% completed therapy, 9% were transferred, 2% lost to follow-up, 1% stopped because of adverse reactions, and 9% died. Ninety-seven percent of the patients' sputum cultures converted to negative.



## Summary

- Consultation with an expert should be obtained in all cases of MDR/XDR-TB.

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- Design of individualized MDR-TB regimens should be based on DST results, prior history of TB treatment, potential for cross-resistance, potential for overlapping drug toxicities, and other key clinical and epidemiologic factors.

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- MDR-TB regimens should contain at least 4-6 likely effective drugs (optimally 5), and XDR-TB regimens should contain at least 6 likely effective drugs.

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- For MDR-TB:
  - The intensive phase of treatment should continue at least 6 months beyond culture conversion.
  - The continuation phase should continue at least 18 months beyond culture conversion.

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- For XDR-TB:
  - The total duration of treatment should be at least 24 months beyond culture conversion.

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- Case management is critical to successful treatment in drug-resistant TB.

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- DOT should be used for all patients with MDR/XDR-TB.

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- New drugs may eventually lead to better outcomes and shorter durations of therapy.

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# 5

# Medication Fact Sheets

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## AMIKACIN (AK) [ 1 of 2 ]

<b>Drug class</b>	Aminoglycoside
<b>Trade name</b>	Amikacin/Amikin
<b>Activity against TB</b>	<b>Bactericidal;</b> has strong anti-TB activity. Cross-resistance with kanamycin and some data suggesting cross-resistance with capreomycin.
<b>Cross-resistance</b>	Kanamycin; variable frequency of cross-resistance with capreomycin has been reported
<b>Dose (all once daily)</b>	<p><b>Adults:</b> 15 mg/kg/day in a single daily dose, 5–7 days per week 15 mg/kg/dose, 2–3 times per week can be used after culture conversion is documented after initial period of daily administration (some experts use up to 25 mg/kg/dose for intermittent therapy; monitor concentrations).</p> <p><b>&gt; 59 yrs of age:</b> Many experienced clinicians prefer to use a lower starting dose of 10 mg/kg/dose (max 750 mg) 5–7 times per week or 2–3 times per week after initial period. Alternatively, 15 mg/kg/dose 3 times per week</p> <p><b>Children:</b> 15–30 mg/kg/day (max 1 gram) 5–7 days per week. 15–30 mg/kg/day (max 1 gram) 3 days per week after initial period daily.</p> <p><b>Renal failure/dialysis:</b> 12–15 mg/kg/dose after dialysis 2-3 times weekly (not daily).</p> <p><b>Markedly obese individuals</b> should have an adjusted dose due to the decreased distribution of extracellular fluids in adipose tissues. Dosing based on actual weight will give supratherapeutic concentrations.</p> <p><b>For dosing, use adjusted weight as follows:</b> Ideal body weight + 40% of 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</p> <p><i>Concentrations should be followed closely.</i></p>
<b>Route of administration</b>	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.
<b>Preparation</b>	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).
<b>Storage</b>	Solution in original vial is stable at room temperature; diluted solution is stable at room temperature at least 3 weeks or in the refrigerator at least 60 days.
<b>Pharmacokinetics</b>	<p>For intravenous administration, infuse over 30-60 minutes for adults; 1–2 hours for children; intramuscular absorption is complete within 4 hours and peak concentrations are achieved at 1–2 hours. Obtaining a drug concentration 90–120 minutes after intravenous infusion allows for complete distribution of drug. An additional concentration collected 4 hours later will allow for a half-life to be calculated and peak to be back-extrapolated.</p> <p><b>Peak concentrations</b> for a 15 mg/kg dose are between 35 and 45 mcg/ml.</p> <p><b>Peak concentrations</b> of 65–80 mcg/ml are obtained after a 25 mg/kg dose.</p> <p>Trough concentrations are generally &lt; 5 mcg/ml in patients with normal renal function.</p>
<b>Oral absorption</b>	There is no significant oral absorption. Intramuscular absorption might be delayed if the same site is used consistently.

# AMIKACIN (AK) [ 2 of 2 ]

<b>CSF penetration</b>	Variable penetration; appears to penetrate inflamed meninges better.
<b>Special circumstances</b>	<p><b>Use in pregnancy/breastfeeding:</b> Generally avoided in pregnancy due to congenital deafness seen with streptomycin and kanamycin. Can be used while breastfeeding.</p> <p><b>Use in renal disease:</b> Use with caution. Concentrations 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 variably cleared by hemodialysis.</p> <p><b>Use in hepatic disease:</b> Drug concentrations 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.</p> <p><b>Diuretic use:</b> Coadministration of loop diuretics and aminoglycoside antibiotics carries an increased risk of ototoxicity.</p>
<b>Adverse reactions</b>	<p>Nephrotoxicity: 9% for general population (may be lower for once-daily use, higher for prolonged use).</p> <p>Ototoxicity (hearing loss): Increased with advanced age and prolonged use.</p> <p>Vestibular toxicity.</p> <p>Local pain with IM injections.</p> <p>Electrolyte abnormalities, including hypokalemia, hypocalcemia, and hypomagnesemia.</p>
<b>Contraindications</b>	<p><b>Pregnancy</b> — relative contraindication (congenital deafness seen with streptomycin and kanamycin use in pregnancy).</p> <p><b>Hypersensitivity to aminoglycosides.</b></p> <p><b>Caution with renal, hepatic, vestibular, or auditory impairment.</b></p>
<b>Monitoring</b>	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 concentrations at baseline if there is any question about renal function. Some experts monitor aminoglycoside concentrations routinely, regardless of renal function. Monitor concentrations serially for patients with impaired renal function.
<b>2012 wholesale cost</b> 30-day supply, 60-kg person	\$176 (outpatient public health pricing) \$324 (community hospital)
<b>Patient instructions</b>	<p><b>Call your doctor right away if you have:</b></p> <ul style="list-style-type: none"> <li>• Problems with hearing, dizziness, or balance</li> <li>• Rash or swelling of your face</li> <li>• Trouble breathing</li> <li>• Decreased urination</li> <li>• Swelling, pain, or redness at your IV site</li> <li>• Muscle twitching or weakness</li> </ul>

## AMOXICILLIN/CLAVULANATE (AMX/CLV) [1 of 2]

<b>Drug class</b>	Penicillin/beta-lactam inhibitor
<b>Trade name</b>	Augmentin XR or Augmentin ES-600 suspension
<b>Activity against TB</b>	Conflicting and limited reports, but possible early bactericidal activity.
<b>Cross-resistance</b>	None reported
<b>Dose</b>	<p><b>Adults:</b> 2000 mg as amoxicillin/125 mg clavulanate twice daily.</p> <p><b>Children:</b> 80 mg/kg/day divided twice daily of the amoxicillin component.</p> <p><b>Renal failure/dialysis:</b> For creatinine clearance 10–30 ml/min dose 1000 mg as amoxicillin twice daily; for creatinine clearance &lt; 10 ml/min dose 1000 mg as amoxicillin once daily.</p> <p><b>Hemodialysis:</b> Single dose every 24 hours and after each dialysis session.</p>
<b>Route of administration</b>	Oral. Imipenem/cilastatin should be used if a parenteral beta-lactam drug is desired.
<b>Preparation</b>	For adults: 1000 mg amoxicillin/62.5 mg clavulanate (Augmentin XR) tablets, 2 tablets twice daily; for pediatric dosing: 600 mg/5ml product (Augmentin ES-600). A less expensive equivalent can be achieved by prescribing generic amoxicillin/clavulanate and additional amoxicillin to achieve the same total daily dose of amoxicillin and clavulanate (for adults: 4000 mg amoxicillin and 250 mg clavulanate divided twice daily).
<b>Storage</b>	Tablets are stable at room temperature; reconstituted suspension should be stored in the refrigerator and discarded after 10 days.
<b>Pharmacokinetics</b>	<p>Time to peak oral concentration is 60–90 minutes.</p> <p><b>Serum concentrations</b> of 17 mcg/ml of amoxicillin were reported following a 2000 mg (as amoxicillin) dose.</p>
<b>Oral absorption</b>	Good oral absorption, best tolerated and well absorbed when taken at the start of a standard meal.
<b>CSF penetration</b>	Approximately 5% of the plasma concentration reaches the CSF.
<b>Special circumstances</b>	<p><b>Use in pregnancy/breastfeeding:</b> Probably safe in pregnancy (no known risk); can be used while breastfeeding.</p> <p><b>Use in renal disease:</b> 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).</p> <p><b>Use in hepatic disease:</b> Clavulanate is cleared by the liver, so care should be used when using in patients with liver failure.</p>
<b>Adverse reactions</b>	<p>Diarrhea and abdominal discomfort are most common.</p> <p>Hypersensitivity.</p> <p>Nausea, vomiting, and rash are also common.</p> <p>Rare side effects have been reported in all other organ systems.</p>

# AMOXICILLIN/CLAVULANATE (AMX/CLV) [ 2 of 2 ]

<b>Contraindications</b>	Penicillin allergy; use with caution with cephalosporin allergies.
<b>Monitoring</b>	No specific monitoring is required.
<b>2012 wholesale cost</b> 30-day supply, 60-kg person	\$241 (outpatient public health pricing) \$294 (community hospital)
<b>Patient instructions</b>	<p>Take at the beginning of a meal.</p> <p>Store tablets at room temperature; store suspension in the refrigerator—throw away after 10 days and refill the prescription.</p> <p><b>Call your doctor right away if you have:</b></p> <ul style="list-style-type: none"><li>• Rash or swelling</li><li>• Trouble breathing</li><li>• Severe diarrhea</li></ul>

# BEDAQUILINE (BDQ) [1 of 2]

<b>Drug class</b>	Diarylquinolone									
<b>Trade name</b>	Sirturo									
<b>Activity against TB</b>	Bactericidal; has strong anti-TB activity. Inhibits adenosine 5'-triphosphate (ATP) synthase with <i>in vitro</i> activity against both replicating and nonreplicating bacilli.									
<b>Cross-resistance</b>	Cross-resistance with clofazimine has been demonstrated in both directions through efflux-based resistance.									
<b>Dose</b>	<p><b>Adults:</b> 400 mg daily for 14 days, followed by 200 mg 3 times weekly for 22 weeks. Has not been studied past 24 weeks of administration.</p> <p><b>Missed doses:</b> After the first 2 weeks of treatment, the dose changes to the 200 mg three times per week, even if doses were missed during the first 2 weeks. Patients should not make up for missed doses during the first 2 weeks of treatment.</p> <p><b>Concomitant medications:</b> Bedaquiline is metabolized by CYP3A4 and co-administration of rifamycins (e.g., rifampin, rifapentine and rifabutin) or other strong CYP3A4 inducers may require dose adjustment. See Section 7 in <a href="http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/204384s000lbl.pdf">http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/204384s000lbl.pdf</a>.</p> <p><b>Children:</b> Has not been studied in children. Based strictly on weight, converting from the adult doses in a 70 kg patient, estimated pediatric doses would be 6 mg/kg daily for 14 days, followed by 3 mg/kg 3times weekly for 22 weeks. However, these doses are not supported by clinical experience.</p> <p><b>Renal failure/dialysis:</b> No dose adjustment needed for mild to moderate renal insufficiency, but should be used with caution in patients requiring renal dialysis.</p>									
<b>Route of administration</b>	Oral.									
<b>Preparation</b>	100 mg tablets.									
<b>Storage</b>	Store at room temperature. Tablets removed from the original packaging should be stored in a tight, light-resistant container and labeled with an expiration date not to exceed 3 months.									
<b>Pharmacokinetics</b>	<p><b>Peak oral absorption</b> occurs approximately 5 hours post dose. Administration with a standard meal increases bioavailability about 2-fold, therefore drug should be taken with food. The drug is highly protein-bound. Bedaquiline has a mean terminal half-life of 5.5 months. This likely reflects slow release from peripheral tissues.</p> <p><b>Peak concentrations</b> typically occur 5-6 hours after the dose is given. Serum concentrations are not clinically available.</p> <p><b>Peak concentrations</b> depend on the size and number of doses:</p> <table border="1"> <thead> <tr> <th>Dose (daily)</th> <th>N doses</th> <th>C<sub>max</sub> (mcg/ml)</th> </tr> </thead> <tbody> <tr> <td>200 mg</td> <td>14th dose</td> <td>2.7 (1.7-4.3)</td> </tr> <tr> <td>400 mg</td> <td>14th dose</td> <td>4.5 (2.4-13.6)</td> </tr> </tbody> </table>	Dose (daily)	N doses	C <sub>max</sub> (mcg/ml)	200 mg	14th dose	2.7 (1.7-4.3)	400 mg	14th dose	4.5 (2.4-13.6)
Dose (daily)	N doses	C <sub>max</sub> (mcg/ml)								
200 mg	14th dose	2.7 (1.7-4.3)								
400 mg	14th dose	4.5 (2.4-13.6)								
<b>Oral absorption</b>	Good oral absorption. Should be given with a meal to increase bioavailability.									
<b>CSF penetration</b>	No data available. Also, there are no data on the treatment of extra-pulmonary TB (e.g., central nervous system) with bedaquiline.									

# BEDAQUILINE (BDQ) [ 2 of 2 ]

<p><b>Special circumstances</b></p>	<p><b>Use in pregnancy/breastfeeding:</b> Pregnancy category B. No fetal harm found in animal studies. The drug is concentrated in breast milk and avoiding nursing should be considered.</p> <p><b>Use in renal disease:</b> No dose adjustment needed for mild to moderate renal insufficiency but should be used with caution in patients requiring peritoneal or hemodialysis. Drug level monitoring may be useful, once available.</p> <p><b>Use in hepatic disease:</b> No dose adjustment is necessary for bedaquiline in patients with mild or moderate hepatic impairment. Bedaquiline has not been studied in patients with severe hepatic impairment and should be used with caution in these patients, and only when the benefits outweigh the risks. Clinical monitoring for bedaquiline -related adverse reactions is recommended.</p>
<p><b>Adverse reactions</b></p>	<p>QTc prolongation, hepatitis, nausea, joint pain, headache, elevated amylase, coughing up blood, chest pain, loss of appetite, and/or rash.</p>
<p><b>Contraindications</b></p>	<p>None, but use with caution if other QTc prolonging agents, such as clofazimine or fluoroquinolones, are being given.</p>
<p><b>Monitoring</b></p>	<p>EKG at baseline, 2, 12 and 24 weeks of treatment. Stop bedaquiline if QTc &gt; 500 and monitor EKGs frequently until QTc returns to normal. Baseline potassium, calcium and magnesium, repeat if QTc prolongation occurs, and monthly if on injectable drug. Baseline and monthly LFTs.</p>
<p><b>Warning</b></p>	<p>An increased risk of death was seen in the bedaquiline treatment group (9/79, 11.4%) compared to the placebo treatment group (2/81, 2.5%) in one placebo-controlled trial. There was no pattern to the causes of death, and cause and effect could not be established. Only use bedaquiline when an effective treatment regimen cannot otherwise be provided.</p> <p>QTc prolongation can occur with bedaquiline. Use with drugs that prolong the QTc interval may cause additive QTc prolongation.</p>
<p><b>2014 wholesale cost</b> 24-week supply, 60-kg person</p>	<p>\$23,070 (outpatient public health pricing) \$30,000 (community hospital)</p>
<p><b>Patient instructions</b></p>	<p>Avoid alcohol. Take medication with food</p> <p><b>Call your doctor and stop the medicine right away if you have:</b></p> <ul style="list-style-type: none"> <li>• <b>serious heart rhythm changes (QTc prolongation).</b> Tell your healthcare provider right away if you have a change in your heartbeat (a fast or irregular heartbeat), or if you faint.</li> <li>• <b>liver problems (hepatotoxicity).</b> Call your healthcare provider right away if you have unexplained symptoms such as nausea or vomiting, stomach pain, fever, weakness, itching, unusual tiredness, loss of appetite, light-colored bowel movements, dark-colored urine, yellowing of your skin or the white of your eyes.</li> </ul>

## CAPREOMYCIN (CM) [ 1 of 2 ]

<b>Drug class</b>	Cyclic polypeptide
<b>Trade name</b>	Capastat
<b>Activity against TB</b>	<b>Bactericidal;</b> has strong anti-TB activity; inhibits protein synthesis. Some data suggesting cross-resistance with amikacin and kanamycin.
<b>Cross-resistance</b>	Amikacin and kanamycin. Variable frequency of cross-resistance has been reported.
<b>Dose (all once daily)</b>	<p><b>Adults:</b> 15 mg/kg/day in a single daily dose, 5–7 days per week 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 concentrations).</p> <p><b>&gt; 59 yrs of age:</b> Many experienced clinicians prefer to use a lower starting dose of 10 mg/kg/dose (max 750 mg) 5–7 times per week or 2–3 times per week after initial period. Alternatively, 15 mg/kg/dose 3 times per week.</p> <p><b>Children:</b> 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.</p> <p><b>Renal failure/dialysis:</b> 12–15 mg/kg/dose 2–3 times weekly (not daily).</p> <p><b>Markedly obese individuals</b> should have an adjusted dose due to the decreased distribution of extracellular fluids in adipose tissues. Dosing based on actual weight will give supratherapeutic concentrations.</p> <p><b>For dosing, use adjusted weight as follows:</b> Ideal body weight + 40% of 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 <i>Concentrations should be followed closely.</i></p>
<b>Route of administration</b>	IV or IM.
<b>Preparation</b>	Capreomycin is available in vials of 1 gram for either IM or IV administration. The contents of the vial should be reconstituted with 2 ml or more of NS or sterile water.
<b>Storage</b>	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.
<b>Pharmacokinetics</b>	<p>Intramuscular peak concentrations are achieved at 2 hours. Obtaining a drug concentration 90–120 minutes after intravenous infusion allows for complete distribution of drug. An additional concentration collected 4 hours later will allow for a half-life to be calculated and peak to be back-extrapolated.</p> <p><b>Peak concentrations</b> for a 15 mg/kg dose are between 35 and 45 mcg/ml.</p> <p><b>Peak concentrations</b> of 65–80 mcg/ml are obtained after a 25 mg/kg dose.</p> <p>Trough concentrations should be &lt; 5 mcg/ml in patients with normal renal function.</p>
<b>Oral absorption</b>	There is no significant oral absorption. Intramuscular absorption might be delayed if the same site is used consistently.
<b>CSF penetration</b>	There is a paucity of data regarding capreomycin's penetration of the meninges.



# CAPREOMYCIN (CM) [ 2 of 2 ]

<p><b>Special circumstances</b></p>	<p><b>Use in pregnancy/breastfeeding:</b> 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.</p> <p><b>Use in renal disease:</b> Use with caution. Concentrations 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 7, <i>Co-morbidities and Special Situations – Renal Failure</i>.</p> <p><b>Use in hepatic disease:</b> Drug concentrations 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.</p>
<p><b>Adverse reactions</b></p>	<p>Similar to the aminoglycosides.</p> <p>Nephrotoxicity: 20%–25% including proteinuria, reduced creatinine clearance, and depletion of potassium and magnesium.</p> <p>Ototoxicity (hearing loss): Occurs more often in elderly persons or those with pre-existing renal impairment; vestibular toxicity.</p> <p>Local pain with IM injections.</p> <p>Electrolyte abnormalities, including hypokalemia, hypocalcemia, and hypomagnesemia.</p> <p>Liver function test abnormalities when used with other TB drugs.</p>
<p><b>Contraindications</b></p>	<p><b>Hypersensitivity to capreomycin.</b> Some experts would not use capreomycin if vestibular side effects resulted from aminoglycoside use.</p> <p><b>Generally avoided in pregnancy</b> due to congenital deafness seen with aminoglycosides and mechanism of ototoxicity may be similar with capreomycin. There are case reports of its safe use in pregnancy (unaffected newborns).</p>
<p><b>Monitoring</b></p>	<p>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 concentrations at baseline if there is any question about renal function. Some experts monitor capreomycin concentrations routinely, regardless of renal function. Monitor concentrations serially for patients with impaired renal function.</p>
<p><b>2012 wholesale cost</b> 30-day supply, 60-kg person</p>	<p>\$349 (outpatient public health pricing) \$3,598 (community hospital)</p>
<p><b>Patient instructions</b></p>	<p><b>Call your doctor right away if you have:</b></p> <ul style="list-style-type: none"> <li>• Rash</li> <li>• Fever or chills</li> <li>• Bleeding or bruising</li> <li>• Problems with hearing, dizziness, or balance</li> <li>• Bleeding or a lump where the shot is given</li> <li>• Decreased urination</li> <li>• Trouble breathing</li> <li>• Muscle weakness</li> </ul>

## CLARITHROMYCIN (CLR) [1 of 2]

<b>Drug class</b>	Macrolide
<b>Trade name</b>	Biaxin
<b>Activity against TB</b>	Much more active against nontuberculous mycobacteria, especially MAC, but some isolates of TB are susceptible <i>in vitro</i> . Does not have proven value for the treatment of TB in humans, and <i>in vitro</i> data are not particularly encouraging. Inhibits protein synthesis by binding to the 50S ribosomal subunit.
<b>Cross-resistance</b>	None reported.
<b>Dose</b>	<p><b>Adults:</b> 500 mg twice daily or 1 gram daily of extended release formulation</p> <p><b>Children:</b> 7.5 mg/kg q 12 hours up to 500 mg</p> <p><b>Renal failure/dialysis:</b> The drug is cleared both hepatically and renally. In severe renal impairment, the interval between doses should be increased, i.e., 500 mg daily.</p>
<b>Route of administration</b>	Oral
<b>Preparation</b>	Oral tablets of 250 and 500 mg. Also available in Extended Release tablets for once daily use. Oral suspension 125 mg/5 ml and 250 mg/5 ml.
<b>Storage</b>	Store tablets and unmixed granules for suspension at room temperature in a well sealed container and protect from light. The mixed suspension should not be refrigerated and can be stored for 14 days.
<b>Pharmacokinetics</b>	<p><b>Peak oral absorption</b> occurs at 2–3 hours after the drug dose.</p> <p><b>Peak concentrations</b> of 2–7 mcg/ml are expected after an oral dose of 500 mg in the nonfasting adult. Because of high intracellular concentrations, tissue levels are higher than in the serum.</p>
<b>Oral absorption</b>	The drug is rapidly absorbed after oral administration and is about 50% bioavailable. It can be given without regard to food. Food slightly delays the peak serum level but also slightly increases the peak concentration achieved.
<b>CSF penetration</b>	There is no information available about CNS penetration
<b>Special circumstances</b>	<p><b>Pregnancy/Breastfeeding:</b> Pregnancy category C and generally should not be used in pregnancy unless no other alternative is available. It is not known if the drug is excreted in human breast milk.</p> <p><b>Use in renal disease:</b> The interval between doses should be increased in severe renal disease. See Chapter 7, <i>Co-morbidities and Special Situations – Renal Failure</i>.</p> <p><b>Use in hepatic disease:</b> No adjustment is necessary.</p>
<b>Adverse reactions</b>	<p>Diarrhea, nausea, abnormal taste, dyspepsia, abdominal pain/discomfort, headache.</p> <p><b>Rare</b> allergic skin reactions, liver toxicity, QT prolongation, <i>C.diff</i> colitis, hearing loss</p>

## CLARITHROMYCIN (CLR) [ 2 of 2 ]

<b>Contraindications</b>	<b>Patients with known hypersensitivity to macrolide antibiotics.</b> <b>Should not be given with the any of the following drugs:</b> Cisapride, pimozone, astemizole, terfenadine, and ergotamine or dihydroergotamine.
<b>Monitoring</b>	No routine laboratory monitoring is indicated.
<b>2012 wholesale cost</b> 30-day supply, 60-kg person	\$16 (outpatient public health pricing) \$271 (community hospital)
<b>Patient instructions</b>	This medication may be taken with or without food. Be sure to tell your doctor what other medications you are taking. Do not take cisapride, pimozone, astemizole, terfenadine, and ergotamine or dihydroergotamine when taking clarithromycin. Stop the medication and call your doctor immediately if you develop severe diarrhea.

## CLOFAZIMINE (CFZ) [ 1 of 2 ]

<b>Drug class</b>	Iminophenazine
<b>Trade name</b>	Lamprene
<b>Activity against TB</b>	<i>In vitro</i> activity against <i>M. tuberculosis</i> without much <i>in vivo</i> data. Generally reserved for cases with few other options.
<b>Cross-resistance</b>	Bedaquiline. Cross-resistance has been reported in both directions through efflux-based resistance.
<b>Dose (all once daily)</b>	<p><b>Adults:</b> 100 to 200 mg daily (oral) have been used. A regimen of 200 mg daily for 2 months, followed by 100 mg daily has been used.</p> <p><b>Children:</b> Limited data, but doses of 1 mg/kg/day have been given.</p> <p><b>Renal failure/dialysis:</b> No adjustment required.</p>
<b>Route of administration</b>	Oral; not available parenterally.
<b>Preparation</b>	50 and 100 mg capsules.
<b>Storage</b>	Room temperature.
<b>Pharmacokinetics</b>	<p>Tissue half-life estimated to be around 70 days.</p> <p><b>Peak concentrations</b> 2–3 hours after a dose are expected to be 0.5–2.0 mcg/ml.</p> <p><b>Peak concentrations</b> occur at 4–8 hours when given with food.</p>
<b>Oral absorption</b>	70% absorption after an oral dose.
<b>CSF penetration</b>	Limited data are available regarding CNS penetration.
<b>Special circumstances</b>	<p><b>Use in pregnancy/breastfeeding:</b> 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.</p> <p><b>Use in renal disease:</b> No dosage adjustment required.</p> <p><b>Use in hepatic disease:</b> Partially metabolized by the liver; use caution and/or adjust the dose for severe hepatic insufficiency.</p>
<b>Adverse reactions</b>	<p>Pink or red discoloration of skin, conjunctiva, cornea, and body fluids.</p> <p>Gastrointestinal intolerance.</p> <p>Photosensitivity.</p> <p>Other side effects include retinopathy, dry skin, pruritus, rash, ichthyosis, xerosis, and severe abdominal symptoms, bleeding, and bowel obstruction.</p>
<b>Contraindications</b>	<b>Allergy to clofazimine.</b>
<b>Monitoring</b>	Symptomatic monitoring.

## CLOFAZIMINE (CFZ) [ 2 of 2 ]

### 2012 wholesale cost

Clofazimine is not commercially available within the United States. Clinicians should contact the FDA's Office of Emergency Operations (866-300-4374 or 301-796-8240) in order to apply for a single patient Investigational New Drug (IND). The drug is made available on a case-by-case basis without charge.

### 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 (CS) [ 1 of 2 ]

<b>Drug class</b>	Analog of D-alanine
<b>Trade name</b>	Seromycin
<b>Activity against TB</b>	<b>Bacteriostatic;</b> inhibits cell wall synthesis.
<b>Cross-resistance</b>	None reported
<b>Dose</b>	<p><b>Adults:</b> 10–15 mg/kg/day usually; 250 mg PO twice a day or 500 mg PO in a single dose; can increase to 250 mg PO 3 times a day or 250 mg QAM and 500 mg PO QHS if peak concentrations are kept below 35 mcg/ml. Some patients may require only alternate day 250 mg and 500 mg dosing to achieve desired blood levels.</p> <p><b>Children:</b> 10–20 mg/kg/day divided every 12 hours (daily maximum 1 gram).</p> <p><b>Vitamin B6:</b> Although supporting data are not extensive, MDR-TB experts recommend that all patients should receive vitamin B6 while taking cycloserine. Adults need 100 mg or more (or 50 mg per 250 mg of cycloserine) and children should receive a dose proportionate to their weight.</p> <p><b>Renal failure/dialysis:</b> 250 mg once daily or 500 mg 3 times per week; monitor drug concentrations to keep peak concentrations &lt; 35 mcg/ml. See Chapter 7, <i>Co-morbidities and Special Situations – Renal Failure</i>.</p>
<b>Route of administration</b>	Oral; not available parenterally.
<b>Preparation</b>	250 mg capsule.
<b>Storage</b>	Room temperature in airtight containers.
<b>Pharmacokinetics</b>	<p><b>Peak oral absorption</b> usually occurs by 2 hours (may be up to 4 hours).</p> <p><b>Peak concentration</b> should be drawn at 2 hours; if delayed absorption is suspected, a concentration at 6 hours will be helpful. A concentration at 10 hours will allow for calculation of the half-life. Allow 3–4 days of drug administration before drawing concentrations due to the long half-life.</p> <p><b>Peak concentrations</b> are expected to be between 20 and 35 mcg /ml. CNS toxicity is associated with concentrations over 35 mcg/ml, but may occur even at lower concentrations. Some MDR-TB clinicians prefer to keep the concentration below 30 mcg/ml.</p>
<b>Oral absorption</b>	Modestly decreased by food (best to take on an empty stomach); not significantly affected by antacids or orange juice.
<b>CSF penetration</b>	Concentrations approach those in serum.
<b>Special circumstances</b>	<p><b>Use in pregnancy/breastfeeding:</b> 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).</p> <p><b>Use in renal disease:</b> Cycloserine is cleared by the kidney and requires dose adjustment for renal failure (see above). Use with caution.</p> <p><b>Use in hepatic disease:</b> Not associated with hepatotoxicity.</p>

## CYCLOSERINE (CS) [ 2 of 2 ]

<b>Adverse reactions</b>	CNS toxicity, including inability to concentrate and lethargy. More serious CNS side effects, including seizure, depression, psychosis, and suicidal ideation, <i>usually</i> occur at peak concentrations > 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.
<b>Contraindications</b>	<b>Significant CNS disease</b> , including seizure disorder, psychotic disease, or alcohol abuse.
<b>Monitoring</b>	Peak concentrations should be obtained within the first 1–2 weeks of therapy and monitored serially during therapy. The peak concentration should be kept below 35 mcg/ml. Baseline and monthly monitoring for depression using a tool such as the Beck Depression Index should be done.
<b>2012 wholesale cost</b> 30-day supply, 60-kg person	\$435 (outpatient public health pricing) \$810 (community hospital)
<b>Patient instructions</b>	<p>Best taken on an empty stomach, with juice or antacids. If food is taken, avoid a large fatty meal. Avoid alcohol.</p> <p>You must also take a high-dose vitamin B6 supplement while on this drug.</p> <p><b>Call your doctor right away if you have:</b></p> <ul style="list-style-type: none"><li>• Seizures</li><li>• Shakiness or trouble talking</li><li>• Depression or thoughts of hurting yourself</li><li>• Anxiety, confusion, or loss of memory</li><li>• Personality changes, such as aggressive behavior</li><li>• Rash or hives</li><li>• Headache</li></ul>



## DELAMANID (DLM) [ 1 of 2 ]

<b>Drug class</b>	Nitroimidazo-oxazole derivative
<b>Trade name</b>	Delyba (in Europe)
<b>Activity against TB</b>	Bactericidal; has strong anti-TB activity. Inhibits mycolic acid biosynthesis.
<b>Cross-resistance</b>	Cross-resistance with investigational drug PA-824, also a Nitroimidazole
<b>Dose</b>	<p><b>Adults:</b> 100 mg twice daily with food for 24 weeks. Administration for more than 6 consecutive months has not been studied.</p> <p><b>Children:</b> The safety and efficacy of delamanid in children under 18 years has not been published. Based strictly on weight, converting from the adult doses in a 70 kg patient, estimated pediatric doses would be 1.5 mg/kg twice daily for 24 weeks. However, these doses are not supported by clinical experience. Studies are ongoing, testing delamanid at 50 mg BID for ages 6-11, and 100 mg BID for ages 12-17.</p> <p><b>Renal failure/dialysis:</b> No dose adjustment needed for mild to moderate renal insufficiency but there are no data regarding use in patients with severe renal impairment. Therefore, delamanid is not recommended for patients with severe renal impairment.</p>
<b>Route of administration</b>	Oral.
<b>Preparation</b>	50 mg film coated tablets.
<b>Storage</b>	Store at room temperature and in original package in order to protect from moisture.
<b>Pharmacokinetics</b>	<p><b>Time of peak oral absorption</b> (<math>T_{max}</math>) occurs approximately 4 hours post dose. Administration with a standard meal increases bioavailability about 3-fold, therefore drug should be taken with food. The drug is highly protein-bound, and displays a large volume of distribution.</p> <p><b>Peak concentrations</b> (<math>C_{max}</math>) at steady state (approximately 14 days of administration) were 369 and 361 ng/ml after the first and second dose, respectively (0.37 and 0.36 mcg/ml).</p>
<b>Oral absorption</b>	25- 47% of the delamanid dose is absorbed following oral administration with food.
<b>Metabolism</b>	The drug is predominantly metabolized in plasma by albumin. Minimal metabolism of delamanid also occurs in human liver microsomes by cytochrome P450 (CYP) 3A4.
<b>CSF penetration</b>	No data are available. Also, there are no data on the treatment of extrapulmonary TB (e.g., central nervous system, bone) with delamanid.

# DELAMANID (DLM) [2 of 2]

<p><b>Special circumstances</b></p>	<p><b>Use in pregnancy/breastfeeding:</b> Delamanid may cause harm to a fetus. It is usually not recommended for use during pregnancy. It is not known if delamanid passes into breast milk in humans. Breastfeeding is not recommended during treatment with delamanid.</p> <p><b>Use in renal disease:</b> No dose adjustment needed for mild to moderate renal insufficiency, but delamanid is not recommended for patients with severe renal impairment.</p> <p><b>Use in hepatic disease:</b> No dose adjustment is necessary for delamanid in patients with mild hepatic impairment, but it is not recommended in patients with moderate to severe hepatic impairment. Delamanid is contraindicated in patients with serum albumin levels &lt;2.8 g/ml.</p> <p><b>Use in cardiac disease:</b> Patients with various cardiac risk factors, including QTc interval prolongation, should not receive delamanid unless the potential benefits of treatment are expected to outweigh the possible risks. For all patients, an ECG is recommended prior to starting delamanid, and then monthly throughout treatment. Patients with serum albumin levels &lt;3.4 g/ml (but at least 2.8 g/ml), or with cardiac risk factors, should receive more frequent ECG monitoring. Serum electrolytes should be checked and corrected as needed.</p>
<p><b>Adverse reactions</b></p>	<p>The most frequent adverse drug reactions noted in controlled trials using delamanid with background regimens were nausea, vomiting, dizziness, insomnia, and upper abdominal pain. QTc prolongation occurred in about 10% of patients receiving 100 mg twice daily. However, no episodes were accompanied by clinical symptoms such as arrhythmias or syncope.</p>
<p><b>Contraindications</b></p>	<p>Hypersensitivity to delamanid</p> <p>Serum albumin &lt; 2.8 g/ml because of an increased risk of QTc prolongation</p> <p>Taking other medications that are strong inducers of CYP3A (e.g. carbamazepine, rifamycins)</p>
<p><b>Monitoring</b></p>	<p>ECG at baseline and monthly during treatment. Baseline electrolytes, repeat if QTc prolongation occurs.</p>
<p><b>2012 wholesale cost</b> 24-week supply, 60-kg person</p>	<p>Not available (outpatient public health pricing) Not available (community hospital)</p>
<p><b>Patient instructions</b></p>	<p>Take medication with food</p> <p>Tell your doctor if you have one of the following conditions:</p> <ul style="list-style-type: none"> <li>• You have low levels of albumin, potassium, magnesium or calcium in the blood</li> <li>• You have been told that you have heart problems or have a history of heart attack</li> <li>• If you have a condition called congenital long QT syndrome or problems with heart rhythm</li> <li>• You have liver or kidney disease</li> <li>• You have HIV</li> </ul> <p>Tell your doctor if you are pregnant or planning on pregnancy.</p>

# ETHAMBUTOL (EMB) [1 of 2]

<b>Drug class</b>	Unspecified
<b>Trade name</b>	Myambutol
<b>Activity against TB</b>	<b>Bacteriostatic</b> 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.
<b>Cross-resistance</b>	None reported
<b>Dose (all once daily)</b>	<p><b>Adults:</b> 15–25 mg/kg/day. 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. Intermittent dosing at 50 mg/kg thrice or twice weekly can be used.</p> <p><b>Children:</b> 15–25 mg/kg/day; doses closer to 15 mg/kg/day should be used if the drug is used for more than 2 months.</p> <p><b>Renal failure/dialysis:</b> 15–25 mg/kg/dose 3 times weekly (not daily).</p> <p><b>Obesity:</b> ATS/CDC Guidelines recommend dosing based on estimated lean body weight.  Lean Body Weight (men) = <math>(1.10 \times \text{Weight(kg)}) - 128 \times (\text{Weight}^2 / (100 \times \text{Height(m)}^2))</math>  Lean Body Weight (women) = <math>(1.07 \times \text{Weight(kg)}) - 148 \times (\text{Weight}^2 / (100 \times \text{Height(m)}^2))</math>  <i>Serum levels may be monitored.</i></p>
<b>Route of administration</b>	Oral; not available parenterally in the U.S.
<b>Preparation</b>	100 mg tablets; scored 400 mg tablets; coated 100 mg tablets; coated, scored 400 mg tablets.
<b>Storage</b>	Room temperature.
<b>Pharmacokinetics</b>	<p><b>Peak oral absorption</b> occurs 2–4 hours after the dose. Draw a peak serum concentration 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.</p> <p><b>Peak concentrations</b> of 2–6 mcg/ml are expected with daily dosing. Intermittent doses of 50 mg/kg can be expected to produce peaks of 4–12 mcg/ml.</p>
<b>Oral absorption</b>	80% bioavailability independent of food.
<b>CSF penetration</b>	Ethambutol penetrates meninges poorly.
<b>Special circumstances</b>	<p><b>Use in pregnancy/breastfeeding:</b> Safe in pregnancy; can be used while breastfeeding.</p> <p><b>Use in renal disease:</b> 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 therapeutic drug monitoring. See Chapter 7, <i>Co-morbidities and Special Situations - Renal Failure</i>.</p> <p><b>Use in hepatic disease:</b> Safe in liver disease.</p>
<b>Adverse reactions</b>	Retrobulbar neuritis (dose-related—exacerbated during renal failure).

# ETHAMBUTOL (EMB) [ 2 of 2 ]

<b>Contraindications</b>	<b>Pre-existing optic neuritis; visual changes on ethambutol.</b>
<b>Monitoring</b>	Patients should be counseled to report any changes in vision. 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).
<b>2012 wholesale cost</b> 30-day supply, 60-kg person	\$20 (outpatient public health pricing) \$140 (community hospital)
<b>Patient instructions</b>	<p>Can be taken with food or on an empty stomach.</p> <p><b>Call your doctor right away if you have:</b></p> <ul style="list-style-type: none"><li>• Any problems with your eyes: vision changes, blurring, color blindness, trouble seeing, or eye pain</li><li>• Swelling of face</li><li>• Rash, hives, or trouble breathing</li><li>• Numbness, pain, or tingling in hands or feet</li><li>• Joint pain</li><li>• Fever or chills</li><li>• Nausea, vomiting, poor appetite, or abdominal pain</li><li>• Headache or dizziness</li></ul>

## ETHIONAMIDE (ETA) [1 of 2]

<b>Drug class</b>	Derivative of isonicotinic acid
<b>Trade name</b>	Trecator-SC
<b>Activity against TB</b>	Weakly bactericidal; blocks mycolic acid synthesis.
<b>Cross-resistance</b>	Cross-resistance to isoniazid may occur when there is low-level resistance to ethionamide due to mutation in inhA or the promoter region.
<b>Dose</b>	<p><b>Adults:</b> 15–20 mg/kg/day frequently divided (max dose 1 gram per day); usually 500–750 mg per day in 2 divided doses or a single daily dose. Most patients will experience GI intolerance with ETA doses greater than 1 gram daily.</p> <p><b>Children:</b> 15–20 mg/kg/day usually divided into 2–3 doses. 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.</p> <p><b>Vitamin B6:</b> Although there is little supporting data, most MDR-TB experts recommend that all patients should receive vitamin B6 while taking ethionamide. Adults need 100 mg and children should receive a dose proportionate to their weight.</p> <p><b>Renal failure/dialysis:</b> No change.</p>
<b>Route of administration</b>	Oral; not available parenterally.
<b>Preparation</b>	Coated 250 mg tablet.
<b>Storage</b>	Store at room temperature.
<b>Pharmacokinetics</b>	<p><b>Peak oral absorption</b> is usually reached in 2–3 hours, but delayed absorption is common; peak concentrations should be drawn at 2 hours.</p> <p><b>Peak concentrations</b> are typically 1–5 mcg/ml.</p>
<b>Oral absorption</b>	Erratic absorption, possibly due to GI disturbances associated with the medication.
<b>CSF penetration</b>	Concentrations approach those in serum; one pediatric study evaluating drug concentrations in the CSF suggests that ethionamide should be dosed on the high end of the range for patients with meningitis.
<b>Special circumstances</b>	<p><b>Use in pregnancy/breastfeeding:</b> Generally avoided during pregnancy due to reports of teratogenicity; little data about use during breastfeeding—an estimated 20% of a usual therapeutic dose is thought to be received (dose the infant with vitamin B6 if breastfed).</p> <p><b>Use in renal disease:</b> No precautions are required for renal impairment.</p> <p><b>Use in hepatic disease:</b> Can cause hepatotoxicity similar to that of INH—use with caution in liver disease.</p>

# ETHIONAMIDE (ETA) [ 2 of 2 ]

<p><b>Adverse reactions</b></p>	<p>Gastrointestinal upset and anorexia: Sometimes intolerable (symptoms are moderated by food or taking at bedtime). Premedication with an antiemetic like ondansetron is often helpful. Low dose Ativan 0.5 mg has also been used successfully.</p> <p>Metallic taste.</p> <p>Hepatotoxicity.</p> <p>Endocrine effects: Gynecomastia, hair loss, acne, impotence, menstrual irregularity, and reversible hypothyroidism—treat with thyroid replacement.</p> <p>Neurotoxicity (patients taking ethionamide should take high doses of vitamin B6). Side effects may be exaggerated in patients also taking cycloserine.</p>
<p><b>Contraindications</b></p>	<p><b>Sensitivity to ethionamide.</b></p>
<p><b>Monitoring</b></p>	<p>Monitor TSH for evidence of hypothyroidism requiring replacement; therapeutic drug monitoring if malabsorption suspected. Monitor liver function tests.</p>
<p><b>2012 wholesale cost</b> 30-day supply, 60-kg person</p>	<p>\$177 (outpatient public health pricing) \$378 (community hospital)</p>
<p><b>Patient instructions</b></p>	<p>Take this medicine with food.</p> <p>You must also take a high-dose vitamin B6 supplement while on this drug.</p> <p><b>Call your doctor right away if you have:</b></p> <ul style="list-style-type: none"> <li>• Any problems with your eyes: eye pain, blurred vision, color blindness, or trouble seeing</li> <li>• Numbness, tingling, or pain in your hands or feet</li> <li>• Unusual bruising or bleeding</li> <li>• Personality changes such as depression, confusion, or aggression</li> <li>• Yellowing of your skin or eyes</li> <li>• Dark-colored urine</li> <li>• Nausea and vomiting</li> <li>• Dizziness</li> <li>• Swollen breasts (in men)</li> </ul>

## IMIPENEM/CILASTATIN (IMP/CLN) [1 of 2]

<b>Drug class</b>	Beta-lactam – carbapenem
<b>Trade name</b>	Primaxin
<b>Activity against TB</b>	<i>In vitro</i> activity—very limited clinical experience.
<b>Cross-resistance</b>	Imipenem and Meropenem are both carbapenems and likely to have a moderate probability of cross-resistance
<b>Dose</b>	<p><b>Adults:</b> 1000 mg IV every 12 hours.</p> <p><b>Children:</b> Meropenem preferred. See <i>Meropenem</i>.</p> <p><b>Renal failure/dialysis:</b> Adjustment in dose based on severity of renal failure—for example, 750 mg every 12 hours for creatinine clearance 20–40 ml/min, 500 mg every 12 hours for creatinine clearance &lt; 20 ml/min.</p>
<b>Route of administration</b>	IV or IM (total IM doses are not recommended more than 1.5 gram/day and are therefore not very practical for treatment of drug-resistant TB). No oral preparation.
<b>Preparation</b>	Lyophilized powder 1:1 ratio of imipenem and cilastatin. Vials are available 250, 500, 750 mg, or 1 gram.
<b>Storage</b>	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.
<b>Pharmacokinetics</b>	<p><b>Peak concentrations</b> occur immediately after IV infusion and 1 hour after IM infusion.</p> <p><b>Peak concentrations</b> of 35–60 mcg/ml occur after infusion of 1 gram.</p>
<b>Oral absorption</b>	No oral absorption.
<b>CSF penetration</b>	Good CSF penetration, but children with meningitis treated with imipenem had high rates of seizures (meropenem preferred for meningitis and for children).
<b>Special circumstances</b>	<p><b>Use in pregnancy/breastfeeding:</b> Little information known regarding use in pregnancy; unknown safety during breastfeeding.</p> <p><b>Use in renal disease:</b> Dose adjustment required (see above); dose after dialysis.</p> <p><b>Use in hepatic disease:</b> Elevated liver function tests have been noted in up to 6% of patients, but no definite liver damage has been documented.</p>
<b>Adverse reactions</b>	Diarrhea, nausea, or vomiting. Seizure (noted with CNS infection).
<b>Contraindications</b>	<b>Carbapenem intolerance; meningitis</b> (use meropenem rather than imipenem).
<b>Monitoring</b>	Symptomatic monitoring.
<b>2012 wholesale cost</b> 30-day supply, 60-kg person	\$702 (outpatient public health pricing) \$2,107 (community hospital)



## Patient instructions

Make sure your doctor knows if you are also taking ganciclovir or have allergy to penicillins or cephalosporins.

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

- Fast or irregular heartbeat
- Seizures
- Severe diarrhea (watery or bloody)
- Skin rash, hives, or itching
- Swelling of the face, throat, or lips
- Wheezing or trouble breathing

# ISONIAZID (INH) [1 of 2]

<b>Drug class</b>	Isonicotinic acid hydrazide
<b>Trade name</b>	INH/Isoniazid/Laniazid/Nydrazid
<b>Activity against TB</b>	<b>Bactericidal</b> , especially for rapidly dividing cells. Affects mycolic acid (cell wall) synthesis. Inclusion of INH in the regimen of patients with strain W MDR-TB and other strains with low-level INH resistance were also associated with improved outcomes.
<b>Cross-resistance</b>	Cross-resistance to ethionamide may occur when there is low-level resistance to isoniazid due to a mutation in <i>inhA</i> or the promotor region.
<b>Dose (all once daily)</b>	<p><b>Adults:</b> 5 mg/kg/day (PO or IV) usual adult dose 300 mg daily; high dose INH (900 to 1500 mg twice or thrice weekly) is sometimes used, especially for patients with low-level INH resistance.</p> <p><b>Children:</b> 10–15 mg/kg/day up to 300 mg (PO or IV); 20–30 mg/kg/dose twice or thrice weekly.</p> <p><b>Renal failure/dialysis:</b> 300 mg once daily or 900 mg thrice weekly.</p> <p><b>Vitamin B6</b> 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.</p>
<b>Route of administration</b>	Oral, intravenous, or intramuscular.
<b>Preparation</b>	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. When given IV, dilute in 25 ml normal saline and infuse as a slow bolus over 5 minutes. Since compatibility information is not available, do not infuse “piggyback” with other drugs through a shared IV line.
<b>Storage</b>	Suspension must be kept at room temperature.
<b>Pharmacokinetics</b>	<p><b>Peak serum concentrations</b> are achieved at 1–2 hours after the oral dose.</p> <p><b>Peak concentrations</b> Collect blood for peak serum concentrations 2 hours after a dose (and if desired at 6 hours after a dose in order to calculate half-life).</p> <p><b>Peak concentration</b> is expected to be 3–5 mcg/ml after daily dose and 9–15 mcg/ml after twice weekly dose.</p>
<b>Oral absorption</b>	Well absorbed orally or intramuscularly; best absorbed on an empty stomach; up to 50% reduction in peak concentration with a fatty meal.
<b>CSF penetration</b>	Concentration equivalent to plasma in inflamed meninges. 20% of concentrations in plasma in non-inflamed meninges.

MEDICATION FACT SHEETS

# ISONIAZID (INH) [ 2 of 2 ]

<p><b>Special circumstances</b></p>	<p><b>Use in pregnancy/breastfeeding:</b> 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.</p> <p><b>Use in renal disease:</b> No dose adjustment for renal failure, but pyridoxine supplementation should be used.</p> <p><b>Use in hepatic disease:</b> May exacerbate liver failure. Use with caution.</p> <p><b>Drug Interactions:</b> Isoniazid is a CYP3A4 inhibitor. INH may increase the concentrations of certain cytochrome P450 enzyme substrates, including phenytoin and carbamazepine.</p>
<p><b>Adverse reactions</b></p>	<p>Hepatitis (age-related).</p> <p>Peripheral neuropathy.</p> <p>Hypersensitivity reactions.</p> <p>Other reactions, including optic neuritis, arthralgias, CNS changes, drug-induced lupus, diarrhea, and cramping with liquid product.</p>
<p><b>Contraindications</b></p>	<p><b>Patients with high-level INH resistance</b> who have failed an INH-containing regimen should not receive INH.</p>
<p><b>Monitoring</b></p>	<p><b>Clinical monitoring of all patients on INH is essential.</b> 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 concentrations of phenytoin or carbamazepine in patients receiving those drugs (increases phenytoin concentrations and risk of hepatotoxicity with carbamazepine), especially when undergoing INH monotherapy. Rifampin tends to lower concentrations of these drugs and balance effect of INH.</p>
<p><b>2012 wholesale cost</b> 30-day supply, 60-kg person</p>	<p>\$1 (outpatient public health pricing) \$3 (community hospital)</p>
<p><b>Patient instructions</b></p>	<p>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).</p> <p><b>Call your doctor right away if you have any of these side effects:</b></p> <ul style="list-style-type: none"> <li>• Loss of appetite for a few days that is not going away</li> <li>• Tiredness, weakness</li> <li>• Moderate stomach pain, nausea, or vomiting</li> <li>• Numbness or tingling of your fingers or toes</li> <li>• Blurred vision, eye pain</li> <li>• Yellow skin or eyes or dark-colored urine</li> </ul>

# KANAMYCIN (KM) [ 1 of 2 ]

<b>Drug class</b>	Aminoglycoside
<b>Trade name</b>	Kantrex
<b>Activity against TB</b>	<b>Bactericidal;</b> has strong anti-TB activity. Cross-resistance with amikacin and some data suggesting cross-resistance with capreomycin; inhibits protein synthesis.
<b>Cross-resistance</b>	Amikacin: high likelihood of cross-resistance because it is associated with the same mutation ( <i>rrs</i> ). However, there are some kanamycin mutations ( <i>eis</i> ) that do not cause amikacin resistance. Some data suggests amikacin cross-resistance with capreomycin.
<b>Dose (all once daily)</b>	<p><b>Adults:</b> 15 mg/kg/day in a single daily dose, 5–7 days per week.</p> <p>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 concentrations).</p> <p><b>&gt; 59 yrs of age:</b> Many experienced clinicians prefer to use a lower starting dose of 10 mg/kg 5–7 times per week or 2–3 times per week after initial period. Alternatively, 15 mg/kg/dose 3 times per week.</p> <p><b>Children:</b> 15–30 mg/kg/day (max 1 gram) 5–7 days per week. 15–30 mg/kg/day (max 1 gram) 3 days per week after initial period daily.</p> <p><b>Renal failure/dialysis:</b> 12–15 mg/kg/dose 2–3 times weekly (not daily).</p> <p><b>Markedly obese individuals</b> should have an adjusted dose due to the decreased distribution of extracellular fluids in adipose tissues. Dosing based on actual weight will give supratherapeutic concentrations.</p> <p><b>For dosing, use adjusted weight as follows:</b> Ideal body weight + 40% of 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</p> <p><i>Concentrations should be followed closely.</i></p>
<b>Route of administration</b>	Intravenous or intramuscular; not absorbed orally.
<b>Preparation</b>	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.
<b>Storage</b>	Store in the refrigerator.
<b>Pharmacokinetics</b>	<p>For intravenous administration, infuse over 60 minutes for adults; 1–2 hours for children; intramuscular absorption is complete within 4 hours and peak concentrations are achieved at 1–2 hours. Obtaining a drug concentration 90–120 minutes after intravenous infusion allows for complete distribution of drug. An additional concentration collected 4 hours later will allow for a half-life to be calculated and peak to be back-extrapolated.</p> <p><b>Peak concentrations</b> for a 15 mg/kg dose are between 35 and 45 mcg/ml.</p> <p><b>Peak concentrations</b> of 65–80 mcg/ml are obtained after a 25 mg/kg dose.</p> <p>Trough concentrations should be undetectable after a 24-hour dose.</p>

# KANAMYCIN (KM) [ 2 of 2 ]

<b>Oral absorption</b>	Not absorbed orally; 40–80% of the dose is absorbed intramuscularly.
<b>CSF penetration</b>	Minimal and variable CSF penetration—slightly better with inflamed meninges.
<b>Special circumstances</b>	<p><b>Use in pregnancy/breastfeeding:</b> Generally avoided in pregnancy due to documented congenital deafness. Can be used while breastfeeding.</p> <p><b>Use in renal disease:</b> Use with caution. Concentrations 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 variably cleared by hemodialysis, see Chapter 7, <i>Co-morbidities and Special Situations – Renal Failure</i>.</p> <p><b>Use in hepatic disease:</b> Drug concentrations 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.</p> <p><b>Diuretic use:</b> Coadministration of loop diuretics and aminoglycoside antibiotics carries an increased risk of ototoxicity.</p>
<b>Adverse reactions</b>	<p>Nephrotoxicity: Appears to be more nephrotoxic than streptomycin.</p> <p>Ototoxicity (hearing loss) and vestibular toxicity: Increased with advanced age and prolonged use; appears to occur slightly more commonly with kanamycin than with streptomycin and about the same frequency as amikacin. Kanamycin seems to have slightly less vestibular toxicity.</p>
<b>Contraindications</b>	<b>Pregnancy</b> (congenital deafness seen with streptomycin and kanamycin use in pregnancy); <b>hypersensitivity to aminoglycosides</b> ; caution with renal, vestibular, or auditory impairment; patients with intestinal obstructions.
<b>Monitoring</b>	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 concentrations at baseline if there is any question about renal function. Some experts monitor aminoglycoside concentrations routinely, regardless of renal function. Monitor concentrations serially for patients with impaired renal function.
<b>2012 wholesale cost</b> 30-day supply, 60-kg person	<p>\$153 (outpatient public health pricing)</p> <p>\$362 (community hospital)</p> <p>Not currently available in the U.S.</p>
<b>Patient instructions</b>	<p><b>Call your doctor right away if you have:</b></p> <ul style="list-style-type: none"> <li>• Problems with hearing, dizziness, or balance</li> <li>• Rash or swelling of your face</li> <li>• Trouble breathing</li> <li>• Decreased urination</li> <li>• Watery or bloody diarrhea</li> <li>• Swelling, pain, or redness at your IV site</li> <li>• Muscle twitching or weakness</li> </ul>

# LEVOFLOXACIN (LFX) [1 of 2]

<b>Drug class</b>	Fluoroquinolone (FQN)
<b>Trade name</b>	Levaquin
<b>Activity against TB</b>	<b>Bactericidal;</b> has strong anti-TB activity. Cross-resistance with other fluoroquinolones, but data suggests greater activity than ciprofloxacin or ofloxacin. Inhibits DNA gyrase.
<b>Cross-resistance</b>	In general, there is a complete class effect cross-resistance among fluoroquinolones <i>in vitro</i> . However, data suggest that moxifloxacin may continue to demonstrate some activity despite <i>in vitro</i> resistance to ofloxacin
<b>Dose (all once daily)</b>	<p><b>Adults:</b> For treatment of TB disease: 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 ≤ 45.5 kg (100 lbs); 750 mg/day if &gt; 45.5 kg (100 lbs).</p> <p><b>Children:</b> 15-20 mg/kg/day once daily or divided BID for younger children (PO or IV)</p> <p><b>Renal failure/dialysis:</b> 750–1000 mg/dose 3 times weekly (not daily) for creatinine clearance &lt; 30 ml/min.</p>
<b>Route of administration</b>	Oral or intravenous.
<b>Preparation</b>	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 is 25 mg/ml.
<b>Storage</b>	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.
<b>Pharmacokinetics</b>	<p><b>Peak oral absorption</b> occurs at 1–2 hours.</p> <p><b>Peak concentrations</b> should be drawn at 2 hours after the dose. A second level drawn at 6 hours post dose can distinguish between delayed absorption and malabsorption.</p> <p><b>Peak concentrations</b> of 8–12 mcg/ml are expected.</p>
<b>Oral absorption</b>	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).
<b>CSF penetration</b>	Concentrations are 65% of that in the serum.
<b>Special circumstances</b>	<p><b>Use in pregnancy/breastfeeding:</b> Fluoroquinolones are generally avoided in pregnancy and breastfeeding due to observation of arthropathy in puppy models. However, there are a few case reports of fluoroquinolones being used safely in pregnancy.</p> <p><b>Use in renal disease:</b> 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.</p> <p><b>Use in hepatic disease:</b> Drug concentrations not affected by hepatic disease. Presumed to be safe in severe liver disease.</p>

# LEVOFLOXACIN (LFX) [ 2 of 2 ]

<b>Adverse reactions</b>	Nausea and bloating. Headache, dizziness, insomnia, or tremulousness. <b>Rare</b> tendon rupture, arthralgias (can usually be treated symptomatically). QTc prolongation, hypoglycemia.
<b>Contraindications</b>	<b>Fluoroquinolone intolerance, prolonged QTc, pregnancy (relative contraindication)</b>
<b>Monitoring</b>	Side effect monitoring, but no specific laboratory monitoring required.
<b>2012 wholesale cost</b> 30-day supply, 60-kg person	\$6 (outpatient public health pricing) \$592 (community hospital)
<b>Patient instructions</b>	Avoid caffeinated foods and beverages while taking this medicine; you can take levofloxacin with food. Drink plenty of beverages. Do not take milk-based products, antacids (especially aluminum-containing), mineral supplements such as iron or magnesium, or multivitamins within 2 hours of this medication. This medicine may cause sun sensitivity; use sunscreens. Do not undertake new strenuous activities. <b>Call your doctor and stop the medicine right away if you have:</b> <ul style="list-style-type: none"><li>• Pain, swelling or tearing of a tendon (such as the back of your ankle, elbow, etc.), or muscle or joint pain</li><li>• Rashes, hives, bruising or blistering, trouble breathing, or tightness in your chest</li><li>• Diarrhea</li><li>• Yellow skin or eyes</li><li>• Anxiety, confusion, or dizziness</li></ul>

# LINEZOLID (LZD) [1 of 2]

<b>Drug class</b>	Oxazolidinones
<b>Trade name</b>	Zyvox
<b>Activity against TB</b>	Has <i>in vitro</i> bactericidal activity—increasing clinical experience; inhibits protein synthesis.
<b>Cross-resistance</b>	None reported
<b>Dose</b>	<p><b>Adults:</b> 600 mg once daily.</p> <p><b>Children:</b> 10 mg/kg/dose every 12 hours.</p> <p><b>Vitamin B6:</b> All patients should receive vitamin B6 while receiving linezolid.</p> <p><b>Renal failure/dialysis:</b> No dose adjustment required.</p>
<b>Route of administration</b>	Oral or intravenous.
<b>Preparation</b>	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.
<b>Storage</b>	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).
<b>Pharmacokinetics</b>	<p>Intravenous doses are administered over 30–120 minutes.</p> <p><b>Peak concentrations</b> are achieved 1–1.5 hours after an oral dose and ½ hour after an IV dose.</p> <p><b>Peak concentrations</b> should be drawn 2 hours after an oral dose or after the end of an IV infusion. A 6-hour post dose concentration can be used to calculate half-life.</p> <p><b>Peak concentrations</b> are expected to be 12–24 mcg/ml.</p>
<b>Oral absorption</b>	Nearly complete oral absorption.
<b>CSF penetration</b>	CSF concentrations are about 1/3 of those in serum in animal models, and linezolid has been used to treat meningitis in humans.
<b>Special circumstances</b>	<p><b>Use in pregnancy/breastfeeding:</b> Not recommended during pregnancy or breastfeeding due to limited data.</p> <p><b>Use in renal disease:</b> No dose adjustment is recommended, but metabolites may accumulate.</p> <p><b>Use in hepatic disease:</b> Rarely associated with increased transaminases.</p>
<b>Adverse reactions</b>	<p>Myelosuppression.</p> <p>Diarrhea and nausea.</p> <p>Optic and peripheral neuropathy – may be irreversible.</p>



# LINEZOLID (LZD) [ 2 of 2 ]

<b>Contraindications</b>	<p><b>Hypersensitivity to oxazolidinones.</b></p> <p><b>Symptoms of neuropathy</b> (pain, numbness, tingling or weakness in the extremities).</p> <p><b>Drug Interactions:</b> Linezolid should generally not be administered to patients taking serotonergic agents, such as monoamine oxidase inhibitors (MAOIs) due to the potential for serious CNS reactions, such as serotonin syndrome. Since MAO type A deaminates serotonin, and SSRIs potentiate the action of serotonin by inhibiting its neuronal reuptake, administration of linezolid concurrently with an SSRI can lead to serious reactions such as serotonin syndrome or neuroleptic malignant syndrome-like reactions.</p>
<b>Monitoring</b>	Monitor for peripheral neuropathy and optic neuritis. Monitor CBC weekly during the initial period, then monthly, and then as needed based on symptoms; there is little clinical experience with prolonged use.
<b>2012 wholesale cost</b> 30-day supply, 60-kg person	\$1,064 (outpatient public health pricing) \$3,724 (community hospital)
<b>Patient instructions</b>	<p>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.</p> <p><b>Call your doctor right away if you have any of these side effects:</b></p> <ul style="list-style-type: none"><li>• Pain, numbness, tingling or weakness in the extremities</li><li>• Black, tarry stools or severe diarrhea</li><li>• Unusual bleeding or bruising</li><li>• Unusual tiredness or weakness</li><li>• Headache, nausea, or vomiting</li><li>• Changes in vision</li></ul>

# MEROPENEM (MPM) [1 of 2]

<b>Drug class</b>	Beta-lactam – carbapenem
<b>Trade name</b>	Merrem I.V.
<b>Activity against TB</b>	<i>In vitro</i> activity—very limited clinical experience.
<b>Cross-resistance</b>	Meropenem and imipenem are both carbapenems and likely to have a moderate probability of cross-resistance.
<b>Dose</b>	<p><b>Adults:</b> Not established. Only published study used 2000 mg IV every 8–12 hours. Based on pharmacokinetic data 1000 mg every 12 hours may be sufficient. Must be given with clavulanate (available as amoxicillin / clavulanate ) 125 mg every 8–12 hours.</p> <p><b>Children:</b> Not established for TB.</p> <p><b>For other bacterial infections:</b> 20 mg/kg/dose and 40 mg/kg/dose for meningitis or particularly severe infections are used IV every 8 hours up to 2 gram per dose.</p> <p><b>Renal failure/dialysis:</b> Adjustment in dose and interval based on severity of renal failure and body weight—for example, 750 mg every 12 hours for creatinine clearance 20–40 ml/min, 500 mg every 12 hours for creatinine clearance &lt; 20 ml/min.</p>
<b>Route of administration</b>	IV only; no oral preparation.
<b>Preparation</b>	Crystalline powder. Product is available in 500 mg, or 1 gram vials.
<b>Storage</b>	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.
<b>Pharmacokinetics</b>	At the end of a 30-minute infusion, peak concentration after a 1 gram dose should be 39–58 mcg/ml. The elimination half-life is approximately 1 hour in patients with normal renal function.
<b>Oral absorption</b>	No oral absorption.
<b>CSF penetration</b>	Adequate CSF penetration
<b>Special circumstances</b>	<p><b>Use in pregnancy/breastfeeding:</b> Little information known regarding use in pregnancy; unknown safety during breastfeeding.</p> <p><b>Use in renal disease:</b> Dose adjustment required (see above); dose after dialysis.</p> <p><b>Use in hepatic disease:</b> Liver disease does not alter the pharmacodynamics of meropenem</p>
<b>Adverse reactions</b>	<p>Diarrhea, nausea, or vomiting.</p> <p>Seizure (noted with CNS infection), but rare compared to imipenem. Rarely elevated LFTs, hematologic toxicity, hypersensitivity</p>
<b>Contraindications</b>	<b>Carbapenem intolerance</b>
<b>Monitoring</b>	Symptomatic monitoring.

# MEROPENEM (MPM) [ 2 of 2 ]

**2012 wholesale cost**  
30-day supply, 60-kg person

\$674 (outpatient public health pricing)  
\$1,109 (community hospital)

## Patient instructions

Make sure your doctor knows if you are also taking valproic acid or have allergy to penicillins or cephalosporins.

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

- Severe diarrhea (watery or bloody)
- Skin rash, hives, or itching
- Swelling in the face, throat, or lips
- Wheezing or trouble breathing

# MOXIFLOXACIN (MFX) [1 of 2]

<b>Drug class</b>	Fluoroquinolone (FQN)
<b>Trade name</b>	Avelox
<b>Activity against TB</b>	<b>Bactericidal;</b> inhibits DNA gyrase; cross-resistance with other fluoroquinolones, but may be more active based on <i>in vitro</i> data.
<b>Cross-resistance</b>	In general, there is a complete class effect cross-resistance among fluoroquinolones <i>in vitro</i> . However, data suggest that moxifloxacin may continue to demonstrate some activity despite <i>in vitro</i> resistance to ofloxacin.
<b>Dose (all once daily)</b>	<b>Adults:</b> 400 mg daily (PO or IV). <b>Children:</b> No established dose. <b>Renal failure/dialysis:</b> No dose adjustment required.
<b>Route of administration</b>	Oral or IV.
<b>Preparation</b>	Tablets (400 mg); aqueous solution (400 mg/250 ml) for IV injection.
<b>Storage</b>	Store oral and IV products at room temperature (do not refrigerate).
<b>Pharmacokinetics</b>	<b>Peak absorption</b> after an oral dose is noted in 1–3 hours. <b>Peak concentrations</b> should be drawn at 2 hours. A 6-hour concentration can be drawn to calculate half-life. <b>Peak concentrations</b> are expected to be 3-5 mcg/ml. Collecting samples at 2 and 6 hours after an oral dose can distinguish between delayed absorption and malabsorption.
<b>Oral absorption</b>	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).
<b>CSF penetration</b>	Good penetration in animal model studies.
<b>Special circumstances</b>	<b>Use in pregnancy/breastfeeding:</b> Fluoroquinolones are generally avoided in pregnancy and breastfeeding due to observation of arthropathy in puppy models. However, there are a few case reports of fluoroquinolones being used safely in pregnancy. <b>Use in renal disease:</b> Excretion unchanged in the face of renal failure; no data on effect of dialysis. <b>Use in hepatic disease:</b> Rarely associated with hepatotoxicity; use with caution. No dose adjustment required for mild or moderate liver disease.
<b>Adverse reactions</b>	Nausea and diarrhea. Headache and dizziness. <b>Rare</b> tendon rupture; arthralgias. Rare hepatotoxicity. QTc prolongation, hypo/hyperglycemia.

# MOXIFLOXACIN (MFX) [ 2 of 2 ]

<b>Contraindications</b>	Fluoroquinolone intolerance, prolonged QTc, pregnancy (relative contraindication).
<b>Monitoring</b>	Symptomatic monitoring.
<b>2012 wholesale cost</b> 30-day supply, 60-kg person	\$80 (outpatient public health pricing) \$684 (community hospital)
<b>Patient instructions</b>	<p>Keep moxifloxacin at room temperature. Moxifloxacin can be taken with food, but do not take milk-based products, antacids (especially aluminum-coating), vitamin supplements, or sucralfate within 2 hours of this medication. Do not undertake new strenuous activities.</p> <p><b>Call your doctor and stop the medicine right away if you have:</b></p> <ul style="list-style-type: none"><li>• Pain, swelling or tearing of a tendon (such as the back of your ankle, elbow, etc.), or muscle or joint pain</li><li>• Rashes, hives, bruising or blistering, trouble breathing, or tightness in your chest</li><li>• Diarrhea</li><li>• Yellow skin or eyes</li><li>• Anxiety, confusion, or dizziness</li></ul>

## PARA-AMINOSALICYLATE (PAS) [ 1 of 2 ]

<b>Drug class</b>	Salicylic acid – anti-folate
<b>Trade name</b>	PASER
<b>Activity against TB</b>	<b>Bacteriostatic.</b>
<b>Cross-resistance</b>	None reported.
<b>Dose</b>	<p><b>Adults:</b> 8–12 grams per day divided 2–3 times per day. Some experts use 6 grams daily.</p> <p><b>Children:</b> 200–300 mg/kg/day divided 2–4 times per day.</p> <p><b>Renal failure/dialysis:</b> No change.</p>
<b>Route of administration</b>	Oral; should be given sprinkled on or stirred into yogurt or similar food. Do not chew the granules; they should be swallowed whole. Not available parenterally in the U.S.
<b>Preparation</b>	4 grams per packet.
<b>Storage</b>	Packets should be kept in the refrigerator or freezer.
<b>Pharmacokinetics</b>	<p>Delayed peak concentration with the PASER formulation (the only product available in the United States) due to its enteric coating and sustained release (1–6 hours).</p> <p><b>Peak concentrations</b> should be collected at 6 hours.</p> <p><b>Peak concentrations</b> are expected to be 20–60 mcg/ml.</p>
<b>Oral absorption</b>	Incomplete absorption—sometimes requires increased doses to achieve therapeutic concentrations.
<b>CSF penetration</b>	Poorly penetrates the meninges (somewhat better with inflammation).
<b>Special circumstances</b>	<p><b>Use in pregnancy/breastfeeding:</b> Not studied, but no teratogenicity known. There is little data regarding use during breastfeeding. In one patient, the milk concentration was 1 mcg/ml compared to a serum concentration of 70 mcg/ml.</p> <p><b>Use in renal disease:</b> Inactive metabolite is cleared by the kidneys.</p> <p>The package insert says to avoid with severe renal failure. Other authorities believe it can be used with caution (no toxicity of metabolite known).</p> <p><b>Use in hepatic disease:</b> Use with caution; 0.5% incidence of hepatotoxicity.</p>
<b>Adverse reactions</b>	<p>Gastrointestinal distress (less with the PASER formulation than with older preparations).</p> <p>Rare hepatotoxicity and coagulopathy.</p> <p>Reversible hypothyroidism (increased risk with concomitant use of ethionamide)—treat with thyroid replacement.</p>
<b>Contraindications</b>	<b>Pregnancy (relative)</b>
<b>Monitoring</b>	Monitor TSH, electrolytes, blood counts, and liver function tests.

## PARA-AMINOSALICYLATE (PAS) [ 2 of 2 ]

**2012 wholesale cost**  
30-day supply, 60-kg person

\$173 (outpatient public health pricing)

### 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. Do not use the packet if expanded 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—this is normal.

**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

# PYRAZINAMIDE (PZA) [1 of 2]

<b>Drug class</b>	Synthetic derivative of nicotinamide
<b>Trade name</b>	Pyrazinamide
<b>Activity against TB</b>	<b>Bactericidal</b> for semi-dormant <i>M. tuberculosis</i> . Mechanism unclear.
<b>Cross-resistance</b>	None reported.
<b>Dose (all once daily)</b>	<p><b>Adults:</b> 25 mg/kg/day. Intermittent dosing at twice or thrice weekly up to 50 mg/kg can be given.</p> <p><b>Children:</b> 30–40 mg/kg/dose.</p> <p><b>Renal failure/dialysis:</b> 25 mg/kg/dose 3 times per week (not daily).</p> <p><b>Obesity:</b> ATS/CDC Guidelines recommend dosing based on estimated lean body weight.</p> <p>Lean Body Weight (men) = <math>(1.10 \times \text{Weight(kg)}) - 128 \times (\text{Weight}^2 / (100 \times \text{Height(m)}^2))</math>  Lean Body Weight (women) = <math>(1.07 \times \text{Weight(kg)}) - 148 \times (\text{Weight}^2 / (100 \times \text{Height(m)}^2))</math></p>
<b>Route of administration</b>	Oral; not available parenterally.
<b>Preparation</b>	500 mg scored or unscored tablet.
<b>Storage</b>	Store the tablets at room temperature.
<b>Pharmacokinetics</b>	<p><b>Peak concentration</b> is 1–4 hours after an oral dose.</p> <p><b>Peak concentrations</b> should be drawn at 2 and 6 hours for therapeutic drug monitoring.</p> <p><b>Peak concentrations</b> of 20–40 mcg/ml are expected after a daily dose. When giving 50 mg/kg intermittently, 60–80 mcg/ml can be expected. An elevated uric acid is an expected finding in every patient on pyrazinamide. If not present, may indicate patient is not taking the drug or there is malabsorption.</p>
<b>Oral absorption</b>	Well absorbed from the GI tract.
<b>CSF penetration</b>	Concentrations equivalent to serum.
<b>Special circumstances</b>	<p><b>Use in pregnancy/breastfeeding:</b> In the United States, 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 susceptible to pyrazinamide (no known teratogenicity). Can be used while breastfeeding.</p> <p><b>Use in renal disease:</b> Cleared by the kidneys; dose 3 times a week and after dialysis.</p> <p><b>Use in hepatic disease:</b> Use with caution; pyrazinamide is associated with hepatotoxicity in about 1% of patients. It can be quite severe and worsen off treatment.</p>



# PYRAZINAMIDE (PZA) [ 2 of 2 ]

<b>Adverse reactions</b>	Gout (hyperuricemia) and arthralgias. Hepatotoxicity. Rash. Photosensitivity. Gastrointestinal upset.
<b>Contraindications</b>	<b>Allergy to pyrazinamide; severe gout.</b>
<b>Monitoring</b>	Monitor transaminases and uric acid.
<b>2012 wholesale cost</b> 30-day supply, 60-kg person	\$35 (outpatient public health pricing) \$106 (community hospital)
<b>Patient instructions</b>	May be taken with or without food; this medicine may cause a rash after sun exposure: limit your sun exposure. <b>Call your doctor right away if you have any of these side effects:</b> <ul style="list-style-type: none"><li>• Skin rash, severe itching, or hives</li><li>• Pain or swelling in the joints</li><li>• Yellowing of the skin or eyes or dark urine</li><li>• Nausea or vomiting</li><li>• Unusual tiredness or loss of appetite</li></ul>

## RIFABUTIN (RFB) [ 1 of 2 ]

<b>Drug class</b>	Rifamycin
<b>Trade name</b>	Mycobutin
<b>Activity against TB</b>	<b>Bactericidal;</b> same mechanism of activity as rifampin (inhibits RNA polymerase). Less than 20% of rifampin-resistant strains are susceptible to rifabutin.
<b>Cross-resistance</b>	Cross-resistance among the rifamycin class of drugs is typical. In <20% of strains that are resistant to rifampin, rifabutin may retain susceptibility <i>in vitro</i> . The clinical significance of this is unknown.
<b>Dose (all once daily)</b>	<p><b>Adults:</b> 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.</p> <p><b>Children:</b> The pediatric dose is not established, but doses of 5–10 mg/kg/day have been used (higher doses have been recommended for children &lt; 1 year of age). Caution should be used in very young children in whom visual changes might not be obvious.</p> <p><b>Renal failure/dialysis:</b> No dose adjustment in mild renal insufficiency. For creatinine clearance less than 30 ml/minute, the usual dose may be used, but monitor drug concentrations to avoid toxicity.</p> <p><b>Concomitant medications:</b> Dosage adjustment may be required, particularly with anti-retroviral therapy use. See <a href="http://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv-guidelines/27/hiv-tb">http://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv-guidelines/27/hiv-tb</a>. If given with ritonavir or cobistat, begin with 150 mg daily. If given with efavirenz, begin with 600 mg daily.</p>
<b>Route of administration</b>	Oral; not available parenterally.
<b>Preparation</b>	150 mg capsule.
<b>Storage</b>	Capsules should be kept at room temperature.
<b>Pharmacokinetics</b>	<p><b>Peak concentration</b> is reached 3–4 hours after a dose.</p> <p><b>Peak serum concentration</b> should be drawn 3 hours after the dose; a second sample 7 hours post-dose is desirable in order to distinguish between delayed absorption and malabsorption.</p> <p><b>The peak concentration</b> should be between 0.3 and 0.9 mcg/ml. Dose adjustments should be considered for patients with concentrations &lt; 0.3 or &gt; 1.0 mcg/ml (low concentrations predict risk of emergence of drug resistance). Rifabutin concentrates in tissues: in lung tissues, concentrations reach 10–20 times that in serum.</p>
<b>Oral absorption</b>	Well absorbed from the GI tract.
<b>CSF penetration</b>	Penetrates inflamed meninges.

# RIFABUTIN (RFB) [ 2 of 2 ]

<p><b>Special circumstances</b></p>	<p><b>Use in pregnancy/breastfeeding:</b> Insufficient data in pregnancy. Unknown effects from breastfeeding.</p> <p><b>Use in renal disease:</b> Used without dose adjustment in mild renal insufficiency. For creatinine clearance less than 30 ml/minute, the usual dose may be used, but monitor drug concentrations to avoid toxicity.</p> <p><b>Use in hepatic disease:</b> Use with caution and additional monitoring in liver disease. Dose adjustments necessary for drug interactions—especially HIV drugs. See <a href="http://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv-guidelines/27/hiv-tb">http://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv-guidelines/27/hiv-tb</a>.</p>
<p><b>Adverse reactions</b></p>	<p>Leukopenia (dose dependent); thrombocytopenia.</p> <p>Rashes and skin discoloration (bronzing or pseudojaundice).</p> <p>Anterior uveitis and other eye toxicities.</p> <p>Hepatotoxicity similar to that of rifampin.</p> <p>Drug interactions with many other drugs—but only 40% of that seen with rifampin. Rifabutin concentrations may be affected by other drugs.</p> <p>Arthralgias.</p>
<p><b>Contraindications</b></p>	<p><b>Rifamycin hypersensitivity.</b> Data are lacking on cross-sensitivity to rifabutin in patients with hypersensitivity. If used, use with caution, with careful monitoring of patient for development of hypersensitivity. Should not be used for patients with MDR-TB unless susceptibility to rifabutin documented.</p>
<p><b>Monitoring</b></p>	<p>Increased liver function monitoring; monitor drug concentrations of interacting medications; blood counts and vision screening.</p>
<p><b>2012 wholesale cost</b> 30-day supply, 60-kg person</p>	<p>\$75 (outpatient public health pricing) \$970 (community hospital)</p>
<p><b>Patient instructions</b></p>	<p>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 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.</p> <p><b>Call your doctor right away if you have any of these side effects:</b></p> <ul style="list-style-type: none"> <li>• Any eye pain, change in vision, or sensitivity to light</li> <li>• Fever, chills, or sore throat</li> <li>• Pain or swelling in the joints</li> <li>• Yellowing of the skin or eyes or dark urine</li> <li>• Nausea or vomiting</li> <li>• Unusual tiredness or loss of appetite</li> </ul>

# RIFAMPIN (RIF) [1 of 2]

<b>Drug class</b>	Rifamycin
<b>Trade name</b>	Rifadin (also known as rifampicin)
<b>Activity against TB</b>	<b>Bactericidal;</b> inhibits protein synthesis; cross-resistance with other rifamycins.
<b>Cross-resistance</b>	Cross-resistance among the rifamycin class of drugs is typical. In <20% of strains resistant to rifampin, rifabutin may retain susceptibility <i>in vitro</i> . The clinical significance of this is unknown.
<b>Dose (all once daily)</b>	<p><b>Adults:</b> 10 mg/kg/dose (PO or IV). Usual dose 600 mg.</p> <p><b>Children:</b> 10-30 mg/kg/day based on age. See Chapter 6, <i>Pediatrics</i>, Table 3 footnote, page 162, for details. (Maximum 600 mg/day.)</p> <p><b>Renal failure/dialysis:</b> No adjustment required.</p> <p><b>Concomitant medications:</b> Dosage adjustment may be required for concurrent medications, including warfarin. After stopping rifampin, warfarin dosage may require downward adjustment to prevent toxicity. Concurrent treatment with most anti-retroviral drugs is not recommended, as anti-retroviral drug concentrations are substantially reduced. On the other hand, rifampin plasma concentrations are not affected by most other drugs, based on current data. See <a href="http://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv-guidelines/27/hiv-tb">http://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv-guidelines/27/hiv-tb</a>.</p>
<b>Route of administration</b>	Oral or intravenous.
<b>Preparation</b>	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.
<b>Storage</b>	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.
<b>Pharmacokinetics</b>	<p><b>Peak time to concentration</b> after an oral dose is 1–4 hours.</p> <p><b>Peak concentrations</b> should be obtained 2 hours after a dose, and if delayed absorption is considered, a concentration at 6 hours should also be collected.</p> <p><b>Peak concentrations</b> of 8 to 24 mcg/ml are expected. Dose increase should be strongly considered for low concentrations (but not for delayed absorption), as rifampin exhibits a dose response in treatment of TB.</p>
<b>Oral absorption</b>	Usually rapid absorption, may be delayed or decreased by high-fat meals.
<b>CSF penetration</b>	Rifampin CSF penetration is variable and typically achieves only 10–20% of serum concentrations in CSF (may be better in the face of inflamed meninges), but this may still be an important contribution to the regimen. Some authors recommend increased doses of rifampin in patients with TB meningitis.
<b>Special circumstances</b>	<p><b>Use in pregnancy/breastfeeding:</b> Recommended for use in pregnancy; can be used while breastfeeding.</p> <p><b>Use in renal disease:</b> Can be used without dose adjustment.</p> <p><b>Use in hepatic disease:</b> Use with caution, can be associated with hepatotoxicity.</p>

# RIFAMPIN (RIF) [ 2 of 2 ]

<b>Adverse reactions</b>	<b>Many drug interactions.</b> Orange staining of body fluids. Rash and pruritus. GI upset, flu-like syndrome (usually only with intermittent administration). Hepatotoxicity. Hematologic abnormalities (thrombocytopenia, hemolytic anemia).
<b>Contraindications</b>	<b>Rifamycin allergy;</b> due to <b>drug interactions</b> , may be contraindicated with concurrent use of certain drugs.
<b>Monitoring</b>	Liver function monitoring if appropriate (if given with other hepatotoxic medications or if there are symptoms of hepatotoxicity); monitor drug concentrations of interacting medications.
<b>2012 wholesale cost</b> 30-day supply, 60-kg person	\$26 (outpatient public health pricing) \$82 (community hospital)
<b>Patient instructions</b>	<p>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.</p> <p><b>Call your doctor right away if you have any of these side effects:</b></p> <ul style="list-style-type: none"><li>• Unusual tiredness or loss of appetite</li><li>• Severe abdominal upset</li><li>• Fever or chills</li></ul>

## RIFAPENTINE (RPT) [1 of 2]

<b>Drug class</b>	Rifamycin
<b>Trade name</b>	Priftin
<b>Activity against TB</b>	<b>Bactericidal;</b> same mechanism of action as rifampin, inhibits RNA polymerase. 100% cross-resistant with rifampin.
<b>Cross-resistance</b>	Cross-resistance among the rifamycin class of drugs is typical. In <20% of strains resistant to rifampin, rifabutin may retain susceptibility <i>in vitro</i> . The clinical significance of this is unknown.
<b>Dose for active tuberculosis disease:</b>	<p><b>Adults:</b> 600 mg once weekly during the continuation phase of treatment. (Not recommended in the U.S. for use during the initial treatment phase and will no longer be recommended in upcoming ATS/CDC treatment guidelines.) Higher daily doses are being studied, with one study suggesting 1200 mg daily with food.</p> <p><b>Children:</b> (12 years of age and older), 600 mg once weekly if <math>\geq</math> 45 kg. 450 mg once weekly if &lt; 45 kg.</p>
<b>Dose for LTBI:</b>	<p><b>Adults:</b> 900 mg once weekly for 12 doses given with INH 900 mg</p> <p><b>Children:</b> (12 and older), once weekly dose for 12 weeks based on weight (10.0-14.0 kg = 300 mg; 14.1-25.0 kg = 450 mg; 25.1-32.0 kg = 600 mg; 32.1-49.9 kg = 760 mg; <math>\geq</math> 50 kg = 900 mg) given with INH 15 mg/kg weekly</p> <p><b>Renal failure/dialysis:</b> No adjustment required. Only 17% of ingested dose is excreted renally.</p> <p><b>Concomitant medications:</b> Dosage adjustment may be required for concurrent medications. Concurrent treatment with most anti-retroviral drugs is not recommended, as anti-retroviral drug concentrations are substantially reduced, as they are with rifampin. On the other hand, rifapentine plasma concentrations are not affected by most other drugs, based on current data.</p>
<b>Route of administration</b>	Oral
<b>Preparation</b>	150 mg tablets
<b>Storage</b>	Tablets should be stored at room temperature
<b>Pharmacokinetics</b>	<p><b>Time to peak concentration</b> after an oral dose is 5–6 hours.</p> <p><b>Peak concentrations</b> after a 600 mg dose are expected to be 8–30 mcg/ml. The half-life is approximately 13 hours.</p>
<b>Oral absorption</b>	Oral bioavailability is 70%. Peak concentration and AUC are increased if given with a meal.
<b>CSF penetration</b>	No information available

# RIFAPENTINE (RPT) [ 2 of 2 ]

<p><b>Special circumstances</b></p>	<p><b>Use in pregnancy:</b> Pregnancy category C. Use only if potential benefit outweighs possible risk.</p> <p><b>Use in renal disease:</b> Insufficient data, but likely to be safe since only minimally excreted by the kidneys.</p> <p><b>Use in hepatic disease:</b> Pharmacokinetics are very similar to normal volunteers in persons with mild to severe liver impairment.</p> <p><b>Dose adjustments:</b> Not necessary to adjust rifapentine dosage due to drug interactions – but may be needed for concurrent drugs, as is the case for rifampin.</p>
<p><b>Adverse reactions</b></p>	<p><b>Many drug interactions.</b></p> <p>Red-orange staining of body fluids</p> <p>Rash and pruritis</p> <p>Hypersensitivity reaction</p> <p>Hepatotoxicity</p> <p>Hematologic abnormalities</p>
<p><b>Contraindications</b></p>	<p>History of hypersensitivity to any of the rifamycins (i.e., rifampin or rifabutin)</p>
<p><b>Monitoring</b></p>	<p>Liver function monitoring if appropriate (if given with other hepatotoxic medications or if there are symptoms of hepatotoxicity); monitor drug concentrations of interacting medications.</p>
<p><b>2012 wholesale cost</b> 30-day supply, 60-kg person</p>	<p>\$54 (outpatient public health pricing) \$109 (community hospital)</p>
<p><b>Patient instructions</b></p>	<p>Rifapentine may produce a reddish coloration of your urine, sweat, sputum, tears, and breast milk – be aware that your contact lenses or dentures may be permanently stained. The reliability of oral or other systemic hormonal contraceptives may be affected; consider using alternative contraceptive measures. If you are prone to nausea, vomiting, or gastrointestinal upset, taking rifapentine with food may be useful.</p> <p><b>Call your doctor right away if you have any of these side effects:</b></p> <ul style="list-style-type: none"> <li>• Fever</li> <li>• Loss of appetite</li> <li>• Malaise</li> <li>• Nausea and vomiting</li> <li>• Darkened urine</li> <li>• Yellowish discoloration of the skin and eyes</li> <li>• Pain or swelling of the joints</li> </ul>

# STREPTOMYCIN (SM) [1 of 2]

<b>Drug class</b>	Aminoglycoside
<b>Trade name</b>	Streptomycin sulfate
<b>Activity against TB</b>	<b>Bactericidal;</b> inhibits protein synthesis; no significant cross-resistance with other aminoglycosides.
<b>Cross-resistance</b>	Rarely may be cross-resistant to kanamycin.
<b>Dose (all once daily)</b>	<p><b>Adults:</b> 15 mg/kg/day in a single daily dose, 5–7 days per week (maximum dose is generally 1 gram, but a large, muscular person could receive more and should have concentrations 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 concentrations).</p> <p><b>&gt; 59 yrs of age:</b> Many experienced clinicians prefer to use a lower starting dose of 10 mg/kg ( 5–7 times per week or 2–3 times per week after initial period). Alternatively, 15 mg/kg/dose 3 times per week.</p> <p><b>Children:</b> 20–40 mg/kg/day (max 1 gram) 5–7 days per week. 20–40 mg/kg/day (max 1 gram) 3 days per week after initial period daily.</p> <p><b>Renal failure/dialysis:</b> 12–15 mg/kg/dose 2–3 times weekly (not daily).</p> <p><b>Markedly obese individuals</b> should have an adjusted dose due to the decreased distribution of extracellular fluids in adipose tissues. Dosing based on actual weight will give supratherapeutic concentrations.</p> <p><b>For dosing, use adjusted weight as follows:</b> Ideal body weight + 40% of 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 <i>Concentrations should be followed closely.</i></p>
<b>Route of administration</b>	Intravenous or intramuscular (has been used intrathecally and intraperitoneally). Not absorbed orally.
<b>Preparation</b>	1 gram vial for injection.
<b>Storage</b>	Store in the refrigerator.
<b>Pharmacokinetics</b>	<p>For intravenous administration, infuse over 60 minutes for adults; 1–2 hours for children; intramuscular absorption is complete within 4 hours and peak concentrations are achieved at 1–2 hours. Obtaining a drug concentration 90–120 minutes after intravenous infusion allows for complete distribution of drug. An additional concentration collected 4 hours later will allow for a half-life to be calculated and peak to be back-extrapolated.</p> <p><b>Peak concentrations</b> for a 15 mg/kg dose are between 35 and 45 mcg/ml.</p> <p><b>Peak concentrations</b> of 65–80 mcg/ml are obtained after a 25 mg/kg dose.</p> <p>Trough concentrations should be &lt; 5 mcg/ml in patients with normal renal function.</p>
<b>Oral absorption</b>	There is no significant oral absorption. Intramuscular absorption might be delayed if the same site is used consistently.
<b>CSF penetration</b>	Variable penetration; appears to penetrate inflamed meninges better.



# STREPTOMYCIN (SM) [ 2 of 2 ]

<p><b>Special circumstances</b></p>	<p><b>Use in pregnancy/breastfeeding:</b> Avoided in pregnancy due to documented cases of congenital deafness. Can be used while breastfeeding.</p> <p><b>Use in renal disease:</b> Use with caution. Concentrations 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 variably cleared by hemodialysis; see Chapter 7, <i>Co-morbidities and Special Situations – Renal Failure</i>.</p> <p><b>Use in hepatic disease:</b> Drug concentrations not affected by hepatic disease (expect 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.</p> <p><b>Diuretic use:</b> Coadministration of loop diuretics and aminoglycoside antibiotics carries an increased risk of ototoxicity.</p>
<p><b>Adverse reactions</b></p>	<p>Nephrotoxicity: Less nephrotoxic than amikacin.</p> <p>Ototoxicity (hearing loss): Increased with advanced age and prolonged use.</p> <p>Vestibular toxicity.</p> <p>Local pain with IM injections.</p> <p>Electrolyte abnormalities, including hypokalemia, hypocalcemia, and hypomagnesemia.</p>
<p><b>Contraindications</b></p>	<p><b>Pregnancy</b> (congenital deafness seen with streptomycin and kanamycin use in pregnancy); <b>hypersensitivity to aminoglycosides</b>; caution with renal, vestibular, or auditory impairment.</p>
<p><b>Monitoring</b></p>	<p>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 concentrations at baseline if there is any question about renal function. Some experts monitor aminoglycoside concentrations routinely, regardless of renal function. Monitor concentrations serially for patients with impaired renal function.</p>
<p><b>2012 wholesale cost</b> 30-day supply, 60-kg person</p>	<p>\$178 (outpatient public health pricing) \$450 (community hospital)</p>
<p><b>Patient instructions</b></p>	<p>Store streptomycin in the refrigerator.</p> <p><b>Call your doctor right away if you have:</b></p> <ul style="list-style-type: none"> <li>• Problems with hearing, dizziness, or balance</li> <li>• Rash or swelling of your face</li> <li>• Trouble breathing</li> <li>• Decreased urination</li> <li>• Watery or bloody diarrhea</li> <li>• Swelling, pain, or redness at your IV site</li> <li>• Muscle twitching or weakness</li> </ul>

## New Anti-TB Drugs in the Pipeline

CLINICAL TRIALS		
PHASE I	PHASE II	PHASE III
<b>TBA-354</b> Nitroimidazole	<b>Sutezolid (PNU-100480)</b> Oxazolidinone	<b>Bedaquiline (TMC 207) with OBR* for MDR-TB</b> Diarylquinoline
<b>Q203-Novel anti-TB agent</b> Imidazopyridine	<b>SQ109</b> Ethylenediamine	<b>Delamanid (OPC-67683) with OBR* for MDR-TB</b> Nitro-dihydro-imidazooxazole Submitted for FDA approval
	<b>Rifapentine for drug-susceptible TB</b> Rifamycin	<b>Petromanid – Moxifloxacin – Pyrazinamide</b> New chemical entity
	<b>Bedaquiline - Pretomanid – Pyrazinamide regimen</b>	<i>*Optimized Background Regimen</i>
	<b>Levofloxacin</b> Fluoroquinolone	

For updated information, see <http://www.newtbdrugs.org/pipeline.php>

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# Pediatrics

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

- Pediatric tuberculosis (TB) can be difficult to confirm bacteriologically due to its generally paucibacillary nature, and because children have difficulty producing sputum for analysis.
- Drug resistance should be suspected in children when the source case has drug-resistant TB or the child originates from a region with high rates of drug resistance.
- Because we have no data from randomized, controlled studies upon which to base our treatment regimens for children, we follow the same regimens required for adult disease.
- To determine the drug-susceptibility pattern of a pediatric TB case, it is often necessary (and critically important) to identify the source case from whom the child likely acquired the organism.
- Diagnosis and treatment of pediatric TB is often based on typical clinical or radiographic features in conjunction with demographic features and exposure history. Failure to diagnosis drug-resistant TB can result in long delays in definitive treatment with resultant risk for the child.

## Magnitude of the pediatric drug-resistant TB burden

The true burden of pediatric TB, especially drug-resistant TB, is unknown. It is estimated that annually at least **8 million children are infected with *Mycobacterium (M.) tuberculosis* worldwide**, at least **1 million develop TB disease**, and approximately **32,000 become sick with MDR-TB**. Recent reports of pediatric contacts of drug-resistant adult cases reveal high rates of MDR-LTBI and MDR-TB. In contact investigations in South Africa, Pakistan, and Peru, 5–20% of children who were household contacts to a case of MDR-TB had TB disease, either upon initial evaluation or during several years of follow up. In a series in Turkey, 10% of children exposed to active MDR-TB developed MDR-TB disease themselves, all within 6 months of source case diagnosis. Unless more widespread contact investigation and treatment of pediatric contacts are undertaken in high-burden, low-resource countries, the burden of pediatric MDR-TB and pool of future drug-resistant TB pose a compelling public health risk.

# Collection of pediatric specimens

## Gastric aspirates

Gastric aspirates are the traditional specimen collected from children suspected of having TB. The stomach is intubated and contents aspirated in order to collect swallowed sputum. Yields are best for children who have fasted overnight, but specimens are sometimes collected after a nap in the clinic. Since most studies report a maximum yield of 40–50% in children treated for TB disease (some recent series report only 10–20% positivity), **3 morning specimens** are collected in order to maximize yield. While each specimen adds yield, **80–90% of positive results are found in the first gastric aspirate collected.**

- Take care to meticulously collect and process the first specimen.
- If the specimen is not processed immediately, neutralize the acidity with sodium carbonate to preserve the viability of the mycobacteria.
- Because the specimen is often collected very early in the morning before the microbiology lab is open and ready to process specimens, it is strongly advised to **neutralize the specimen** at the bedside by collecting it into a pre-prepared tube.
- The **youngest infants, children with extensive pulmonary disease, and those who are symptomatic have the highest yield** from gastric aspirate collection.
- The child should not eat or drink anything (even medications) for 6 hours before the procedure as this may prompt stomach emptying.
- Several strategies can be helpful if there is not return of mucus with the first aspiration: the operator can quickly instill up to 20 mL of **non-bacteriostatic** sterile water and immediately aspirate again, roll the child, or advance and withdraw the tube— aspirating the entire time.
- When tap water is used for collecting or processing the specimen, false-positive smear results have sometimes been reported.
- If there is a high suspicion of drug-resistant disease and the child is hospitalized for a prolonged period of time, additional specimens can be collected to further increase yield.

## Sputum collection

Spontaneously-expectorated sputum can be collected from **older children**, especially with careful coaching.

- Advise the family to have the child **drink plenty of liquids** the night before the collection.
- **First morning specimens** have the highest yield.
- Serial big breaths held for 5 seconds should be followed by a robust cough.
- Children should be trained to **spit the thick mucus**, rather than the thin saliva, into the specimen cup.
- If a child is unable to collect specimen in the clinic, sometimes they are able to collect sputum after **serial slow, big breaths in a hot shower** at home first thing in the morning. They should be advised to try this before eating or drinking anything.
- Some protocols suggest rinsing the mouth with water, gargling with 3% saline, and/or brushing the teeth in order to minimize contamination with mouth flora.



- It can also be helpful to have the child carry specimen cups throughout the day for the random productive cough. If the specimen cup is stored in the refrigerator, serial small sputum specimens can be collected to maximize yield.

**Sputum induction** is the process of collecting sputum after the child inhales hypertonic saline (3–10%) using an ultrasonic nebulizer. **Induction improves the yield of sputum collection for patients of all ages.**

- The specimen has the highest yield first thing in the morning and the child should be NPO (nothing by mouth) for at least 4 hours before the procedure.
- Twenty to 45 minutes of inhalation with occasional deep breaths are often required to induce productive cough and collect sufficient specimen.
- Use of a mask provides maximal saline inhalation, but is poorly tolerated by some children. Pre-treatment with a bronchodilator is recommended as bronchospasm can occur, particularly among patients with asthma or when higher concentrations of hypertonic saline are used.
- Some protocols recommend gargling with 3% sodium chloride beforehand to remove oral contaminants.
- Older children can be taught to collect the sputum into a sterile specimen cup, but younger children might require nasopharyngeal or oropharyngeal aspiration by a skilled health care worker when they begin to cough in order to collect the mucus.

**Bronchoscopy** with bronchoalveolar lavage is usually reserved for specimen collection when TB is only one of many potential diagnoses. Gastric aspirates and induced sputum can have similar or superior yields without the expense and invasiveness of a bronchoscopy.

Collection of other specimen types, such as **nasopharyngeal aspirate (NPA)** and **stool culture**, are promising. The NPA seems to be the quickest specimen as it does not involve prior treatment with a bronchodilator or nebulized saline, and the child is only intubated into the posterior nasopharynx. In some series, the yield is almost equivalent to those found at the same centers by gastric aspiration. Series describing stool cultures have not shown improved yield over traditional specimens.

It is unlikely that any specimen or any technology will have sufficient sensitivity to “rule out” TB disease in the pediatric population. The community of pediatric TB providers should continue to seek refinements in technique and technology to improve yield and shorten the time to diagnosis of laboratory-proven TB disease, and drug resistance, in particular.

**Culture yield from children is suboptimal, and it is important to pursue susceptibility data from the likely source case.** Clinicians rely on their public health partners to seek a likely source case for pediatric cases and to collect high-quality specimens for prompt processing.



## Molecular and microbiologic techniques for analyzing pediatric specimens

As children have a low bacillary load and rarely have cavitory disease, they are **unlikely to have smear-positive sputum or gastric aspirate specimens**. Culture techniques have markedly improved with the use of liquid media, but pediatric specimens still have a yield much lower than that of adults treated for TB disease. Pediatric specimens often take several weeks to yield a positive result and several more weeks to provide drug susceptibility results. The areas of the world with the highest rates of drug-resistant TB do not have universal access to state-of-the-art testing technologies. Many areas have no access to routine culture techniques, or only use solid media, a technique that is less sensitive and takes much longer to detect growth.

**Molecular methodologies are most sensitive in smear-positive specimens, but are promising in pediatrics.** Nucleic acid amplification tests (NAAT) are used by most U.S. labs to quickly identify an acid-fast bacilli (AFB) smear-positive sputum as *M. tuberculosis* complex. Depending on lab protocol and provider requests, these rapid tests may be performed on smear-negative sputum or other specimens (which will have a lower yield than smear-positive sputum). Since the vast majority of pediatric specimens are smear-negative, it naturally follows that NAAT tests will have a lower yield for pediatric specimens. Some series have also noted occasional false-positive results from pediatric gastric aspirate specimens. Newer molecular techniques identify both *M. tuberculosis* complex **and** resistance genes from clinical specimens or growth from culture techniques. Few studies have evaluated these newer techniques in children.

The **Xpert-MTB/RIF assay** is licensed in the United States and uses a fully automated amplification system for the detection of *M. tuberculosis* complex, as well as simultaneous detection of rifampin (RIF) resistance via the *rpoB* gene. The main advantage of the Xpert-MTB/RIF assay is that **results are available the same day** that the specimen is processed. However, **it is not as sensitive as culture for pediatric sputum or gastric aspirate specimens**. Over 2,600 children have been studied and reported in at least 16 studies involving Xpert-MTB/RIF.

*A negative result from the Xpert-MTB/RIF assay never rules out active TB disease in a child.*

- Compared to culture, the Xpert MTB/RIF was less sensitive (66%) and >98% specific (rare false positives) for pediatric sputum or gastric aspirate specimens.
- Importantly, in these same series, Xpert MTB/RIF was superior to smear microscopy in rapidly diagnosing tuberculosis in children.

**Most pediatric TB is culture-negative**, even using the most aggressive specimen collection technique and collecting multiple specimens.

In one series of TB diagnosed on clinical grounds by a provider, Xpert MTB/RIF was positive in only 4% of induced sputa and only 15% of gastric aspirates. International guidelines updated by the World Health Organization (WHO) in 2013 recommend that for adults and children, **Xpert MTB/RIF should be used as the initial diagnostic test in individuals suspected of having MDR-TB or HIV-associated TB**, and may be used in all children suspected of having TB. Xpert MTB/RIF may be considered as an additional test

after microscopy in settings where MDR-TB or HIV is of lesser concern, especially in further testing of smear-negative specimens. See **Chapter 3, Laboratory**, for more information about molecular testing.

## Treatment of children with drug-resistant disease

Since the original publication and second edition of this *Survival Guide*, there has been an explosion of publications concerning pediatric drug-resistant TB (primarily from South Africa, which has an enormous burden of TB, drug-resistant TB, and HIV). In 2012, a meta-analysis of treatment outcomes for a total of 315 children with MDR-TB analyzed a geographically and clinically diverse group of 8 studies published between 2003 and 2011. Across all sites, only 5.9% of children died and 82% enjoyed treatment success. Not surprisingly, 39% had a drug-related adverse event. Of the 4 studies that reported the number of drugs used in a regimen, an average of 5.8 drugs were used: all drugs were not necessarily employed for the entire duration of therapy.

Two studies within the meta-analysis reported that the duration of therapy was measured after culture conversion (9-12 months), 2 studies did not report duration of therapy, and the remaining 4 studies reported an average of 15.7 months of treatment. Twenty-two children (5.9%) died and 19 children (6.2%) defaulted from care. The only variable which was statistically associated with successful outcome was the **use of an injectable drug**. Because of the nature of the meta-analysis, variables could not be evaluated on an individual level, but the studies reporting that most of the patients received an injectable drug had a composite successful outcome rate of 87.2%, compared to those sites in which injectable drugs were rarely used (success 62.6%). While not statistically significant, 3 of the 4 reports with below-average success rates also had the highest rates of HIV infection. Success rates were 53-79% for the 3 series with an average of 37% HIV-positive patients, compared to 79-97% success rates for the series with an average of 2% HIV-positive children.

### General principles

Many guidelines have been published recently regarding treatment of adult and pediatric MDR-TB. In the absence of efficacy data derived from randomized, controlled trials, the following are generally accepted principles for treatment of MDR-TB in children:

- Because pediatric cases are often culture negative and lack susceptibility data, treatment regimens are often constructed based on the **drug-resistance pattern of the presumed source case**.
- **For MDR-TB, at least 4-6 likely effective drugs should initially be employed**, including a fluoroquinolone and an injectable agent.
  - “Likely effective drugs” are those that have not been taken previously by the patient (or source case) and/or to which in vitro drug susceptibility has been documented.
- Since a regimen is often initiated before full drug-susceptibility data are available for either the child or source case, **it is appropriate to empirically start therapy with 5 or 6 likely effective drugs if risks for drug resistance are identified**.

- Choose drugs based on: **site of the infection** (better central nervous system [CNS] penetration for meningitis, for example); **drugs that have not previously been used** in the child or source case regimen; **and drugs that are readily available.**
- **When all the drug-susceptibility data are available, 1 or 2 drugs can sometimes be stopped** depending on the response to treatment and the extent of disease. If the isolate is susceptible to all the drugs in the regimen, this strategy allows the provider to stop a drug that is poorly tolerated by the patient, and this can create a big psychological boost to the patient, family, and team. If the isolate is not susceptible to some of the drugs in the regimen, the clinician has usually not lost time or risked extension of resistance by starting with too modest a regimen.
- If the child is old enough to submit sputum, **serial sputum** should be collected for smear and culture throughout the treatment course.
- In the case of asymptomatic children with minimal disease (i.e., hilar adenopathy found as part of contact investigation), a minimal total duration of treatment of 16 months may be acceptable. (This shorter duration may be supported by 2012 meta-analysis findings).
- In all other cases, particularly symptomatic children or children with extensive radiographic disease, treatment durations consistent with adult recommendations can be considered:
  - **Intensive phase duration:** for the use of the injectable agent, at least 6 months beyond microbiologic, clinical or radiographic improvement
  - **Total duration of treatment:** at least 18 months beyond microbiologic, clinical or radiographic improvement

These recommendations are based on current U.S. expert opinion and practice.

## Administering oral TB drugs in children

*Very few anti-tuberculosis drugs are available in liquid preparations or in chewable 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. Using this strategy, 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**
- **Mix crushed tablets or capsule contents into a small amount of food as a vehicle to deliver the dose.**
  - Give a small amount of plain vehicle before the medication dose, between spoonfuls and after the dose.
  - 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 lessening drug taste in the vehicle itself).
- **Immediately after the medication is given, give 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.**

## TB drug dosages in children

Over the years, guidelines from the American Academy of Pediatrics (AAP), American Thoracic Society (ATS), Centers for Disease Control and Prevention (CDC), WHO and national TB programs have advised **very different doses** for TB drugs for children. In the past ten years, the data regarding pediatric pharmacokinetics for TB drugs have markedly increased.

The ***Sentinel Project on Pediatric Drug-Resistant Tuberculosis*** describes itself as a “global partnership of researchers, caregivers, and advocates who share a vision of a world where no child dies from this curable disease. We are collaborating to raise the visibility of this vulnerable population of children, and to share evidence and resources that can increase children’s access to prompt and effective treatment.” The Sentinel Project recently solicited published and unpublished pharmacokinetic data from colleagues around the world and scrutinized appropriate pediatric TB dosing regimens. The Sentinel Project published a user-friendly guide for management of pediatric MDR-TB as well as a one-page, weight-based table for all the second-line TB drugs. [See **Resources** at the end of this chapter.]

It is now clear that **children metabolize most TB drugs more rapidly than adults** and that **higher weight-based doses are required** to achieve the same serum concentrations (expected to be associated with clinical and microbiologic success). **Neonates and young infants, however, often have immature drug clearance and may not tolerate those same doses.** Studies are underway to define optimal doses. Consult a pediatric TB expert for dosing advice.

In general, **pediatric drug doses should be used for children through age 14 years**, or until their weight-based dosing is that of the adult dosing (whichever comes first).

Table 1 lists the doses of pediatric TB drugs recommended by 2 organizations.

TABLE 1.

**AAP and Sentinel Project daily drug dosing**

<b>Drug</b>	<b>AAP</b>	<b>Sentinel Project</b>
<b>Isoniazid (INH)</b>	10-15 mg/kg/day (max 300 mg/day or twice a week 900 mg)	High dose for low-level drug resistance 15-20 mg/kg/day
<b>Rifampin (RIF)</b>	10-30 mg/kg/day based on age* See Table 3 footnote, page 162, for details. (max 600 mg/day)	10-20 mg/kg/day
<b>Pyrazinamide (PZA)</b>	30-40 mg/kg/day (max 2 g/day)	30-40 mg/kg/day
<b>Ethambutol (EMB)</b>	15-25 mg/kg/day (max 1000 mg/day*)	15-25 mg/kg/day
<b>Amikacin (AK)</b>	15-30 mg/kg/day (max 1000 mg/day)	15-20 mg/kg/day (max 1000 mg/day)
<b>Capreomycin (CM)</b>	15-30 mg/kg/day (max 1000 mg/day)	15-20 mg/kg/day (max 1000 mg/day)
<b>Cycloserine (CS)</b>	10-20 mg/kg/day divided into 2 daily doses (max 1000 mg/day)	15-20 mg/kg/day
<b>Ethionamide (ETA)</b>	15-20 mg/kg/day divided into 2 or 3 daily doses (max 1000 mg/day)	15-20 mg/kg/day
<b>Kanamycin (KM)</b>	15-30 mg/kg/day (max 1000 mg/day)	15-20 mg/kg/day (max 1000 mg/day)
<b>Levofloxacin (LFX)</b>	15-20 mg/kg/day (max 1000 mg/day)	15-20 mg/kg/day divided into 2 doses (< 5 yo) 7.5-10 mg/kg/day once daily (> 5 yo)
<b>Moxifloxacin (MXF)</b>	7.5-10 mg/kg/day (up to 400)	7.5-10 mg/kg/day
<b>Para-aminosalicylate (PAS)</b>	200-300 mg/kg/day divided bid – qid (max 10g/day)	200-300 mg/kg/day divided into 2 daily doses
<b>Streptomycin (SM)</b>	20-40 mg/kg/day (max 1000 mg/day)	20-40 mg/kg/day (max 1000 mg/day)
<b>Clofazimine (CFZ)</b>		2-3 mg/kg once daily; if the child is <25kg give 100 mg every second day (max 200 mg/day)
<b>Amoxicillin/ clavulanate (AMX/CLV)</b>		80 mg/kg/day in 2 divided doses based on the amoxicillin component (max 4000 mg/day amoxicillin, 500 mg/day clavulanate)
<b>Meropenem (MPM)</b>		20-40 mg/kg IV every 8 hours (max 6000 mg/day)
<b>Linezolid (LZD)</b>		10 mg/kg/dose twice daily for children <10 years of age 300 mg daily for children ≥10 years of age (max 600 mg/day) Also give vitamin B6

\*See pages 162 and 163 for updated RIF and EMB dosages based on the 2018 AAP Red Book.

## Specific TB drugs

See also **Chapter 5, Medication Fact Sheets**, for information about monitoring, side effects and pharmacokinetics.

### 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 been no 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 to 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 15–20 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 and children require higher doses than do adults to achieve the same levels. Providers sometimes use doses closer to 25 mg/kg/dose in the initial phase of treatment while the bacillary loads are highest, and then decrease the dose for the long-term management.
- 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 small items (e.g., 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 and can be crushed fairly easily into liquid or food. It can also be given without food.

### Ethionamide (ETA)

- Better tolerated by children than adults with fewer gastrointestinal (GI) side effects.
- Dose: 15 to 20 mg/kg/day (recommended by AAP and Sentinel Project) 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 to 5 days (drug-ramping). After a few weeks of a full dose divided twice a day, the child could try the dose in a single daily dose with food.
- ETA 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 achieve an accurate dose over the course of several doses.
- As with adults, children should be supplemented with **pyridoxine** when taking ETA, and **thyroid function** should be monitored.

### Cycloserine (CS)

- Generally well-tolerated in children, though there have been reports of **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. See **Chapter 3, Laboratory**, section on **Therapeutic drug monitoring**.
- As with adults, children should be supplemented with pyridoxine when taking CS.

## Fluoroquinolones

- Fluoroquinolones have generally been avoided in children because arthropathy has been observed in animal models. Many thousands of children have received courses of fluoroquinolones (usually for short periods of time) and **none have been found to have irreversible 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 hundreds of children treated with fluoroquinolones for more than 6 months have been reported without irreversible arthropathy. Rates of reversible arthralgia have been similar to those in adults, and cases of Achilles tendon rupture have been reported in adolescents.
- **National guidelines endorse the use of fluoroquinolones in the treatment of children with MDR-TB if the drug is vital to the regimen. Parents and care providers should carefully watch for musculoskeletal complaints.**
- **Levofloxacin (LFX)** has significantly better activity against TB than ciprofloxacin (which is licensed for treatment of complicated urinary tract infection in children). LFX has been studied for otitis media and community-acquired pneumonia in children. Two recent studies support the use of 15-20 mg/kg/day in a single daily dose for children of all ages outside the neonatal period (up to the adult doses of 750-1000 mg daily) in order to achieve the goal serum levels for TB treatment. LFX comes as unscored 250- and 500-mg tablets. An oral suspension of 25 mg/mL is available.
- There is one published pharmacokinetic data report about the use of **moxifloxacin (MFX)** in children (and a few anecdotal reports), showing that recommended doses of 7.5–10 mg/kg/day are insufficient to achieve serum levels obtained by adults receiving 400 mg doses.
- Fluoroquinolone use in children should be undertaken with informed consent of the parents. Parents and all caregivers should be observant for any signs or symptoms of toxicity, including extremity pain, swelling, or range of motion limitation.

## Para-aminosalicylate (PAS)

- PAS is marketed in a reasonably well-tolerated formulation of **granules**. The packets of granules contain 4 grams of PAS.
- AAP pediatric dose: 200 to 300 mg/kg/day in 2 to 4 divided doses (most children can tolerate the dose divided in only 2 daily doses). Maximum daily dose is 10 gm. A recent study evaluated 150 mg/kg/day in either a single daily dose or divided twice daily and found levels consistent with adult serum levels. This is the internationally-recommended dose.
- Lucane Pharma developed a **pediatric dosing spoon** calibrated to dispense PAS in dosing ranges acceptable for children. The spoon has cut-off marks for the different doses of PAS based on weight-band doses. See **Resources** at the end of this chapter for information about how to obtain the dosing spoon.
- To measure the granules without a dosing spoon, 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. **PAS granules should not be chewed by the patient.**



- Warn the family that the drug leaches out of the granules and that the empty spheres (skeletons) will be visible in the stool.

## Linezolid

- There is not extensive experience with the use of linezolid for pediatric TB. Doses of 10 mg/kg twice daily have been used successfully in children under twelve years of age. An alternate dosing recommendation is 10 mg/kg twice daily if the child weighs less than 30 kg, and 10 mg/kg once daily (or 300 mg once daily) for children over 30 kg. The typical adult dose is 600 mg once daily. Some clinicians use the 600 mg once-daily dose for adults for the first several months (initiation phase), followed by 300 mg once daily in the continuation phase. **Many children and adults require dose reduction** due to adverse events (preferably after the first few months of therapy).
- Children taking linezolid should be **followed carefully for hematologic toxicity, symptoms of peripheral neuropathy, and optic neuropathy.**

## Injectable drugs

- A cornerstone in the treatment of MDR-TB in adults, **an injectable drug should be included in the treatment of children with MDR-TB.** Most guidelines suggest using an injectable drug for at least 4–6 months from culture conversion, and ideally longer when there is more extensive drug resistance (fewer good drugs in the treatment regimen) or more extensive disease.
- Newer international data suggest good drug levels using **slightly lower doses** (see Table 1), **which should lead to fewer side effects** (hearing loss in particular). Children receiving aminoglycosides or capreomycin (CM) should be monitored, as are adults, with hearing and vestibular screens and renal function monitoring.
- Injectables are initiated at 5–7 days per week. Intermittent dosing of 3 times per week can be used after culture conversion or clinical/radiographic improvement is documented.
- While some adults elect to receive the drugs intramuscularly, most children should have an 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.
- In rare situations when intramuscular (IM) injection must be used for administering the injectable drug, **take care to select an injection site appropriate for the child's age and muscle development.**
  - The middle third of the vastus lateralis muscle, located along the anterolateral aspect of the thigh, is the only recommended IM site for a child younger than 18 months and is the preferred site for children younger than 3 years old.
  - The ventrogluteal muscle may be a good alternate IM injection site in children older than 18 months, although the target injection area is small and site rotation may be necessary to avoid overuse.
  - The deltoid muscle may be considered as an alternate rotation site in children older than 18 months if the volume of injectable medication is less than or equal to 1 mL; however, it is not recommended for repeated injections given its small size.
  - The dorsogluteal muscle should be **avoided** in children younger than 3 years old.
- The site of IM injection should be recorded to facilitate appropriate **rotation of the injection** and assessment for injection-associated complications.

## Pediatric drug dosing for tablets, capsules, granules

The following tables are designed to help clinicians select pediatric doses based on fractions of tablets, capsules, or packets of granules.

For dosing of injectables and oral suspensions, see **Table 1: AAP and Sentinel Project daily drug dosing.**

TABLE 2. **ISONIAZID**

Child's weight		Daily isoniazid dose 10-15 mg/kg/dose		
KILOGRAMS	POUNDS	MILLIGRAMS	100 mg TABS	300 mg TABS
3-5	6.6-11	50 mg	1/2	0
5-7.5	11-16.4	75 mg	3/4	0
7.5-10	16.5-22	100 mg	1	0
10-15	22-33	150 mg	0	1/2
15-20	33-44	200 mg	2	0
Over 20	Over 44	300 mg	0	1

**Maximum daily isoniazid dose is 300 mg**

TABLE 3. **RIFAMPIN** *updated 9-25-19*

Child's weight		Daily rifampin dose			
KILOGRAMS	POUNDS	MILLIGRAMS	150 mg CAP	300 mg CAP	mg/kg/dose
< 3.3 over 28 days	7.3	75 mg	1/2	0	22.7+
3.3-5	7.3-11	100 mg	2/3	0	20 - 30
5-7.5	11-16.5	150 mg	1	0	20 - 30
7.5-11	16.5-24	225 mg	1.5	0	20 - 30
11-15	24-33	300 mg	0	1	20 - 27
15-20	33-44	375 mg	1/2	1	19 - 25
20-27	44-59	450 mg	1	1	17 - 22
Over 27	Over 59	600 mg	0	2	< 22

**Maximum daily rifampin dose is currently 600 mg (higher adult doses are being evaluated)**

Recent studies suggest that young children metabolize rifampin more quickly and that doses of rifampin used in the past have not been achieving adult serum levels. Hence, the 2018 AAP Red Book notes: Many experts recommend using a daily rifampin dose of 20-30 mg/kg/day for infants and toddlers, and for serious forms of tuberculosis such as meningitis and disseminated disease. Neonates (<28 days of age) should receive rifampin 10 mg/kg/day

When isoniazid in a dosage exceeding 10/mg/kg/dose is used in combination with rifampin, the incidence of hepatotoxic effects may be increased.

## Pediatric drug dosing

TABLE 4. **PYRAZINAMIDE** revised 6/7/16

Child's weight		Daily pyrazinamide dose 30-40 mg/kg/dose	
KILOGRAMS	POUNDS	MILLIGRAMS	500 mg TABS
3-4.2	6.6-9.2	125 mg	1/4
4.3-6.2	9.4-13.6	187.5 mg	3/8
6.3-8.9	14-20	250 mg	1/2
9-12.5	20-27.5	375 mg	3/4
12.6-18	27.7-40	500 mg	1
18.1-25	40-55	750 mg	1 1/2
25.1-33.3	55-73	1000 mg	2
33.4-41.5	73-91	1250 mg	2 1/2
41.6-50	91-110	1500 mg	3
50.1 & over	Over 110	2000 mg	4

Dose obese children on lean body weight

**Maximum daily pyrazinamide dose is 2 grams**

TABLE 5. **ETHAMBUTOL** updated 7-26-18 to align with 2018 AAP Red Book

Child's weight		Daily ethambutol dose 15-25 mg/kg/dose		
KILOGRAMS	POUNDS	MILLIGRAMS	100 mg TABS	400 mg TABS
4-6	9-13	100 mg	1	0
6-8	14-17	150 mg	1 1/2	0
8-12.5	18-27	200 mg	2	0
12.5-17.5	28-38	300 mg	3	0
17.5-22.5	39-49	400 mg	0	1
22.5-27.5	50-60	500 mg	1	1
27.5-32.5	61-71	600 mg	2	1
32.5-37.5	72-82	700 mg	3	1
37.5-55	83-121	800 mg	0	2
56-75	123-165	1200 mg	0	3

Dose obese children on lean body weight

**Maximum daily ethambutol dose: See note**

Note: AAP recommends 1 gram as a maximum daily ethambutol dose for children. TB pharmacologists suggest dosing based on lean weight. Max daily dose might exceed 1 gram for a muscular teen.

# Pediatric drug dosing

TABLE 6. **CYCLOSERINE**

Child's weight		Daily cycloserine dose 10-20 mg/kg/day divided bid	
KILOGRAMS	POUNDS	MILLIGRAMS	250 mg CAP
8-12	17-26	83 mg po bid	1/3 po bid
12-16	27-35	125 mg po bid	1/2 po bid
16-25	35-55	166 mg po bid	2/3 po bid
25-38	55-84	250 mg po bid	1 po bid
Over 38	Over 84	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	
<b>Maximum daily cycloserine dose is 1 gram</b>			

TABLE 7. **ETHIONAMIDE**

Child's weight		Daily ethionamide dose 15-20 mg/kg/day divided bid		
KILOGRAMS	POUNDS	INITIAL DOSE	DOSE SIZE	FINAL DOSE
8.4-11	18.5-24	82.5 mg po qhs	1/3 tablet	82.5 mg po bid
11.1-16.6	24-36.5	125 mg po qhs	1/2 tablet	125 mg po bid
16.7-20	36.5-44	165 mg po qhs	2/3 tablet	165 mg po bid
20-25	44-55	187 mg po qhs	3/4 tablet	187 mg po bid
25-33.3	55-73	250 mg po qhs	1 tablet	250 mg po bid
Over 33.3	Over 73	250 mg po qhs	1 tablet	250 mg po bid 500 mg po qhs
<b>Maximum daily ethionamide dose is 1 gram</b>				

TABLE 8. **PARA-AMINOSALICYLATE (PAS)**

Child's weight		Daily PAS dose 200-300 mg/kg/day in divided doses	
KILOGRAMS	POUNDS	GRAMS	PACKET
8-10	17-22	1 gram po bid	1/4 packet
10-15	22-34	1.5 grams po bid or 1 gram po tid	3/8 packet bid or 1/4 packet tid
15-20	35-44	2 grams po bid	1/2 packet
20-30	45-66	3 grams po bid	3/4 packet
30-40	67-88	4 grams po bid	1 packet
Over 40	Over 89	5 grams po bid	1 1/4 packet
<b>Maximum daily PAS dose is 10 grams</b>			

## When to start a drug-resistant TB regimen in children

Symptomatic children diagnosed with TB disease and with high risk of drug resistance should be treated with an expanded empiric regimen just like an adult in the same situation. Features that suggest risk for drug resistance include:

- **Previous treatment for TB** in the child or a close contact
- Known **exposure to drug-resistant TB**
- Known **exposure to someone who has failed TB treatment, died from TB, or been poorly adherent to TB treatment**
- **Failure to improve** clinically or microbiologically on TB treatment

Every effort should be made to collect high-quality specimens from the child and all possible source cases. Specimens should be submitted for both traditional culture and susceptibility testing as well as molecular drug-susceptibility testing. Some of these rapid tests will be available at larger local hospital laboratories, but it may be necessary to submit specimens to a regional or state reference laboratory. See **Chapter 3, Laboratory**, section on **Molecular methods**. Close communication through the appropriate channels with the correct paperwork and documentation will facilitate rapid processing of specimens and best results for the patient. Consultation with a regional pediatric TB expert through the Regional TB Training and Medical Consultation Center (RTMCC) network is often very helpful. See **Appendix 1: Expert Resources for Drug-Resistant TB**.

The treatment of asymptomatic children who have abnormal chest radiographs can sometimes be deferred for a few weeks while drug-susceptibility testing is completed. This sometimes allows the best initial regimen, exposes the child to the least toxic medications, and increases adherence and tolerability through the whole course of treatment. The youngest children have the highest rates of development of TB disease and dissemination. For infants, deferral of treatment of presumed TB disease should only be undertaken with caution and with expert consultation.

**Subtle abnormalities** of chest radiographs sometimes reflect viral disease, community-acquired pneumonia, reactive airways disease, reversible atelectasis, or technique. Repeat testing 2–3 weeks later often yields a normal chest radiograph and avoids unnecessary treatment for TB disease. If a radiograph is improving and the child is still asymptomatic, you can continue to defer treatment (as long as the child will not be lost to follow-up) and re-evaluate at 2- to 3-week intervals. Persistent atelectasis can also be the only finding of TB disease on plain film radiography. It is usually caused by lymphadenopathy which is not always visible on plain film.

**Do not start a regimen for treatment of drug-susceptible or drug-resistant LTBI until TB disease is excluded.**

# Treatment of children with drug-resistant LTBI

**Latent TB Infection (LTBI)** is diagnosed when a child has a positive tuberculin skin test (TST) or interferon gamma release assay test (IGRA) and has no evidence of TB disease based on high quality chest radiographs (ideally 2 views, frontal and lateral) and focused history and physical exam.

## TST or IGRA?

National guidelines endorse the interchangeable use of IGRA tests and TST in children 5 years of age and older.

The IGRA tests are more specific for TB infection because they evaluate the lymphocytic response to 2 or 3 proteins which are present in TB, but not in the bacille Calmette-Guérin (BCG) vaccine and not in most nontuberculous mycobacteria (NTM). Because there is generally less experience and fewer published data with IGRAs in young children, these tests are not uniformly used in the evaluation of young children. The IGRA tests are recommended preferentially for children who have received BCG vaccine in the past.

AAP now endorses the use of IGRA tests in children as young as 3 years of age in certain circumstances:

- in children with a negative TST, but high clinical suspicion for TB disease and/or high risk for infection, progression, or poor outcome.
- in children with a positive TST, but the child is healthy with low risk for TB infection; when additional information is required to ensure adherence with LTBI treatment (parents are reluctant to accept LTBI treatment without further validation); or when the child is suspected of having NTM.

IGRA tests can be used in any age child, but there may be an increased rate of false-negative or indeterminate test results in young children – both TST and IGRA tests result in more false negative results in young children in whom the immune system is not fully developed.

The diagnosis of drug-resistant LTBI is based on the presumption that an individual with known drug-resistant TB is the source of the LTBI for the child being evaluated. (See **Chapter 10, Contacts**). Since treatment of drug-resistant LTBI requires use of more expensive drugs with potentially more side effects than isoniazid (INH), the diagnosis should be made carefully. Consider the following features:

- the **degree of exposure** to the source case (duration and proximity)
- the **infectiousness** of the source case (as evidenced by smear positivity and evaluation of other contacts exposed to the source case)
- the **likelihood that the child was infected recently**, rather than remotely

The use of INH for treatment of LTBI has been well studied in adults and children. INH markedly decreases the risk of developing TB disease after drug-susceptible infection. Unfortunately, such data are not as robust in children with drug-resistant infection.

**The treatment of LTBI after exposure to a source case with INH mono-resistant TB is rifampin.**

**AAP now endorses a 4-month duration of rifampin therapy for LTBI (non-MDR).**

## Treatment options for MDR-LTBI

Many different regimens have been reported for treatment of MDR-LTBI, but there are **no randomized controlled trials upon which to make evidence-based recommendations.**

Several small studies have evaluated pediatric MDR-LTBI treatment. Among 42 children with LTBI treated by directly observed therapy (DOT) in Micronesia and the Marshall Islands after widespread exposure to MDR-TB, no children developed TB disease when treated with either 1 year of LFX monotherapy (older children) or LFX plus EMB. There were too few children studied to reach statistical significance, but 20 children had developed MDR-TB in the 2 years prior to instituting the use of MDR-LTBI therapy. In a South African study, rates of progression to TB disease after exposure to MDR-TB were reduced from 20% to 5% by treatment with a multidrug regimen for 6 months. In a second South African study, of 186 children treated with 6 months of ofloxacin, EMB and high-dose INH following exposure to a case of MDR-TB (40% of the children were TST positive), only 6 (3.2%) developed TB disease and 4 of those were not completely adherent to treatment. No children treated with DOT developed TB disease.

The AAP does not give a specific recommended regimen for treatment of MDR-LTBI, but suggests consulting a TB specialist. The 2000 ATS/CDC guidelines state: *“For persons who are likely to be infected with MDR-TB and at high risk of developing TB, pyrazinamide and ethambutol or pyrazinamide and a fluoroquinolone (i.e., levofloxacin or ofloxacin) for 6–12 months are recommended, if the organisms from the index case-patient are known to be susceptible to these agents. Immunocompetent contacts may be observed without treatment or treated for at least 6 months.”*

Other 2-drug regimens have been used and reported in children including regimens that included CS and ETA. Two series in the United States have reported very poor tolerability to the combination of LFX with PZA.

**Although it is impossible to make a definitive recommendation regarding treatment of MDR-LTBI, consider the following:**

- Since children less than 5 years of age and immunocompromised individuals are at highest risk for development of TB disease after infection, they should be targeted early in a contact investigation.
- In children under age 6 months and in HIV-positive close contacts, **consider treating for presumed MDR-LTBI** even in the absence of positive test for LTBI, especially in the environment of documented transmission (converters, secondary cases).
- Many experts would treat **MDR-LTBI in young children less than 5 years of age with 2 drugs to which the source case isolate is presumed to be susceptible** (including a fluoroquinolone such as LFX).
- Alternatively, **fluoroquinolone monotherapy** for pediatric and adult MDR-LTBI is used by many U.S. experts (even in young children).
- Another alternative used by some experts is a 2-drug regimen for 3 – 6 months followed by fluoroquinolone monotherapy (up to 1 year total).
- **LFX has advantages over other fluoroquinolones:** better anti-tuberculosis activity than earlier generations of fluoroquinolone, much more pharmacokinetic data in children than MFX, and an oral suspension available in the United States.
- Duration of therapy is unknown, but published series have employed **6-month regimens using multiple drugs, and 9- to 12-month durations for 1- or 2-drug regimens.**

The use of **fluoroquinolones** in children was once avoided due to the association of **arthropathy** in research models using puppies. Thousands of children have received fluoroquinolones (including long courses for drug-resistant TB and serial courses for children with cystic fibrosis) and there have been **no reported cases of irreversible arthropathy**. In the Micronesia study and in South African reports, fluoroquinolones, alone or in combination with other TB drugs, were well tolerated for treatment of MDR-LTBI.

The **second drug in an MDR-LTBI regimen** depends on source case susceptibility, and **EMB** and **PZA** have been the most commonly reported in the literature. Unfortunately, the **combination of LFX and PZA is generally poorly-tolerated** and often associated with failure to complete the prescribed regimen. **CS** and **ETA** are the 2 other drugs that have been used, but both can lead to unpleasant side effects (albeit fewer in children than in adults).



## Window prophylaxis

**Window prophylaxis** is the practice of treating a patient—typically a child less than 5 years of age or a significantly immunocompromised individual—who has been exposed to a potentially infectious source case, but has no current evidence of TB disease or infection (negative TST or IGRA, and normal 2-view chest radiograph and exam).

**Window prophylaxis** treatment typically continues until it has been **8–10 weeks since the last exposure to the source case, or since the source case has become non-infectious if contact was ongoing**. Since it can take 2 to 10 weeks for an intact immune system to recognize a TB infection (and therefore to produce a positive TST or IGRA test), early treatment can potentially abort an early infection or prevent rapid transition from early TB infection to TB disease in vulnerable hosts.

While window prophylaxis is widely used to prevent infection and disease in young children exposed to drug-susceptible disease, there are no consensus guidelines recommending the use of window prophylaxis when a child is exposed to a source case with drug-resistant disease. Despite the lack of consensus, **window prophylaxis is used by many clinicians in an effort to prevent drug-resistant TB disease in vulnerable contacts**.

The drug regimens for window prophylaxis are the same as those used for drug-resistant LTBI and usually include a fluoroquinolone (LFX has the most PK/safety data) as monotherapy, or in combination with PZA, EMB, ETA or CS.

For children with intact immune systems (and at least 6 months of age), **if the follow-up TST or IGRA remains negative** (after the 8- to 10-week window period), window prophylaxis can be stopped. For **young infants and for children who are immunocompromised, a full LTBI course should be administered** because the TST/IGRA may not be sufficiently sensitive to rule out infection.

It is also important to review the child's household members and other close contacts to ensure that there is not a secondary TB case who has not yet been identified or treated.

## Monitoring

All patients receiving LTBI treatment or window prophylaxis for either drug-susceptible or drug-resistant disease should be **monitored regularly** during treatment.

- **Adherence** to therapy should be reviewed and reinforced.
- Potential **side effects** should be monitored and addressed if present.
- **Symptoms of TB disease** should be solicited as some patients develop TB disease despite LTBI treatment or window prophylaxis.
- **Pediatric contacts who did not receive LTBI treatment or window prophylaxis** should also be monitored closely for signs and symptoms of TB disease so that early treatment can be initiated if they do develop disease
  - Evaluate with clinical exam and symptom review every 3 to 6 months for 2 years (with chest radiographs as clinically indicated). If clinical or radiographic findings are suggestive of active TB disease, obtain specimens for diagnostic testing, and consider initiation of a drug-resistant TB regimen.

## Summary

- Drug-resistant TB disease in children is a challenge for the provider as well as for the child and family. A culture-confirmed diagnosis is often not possible due to the difficulties in collecting sputum/respiratory specimens from children.

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- Whether a child is identified as a potential case of TB because of symptoms, screening, or a contact investigation, high quality specimens for culture should be collected from both the child and any adult contacts who might have TB disease.

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- If drug resistance is suspected or if other high-risk conditions exist (young or immunocompromised contacts, highly infectious source case, patient comes from an area of high rates of drug resistance), specimens should be submitted for molecular susceptibility testing.

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- Before drug-susceptibility data are available, some patients should be treated with an expanded empiric regimen if they have high risk of drug-resistant TB. For relatively asymptomatic children, it is sometimes appropriate to delay/defer treatment and follow the patient clinically and with chest radiography until the drug-susceptibility pattern can be established; seek guidance from a pediatric TB expert.

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- MDR-TB treatment for children is similar to that in adults. Treatment should include all first-line drugs to which the isolate is susceptible, a fluoroquinolone, an injectable drug, and other second-line drugs as appropriate. Since a regimen is often initiated before full drug susceptibility data are available, it is appropriate to empirically start therapy with 5 or 6 likely effective drugs.

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- In the case of asymptomatic children with minimal disease, a minimal total duration of treatment of 16 months may be acceptable.

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- In all other cases (symptomatic children or children with extensive radiographic disease), consider treatment durations consistent with adult recommendations:
  - Intensive phase duration: for the use of the injectable agent, at least 6 months beyond microbiologic, clinical or radiographic improvement documented
  - Total duration of treatment: at least 18 months beyond microbiologic, clinical or radiographic improvement documented.
  - Children on MDR-TB treatment require daily DOT as well as close monitoring for toxicity, including blood tests and hearing screens (vision screens if EMB is used). Use of a standard protocol and tracking tools will help in this process.

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- Many providers treat children for MDR-LTBI, although efficacy data from randomized controlled trials are lacking. Fluoroquinolone monotherapy is sometimes used, especially in older children. Two-drug therapy usually includes a fluoroquinolone and either PZA, EMB, ETA or CS. Duration of therapy is unknown, but series have described 6-month regimens for multiple drugs, and 9- to 12-month durations for 1- or 2-drug regimens.

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- The use of window prophylaxis in children exposed to MDR-TB who have a negative TST or IGRA and no evidence of TB disease on physical exam and 2-view chest radiography has not been studied, but it is sometimes employed with the goal of preventing extension or dissemination of early infection. The child is often treated with an appropriate LTBI regimen, and the TST or IGRA is repeated at least 8-10 weeks after the source case is deemed to be non-infectious or the contact with the source case has been broken. If the TST or IGRA is still negative, the prophylaxis is discontinued and the child is monitored clinically.

# Resources

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## Collecting Gastric Aspirates

See [http://www.currytbcenter.ucsf.edu/pediatric\\_tb/resources.cfm](http://www.currytbcenter.ucsf.edu/pediatric_tb/resources.cfm) for detailed instructions and <http://www.currytbcenter.ucsf.edu/products/pediatric-tuberculosis-guide-gastric-aspirate-procedure/video> for a video demonstration. Accessibility verified November 1, 2015.

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## Instructions for sputum collection

<http://www.health.state.mn.us/divs/idepc/diseases/tb/factsheets/sputum.html>  
Accessibility verified November 1, 2015.

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## Sentinel Project on Pediatric Drug-Resistant Tuberculosis

<http://sentinel-project.org/>  
Dosing chart: <http://sentinel-project.org/2014/06/21/dosing-chart-second-edition-2/>  
Accessibility verified January 28, 2016.

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## Pediatric dosing spoon for PAS granules

Contact Jacobus Pharmaceutical Company, Inc., Princeton, New Jersey, to request the PAS dosing spoon (pediatric use only). (609) 921-7447, ext 209.

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# Co-morbidities & Special Situations

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Managing drug-resistant TB, never a simple endeavor, requires additional considerations in the presence of co-morbidities and special situations. Expert consultation is advised.

## Extrapulmonary TB

There is scant information regarding extrapulmonary drug-resistant tuberculosis (TB) in the medical literature. The limited clinical data on MDR-TB suggest that the lessons from the treatment of drug-susceptible extrapulmonary TB are applicable to MDR-TB. Extrapulmonary involvement was not a risk factor for treatment failure in the 2012 summary by Kurbatova of outcomes in 4 large MDR-TB programs.

Many of the series from New York in the 1990s reported large proportions of HIV-positive individuals, who are known to have higher rates of extrapulmonary TB than HIV-negative 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. Although similar efficacy data are not available for patients with drug-resistant TB, expert opinion supports use of corticosteroids in cases of central nervous system (CNS) and pericardial disease.
- **Some forms of TB (particularly scrofula and intrathoracic adenopathy) are known to worsen as the TB is being successfully treated.** This is due to immune reconstitution as the organism is being eliminated and is particularly common in HIV-positive individuals, but known to occur in immunocompetent patients as well. This phenomenon is known as a “paradoxical reaction” or the immune reconstitution inflammatory syndrome (IRIS) and is a condition of exclusion. Other diagnoses, unrecognized drug resistance and microbiologic failure should be excluded first before the diagnosis of IRIS is accepted. If these other etiologies are not appropriately excluded, 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: 1) known penetration of first-line anti-tuberculosis drugs into tissues; 2) clinical experience; and 3) limited clinical trials.** Unfortunately, much less is known regarding the penetration of second-line drugs into tissues.
- **Serial cultures are often not available.** Clinical and radiographic assessments should be used to determine duration of therapy. Other imaging modalities, such as computed tomography, ultrasound or MRI, are often useful in following treatment progress in these patients.

## Role of surgery

Some forms of extrapulmonary TB (e.g., vertebral involvement) 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 CNS TB

Several reports detail poor outcomes of drug-resistant TB meningitis. Most of the patients in these series were HIV-positive and many developed meningitis while already receiving treatment for MDR-TB. Mortality in two series from South Africa—one in adults and one in children—ranged from 57% to 88%. The majority of patients were HIV-positive. Any degree of drug resistance will hinder the treatment of TB meningitis or other 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. Because of this, some experts recommend the use of higher-dose INH in MDR-TB meningitis, especially in the setting of low-level INH resistance.

**Rifampin (RIF), rifabutin (RFB), ethambutol (EMB), and para-aminosalicylate (PAS) penetrate** poorly into the CSF with non-inflamed meninges, but better with inflamed meninges. For RIF, CSF levels reach 10-20% of serum levels in the setting of inflamed meninges (still exceeding the minimum inhibitory concentration [MIC] of sensitive isolates). However, in one study of RIF, CSF with uninflamed meninges showed similar results, with CSF levels 13% to 42% of serum. High-dose RIF (900 mg IV daily) in the initial treatment of TB meningitis was associated with a better outcome in one 2013 study.

**Streptomycin (SM) and the other aminoglycosides** do not enter the CSF in very high concentrations, although 20% or more of serum concentrations may be achieved (CSF concentrations of 1-9 µg/mL in most patients). Successful use of intrathecal administration has been described in at least one case of CNS MDR-TB.

**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 (ETA)** and **cycloserine (CS)** also have good CNS penetration, with levels in CSF approaching that in serum, but a South African study evaluated CSF levels of ETA and concluded that doses of 20 mg/kg/day should be used in order to achieve useful levels in the CSF.

**Levofloxacin (LFX)** and **moxifloxacin (MFX)** both have moderate CNS penetration, even with uninflamed meninges. In one study, LFX levels in the CSF were 37% of serum levels. Levels up to 65% of serum have been found in CFS in the setting of inflamed meninges. In the same study, MFX CSF levels were 23% of levels in serum. MFX has shown good CSF penetration in several animal studies (CSF levels approximately 50% of serum). Both LFX and MFX have been used successfully in MDR-TB meningitis.

**Linezolid (LZD)** has good CNS penetration. One study of patients undergoing neurosurgery found levels in CSF that averaged 70% of serum levels after a single 600 mg dose. The drug has been successfully used to treat gram-positive drug-resistant meningitis in patients.

Data on the CSF penetration of **clofazimine (CFZ)** and **bedaquiline (BDQ)** are not available.

### Route of administration

If the patient is obtunded or severely ill, consider using drugs that can be given parenterally: INH, RIF, fluoroquinolones, and aminoglycosides. Oral-gastric or nasogastric administration of medications has also been effective.

Two reports of treatment of MDR-TB meningitis in HIV-negative individuals describe the use of intrathecal aminoglycosides and fluoroquinolones via Ommaya reservoir with good success and tolerability. Since most of the reports of fatal MDR-TB meningitis were in HIV-positive 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.
- In general, extrapulmonary involvement other than meningitis is not a risk factor for treatment failure in drug-resistant TB.
- Surgical resection (scrofula) and drainage (empyema, abscesses, vertebral disease, 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 later-generation fluoroquinolones may improve outcome and should be evaluated prospectively.



# HIV

Patients with HIV/AIDS are at increased risk of developing TB once infected compared to immunocompetent individuals. Additionally, TB increases HIV replication, promoting a vicious cycle of viral and mycobacterial proliferation. Patients who are HIV-positive with low CD4 counts 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 may be less likely to have cavitory disease and more likely to have mid- and lower-lung disease than are individuals who are HIV-negative.

TB progresses much more rapidly among persons with severe immunodeficiency; therefore, clinicians should have a lower threshold to use regimens with expanded coverage for drug resistance among patients with advanced HIV disease and who have risk factors for infection with a drug-resistant strain of *M. tuberculosis*.

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

- **Previous exposure to rifamycins (e.g., the use of rifabutin [RFB] to prevent disseminated *Mycobacterium avium* intracellulare disease)**
- **Use of highly intermittent rifamycin treatment**
- **Malabsorption of drugs**
- **Drug-drug interactions (e.g., inadequate rifamycin dosing due to antiretroviral coadministration)**
- **Residence in congregate settings**
- **Co-morbid conditions, including those that may interfere with adherence (e.g., substance abuse issues)**
- **CD4 lymphocyte count below 100 cells/mm<sup>3</sup>**

Unfortunately, HIV-positive individuals with MDR-TB have higher mortality rates than HIV-negative patients with MDR-TB, particularly 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. A large series of HIV-positive persons with TB from Thailand showed that early detection and optimal treatment of MDR-TB improved survival, as did anti-retroviral therapy (ART). ART should be initiated in all patients with HIV and TB.

*Patients with HIV are more likely to have atypical presentations of TB.*

Knowledge about the metabolism of the traditional second-line drugs (ethionamide [ETA], cycloserine [CS] and para-aminosalicylic acid [PAS]) is incomplete because they were licensed decades ago. However, based on knowledge of chemical structure and/or metabolism of related agents, these drugs should not have significant drug-drug interactions with antiretroviral medications. Second-line injectable drugs are primarily renally excreted unchanged and should not have interactions with antivirals. The fluoroquinolones are also unlikely to have significant interactions with antiretrovirals. Nonetheless, overlapping toxicities such as nephrotoxicity, QT prolongation on ECG, psychiatric side effects and gastrointestinal (GI) intolerance may limit options for treating co-existing MDR-TB and HIV.

## Treatment of drug-resistant TB in HIV-positive 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
- Overlapping drug side effects of medications used to treat 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 (TB disease appears to worsen when immune reconstitution occurs)
- Complex social, mental health, and substance abuse confounders
- Coinfection with hepatitis C or hepatitis B, which increases the risk of hepatotoxicity, especially when combined with some types of HIV therapy
- Variable penetration of second-line drugs into CNS sites of disease

*Identify all HIV-positive patients by screening all patients with TB disease for HIV.*

## To maximize care of HIV-positive patients:

- Identify all HIV-positive patients by screening all patients with TB disease for HIV.
- Utilize rapid molecular diagnostic testing for earlier diagnosis for both TB disease and drug resistance.
- 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.
- It is critically important to appropriately treat the HIV infection as well as the drug-resistant TB. Consider the best HIV regimen for immune reconstitution as well as the timing of initiation of ART for antiretroviral-naïve patients. Initiation of ART 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 50, it is reasonable to delay ART for 2-8 weeks.**
  - **In patients with CD4 less than 50, it is advisable to begin ART as soon as TB therapy is well tolerated (ideally within 2 weeks). The exception may be CNS TB** in which early initiation of antiretrovirals in drug-susceptible TB has been associated with poorer outcomes due to occurrence of IRIS within the CNS.

### Consider alternate drugs when interactions between TB and HIV drugs are present (e.g., RFB in place of rifampin [RIF]).

- **Rifamycins are inducers of cytochrome P-450 and interact with many drugs.** RIF in particular leads to lower levels of protease inhibitors and non-nucleoside reverse transcriptase inhibitors (NNRTIs). Current recommendations about concomitant use of rifamycins (RIF and RFB) and ART should be consulted. (See **Resources** at the end of this chapter.)
- **The rifamycins and other TB drugs interact with a number of the anti-infectious agents that may be taken by HIV-positive patients,** including the macrolide drugs, cidofovir, anti-fungal drugs, and others.

- 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.
- Efavirenz increases the clearance of PAS by approximately 50%.
- Use of lopinavir/ritonavir alters the metabolism of bedaquiline (BDQ) and leads to higher serum levels and effects of BDQ.
- Intervene to avoid or treat symptomatic toxicity. Peripheral neuropathy, cutaneous reactions, GI side effects, renal impairment, and neuropsychiatric effects may all be worse in HIV/TB patients.
- Use daily directly observed therapy (DOT). During treatment for drug-resistant-TB, also consider DOT of antiretroviral drugs.
- Closely monitor signs and symptoms of malabsorption: diarrhea, abnormal stools, abnormal nutritional studies, evidence of vitamin deficiencies, and weight loss.
- 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 who are HIV-positive 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.
- Antiretroviral therapy is a critical part of the treatment of drug-resistant TB in HIV-positive persons
- HIV-positive patients can be cured of their drug-resistant TB disease, but require special monitoring and concurrent care of their HIV disease. Early initiation of ART increases survival.
- Malabsorption and drug interactions increase risk of drug-resistant TB as well as complicate its treatment.
- Rifamycins can be used in HIV-positive patients on ART, but dose adjustments may be required. RFB generally has fewer drug interactions than does RIF.

# Diabetes mellitus

The association of diabetes mellitus (DM) with TB was noted millennia ago. As treatment became available for both diseases in the last century, this association was no longer thought to be important and there was little interest in research on TB in persons with diabetes. However, the emergence of an epidemic of diabetes throughout the developing world has led to an increased awareness of this important syndemic.

There is little controversy about the **increased risk of progression to active TB among persons with latent TB infection (LTBI) and diabetes**. However, it has only been appreciated recently that outcomes for patients who have both TB and diabetes are poorer than for TB patients without diabetes. The role of DM in furthering drug resistance has remained controversial, but **new evidence is accumulating that diabetes does increase the risk of drug-resistant TB**.

One mechanism for poorer outcomes and acquired drug resistance has been linked to **sub-optimal drug levels**, particularly of rifampin (RIF). This was first described in diabetic patients in an Indonesian cohort, and associated with the higher body mass index of patients with TB and diabetes. More recently, researchers at the University of Virginia have reported on the results of therapeutic drug monitoring for first-line drugs in patients who were slow to respond to therapy, defined as no improvement in symptoms or persistent smear positive at 6 weeks of treatment. **Diabetic patients were 6.3 times more likely to be slow responders** when adjusted for age, gender, country of origin, prior TB cavity disease, HIV, alcohol and tobacco use. They found that 82% of these slow responders had low levels of either isoniazid (INH) or RIF, with statistically significantly lower serum rifampin levels.

A recent study from Taiwan followed 192 patients (60 with DM and TB, 132 with TB only) who were treated for a full course of anti-TB medication and prospectively followed for over one year. The DM and TB patients had **higher treatment failure rates** (17% vs. 2%) and longer time to clearance of mycobacteria from sputum (2.5 months vs. 1.6 months) than did the TB only patients. After one year, 3 DM and TB patients (5.0%) and one TB-only patient (0.8 %) had MDR-TB.

Once patients with DM and TB have MDR-TB, there is evidence that **outcomes of treatment are also poorer**. A recent Korean study looked at 1,407 patients with MDR-TB treated between 2000 and 2002 and followed them for 8-11 years. Diabetes was present in 239 of these or 17%. Patients with MDR-TB and DM had a significantly lower treatment success rate than those without DM (36.0% vs. 47.2%). DM was a significant predictor of poor long-term survival in multivariate analyses.

Patients with diabetes and MDR-TB may be at **increased risk of adverse events** since many of the anti-TB drugs have side effects that place diabetic patients at special risk. Patients with long-standing diabetes may have underlying **renal impairment** that can be worsened by the second-line injectable drugs used in MDR-TB. **Neuropathy** is a common complication of diabetes and also can be worsened by several drugs used to treat MDR-TB such as high-dose INH, cycloserine (CS), linezolid (LZD), and the fluoroquinolones. Patients with diabetes may have **decreased gastric motility** (gastroparesis) and may be at **increased risk of nausea and vomiting** with medications like ethionamide (ETA) or other MDR-TB medications.

### Recommendations when treating patients who have MDR-TB and diabetes

- Follow renal function carefully and use intermittent dosing for injectable drugs if there is pre-existing or newly developing renal impairment.
- Treat symptoms of gastroparesis aggressively with gastric motility agents such as metoclopramide.
- If neuropathy develops, change the offending drug, if possible. If that cannot be done safely, consider use of agents such as tricyclic anti-depressants, gabapentin, and/or adding or increasing the dosage of Vitamin B-6.
- Consider therapeutic drug monitoring to be sure that adequate blood levels are being obtained, and adjust doses if levels are low.

In addition, for diabetic patients who have initial INH mono-resistance, consider obtaining blood levels of RIF and ethambutol (EMB) to be sure that adequate blood levels are present.

### Summary **DIABETES**

- Diabetes adversely affects treatment outcomes for TB.
- Blood levels of anti-TB medications may be lower and sub-therapeutic in patients with diabetes.
- Diabetic patients are at increased risk of adverse reactions to anti-TB drugs.
- Follow recommendations for treating patients who have diabetes-complicating TB.

## Liver disease

Many 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 drug-resistant disease do not affect the liver. The following is a list of anti-tuberculosis medications and their effects on the liver:

Drug	Effect on Liver
<b>Isoniazid (INH)</b>	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.
<b>Rifampin (RIF)</b>	RIF more commonly causes a cholestatic jaundice, but can potentiate the hepatocyte damage caused by INH.
<b>Pyrazinamide (PZA)</b>	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.
<b>Ethionamide (ETA) Para-aminosalicylate (PAS)</b>	ETA and PAS have also been implicated in hepatotoxic drug reactions.
<b>Fluoroquinolones</b>	Some of the fluoroquinolone drugs ( <b>ciprofloxacin and moxifloxacin</b> ) have been associated with occasional cases of liver damage. <b>Travafloxacin</b> has been associated with severe liver toxicity in rare cases.
<b>Aminoglycosides Bedaquiline (BDQ) Clofazimine (CFZ) Cycloserine (CS) Ethambutol (EMB) Linezolid (LZD)</b>	Not commonly associated with liver dysfunction.

Treatment of drug-resistant TB in the setting of liver failure is complicated and depends on the degree of liver damage. At least one patient has successfully undergone liver transplantation for toxicity of multidrug-resistant (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 TB disease), **consider avoiding all hepatotoxic drugs.** The use of LFX, EMB, an aminoglycoside, and CS should be considered, if appropriate. LZD, BDQ, and CFZ are additional alternatives.
- 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.

See **Chapter 9, Adverse Reactions**, for more information regarding response to hepatotoxicity encountered during TB therapy.

## Renal failure

Compared to the general population, patients with chronic renal failure undergoing hemodialysis are at a 10- to 25-fold increased risk of developing TB disease once infected. 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 available. 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 through 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.**

TABLE 1.

## Dosing recommendations for adult patients with reduced renal function and for adult patients receiving hemodialysis

Drug	Change in frequency?	Recommended dose and frequency for patients with creatinine clearance < 30 ml / min or patients receiving hemodialysis
Isoniazid (INH)	No change	300 mg once daily, or 900 mg 3 times/week
Rifampin (RIF)	No change	600 mg once daily, or 600 mg 3 times/week
Pyrazinamide (PZA)	Yes	25–35 mg/kg/dose 3 times/week (not daily)
Ethambutol (EMB)	Yes	15–25 mg/kg/dose 3 times/week (not daily)
Levofloxacin (LFX)	Yes	750–1000 mg/dose 3 times/week (not daily)
Moxifloxacin (MFX)	No change	400 mg daily
Cycloserine (CS)	Yes	250 mg once daily, or 500 mg/dose 3 times/week*
Ethionamide (ETA)	No change	15–20 mg/kg/day (can be in divided doses)
Para-aminosalicylate (PAS)	No change	4 gm/dose twice daily
Linezolid (LZD)	No change	600 mg daily
Clofazimine (CFZ)	No change	100–200 mg daily
Amikacin (AK)	Yes	12–15 mg/kg/dose 2–3 times/week (not daily)
Capreomycin (CM)	Yes	12–15 mg/kg/dose 2–3 times/week (not daily)
Kanamycin (KM)	Yes	12–15 mg/kg/dose 2–3 times/week (not daily)
Streptomycin (SM)	Yes	12–15 mg/kg/dose 2–3 times/week (not daily)

**Note:** Bedaquiline (BDQ) needs no change with mild to moderate renal dysfunction but should be used with caution in severe renal disease.

- 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.
- Refer to **Chapter 5, Medication Fact Sheets** for dosing of aminoglycosides, pyrazinamide, and ethambutol in obese patients.

Table adapted from the American Thoracic Society Treatment Guidelines.

\* The appropriateness of the 250 mg daily dose has not been established.

### 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)

**Creatinine clearance calculator:** <http://reference.medscape.com/calculator/creatinine-clearance-cockcroft-gault>



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 (e.g., 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 to 3 hours post-dose) generally should be maintained within the normal range of 2 to 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 link to calculator in **Estimated creatinine clearance calculations box**, following Table 1)
- Monitor carefully for red-green color discrimination and visual acuity changes

### Aminoglycosides (Streptomycin [SM], Kanamycin [KM], Amikacin [AK]) and Capreomycin [CM]

- 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 AK 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).
- For patients with creatinine clearance less than 30 mL/min or those receiving hemodialysis, 12-15 mg/kg 2 to 3 times per week is recommended. Some experts would recommend considering 3 times per week dosing for patients with creatinine clearance 50-70 mL/min, and twice-weekly dosing if less than 50 mL/min.

### Levofloxacin (LFX)

- Cleared more extensively by the kidney than is moxifloxacin (MFX).
- A dose of 750 to 1000 mg/dose 3 times weekly (not daily) is recommended for treatment of TB. The manufacturer's literature for dosing LFX 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 (MFX)

- In one small study, MFX clearance was unaltered in the presence of renal insufficiency following single oral doses. Another recent study found that MFX pharmacokinetics in critically ill patients who had acute renal failure and were undergoing dialysis was similar to those in healthy subjects without renal impairment. Therefore, MFX dosage should not be altered in patients with renal disease.

### Cycloserine (CS)

- 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 to 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 use of PAS in patients with renal failure not yet on dialysis, but no clear evidence of toxicity.

## Summary RENAL FAILURE

- INH, RIF, MFX, ETA, PAS, LZD, and CFZ 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 CS, and may be helpful for other medications as well.

# Pregnancy

Treatment of drug-resistant TB during pregnancy is very challenging. All female patients of childbearing age with MDR-TB should be strongly advised to **avoid pregnancy**, and if sexually active, to **use highly effective forms of contraception** (e.g., IUDs or implantable hormonal contraceptives). 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. For these reasons, there has been a reluctance to aggressively treat pregnant MDR-TB patients. However, this view is changing.

The largest case series published to date included 38 pregnant patients with MDR-TB. Outcomes were comparable to non-pregnant patients. Of the 38 pregnancies, 5 ended in spontaneous abortions, and 1 child was stillborn. One study in 2005 described long-term follow-up of 6 children (average age 3.7 years) exposed to MDR-TB drugs while *in utero*. All 6 showed normal development. One child demonstrated mildly increased thresholds on auditory brainstem response testing, but his language development was normal, as was an otorhinolaryngological assessment. The majority of these children were exposed to both an injectable agent and a fluoroquinolone *in utero*.

- **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, use of **pyrazinamide (PZA)** is generally avoided in the United States due to lack of safety data. In the case of drug-resistant TB, PZA should be used when the isolate is susceptible.

Resistance	Medications	Duration
INH monoresistance	RIF + EMB + PZA	6–9 months
PZA monoresistance ( <i>M. bovis</i> )	INH + RIF + EMB Followed by INH and RIF	2 months At least 7 more months
RIF monoresistance <i>Consider addition of a fluoroquinolone or injectable drug after delivery to shorten course.</i>	INH + EMB + PZA	At least 18 months

## Several options face the pregnant MDR-TB patient and her team of healthcare providers:

- Treatment of drug-resistant TB with the best possible, albeit frequently weak, MDR-TB regimen, avoiding the known (potential) teratogens: the aminoglycosides and ethionamide (ETA). The regimen can be strengthened after the baby delivers. A potential regimen might include cycloserine (CS), para-aminosalicylate (PAS), and EMB or PZA if still susceptible. Experience with the fluoroquinolones during pregnancy is still limited, but small series have not shown teratogenicity.
- Using a standard MDR-TB regimen with an injectable agent and/or a fluoroquinolone and additional second-line agents as guided by susceptibility testing. It is

essential to discuss the potential risks and benefits with the patient and family prior to beginning such a regimen.

- No treatment at all for very stable disease pending delivery of the baby. An example might be an asymptomatic patient picked up during screening who has a small infiltrate, is smear-negative, and is within a month or two of delivery.
- 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 (SM)** and **kanamycin (KM)** 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 (AK)** and **capreomycin (CM)** are also not recommended during pregnancy, but have been used safely in some reports.
- **ETA** 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 (LFX)** 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 women in the United States 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 jurisdictions in the United States), and toxicity to the fetus has not been documented. For women who are HIV-positive or have drug-resistant TB disease, PZA should be included in the TB regimen if the isolate is susceptible.
- **INH, RIF, and EMB** have not been associated with teratogenic effects. **Rifabutin (RFB), CS, and PAS** have not been extensively studied, but animal models and anecdotal human reports have not shown toxicity. **Linezolid (LZD)** is classified by the FDA as pregnancy category C. Some animal studies failed to reveal evidence of fetal harm; however, studies using high doses demonstrated fetotoxicity and teratogenicity. There are no controlled data in human pregnancies. **LZD** should only be given during pregnancy when benefit outweighs risk.

## Infection control during pregnancy and childbirth

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 TB disease 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 receiving INH, CS and ETA and their breastfed infants 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, ATS does not recommend use of fluoroquinolones during breastfeeding. However, in the setting of MDR-TB, where fluoroquinolones play such an essential role, the potential benefit may outweigh the potential risk. In these situations, the family should be informed of the theoretical risk.

## 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 TB disease should include physical examination to evaluate for these findings as well as a chest radiograph. Abdominal ultrasound is also sometimes helpful to evaluate for hepatosplenomegaly.
- Culture and examination of the placenta by a pathologist is sometimes helpful. Granulomata in the placenta increase 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. **See Chapter 6, Pediatrics, for details on obtaining gastric aspirates.** Lumbar puncture for cell count, protein, glucose, bacterial and acid-fast bacilli (AFB) smear and culture should be performed for a child with suspected congenital TB. Mycobacterial culture of blood, skin lesions, and ear drainage are also sometimes helpful.

Evaluation of the sick newborn for neonatal sepsis and other congenital infections should also be considered, given the rarity of congenital TB.

## Treatment of suspected congenital TB

If a newborn is suspected of having active or congenital TB, treatment for TB disease should be initiated as soon as the aforementioned studies are collected (collect 2 to 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 infectious with drug-resistant TB, mother and baby should be separated until the mother is not infectious. However, mother-infant bonding is important and there are trade-offs to be considered in making a decision about separating a newborn and its mother. Options such as outdoor visitation with the mother wearing a mask may be appropriate.
- If an infant whose mother has known infectious or suspected TB disease is vigorous, afebrile, and has a **completely** normal physical exam and chest radiograph, consider treating the infant prophylactically for latent TB infection (LTBI), in case the baby has been infected during the birth process and does not yet have TB disease, 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, seek the advice of a pediatric TB expert.
- 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, ETA, or CS, 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 prevents some 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. (See **Resources** at the end of this chapter for information about how to obtain and administer the BCG vaccine.)
- If the baby is asymptomatic and the mother has been receiving effective TB therapy and is deemed to be non-infectious, and there are no other potentially infectious source cases in the infant's home, close monitoring without chest radiograph or prophylactic treatment is appropriate.

## TST/IGRA

The TST and interferon gamma release assay (IGRA) tests are rarely positive in newborns, and a negative result contributes little to the early evaluation. The TST is not contraindicated in infants. Most experts recommend considering the skin test reliable after 6 months of life for immunocompetent children. Note that this practice differs from current guidance from the American Academy of Pediatrics, which recommends repeating a TST/IGRA at 3-4 months in infants potentially exposed to perinatal TB. IGRAs may be less reliable than the TST in children under age 3, but may be used on a case-by-case basis.

### 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.

## Solid organ transplant

The occurrence of TB among solid organ transplant (SOT) recipients varies based on the background rates of TB in the general population. It has been estimated that TB among the SOT population is 20-74 times higher than that of the general population. True incidence estimates in the SOT population are often difficult to measure because most studies have calculated a cumulative prevalence of TB. The prevalence of TB in the SOT population in low TB burden regions ranges from 0.2% to 6.5%. TB among persons who have received a SOT is associated with a mortality of 6%-22%, which is substantially higher than the 5% mortality among all TB patients in the United States.

TB can occur in a person who has received a SOT due to five reasons:

- 1) reactivation of latent TB infection (LTBI)
- 2) relapse of previously treated TB
- 3) donor-derived reactivation
- 4) transmission of TB
- 5) person with active TB requiring urgent transplantation (e.g., drug-induced hepatotoxicity)

The most common scenario is **reactivation of LTBI**.

Although the onset of TB varies based on the reason, the majority of TB cases occur during the first 6 months post-transplant. However, for renal transplant patients the onset can be later. The diagnosis of TB among persons who have received a SOT can be challenging due to the lack of traditional TB risk factors, atypical symptoms at presentation,

and a wide range of radiographic manifestations including focal infiltrate, miliary pattern, pulmonary nodules, and pleural effusions. Although most SOT patients are diagnosed with pulmonary TB, 16% have extrapulmonary disease and 33% have disseminated TB disease, which can also make the diagnosis difficult.

Treatment of MDR-TB in a person who has received a SOT can be complicated, primarily due to the **interactions between TB medications and immunosuppressive medications**. Treatment of MDR-TB in a person who has received a SOT will require close coordination between the TB clinician and the transplant team to determine whether the dose of immunosuppressants can be safely reduced during TB treatment. Common interactions between MDR-TB drugs and immunosuppressants are summarized in Table 1. Due to the occurrence of these interactions, MDR-TB treatment will require **close monitoring and consideration of use of intermittent dosing of medications** (e.g., aminoglycosides or capreomycin, and linezolid) to ensure completion of a course of treatment.

TABLE 1.

**Interactions between immunosuppressants and commonly used MDR-TB medications**

Immunosuppressant	Pyrazinamide	Ethambutol	Aminoglycoside or capreomycin	Moxifloxacin or Levofloxacin	Linezolid
Corticosteroids	None	None	None	Increased risk of tendonitis	None
Cyclosporine A	None	None	Combination increases nephrotoxicity	May increase cyclosporine levels (usually, LFX only)	None
Tacrolimus	None	None	Combination increases nephrotoxicity	None	None
Rapamycin/sirolimus	None	None	None	None	None
Mycophenolate mofetil (Cellcept)	None	None	None	May decrease mycophenolate level	None
Azathioprine	None	None	None	None	May increase risk of bone marrow suppression

From Bumacea D, Arend SM, Eyuboglu F, et al.



# Resources

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**Guidelines for the use of antiretroviral agents in HIV-positive adults and adolescents.** Considerations for antiretroviral use in patients with coinfections. *M. Tuberculosis* disease with HIV coinfection. <http://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv-guidelines/27/hiv-tb> Accessibility verified January 31, 2016.

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**Information about how to obtain BCG:**

BCG can be ordered from any wholesaler that distributes Merck vaccines. You may also contact Merck (800-672-6372) directly to determine if the product is available as short-ages may occur. It is important to clarify your request for BCG vaccine for percutaneous use (not the BCG live for intravesical administration for bladder cancer).

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**Instructions for BCG application.**

[http://www.merck.com/product/usa/pi\\_circulars/b/bcg/bcg\\_pi.pdf](http://www.merck.com/product/usa/pi_circulars/b/bcg/bcg_pi.pdf)  
Accessibility verified January 31, 2016.

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# Monitoring & Case Management

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Careful monitoring of drug-resistant TB patients, using a case management approach, is a critical component of effective TB control.

## Case management of drug-resistant TB

### Case management is:

“A collaborative process that assesses, plans, implements, coordinates, monitors, and evaluates the options and services required to meet the client’s health and human service needs. It is characterized by advocacy, communication, and resource management and promotes quality and cost-effective interventions and outcomes.”  
—*Commission for Case Manager Certification*

The goal of tuberculosis (TB) case management is to provide patient-centered care for completion of treatment, and to ensure all public health activities related to stopping transmission are completed.

Public health departments (i.e., under TB or communicable disease control programs) are encouraged to assign a specific health department employee (case manager) the primary responsibility for ensuring the patient is educated about drug-resistant TB, that therapy is continuous, and that contacts are examined. Some specific responsibilities may be assigned to other persons.

## Roles and responsibilities

Providing care for patients with drug-resistant TB is a team effort and a variety of staff and community members may be involved. It is very important that roles and responsibilities are clearly delineated and understood and that effective lines of communications are maintained. Duties and responsibilities may change throughout care as the patient’s needs change.

### Case manager

The case manager coordinates the care provided by the treating clinician(s), specialists, 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:

- Establishing a trusting relationship with the patient.

- Educating the patient and significant others about drug-resistant TB and its treatment.
- Developing an individualized case management plan.
- Ensuring the patient adheres to and completes treatment via DOT.
- Ensuring patient referral to appropriate supportive services.
- Ensuring individuals in contact with the patient are identified, located, prioritized, evaluated, and treated as needed.
- Ensuring response to therapy is evaluated regularly. If response is not in accordance with expected outcomes, ensure the treating clinician is informed.
- Monitoring for adverse effects of treatment and notifying the treating clinician if present.

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 the role of liaison or coordinator-of-care. In addition to the previously listed 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.

## Treating clinician

The treating clinician provides the direct medical care of the patient. Given the toxicities of the second-line drugs and importance of ensuring response to treatment, it is recommended that the treating clinician evaluates the multidrug-resistant (MDR)-TB patient regularly. See section: **Monitoring treatment response.**

When the treating clinician is not part of the public health team (e.g., private or community practice), it is essential to establish linkage with the public health department for case reporting, case management, and provision of DOT.

## DOT worker

The role of the DOT worker for patients with drug-resistant TB is similar to that for patients with pan-susceptible TB. However, because of the large number of pills needed and toxicity of second-line drugs, the DOT worker will need additional training to become familiar with expected side effects and strategies to support the patient in taking medications. In general, the DOT worker is responsible for:

- Watching the patient take pills
- Checking for side effects
- Protecting confidentiality

- Documenting the visit
- Communicating with the case manager and prescribing clinician regularly and immediately about symptoms of serious side effects
- Other duties, including helping patients keep appointments, providing education and offering incentives and enablers

The DOT worker may be the first person to identify a change in a patient's condition or development of an adverse reaction. DOT providers often develop strong relationships with MDR-TB patients because they see them daily and provide ongoing encouragement and support.

### Clinic staff

Nurses and other personnel at the TB or outpatient clinic may be involved with providing DOT, intramuscular (IM) injections, and assessments, as well as alerting the case manager and treating clinician about symptoms of serious side effects.

### Other staff

Other health department staff such as contact investigators, social workers, and community health workers may have important roles in the management and support of drug-resistant TB patients. This would include alerting the case manager and/or treating clinician about symptoms of side effects the patient may be experiencing. Additionally, staff in other organizations or outside the health department may have a role in supporting and/or treating the patient during treatment.

## Initiating treatment

### Initial evaluation

The important task of case managing and monitoring the patient with drug-resistant TB begins with a thorough and organized initial evaluation. The objective of the initial evaluation is to identify those patients at greater risk of adverse effects and to establish a baseline for monitoring.

### Medical history and physical evaluation

- Demographic information (name, address, date of birth, race and ethnicity, etc.)
- Past medical history (including allergies, HIV status or other immunocompromising conditions, diabetes mellitus, hypertension, acute or chronic renal insufficiency, acute or chronic liver disease, psychiatric history, thyroid disease, drug or alcohol dependence, pregnancy, chronic epilepsy or seizure disorder, and other complicating conditions as well as medication taken for these conditions)
- Full TB history including previous treatment (anti-TB medications, duration and dates taken, as well as location where treatment was given), TB symptoms and date of onset, surgeries, and complications; it may be helpful to document prior drug treatment in **Tool 1: Drug-O-Gram**
- Social history including: country of birth, lifestyle and habits, local family and social support network, employment, housing history, travel, as well as history of substance use, migration and incarceration



- Review of systems
- Focused physical exam
- Weight and height to assess nutritional status and calculate body mass index (BMI) and lean body weight
- Source case and contact information including incarceration history, previous residences, household contacts, and visitors

## Baseline examinations

- **Laboratory exams** should include HIV test, CBC, TSH, pregnancy test for women of childbearing age, and a comprehensive metabolic panel (obtain 24-hour creatinine clearance for any elevation of creatinine or question of renal insufficiency). **Tool 4: Laboratory Flow Sheet** may be helpful in summarizing bloodwork results that will be assessed at baseline and throughout treatment.
- **Hearing, vision** (acuity and color), **and vestibular function** should be assessed at baseline and results documented. **Tool 5: Vision Screening Flow Sheet** and **Tool 6: Hearing and Vestibular Flow Sheet** may be helpful for tracking these serial monitoring results.
- **Radiography** should be obtained prior to treatment initiation. Posteroanterior (PA) views (and lateral in children) of the chest for pulmonary disease are recommended. Additional views and/or CT scan may be helpful in some instances.
- **Sputum for nucleic acid amplification test (NAAT), acid-fast bacilli (AFB) smear, culture and drug-susceptibility testing (DST):** At the start of treatment, obtain 3 sputa for AFB smear and culture. Note: In a patient started on a standard TB regimen (RIPE) for 4 weeks or more prior to starting an MDR-TB regimen and for whom the initial isolate was not known to be resistant to **all** first-line drugs at baseline, request a repeat DST from a subsequent positive TB culture obtained near the time of MDR-TB regimen initiation. This will help to ensure that no additional resistance developed during the initial period of therapy. **Tool 3: Bacteriology Flow Sheet** may be helpful for summarizing the important microbiology, molecular tests, and DST results.
- **Rapid molecular assays for identification of drug resistance.** If not already obtained (and conventional DST results are still pending), all patients in whom a clinical suspicion for drug-resistant active pulmonary TB exists should have a sputum specimen submitted for Xpert MTB/RIF or other NAAT that evaluates for rifampin (RIF) and/or isoniazid (INH) resistance.
- **EKG:** For patients who will be taking bedaquiline (BDQ), a baseline EKG is recommended. If such patients have a known QT prolongation, hypokalemia (low potassium), or are being considered for other drugs that prolong the QT interval (e.g., moxifloxacin [MXF] and/or clofazimine [CFZ]), a cardiology consultation should also be obtained.
- **Psychosocial assessment:** Assess for existing mental health and social conditions that may impact treatment. See section: **Psychosocial Support**.

## Initial patient education

Many people will only be able to process a small amount of information during the diagnosis and early treatment period. Constant education and support will help patients and families to anticipate toxicities and to tolerate inconveniences during the long course of treatment.

**The first phase** of treatment is likely to be quite intensive as the patient may be very ill, in airborne infection isolation, and facing many toxic drugs. If the patient's primary language is not English, identify and secure a trained interpreter to assist with the delivery of this initial patient education:

- **Assess patient's understanding** of the diagnosis and plan for treatment
- **Involve the family** and/or significant others in provision of initial patient education
- **Keep information simple** with a focus on the following: gaining mutual commitment to the case management plan; minimizing transmission; obtaining information about contacts; and explaining legal requirements

### Help the patient to understand:

- He/she may feel worse before they feel better.
- The toxicity **symptoms will diminish over time** as the patient's body adjusts to the treatment.
- **Steps can be taken to minimize the side-effects** if and when they occur.
- In the long run, the **treatment will cure the disease**, save the patient's life, and prevent transmission to loved ones.

## Use of case management tools

### ***Drug-O-Gram, MDR-TB Monitoring Checklist and Case Management Plan***

The case manager should develop an individualized case management plan based on the patient's treatment regimen, co-morbidities, and psychosocial assessment. The plan format may vary among health departments depending on their record-keeping processes. Specialized tools such as the ***Drug-O-Gram*** and the ***MDR-TB Monitoring Checklist*** can be part of the case management plan to organize data regarding prior treatment, evaluation, and other notable events in a concise, summarized fashion.

The ***Drug-O-Gram*** is an important case management tool for following the patient's progress through TB treatment. The ***Drug-O-Gram***:

- Documents previous and current drug treatment, weights, microbiology including molecular results, radiology and DST results, and other important information in an easy-to-read, summary format.
- See **Tool 1: *Drug-O-Gram***.

Drug-resistant TB, particularly MDR-TB, requires that close attention be paid to the patient's response to treatment as well as prompt remediation of adverse events that may

arise. A monitoring checklist can help the case manager keep track of the various required examinations as the patient moves through treatment. The individualized **MDR-TB Monitoring Checklist**:

- Delineates the important monitoring events that should occur throughout treatment to assess for clinical response to treatment as well as toxicity based on the patient's drug regimen and underlying comorbidities.
- Ensures that elements of care are not neglected and can be reviewed with patients so they can anticipate upcoming events.
- See **Tool 2: MDR-TB Monitoring Checklist**, for a sample of how this checklist can be customized for individual patients.

**Use a systematic approach to monitoring.**

## Monitoring throughout treatment

Patients with drug-resistant TB will require regular monitoring throughout treatment to document sputum culture conversion and to watch for the development of toxicities. Patients should also be monitored closely for signs of treatment failure. 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 clinician. See **Chapter 9, Adverse Reactions**.

## Monitoring treatment response

Monitoring response to treatment is done through regular evaluation of microbiology results, symptoms, weight, and radiography and other imaging.

TABLE 1.

## Activities for monitoring treatment response for MDR-TB

Adapted from: *Companion Handbook to the WHO Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis*, 2014

Monitoring evaluation	Recommended frequency
<b>Evaluation by clinician</b>	<p><b>During the intensive phase:</b> Every day during the first weeks if hospitalized and at least every week if treated as outpatient, until the treatment is well tolerated.</p> <p>Once stable, the patient is seen twice a month or once a month.</p> <p><b>During the continuation phase:</b> Monthly assessments unless there is a medical necessity to see the patient more often. The DOT provider sees the patient daily between consultations and signals any concerns to the case manager and clinician.</p>
<b>Treatment adherence and tolerance</b>	Daily at every DOT encounter by the DOT worker.
<b>Sputum smears and culture</b>	Obtain 3 sputa at the start of treatment and every 2 weeks until smear conversion, followed by 2-3 sputa every month until culture conversion, and then at least 1 sputum monthly throughout treatment.
<b>Weight</b>	At start of treatment, weekly until stable, and then monthly throughout treatment.
<b>Height</b>	At start of treatment for all (to be able to assess lean body weight or BMI); monthly for children (to assess growth).
<b>Drug-susceptibility testing (DST)</b>	At baseline for first- and second-line anti-TB drugs. Repeat DST for patients who remain culture-positive at month 3 or revert after month 4 (see <b>Chapter 2, <i>Diagnosis</i></b> for more information on DST).
<b>Chest radiograph</b>	At baseline, every 3 to 6 months during treatment, and at the end of treatment.

### Microbiology

Monitoring 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.

- Most MDR-TB patients who are adherent to an effective regimen will convert cultures to negative within 3 months. Patients with fewer effective drugs in their treatment regimens (e.g., XDR-TB patients) will convert more slowly.
- At the start of treatment, obtain 3 sputa for AFB smear and culture. Sputum specimens should be collected at least 8 hours apart. At least 1 specimen should be an early morning specimen. Some patients will be able to produce higher quality specimens if all of them are collected first thing in the morning. Consider supervision of collections and/or sputum induction.

- Repeat sputum collection every 2 weeks until smear conversion.
- Once AFB smears become negative, continue to collect 2 to 3 sputum samples monthly until TB cultures become negative.
- Once the culture has consistently converted to negative, obtain **at least 1** specimen of sputum for AFB smear and culture **monthly** throughout the remaining course of treatment, and more frequently if indicated. Keep track of these smear and culture results using tools such as **Tool 1: Drug-O-Gram** and **Tool 3: Bacteriology Flow Sheet**.
- Whenever sputum is being collected, give appropriate attention to infection control. Collect sputum in a secure isolation area or an outdoor environment. **If the patient cannot spontaneously expectorate sputum, perform sputum induction with hypertonic saline in an appropriately engineered environment.**
- Serial culture collection in children can be difficult. For information on the best methods for collecting specimens for smear and culture in children, see **Chapter 6, Pediatrics**.
- Obtain sputum for AFB smear and culture at the end of treatment.
- An important 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 to 10 mL in volume. Route specimens to the appropriate reference laboratories, request tests for specific detection of drug resistance, and communicate results as quickly as possible to the treating clinician.
- Patients whose sputa are still culture-positive after 3 months of treatment should be reevaluated fully, including repeat DST for the possibility of further development of resistance. Patients are considered to have failed therapy when their sputum cultures are still positive after 4 months of treatment. See section: **Assessment for treatment failure**.

## Extrapulmonary TB

Microbiologic monitoring of **extrapulmonary** disease is more difficult, and serial biopsies or aspirates are rarely indicated. However, if the patient is not responding to treatment, or if there is any reason to suspect that the treatment is failing, strongly consider repeat specimen collection.

## Symptoms

*“The classic symptoms of TB—cough, sputum production, fever and weight loss—generally improve within the first few weeks of treatment.”*

—WHO Companion Handbook

- Early in the course of treatment, assess for symptoms of TB weekly, and then monthly throughout treatment thereafter.
- Document resolution of symptoms that were present at diagnosis.
- Patients with chronic, progressive symptoms such as cough, fever, chest pain, and weight loss will often notice improvement or resolution of these symptoms within weeks of starting effective treatment.

### Systemic symptoms

- Assess and monitor improvement of the following symptoms commonly reported in TB patients: **fever, loss of appetite, pain, and fatigue.**
- Monitor TB site-specific symptoms, and document changes from 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 diabetes and 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.
  - HIV, diabetes mellitus, and other diarrheal and malabsorption syndromes affect drug absorption and may undermine TB treatment, resulting in treatment failure, amplification of drug resistance, or increased risk for relapse. If a patient is at risk for poor absorption, monitor for diarrhea and other symptom changes. For more information, see **Chapter 7, Co-morbidities and Special Situations.**

### Respiratory symptoms

Routinely monitor the patient's cough, respiratory status, and sputum production. Most MDR-TB patients' respiratory symptoms should begin to improve within weeks of starting on appropriate MDR-TB treatment.

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

- **Other respiratory infection or process** (e.g., malignancy)
- **Non-adherent with therapy or not achieving therapeutic concentrations**
- **TB treatment failure? If failure is suspected:**
  - Repeat cultures and DST, including rapid molecular diagnostics for additional acquired resistance
  - 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, co-morbidities, and microbiologic response to treatment

### Weight

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

- Check weight weekly until weight gain stabilizes, and then monthly throughout the course of treatment and follow-up.
- Lean body weight may be calculated for obese individuals to adjust medication dosage. BMI may be calculated for underweight patients to assess nutritional status.

- Occasionally, patients will lose weight while on treatment due to side effects; monitor patients closely to ensure no other signs of treatment failure and investigate the likely cause.
- Very young children with drug-resistant TB may need more frequent weight monitoring as well as monitoring of other indices of growth and development.

**NOTE:** Drug dosages may need to be adjusted as weight changes, particularly in young children and patients who have sustained significant weight loss prior to diagnosis.

### Nutritional support and use of supplements

- Maximize the nutrition of undernourished patients.
  - Offer hospitalized patients flexible meals of their choice, solicit dietary consultation, and offer dietary supplementation.
  - Some patients feel best and gain the most nutritional benefit from small, frequent meals (mini-meals) throughout the day.
  - Occasionally, tube feedings for supplementation are required, and rarely, parenteral nutrition is used (especially prior to surgery to improve post-operative healing).
- Customize outpatient management based on the nutritional status of the patient. Some patients will only need to have their weights monitored, and others will require food diaries, regular nutritional labs, and ongoing nutrition consultation.
- Consider cultural differences and arrange for foods to which the patient is accustomed.
- Some food supplements (such as Ensure and multi-vitamins) interfere with absorption of fluoroquinolones and should be offered at least 2 hours before or after the drug.
- Refer patients with co-morbidities affected by nutritional intake (such as diabetes) for dietary consultation.

### Radiography

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

#### Obtain routine chest radiographs:

- Every 3 to 6 months during treatment
- At the end of therapy
- 6, 12, and 24 months after treatment is completed or as clinically indicated

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

**In particular, CT scans should be obtained to assist in evaluating the differential diagnosis or 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. In very complex cases, an end-of-treatment CT is often useful as a baseline for future follow-up. 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**

## Assessment for treatment failure

Patients are considered to have failed therapy when their sputum cultures are still positive after 4 months of treatment.

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

- Adherence to therapy
- Accurate dose calculation and administration
- Drug absorption
- Adequacy of the drug regimen
- Development of acquired 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)
- Presence of conditions that may delay culture conversion (e.g., uncontrolled diabetes, malabsorption, extensive disease)



## Monitoring for drug toxicity

Screening for drug toxicity and adverse effects is an important part of MDR-TB treatment. Close monitoring is needed to ensure side effects are responded to promptly, particularly when treatment is initiated in an outpatient setting.

### General principles

- **Counsel every patient** beginning any TB therapy to anticipate toxicity.
  - Even patients taking INH monotherapy frequently feel poorly in the first few weeks of therapy. If patients do not anticipate this reaction and are not reassured that it will improve, they may stop the therapy.
  - Monitor patients for general toxicities and drug-specific toxicity at every health-care visit (including during DOT encounters). See **Tool 2: MDR-TB Monitoring Checklist**.
  - Patients with drug-resistant TB may experience more toxicity than patients treated for drug-susceptible disease. Most of the second-line TB drugs are associated with significant side effects.
- 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.
  - **Supplemental ancillary medication** can be helpful in addressing some common side effects.
  - **Non-pharmaceutical approaches** should also be considered. Examples might include:
    - **Change the timing of the dose** to minimize toxicity (e.g., dose at bedtime).
    - **Dose some medicines with food** (have patient try different foods to find something palatable).
    - **Relaxation techniques** can sometimes be helpful.
  - See **Chapter 9, Adverse Reactions**, for approaches to address common adverse events.

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

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### Routine toxicity monitoring

Screening is necessary to detect adverse effects that are not apparent through physical exam or observed by the patient. For patients with MDR-TB or XDR-TB, routine monitoring for drug toxicity frequently includes the following:

- **Screening for bone marrow suppression:** Complete blood counts intermittently as clinically indicated; monthly for patients on **linezolid (LZD)**.
- **Monitoring renal function:** Creatinine at least monthly for patients receiving **aminoglycosides** or **CM**.
  - Baseline creatinine clearance should be documented in persons with serum cre-

atinine greater than expected, or if any concerns arise. (See **Chapter 5, Co-morbidities and Special Situations, Renal Failure, Table 1**, for creatinine clearance calculations.)

- Calculate creatinine clearance especially for patients with small body weight, older age, and in those with diabetes.
- **Monitoring liver function:** Liver function tests (LFTs) monthly (AST, ALT, total bilirubin) for patients taking **pyrazinamide (PZA)**, **ethionamide (ETA)**, or **para-aminosalicylate (PAS)**.
- **Monitoring serum electrolytes:** Potassium, calcium, and magnesium monthly for patients on **CM** and **aminoglycosides**.
- **Screening for hypothyroidism:** Thyroid function (TSH) every 3 months for patients receiving **ETA** or **PAS**.
  - Monitor TSH sooner if symptoms of hypothyroidism develop or if baseline thyroid testing shows abnormalities.
  - Use thyroid replacement if hypothyroidism is documented.
- **Screening for hearing loss and vestibulopathy.** Assess audiometry and vestibular function monthly for patients receiving **aminoglycosides** or **CM**. See **Tool 6: Hearing and Vestibular Screening Flow Sheet** for a sample tool that can be used to assess vestibular function and keep track of monthly vestibular and audiogram screening results. A change in hearing or vestibular function from baseline should be brought promptly to the treating clinician's attention, and the patient should be referred for further evaluation. Some sequela resulting from ototoxicity can be permanent (hearing loss, vertigo, and tinnitus). Early identification and referral is important to enable appropriate modification to the drug regimen to limit or prevent these outcomes. See **Chapter 9, Adverse Reactions**, for information on the management of ototoxicity.
- **Screening for visual changes:** Screen monthly for visual acuity and color discrimination for patients on **ethambutol (EMB)**, **LZD**, and **CFZ**. Refer a patient for further evaluation if changes in vision (acuity or color) or complaint of eye pain is noted. See **Tool 5: Vision Screening Flow Sheet** for tracking of monthly visual acuity and color vision screening results. Watch for evidence of uveitis for patients on **rifabutin (RFB)**.
- **EKG** at least 2, 12 and 24 weeks into treatment for patients on **BDQ**, or weekly if **BDQ** is combined with other medications that may prolong the QT interval.
- **Screening for peripheral neuropathy:** Monitor for peripheral neuropathy monthly while patient is on **LZD** and as clinically indicated for patients on fluoroquinolones (or high-dose INH).
- **Screening for depression, agitation, and psychosis:** Monitor for depression and mood changes (including agitation) monthly for patients taking **cycloserine (CS)**. The most common toxicities associated with CS are depression, psychosis, and suicidal thoughts. Standardized tools for assessing and documenting mental health symptoms are very helpful. It is also important to educate family members to notify the case manager or clinician if they notice any changes in the patient's mood since the patient may not be aware of these adverse effects. See **Resources** at the end of this chapter for examples of screening tools.

See **Tool 2: MDR-TB Monitoring Checklist** and **Chapter 5, Medication Fact Sheets**.

## Drug interactions

Many drugs interfere with TB therapy or contribute to toxicity.

- Monitor patients as to any new medication started. This should include over-the-counter therapies such as:
  - Vitamin/mineral supplements
  - Antacids
  - Traditional medicine, home remedies, and “alternative” or herbal supplements

## Therapeutic drug monitoring

The case manager also frequently coordinates collection and transport of blood samples for therapeutic drug monitoring. Few reference laboratories perform these levels, and factors such as cost and a patient’s insurance status require the expertise of the case manager. For details about timing of blood draws, processing, and shipping of samples, see **Chapter 3, Laboratory**, section on **Therapeutic Drug Monitoring**.

Situations in which serum drug concentrations are commonly used:

- In patients with known **renal insufficiency**
  - **Aminoglycoside** concentrations—target trough drug concentrations are generally <5 mcg/mL in patients. (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 peak concentrations in all patients.)
  - **EMB** concentrations (when it may be necessary to use this drug in patients with significant renal impairment).
- When using **second-line drugs with a narrow therapeutic window** in order to achieve target concentration and minimize toxicity
  - **CS** concentrations, particularly early in the course of treatment, can help the clinician to determine appropriate dose, minimize CNS adverse reactions, and prevent seizure activity. Target concentrations are ideally between 20–30 mcg/mL (below 35 mcg/mL to help avoid CNS side effects). Dose initiation may be done in a “ramped” manner; see **Chapter 4, Treatment**, section on **Escalation of Dosages (Drug Ramping)**.
  - Some experts may also routinely check **ethionamide** and **PAS** levels.
- When few effective drugs are available to include in the regimen, in order to optimize the effect of available drugs
- In patients with co-morbid conditions in which there may be known or suspected malabsorption or when a patient fails to show clinical response to treatment (i.e., remains culture-positive despite appropriate drug regimen, doses and DOT)
- When there is concern for potentially significant drug-drug interactions (such as rifamycins and antiretrovirals)

## Monitoring tools and strategies

As previously noted, the use of monitoring tools will help keep track of the many details of case management, enabling the case manager and treating clinician to keep results organized, to anticipate problems and manage them as they occur. Additional helpful strategies include:

- **Scheduling regular visits** with the patient, initially weekly and then monthly, to perform a thorough assessment until treatment is completed.
- **Real-time reminders** on the computer or mobile phone, a tickler system, etc.
- Seeking **expert consultation** from regional resources such as state TB Control programs and Regional Training and Medical Consultation Centers (RTMCCs). The learning curve is very steep during case management of the first case or two of drug-resistant TB, and use of the resources included in this book and discussions with experts will help with the rapid acquisition of information required. See **Appendix 1: Expert Resources for Drug-Resistant TB**.

## Post-treatment monitoring

At the end of treatment, a sputum culture and chest radiograph (CXR) should be obtained. The patient should undergo post-treatment monitoring for a minimum of 2 years to monitor for relapse. At 6, 12 and 24 months post-treatment (or as clinically indicated), the patient should be monitored with:

- Symptom review
- Medical evaluation
- Sputum for AFB smear and culture
- Chest radiograph

## Patient-centered care and ensuring adherence

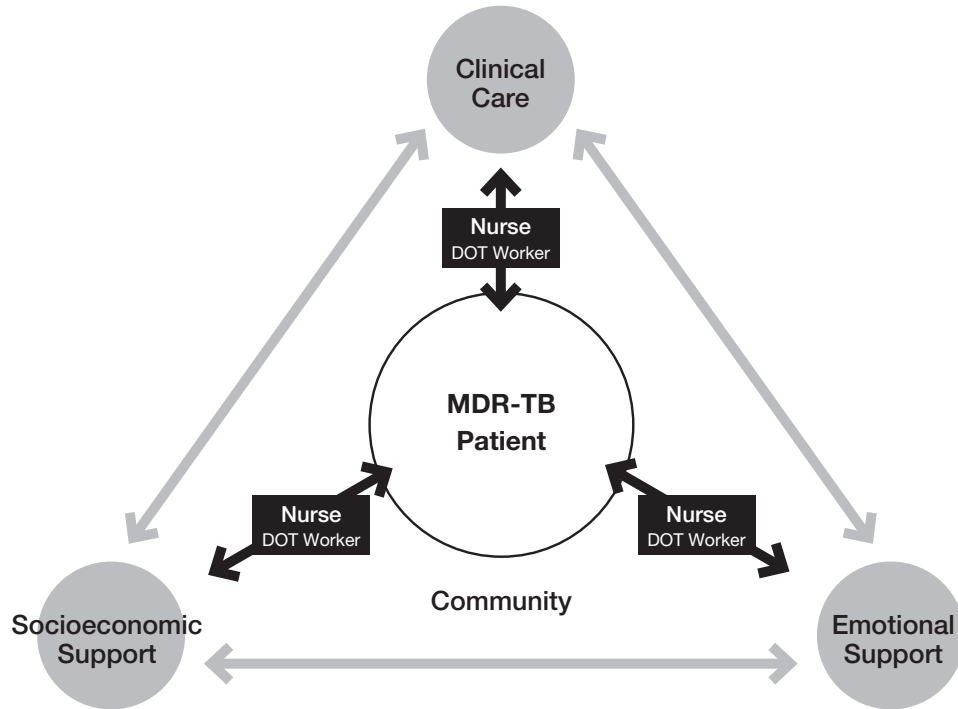
### Standard 9 of the *International Standards for TB Care*

*“Patient-centered approach to treatment should be developed for all patients in order to promote adherence, improve quality of life, and relieve suffering. This approach should be based on the patient’s needs and mutual respect between the patient and the provider.”*

Model programs utilizing a case management and patient-centered care approach in community-based care of drug-resistant TB patients (Figure 1) demonstrate high levels of treatment success.

FIGURE 1.

## Community-Based Model of MDR-TB Treatment



Adapted with permission from *The Community Based Model of Multidrug-Resistant Tuberculosis Treatment*, Jaime Bayona, MD, MPH, Socios En Salud Sucursal, Peru

Adherence to MDR-TB treatment is essential to prevent the amplification of resistance, to increase the chances of treatment cure, and to prevent ongoing transmission in the community. Even in high-resource settings, adherence to MDR-TB treatment can be challenging due to the long duration of treatment, the frequent and serious side effects, and the social and economic burdens to patients and their families.

A variety of factors influence adherence to treatment, including: the provision of DOT; the individual's knowledge and beliefs; social and emotional support available to the patient; and economic support to cover the cost of treatment and potential loss of income to the patient and family while the patient is unable to work or attend school. In order to promote adherence and support the patient, the case manager will be providing or coordinating the following activities:

- **DOT** (including arrangements for the injectable agent)
- **Information support** (education to the patient and family)
- **Psychological/social support** (including use of culturally appropriate resources)
- **Material support** (including use of incentives and enablers, and linkage to health care coverage)
- **Use of legal orders** when indicated

## 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**. DOT is the most effective strategy for ensuring patients take their medications correctly. It is recommended as a standard of care worldwide. Achieving this standard of care, however, requires far greater time and commitment in the setting of drug-resistant TB than of drug-susceptible disease. Weekend doses, drugs given more than once a day, and drugs tolerated only at bedtime will provide programmatic challenges, and DOT may need to be a shared responsibility.

*DOT is so important to the treatment of drug-resistant TB that experts in the field of TB control around the world consider it an essential strategy.*

DOT means that a health care worker or other designated individual watches the patient swallow every dose of the prescribed regimen. Since there are often many pills to swallow, DOT workers will need ample time to sit with the patient. The DOT worker may also be observing that the patient completes the infusion of the injectable agent when patients have been taught to administer the infusion at home. See section: **Roles and responsibilities—DOT worker**.

The case manager must keep an open line of communication with the DOT worker and ensure that he/she can assess which signs and symptoms indicate potential medication toxicity.

- When 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 the initial 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 side effects warrant at least temporary discontinuation of the offending drug. Any toxicity must be quickly identified, reported, and acted upon (see **Chapter 9, Adverse Reactions**). Address all complaints, even if no change can be made.
- It is very important to use standardized forms to record DOT doses and toxicities for these complicated patients.
- Some programs have patients complete a DOT acknowledgement or patient contract so that expectations are clearly explained and agreed upon.

*No detail regarding medication administration should be assumed or left to chance.*

### Routinely ask patients:

**“How did you take your medication?”** (when medications are taken over the weekend or when the dose is self-administered)

**“Have you eaten any milk-based products, antacids, or vitamin products within 2 hours of taking medications?”** (these inhibit the absorption of fluoroquinolones)

**“Did you throw up after taking your medicine?”** (important to ask even if medications are given by DOT in case the patient is vomiting after the DOT worker leaves)

## Providing the injectable agent

Arranging for and providing the administration of an injectable agent for MDR-TB patients can be challenging as many local health departments are not staffed to provide either infusions or injections. Although providing the injectable agent may be daunting, it is important that the patient and staff understand the importance of the injectable agent in the regimen.

### INJECTABLE AGENTS

**Why:** Bactericidal agent

**When:** 5-7 times per week at start of treatment, often drops to 3 times per week after culture conversion to minimize toxicity

**Where:** Hospital, home, clinic, infusion center

**How:** Intramuscular (IM) or intravenous (IV)

**How long:** Usually 6 months post culture conversion unless toxicity develops

A number of factors contribute to the decision for whether the patient will receive the injectable agent as an IM injection or via a peripherally inserted central catheter (PICC), including: insurance, patient preference, health department capacity to provide injection or infusion, DOT arrangements, and availability of home health for IV infusions. Patients without health insurance are often unable to afford placement of a PICC line, and IM injections may be the only option. If there is the choice of either IM or IV administration, patient preference should be strongly considered in addition to safety concerns, ability to provide DOT of the injectable agent, and logistics.

### IM injections

Initially, staff may be skeptical that a patient can tolerate IM injections for 6-plus months. However, many MDR-TB programs in the United States and internationally administer IM injections for all their MDR-TB patients with excellent outcomes. Some programs provide the IM injection in the patient's home, which can be more comfortable and convenient for the patient. Alternatively, patients can come into the clinic/provider office to receive the injection as long as appropriate infection control is in place while the patient is still infectious. Public health and/or clinic nursing staff may require additional in-service training if they have not had recent experience in providing injections. Good injection technique can make the experience less painful for the patient. Lidocaine can be added to the injection to lessen the pain. See **Resources** at the end of this chapter for additional information.

### IV infusions

Patients may prefer to receive infusions versus IM injections. A major challenge in providing infusions is finding staff to perform the infusion. Typically, public health nurses are not trained to provide infusions—or it falls outside of their scopes of practice—and a home health agency may be needed to provide home-based infusions. Often, home health agencies train family members to administer medications; the agencies visit once-a-week to assess the insertion site of the PICC line (or other intravenous catheter) and provide the supply of medications. It is important that the case manager communicate closely with

the home health agency regarding the assessment of whether the patient or family member can safely administer the infusion using proper clean technique.

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**NOTE: Amikacin (AK) may be a better option than capreomycin (CM) for home infusion.** Pharmacies typically provide premixed solutions of AK as it remains stable at room temperature for at least 3 weeks. Patients receiving CM may need to learn to reconstitute the powder as it is not considered stable after 24 hours upon refrigeration (refer to package insert for full instructions).

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Even if the case manager is not directly administering the infusion, it is important that he/she be aware of and assess for signs of infection. Additionally, when the patient or family member administers the infusion, arrangements for DOT of both parenteral and oral medications are needed. Some programs coordinate the DOT of the oral medications with the timing of the infusion. For example, the DOT worker arrives as the infusion is finishing. Programs should establish protocols and procedures for the DOT workers to document administration of the infusion. Once a patient is no longer considered infectious, another option is to use an infusion center.

### Calculating the concentration and volume for administering injectable agents requires careful attention.

For example: CM comes in a powder form and when the diluent is added, the volume expands (i.e., exceeds the volume of diluent added).

**CASE EXAMPLE:** Patient who weighs 55 kg has an order to receive 15 mg/kg CM (825 mg) IM 5 days per week. The nurse reviews the packet insert and sees that when 3.3mL diluent is added to the 1g, 10mL vial, the concentration is approximately 260 mg/mL.

The nurse performs the following calculation to determine the volume of solution to inject to provide 825 mg of CM:

$$260 \text{ mg} / 1 \text{ mL} = 825 \text{ mg} / x \text{ mL}$$

$$X \text{ mL} = 825 \text{ mg} / 260 \text{ mg}$$

$$X \text{ mL} = 3.17 \text{ or } \mathbf{3.2 \text{ mL solution}}$$

It is important for the nurse to review the package insert for each injectable medication to determine the appropriate volume.



## Patient education

All patients and their family members should receive education about MDR-TB, its treatment, and the need for adherence to therapy. Education may be provided by physicians, nurses, community health workers, and other health care providers. The case manager will have a key role in providing education, coaching, and support to the patient throughout treatment. Health care providers are encouraged to communicate with patients in a manner that is respectful, supportive and helps to build a positive partnership. Providers should avoid “talking at” patients and refrain from language that is judgmental or punitive (e.g., “If you don’t take your medications, you will make other people sick...”).

*Ongoing TB education is essential...*

### Tips for delivering key information to the MDR-TB patient

- Always use a venue that guarantees confidentiality in communication.
- Use language that promotes mutual respect and esteem between the patient, caregivers, and health-care providers.
- Do not make promises that the health-care service cannot keep.
- Respect the patient’s right to choose.
- Enable the patient to counteract stigma and discrimination by reassuring that his/her disease is not the result of any socially or morally inappropriate behavior that he/she has made in the past, and that many other patients have successfully completed treatment.

Adapted from: *Companion Handbook to the WHO Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis*, 2014

The following phases may not fit the treatment course for all MDR-TB cases, but will provide a context for case managers to anticipate their patients’ educational capacities and needs. The analogy of preparing for a marathon has been suggested to emphasize the key role the case manager can play in coaching the patient through the various phases of treatment and by setting achievable interim goals.

### 1. First phase

The first phase spans from diagnosis through the period of time the patient may require airborne infection isolation. (See section: **Initiating treatment, initial patient education**). If the patient’s medical needs are not given careful attention during this first phase, the patient is at higher risk for becoming discouraged. Information to share and discuss includes:

- **Major concepts:** MDR-TB, like regular TB, is a contagious disease, which means it can be spread from person to person. TB generally lives in the lungs, but it can also infect other parts of the body. If MDR-TB is left untreated, it can kill the patient. **MDR-TB can be cured** with the right medicine.
- **Recognize and address the patient’s fears and concerns.** Patients are less likely to comprehend treatment information if they are fearful or preoccupied with worries about their jobs or family members.

- **Clarify how drug-resistant TB can be transmitted and how it cannot be transmitted** (i.e., not through sexual relations, sharing food, etc.).
- **Simple infection control practices**, such as covering the mouth when coughing.
- **Airborne infection isolation plans, strategies for keeping the home well-ventilated** with fresh air, and adhering to visitor restrictions if isolated at home.
- Patient's **plans regarding work, travel, or moving**.
- **Expected side effects** and what to do should they occur, including reporting to the DOT provider.
- **How to contact the DOT worker, case manager and/or clinician** in case of an urgent issue when the health department is closed.
- **Available educational and social support resources** in the community and online as appropriate. See **Resources** at the end of this chapter.
- **Criteria for non-infectiousness** (i.e., when home isolation can be discontinued per program protocols and the patient will be allowed to return to work or school).

## 2. Second phase

Once the patient is stabilized on treatment, the emphasis of education will shift. During this phase, **focus on helping the patient manage any side effects, maximizing nutrition** and working together to **identify barriers to adherence**. 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. Information to share and discuss includes:

- **Patient's knowledge and understanding of the disease, treatment plan** and potential serious side effects of treatment
- **Management of side effects** (see **Chapter 9, Adverse Reactions**)
- **Arrangements for DOT and clinical response monitoring**
- **Incentives and enablers** that might aid adherence to treatment (see section: **Use of incentives and enablers**)
- **Management and care for co-morbid conditions**
- **Appetite, nutritional status, and physical activity** as tolerated
- **Signs of clinical improvement**
- **Management of injection site(s)** (care of IM/IV sites)
- Patient's **plans concerning work, travel, or moving**

## 3. Third phase

If 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 have another year or more of oral medication to complete before reaching the finish line. Information to share and discuss includes:

- Patient's plans concerning work, travel, or moving
- Management of side effects (different side effects may develop later into therapy requiring additional management and sometimes a change of medication)

- **Arrangements for DOT and clinical response monitoring**
  - As the patient's circumstances change (e.g., return to work), make necessary adjustments in collaboration with the patient
  - Continually reassess the patient's belief in and understanding of the importance of uninterrupted treatment to prevent treatment failure and relapse
- **Identifying acceptable interventions and strategies for addressing potential barriers** as needed

#### 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 2 years to ensure that if a relapse occurs, it will be identified and acted upon quickly. Information to share and discuss includes:

- Ensure that the patient is **knowledgeable about signs and symptoms of TB and what to do** should he/she experience them.
- **Schedule and inform the patient of follow-up appointments.** Arrange for reminder notification suitable to the patient.
- Revisit the patient's **plans concerning work, travel, or moving.** Provide the patient with appropriate referral and contact information as indicated.

### Psychosocial support

Patients with MDR-TB face many stressors, including the diagnosis of a potentially life-threatening disease, issues of stigma, serious side effects, and economic hardships. A 2006 report by Chalco and colleagues found that many patients with MDR-TB experience strong feelings of guilt and in some cases, the stigma may not come from the social surrounding, but rather from the patient's own family; relatives may react in accordance with past experiences and cultural beliefs. Most patients will need ongoing social and emotional support to cope with these challenges. The case manager often plays a key role in providing emotional and social support by listening to the patient, and talking with patient and family to reduce stigma, fear, and misunderstandings about the disease.

Engage family members in the patient's care; encourage and praise their support. Do everything possible to get the family 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.

Assess the patient's social support network and the strengths and barriers to adherence. Ensure that plans are in place for addressing issues such as mental illness, substance abuse, and homelessness.

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

- Social services and programs for the medically indigent
- Community-based organizations
- Immigration law counsel
- Drug and alcohol counseling
- Mental health programs

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. Ideally, case managers will have familiarity with and ongoing relations with valuable community resources prior to their first cases of drug-resistant TB.

## Substance abuse and mental illness

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 adherent to TB therapy.

- Closely monitor a patient's success and/or relapse with substance abuse issues during TB treatment in order to anticipate toxicity and to avoid adherence complications. Facilitate referral to programs and services that can work with the patient on harm reduction.

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 can affect many patients and can be quite debilitating. **CS**, which is often used to treat MDR-TB, is known to be associated with significant neurotoxicity resulting in depression and sometimes psychosis, particularly when serum drug concentrations are high. Monitor patients for these symptoms and provide support and referral as needed. See **Resources** at the end of this chapter for tools to monitor for depression and psychosis.

- Be aware that some drugs to treat depression such as **selective serotonin reuptake inhibitors (SSRIs)** are not recommended for patients on **LZD**.

## Cultural and religious background

The proportion of patients with MDR-TB in the United States who are foreign-born is substantial (approximately 90% in 2013). A patient's cultural background, spiritual traditions, prior experiences of treating illness, and history of access to care may impact how he/she views the path towards health. Assessing patients' understanding of and beliefs about their diagnoses and treatment plans can provide case managers and providers with important information to negotiate mutually acceptable approaches to treatment.

TABLE 2.

## Leveraging cultural- and religious-related resources during MDR-TB diagnosis and treatment

Examples of potential barriers	Strategies to build on cultural strengths
<ul style="list-style-type: none"> <li>• Cultural stigma about TB</li> <li>• Concern that the illness might interfere with immigration process and/or result in deportation</li> <li>• Hindered access to health care because of:               <ul style="list-style-type: none"> <li>• Lack of health insurance coverage and/or eligibility</li> <li>• Language or cultural barriers combined with the general difficulty of navigating complex health care systems in the United States</li> </ul> </li> <li>• Patient's preference to:               <ul style="list-style-type: none"> <li>• Seek traditional medicine and healing modalities when ill</li> <li>• Seek out a physician from his/her own culture, who may not be familiar with diagnosis and treatment of drug-resistant TB</li> </ul> </li> <li>• For women: Loss of importance to her family if she cannot continue her usual activities or if she experiences disapproval from her spouse</li> <li>• Fear of the diagnosis itself if the individual has lost a friend or family member due to drug-resistant TB</li> </ul>	<p><b>Explore local resources to help bridge the barriers and develop partnerships with the patient to facilitate communication and understanding:</b></p> <ul style="list-style-type: none"> <li>• Trained medical interpreters</li> <li>• Trained patient navigators</li> <li>• Bilingual health department staff</li> <li>• Cultural health brokers</li> <li>• Healthcare professionals from the patient's culture</li> <li>• Community leaders, community organizations</li> <li>• Church-based services</li> <li>• Traditional healers</li> <li>• Other local health departments with experience working with specific ethnic groups</li> <li>• Court interpreters, telephone-accessed interpreters, university language departments</li> <li>• Refugee health and social service programs</li> </ul> <p><b>Connect patients to supportive services and care:</b></p> <ul style="list-style-type: none"> <li>• Legal resources, especially immigration</li> <li>• Counseling services and/or peer support groups</li> <li>• Access to spiritual or religious counsel, particularly during the isolation period</li> </ul>

Few translated patient materials that pertain 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 4, *Multicultural Resources***.

### Economic support

Patients with drug-resistant TB may face economic hardship due to the cost of treatment, loss of work, interruption in schooling, and stigma. Costs associated with the treatment and management of patients with drug-resistant TB may 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 the cost of drugs, diagnostic exams, and surgery may pose an extreme financial burden on individuals and families.

## Health care coverage

- In states that have expanded Medicaid access under the Patient Protection and Affordable Care Act (PPACA or ACA), inpatient and outpatient TB care can be provided to adults who meet income and legal eligibility criteria through full-scope Medicaid. These patients also may be eligible for TB Medicaid that often provides outpatient services with no share of cost, in addition to full-scope Medicaid.
- In some jurisdictions, all TB care may be provided free of charge in the public health setting.
- Patients who are undocumented immigrants may also be able to enroll in full-scope Medi-Cal. See **Resources** at the end of this chapter for more information.
- Organizations that provide *pro bono* immigration legal services can be very helpful in exploring options available to undocumented persons or low-income immigrants.

Many patients experience a period of prolonged unemployment associated with the period of infectiousness and due to employment discrimination. The case manager may intervene and educate employers to help protect a patient's job during the period the patient must remain on respiratory isolation. The case manager may also be instrumental in assisting to find alternative sources of income and/or other assistance (i.e., obtaining disability benefits) for the patient and his/her family while he/she cannot work (see sections: **Patient assistance programs** and **Incentives and enablers**).

**Addressing any financial challenges early in the patient's course of treatment will go a long way in establishing a foundation of confidence and trust.**

## Patient assistance programs

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. Table 3 displays some drugs used to treat drug-resistant TB that are known to be included in PAPs. Please note that PAP information changes periodically and some offers are time-limited.

The AIDS Drugs Assistance Program (ADAP), funded by Ryan White CARE Act dollars, provides HIV-positive individuals with low- or no-cost prescription medications to treat HIV/AIDS and related conditions. In October 2007, ADAP announced that 8 drugs used to treat MDR/XDR-TB were added to the ADAP formulary: moxifloxacin, CM, ETA, CS, p-aminosalicylic acid, imipenem/cilastin, LZD, and levofloxacin. The ADAP formulary now includes most if not all of the drugs used to treat pan-susceptible TB and drug-resistant TB. To inquire about a patient's eligibility for this program, contact the local ADAP coordinator at the state health department.

TABLE 3.

**TB Medications and Patient Assistance Programs (PAPs)\***

Brand name	Generic name	Manufacturer / Assistance Program	Eligibility criteria	PAP telephone / contact information
Treactor-SC	Ethionamide	Pfizer/ RxPathways PAP	Resident of U.S., Puerto Rico, or Virgin Islands without insurance or under-insured	866-706-2400 www.pfizerrxpathways.com
Levaquin	Levofloxacin	Janssen Pharmaceuticals/ Johnson & Johnson Patient Assistance Foundation	Resident of U.S. or U.S. Territory without sufficient resources	800-652-6227 www.janssenprescriptionassistance.com/levaquin-cost-assistance
Avelox	Moxifloxacin	Merck Sharp and Dohme Corp.	U.S. resident without prescription insurance coverage <b>and</b> meets income stipulations	800-727-5400 Merck Helps PAPs www.merckhelps.com/Programs.aspx
Zyvox	Linezolid	Pfizer/Zyvox Assist	Resident of U.S. or Puerto Rico without insurance or under-insured	866-706-2400 Pfizer RxPathways www.pfizerrxpathways.com  My Pfizer Brands www.mypfizerbrands.com  Zyvox Assist: 855-239-9869 www.zyvoxassist.com Note: this is a one-time coupon that expires 12/31/2016
Augmentin	Amoxicillin/ clavulanate	GlaxoSmithKline/ Bridges to Access	U.S. resident, without resources	866-PATIENT 866-728-4368 www.bridgestoaccess.com
Lamprene	Clofazimine	Novartis	MDR-TB	301-796-8240 FDA, single patient Investigational New Drug (IND)

\*Please note: PAP information changes periodically. Information in this table is current as of October 1, 2015.

## Use of incentives and enablers

The use of **incentives and enablers** is another strategy reported to be effective in assisting patients in maintaining adherence to treatment. Enablers such as transportation and food vouchers can be used to address some of the economic hardships experienced during treatment. Additionally, patient motivation commonly wanes once the patient begins to feel better and may affect the patient's commitment to the treatment plan. Simple interventions geared at making the patient's experience easier, as well as that of their family, can go a long way towards gaining commitment to treatment.

For more information about incentives and enablers, see **Resources** section at the end of this chapter.

## Homelessness

When MDR-TB is diagnosed in someone who is homeless or at risk of becoming homeless, additional support is necessary to ensure stable housing can be procured and co-morbidities addressed and managed early on.

- A 2014 study by Marks, et al., indicated that TB patients who were recently homeless were 5 times more likely to acquire drug resistance during treatment than were patients without a recent history of homelessness.
- Closer monitoring of MDR-TB patients who have recently experienced homelessness may be necessary to ensure they are showing response to treatment.
- See **Resources** at the end of this chapter.

## Use of legal orders

Legal measures are sometimes required when a patient with infectious, drug-resistant TB remains non-adherent despite interventions to overcome barriers and to gain the patient's cooperation. The case manager should be knowledgeable about the process for referring such patients, and must ensure that all lesser restrictive measures that have been employed have been documented. When recalcitrance persists, local, regional, and/or state TB control programs can provide additional information on the state laws and regulations pertaining to TB.



# 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 treatment. When the drug-resistant TB patient moves between facilities (such as a hospital or jail) and the community during treatment, the case manager must ensure that appropriate treatment, monitoring, and education of the patient continues. This may require:

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

## Hospitalization and discharge planning

Some patients may require inpatient admission to enable prompt management of drug side effects and adverse reactions.

- **If the patient is hospitalized, the case manager will need to provide support to the patient as well as to 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.
- Hospital staff should be encouraged to seek expert consultation when necessary.

Frequent and timely communication with the patient's hospital-based treatment team regarding **discharge planning** should include:

- Procurement of medications prior to discharge
- Plan for DOT
- Coordination of infusion therapy services if the health department cannot provide them
- Plan for home isolation if the patient will be discharged while still considered infectious (see **Table 4** and section on **Infection control—Home isolation** for further guidance when a patient is still considered infectious)
- Plan for addressing psychosocial issues (such as mental illness, homelessness and substance abuse)
- Scheduling of follow-up clinic appointments and monitoring tests, and providing a contact number to call should problems arise
- Ensuring the hospital is working with the patient to address **ongoing care of co-morbid conditions**, such as HIV, diabetes mellitus, and renal disease.

## Interjurisdictional transfers

If the patient moves out of the case manager's jurisdiction, concrete plans for transfer of care need to be in place before the move. Even if the patient moves out of country, an accepting provider and responsible jurisdiction need to be identified and apprised of the patient's disease and treatment history. (See **Resources** for CDC website on international notification of TB cases.) Provide the patient with enough medications to last through the travel period until he/she can re-establish DOT in the new jurisdiction. Contact information

for family and friends, both in your area and in the destination, may be helpful if the patient does not arrive at the destination in a timely manner.

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 a move prior to completion of therapy. **Note:** Availability of second-line medications, TB cultures, and DOT may be limited in some countries.

- **CureTB** is a binational referral program based in San Diego, California, for patients with TB who move between the United States and Mexico or Central America. CureTB will link patients to TB providers in the countries to which they are traveling, and will share relevant clinical information with the receiving providers.
- **TBNet** is an international tuberculosis patient navigation program under the Migrant Clinician's Network. This program is designed to provide bridge case management for mobile, underserved TB patients inside and outside of the United States. TBNet enrollment is strongly recommended for any MDR-TB patient with suspicion of movement. This program also provides a treatment outcome report to the enrolling site upon case closure. Note: TBNet requires patient consent for enrollment.

See **Resources** for contact information for CureTB and TBNet.

## Co-management 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.
- Explain your role and legal responsibility to monitor the patient throughout the course of treatment, and **explain the regulations** in your state or jurisdiction regarding the provider's responsibility to report information to the health department.
- Convey through your actions and words the specific areas, such as DOT, that you and the health department team can assist in the co-management of the patient.
- Explain the absolute **necessity of DOT**, and emphasize to the provider the benefit of DOT to the patient. Daily contact with the patient through the provision of DOT will ensure that any problems the patient may experience are identified and addressed quickly. Patients frequently take their cues from their clinicians; enlist the provider's support in encouraging the patient to accept DOT.
- Explain the **infection control** practices required to keep office staff and other patients safe.
- Point the provider to resources that may be available to help manage the patient's co-morbid conditions, such as diabetes, malnutrition, and HIV.
- **Share this *Survival Guide* and a list of consulting resources** with the provider. 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, *Expert Resources for Drug-Resistant TB***.
- If the provider and staff have the infrastructure and resourcefulness to problem-solve with 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 detection of drug-resistance testing, blood levels, etc.), stay actively involved to ensure that **everything** gets done and is followed up appropriately.

- Touch base with the office staff regularly. Ensure essential monitoring tests are performed as indicated. 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 whom the patient trusts.
- Ensure that the office staff has been appropriately evaluated if unprotected exposure to the patient has occurred.

**Reach an agreement about how and when important information (sputum and other laboratory results and radiographic results) will be shared between the private provider and public health agency.**

## Incarcerated patients

Special coordination of care is necessary when an MDR-TB patient is incarcerated at the time of diagnosis or during the course of treatment. Below are some areas for special attention:

- **Airborne infection isolation:** Patients will require isolation and may not be returned to the general population until they are considered non-infectious (see section: **Infection control** for suggested criteria). The need for respiratory isolation may require movement to a hospital or different facility and additional coordination to ensure all providers involved know the treatment plan. Occasionally, patients are in isolation for prolonged periods and may require physical and/or occupational therapy to prevent physical deconditioning and situational depression due to lack of movement and stimulation.
- **Adherence and DOT:** It will be important to educate facility staff regarding DOT; do not assume that medications are always observed when given in a correctional facility. Patients cannot be forced to take medications while incarcerated, and staff will need to work closely to address side effects and potential barriers to adherence.
- **Inmate movement:** During the long course of treatment, patients may move to different facilities or be paroled to the community. To ensure a patient is not moved without the awareness of medical staff, a stop sign or letter can be placed in the inmate's record indicating the need to ensure continuity of TB care. For a TB patient who is likely to move, enrollment in TBNet is strongly encouraged to ensure interruptions in treatment are minimized, appropriate follow-up and transfer of care occurs, and outcomes are reported.
- **Coordination of care:** The local TB program should be closely involved with the management of MDR-TB treatment and may also enlist an MDR-TB expert to provide consultation. The case manager should maintain regular communication with the facility's nursing and clinical staff and be proactive in coordinating care when an inmate will be moved to another facility (e.g., schedule a teleconference with staff from both facilities to review the care plan). Other key members to involve in the coordination of care include the facility pharmacist, state correctional medical officers, and the facility administrator.
- **Federal custody:** Give special consideration to MDR-TB patients who are in federal custody or who may transfer to the custody of a federal law enforcement agency. For patients who are diagnosed with MDR-TB while incarcerated or detained, health department staff should verify which agency has legal custody.

Health department staff should communicate with the respective law enforcement agency's health service staff to coordinate continuity of care and prepare and plan for possible transfer, release, or deportation. Transfers may occur to another jurisdiction and/or to the custody of a different law enforcement agency for reasons unrelated to health status. It is important to keep in mind that the law enforcement agency having legal custody may differ from the correctional or detention facility providing housing, security, and care for the prisoner, detainee, or inmate.

- **Deportation:** MDR-TB patients may be at risk for deportation if they are ordered removed by a federal immigration judge. Health department staff should ascertain whether the patient is in the custody of U.S. Immigration and Customs Enforcement (ICE), or if they have an ICE detainer and are scheduled to transfer to ICE custody upon completion of the sentence or resolution of criminal charges. Health department staff should promptly communicate with the ICE Health Service Corps, Public Health, Safety, and Preparedness Unit to coordinate case management and prepare for any possible outcome to the legal proceedings. TBNet enrollment should be verified to ensure continuity of care services for these patients. See **Resources** for contact information.

## Infection control

As noted in the WHO 2014 guide for programmatic management of drug-resistant TB, drug-resistant TB is similar in transmissibility to drug-susceptible TB and requires similar infection control strategies. In order to halt the transmission of *M. tuberculosis* complex, including drug-resistant TB, the correct diagnosis must first be considered, the appropriate treatment initiated, and appropriate infection control measures instituted. Infectious or potentially infectious drug-resistant TB patients should be housed within a negative pressure room in the hospital setting, or if they are outpatients, they should be separated from medically vulnerable family or friends.

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 is limited data on the efficacy of treatment of latent MDR-TB in exposed contacts. Unfortunately, infection control practices and isolation are a significant hardship for the patient and family and may unnecessarily perpetuate and exaggerate stigmatization of the patient with drug-resistant TB. When determining the duration of isolation, the safety of the public and the patient's family and contacts must be weighed against the mental health and morale of the patient as well as the resources required to isolate a patient.

- See **Resources** at the end of this chapter for publications that reflect current standard practices regarding TB and infection control. Local health jurisdictions are an important resource and may have specific guidelines.

### Assessing infectiousness and criteria for release from airborne infection isolation

The following information may be used to guide decisions in assessing infectiousness and determining when isolation may be discontinued:

- 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. However, a 1999 molecular epidemiology study in San Francisco

documented TB transmission following exposure to AFB smear-negative, culture-positive TB cases accounting for 17% of secondary cases. Subsequent studies in the Netherlands and China substantiated this finding. See **Chapter 10, Contacts** for additional considerations regarding transmission and assessment for infectiousness.

- For drug-susceptible TB, a patient receiving TB treatment is deemed to be non-infectious when: he/she has taken and tolerated 2-3 weeks of an appropriate treatment regimen; he/she is clinically improving; and AFB smears have shown improvement if initially smear-positive. If initially AFB smear-negative, the patient can be deemed non-infectious after 5 days of effective treatment with clinical response. In a 2014 report from South Africa, MDR-TB patients became non-infectious once they were AFB smear-negative, started an effective regimen, and had evidence of clinical improvement.
- Because the transmission of MDR-TB has more serious potential consequences for contacts, **it is appropriate to be more cautious about returning MDR-TB patients back to their homes, schools, work sites, and congregate settings. All settings should be assessed by the local health department before determining whether a patient may safely return.**
  - **Take particular care 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** infectious as long as their sputum cultures remain positive. These experts recommend isolation while hospitalized and would not release MDR-TB patients to high-risk settings until sputum cultures are negative. See **Table 4 for an example of criteria used to determine when a patient with MDR-TB or suspected MDR-TB may be released from isolation to either a high-risk or low-risk setting.**

TABLE 4.

## Criteria for Release from Isolation to High and Lower Risk Settings\*

Patient Category	Setting	Criteria
<b>TB case (or suspect on treatment for TB) at increased risk for MDR-TB</b>	High or Lower risk	<ul style="list-style-type: none"> <li>Obtain direct NAAT, if available, for RIF and/or INH resistance.</li> <li>If direct NAAT not available, while phenotypic DST for RIF is pending, at the discretion of the local TB controller, either criteria for patients with known MDR-TB or criteria for patients not at increased risk of MDR-TB may be applied.</li> </ul>
<b>Known MDR-TB case</b>	High risk	<ul style="list-style-type: none"> <li>Three consecutive respiratory specimens collected on separate days, including at least one early AM or induced sputum, or BAL, are AFB smear negative, and no subsequent sputum specimen is AFB smear positive;</li> <li>At least 14 daily doses of treatment for MDR-TB taken and tolerated by DOT;</li> <li>Clinical improvement; and</li> <li>At least 2 consecutive negative sputum cultures without a subsequent positive culture.</li> </ul>
	Lower risk**	<ul style="list-style-type: none"> <li>Three consecutive sputum specimens collected on separate days are AFB smear negative;</li> <li>At least 14 daily doses of treatment for MDR-TB taken and tolerated by DOT; and</li> <li>Clinical improvement.</li> </ul>

### Definitions:

#### High Risk Setting

- A housing or work setting in which others will share air with the TB patient and which is characterized by 1 or more of the following factors:
  - A large number or high density of persons.
  - The presence of persons at high risk of progression to active TB disease (e.g., children < 5, persons with HIV infection)
  - The presence of persons who have not been previously exposed to the TB patient.

#### Lower Risk Setting

- A **residential** setting not characterized as high risk, and:
  - No other persons will share the air with the TB patient; OR
  - Other persons who will share the air with the TB patient are not at increased risk for progression to TB disease if infected; OR
  - All persons at increased risk of progression to TB disease if infected, including all children under the age of 5 years, who will share the air with the TB patient, have been previously exposed to the TB patient, have had a complete medical evaluation and have been started on therapy, including window period treatment for presumed LTBI (TB1), as appropriate.
- A **work** setting not characterized as high risk, and in which no contacts are known or reasonably expected to be at increased risk of progression to TB disease if infected

\*Adapted from CDPH/CTCA Joint Guidelines for the Assessment of Tuberculosis Patient Infectiousness and Placement into High and Lower Risk Settings 2009

\*\*A patient may be considered for placement in a lower risk setting without meeting these criteria if no previously unexposed persons will be present (see section: **Home isolation**)

## Home isolation

Many patients with drug-resistant TB do not require hospitalization and may be on home isolation at the start of treatment. Some patients may be hospitalized to initiate treatment and become ready for discharge prior to becoming non-infectious. A number of factors should be taken into account when considering whether home isolation is appropriate:

- Physical environment (is the home very small and crowded with little air flow?)
- Medical risks of household members (young children, immunocompromised?)
- Stability of household (relative likelihood that no new members will enter)
- Anticipated adherence by the patient
- 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.

When caring for drug-resistant TB patients who are considered potentially infectious, healthcare and other service providers entering the home to deliver DOT and/or other healthcare services (e.g., patient interviews, home infusions) must comply with current infection control measures to prevent occupational exposure. For information that is essential to consider when preparing for the care of infectious TB patients in the home setting, consult with national (National Institute for Occupational Safety and Health [NIOSH]) and state occupational health and safety programs, your state TB program, or your RTMCC.

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

In some cases, home isolation will not be possible. In these cases, if resources permit, consider:

- Patients can sometimes be housed in a motel room which has an air supply that vents to the outdoors.
- A mobile home or trailer may be rented or purchased and used to house the patient until they are non-infectious.

## Transportation

Considerations for transporting the infectious drug-resistant TB patient:

- **Private car:** Have windows down, mask patient if possible, eat outdoors at stops.
- **Ambulance:** Identify an ambulance company that has vehicles with negative pressure and high efficiency particulate air (HEPA) filtration. Patients should wear surgical masks, and providers and drivers should wear N-95 masks.
- **Commercial airline flights:** WHO guidelines consider patients with MDR-TB to be infectious until their sputa are culture-negative, and forbids travel in public airplanes or other public transportation until their sputa are culture-negative (see **Resources**).
- **Air ambulance:** Contact the patient's insurance company, your hospital social worker or case manager, or your expert resources to identify an air ambulance company or private flight arrangements to safely transport your patient. WHO and International Air Transport Association have published guidelines regarding transporting potentially infectious tuberculosis patients by airline (see **Resources**).



# Drug supply management

## Drug availability

Many second-line TB medications are not regularly in stock at local pharmacies or wholesalers. 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 a pharmacy or wholesaler states a drug is not available or “in stock,” additional steps can help determine if the drug is truly unavailable.

1. Check the U.S. Food and Drug Administration (FDA) Drug Shortage website, or the American Society of Health-System Pharmacists Drug Shortage website to see if a drug shortage has been reported (see **Resources**).
2. Ask the pharmacy or wholesaler to check with other distribution centers.
3. Call (or ask the pharmacy to call) the drug manufacturer directly and ask:
  - If there is stock
  - How the drug can be obtained (e.g. through wholesalers and/or directly from the manufacturer)
  - If the drug is on allocation that requires a special request (as has been the case for AK)
  - If the drug is short-dated (expiration date is imminent and wholesalers will not keep in stock and may require special agreement to release the drug)
  - If out of stock, anticipated date of availability

If **not available** from the pharmacy or manufacturer:

- Contact the TB nurse consultant at the state health department or the state TB controller; if your state TB program supplies TB medications, its central pharmacy may carry or have access to second-line drugs.
- Contact local hospitals to see if they have supply to share.
- Try to identify a patient in the area who has recently been taking the drug and see how that patient’s case manager obtained the drug.

Additionally, 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.

## Drug shortages

Drug shortages have become increasingly common in the United States and most TB programs have been impacted by shortages of first- and second-line TB drugs. CDC has received reports of difficulty obtaining INH, RIF, streptomycin (SM), CS, ETA, AK, and CM.

Suggestions for managing drug supply and addressing drug shortages:

- 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 and complete the *TB Drugs & Diagnostics Shortages Reporting Form* at the National TB Controllers Association website. The FDA is also a potential resource. See **Resources**.



TB drug supply can also be impacted by insurance company policies. Some insurance companies will limit the number of days or weeks a pharmacy can supply certain medications. Fluoroquinolones and macrolides in particular, may require special treatment authorization from the insurance company. Suggestions for addressing this issue include:

- Ask the pharmacy to help you anticipate any such restrictions on the patient's prescription plan.
- Write a letter to the insurer explaining the medical condition, duration of anticipated use of the drug, and need for that particular drug over another formulary drug to request authorization for prescription coverage. For most efficient processing, include the patient's name, date of birth, insurance ID and policy numbers, as well as the subscriber information.

### **Drug storage and safety**

- Most of the drugs used to treat drug-resistant TB can be stored at room temperature (59° to 86°F; 15 to 30°C); however, keep the following medications **refrigerated**:
  - **PASER granules**—store below 59°F (15°C); can also be stored in freezer
- Work with the agency providing parenteral medications to make sure the suspended forms do not exceed their safe shelf lives.
- Ensure safety of needle handling and disposal.

See **Chapter 5, Medication Fact Sheets**, for more details about each drug.



# Tool 2: MDR-TB Monitoring Checklist\*

Patient Name: SAMPLE PATIENT Treatment Start Date: May 5, 2015 Treatment Regimen: EMB, Moxifloxacin, Amikacin, Linezolid, PAS

Activity	Month of Treatment																		
	Baseline	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Date	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov
<b>CLINICAL MONITORING</b>																			
Sputum smear and culture <sup>1</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
CXR <sup>2</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Weight <sup>3</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Symptom review <sup>4</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
DST <sup>5</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>LAB MONITORING FOR TOXICITY / CO-MORBIDITIES</b>																			
CBC <sup>6</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Creatinine <sup>7</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
LFIs <sup>8</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
K+, Ca, Mg++ <sup>9</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Drug level <sup>10</sup>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
TSH <sup>11</sup>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
HIV <sup>12</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Pregnancy	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>MONITORING PROCEDURES</b>																			
Audiogram <sup>13</sup>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Vestibular exam <sup>14</sup>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Vision exam <sup>15</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Peripheral neuropathy <sup>16</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Arthralgias <sup>17</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Depression <sup>18</sup>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
EKG <sup>19</sup>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>*Important: Monitoring recommendations may change if treatment regimen or patient status changes. A box indicates monitoring activity is recommended. Check box when activity is completed.</b>																			
<ol style="list-style-type: none"> <li>Collect three AFB smear and culture specimens every 2 weeks until smear conversion, and then 2-3 specimens monthly until cultures have converted to negative. Once cultures have converted, obtain at least 1 specimen monthly throughout therapy.</li> <li>Obtain baseline CXR and monitor q 3 months during the first year and q 6 months in the second year of treatment.</li> <li>Monitor weight monthly and adjust medications as needed.</li> <li>Monitor for symptoms monthly.</li> <li>Obtain first- and second-line DST results at baseline. Repeat if patient on RIPE and remains culture positive prior to MDR-TB Rx, and again if patient fails to convert culture after 3 months on treatment.</li> <li>Obtain weekly for first month, then monthly for patients on linezolid.</li> <li>Obtain creatinine at baseline and monthly while patient is on an injectable agent.</li> <li>LFIs at baseline and then monthly while patient is on PZA, ethionamide or PAS.</li> <li>K+, Ca++, and Mg++ at baseline and monthly while patient is on an injectable agent.</li> <li>Therapeutic drug levels (TDM) should be obtained for patients receiving cycloserine after 2 weeks on therapy and if signs of toxicity develop. TDM may be obtained for other drugs as clinically indicated.</li> <li>Monitor TSH at baseline and every 3 months while patient is on ethionamide or PAS, and more frequently if symptoms or abnormalities.</li> <li>Obtain baseline HIV.</li> <li>Perform audiogram at baseline and monthly while patient is on an injectable agent.</li> <li>Perform vestibular exam at baseline and monthly while patient is on an injectable agent.</li> <li>Perform visual acuity plus color discrimination exams at baseline and monthly while patient is on ethambutol or linezolid.</li> <li>Monitor for peripheral neuropathy at baseline and monthly while patient is on linezolid and as clinically indicated for patients on fluoroquinolones.</li> <li>Monitor for arthralgias at baseline and monthly while patient is on PZA or fluoroquinolone.</li> <li>Monitor for depression, agitation, or mental status change at baseline and monthly while patient on cycloserine.</li> <li>Obtain EKG at baseline and at least 2, 12, and 24 weeks for patients on bedaquiline and at baseline and after treatment start for patients on fluoroquinolones as clinically indicated.</li> </ol>																			

Adapted from a checklist developed by the California Department of Public Health TB Control Branch, MDR-TB Service

MONITORING & CASE MANAGEMENT



# Tool 4: Laboratory Flow Sheet

	<b>DATE:</b>								
<b>HEME</b>	WBC								
	Hgb/Hct								
	Platelets								
<b>Chemistry</b>	Na+								
	K+								
	Cl-								
	CO <sub>2</sub>								
	Ca <sup>++</sup>								
	Mg <sup>++</sup>								
	Total Bili								
	Glucose								
	BUN								
	Creatinine								
	Uric Acid								
	Alk Phos								
	AST (SGOT)								
	ALT (SGPT)								
	T. Protein								
	Albumin								
<b>ABG</b>	PH								
	PaO <sub>2</sub>								
	PaCO <sub>2</sub>								
	HCO <sub>3</sub>								
	O <sub>2</sub> Sat								
<b>Urine</b>	Spec. Gravity								
	pH								
	Ketone								
	Glucose								
	Protein								
	Heme								
	Cr Clearance								
<b>Other</b>	TSH								
	PT/PTT								
	HgbA1C								
	CD4								
	Viral Load								
	Pregnancy								
<b>Drug Levels</b>									

Revised September 2015. Adapted from a laboratory flow sheet developed by the Los Angeles County TB Control Program.

MONITORING & CASE MANAGEMENT



# Tool 6: Hearing and Vestibular Screening Flow Sheet

Date	Change in hearing, ringing or fullness in ears?	Dizzy, weak or unsteady?	Romberg	Walking	Heel-to-Toe Walk	Audiogram		Signature	Comment/Action
						Left	Right		
Baseline	Left ear: Y / N Right ear: Y / N	Yes / No	Normal Loss of balance	OK Weaves Staggers	Does well Jerky Hesitates Sways	WNL Abn Stable	WNL Abn Stable		
	Left ear: Y / N Right ear: Y / N	Yes / No	Normal Loss of balance	OK Weaves Staggers	Does well Jerky Hesitates Sways	WNL Abn Stable	WNL Abn Stable		
	Left ear: Y / N Right ear: Y / N	Yes / No	Normal Loss of balance	OK Weaves Staggers	Does well Jerky Hesitates Sways	WNL Abn Stable	WNL Abn Stable		
	Left ear: Y / N Right ear: Y / N	Yes / No	Normal Loss of balance	OK Weaves Staggers	Does well Jerky Hesitates Sways	WNL Abn Stable	WNL Abn Stable		
	Left ear: Y / N Right ear: Y / N	Yes / No	Normal Loss of balance	OK Weaves Staggers	Does well Jerky Hesitates Sways	WNL Abn Stable	WNL Abn Stable		
	Left ear: Y / N Right ear: Y / N	Yes / No	Normal Loss of balance	OK Weaves Staggers	Does well Jerky Hesitates Sways	WNL Abn Stable	WNL Abn Stable		
	Left ear: Y / N Right ear: Y / N	Yes / No	Normal Loss of balance	OK Weaves Staggers	Does well Jerky Hesitates Sways	WNL Abn Stable	WNL Abn Stable		

**NOTE:** If changes from baseline noted during monthly screening, inform treating clinician and refer for further evaluation.

Adapted from the Texas Center for Infectious Disease Hearing/Vision/Vestibular Report

# Resources

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## MONITORING THROUGHOUT TREATMENT

### Screening for depression and psychosis

*Beck Depression Inventory* (available in English and in Spanish)  
Harcourt Assessment, San Antonio, TX; <http://www.pearsonclinical.com/psychology/products/100000159/beck-depression-inventoryii-bdi-ii.html>

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*Personal Health Questionnaire Depression Scale* (PHQ-9)  
[http://cqaimh.org/pdf/tool\\_phq9.pdf](http://cqaimh.org/pdf/tool_phq9.pdf)

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*Zung Self-Rating Depression Scale*  
<http://healthnet.umassmed.edu/mhealth/ZungSelfRatedDepressionScale.pdf>

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*Mental Health Assessment Tool*—Heartland National Tuberculosis Center (2013)  
[http://www.heartlandntbc.org/assets/products/mental\\_health\\_screening\\_tool.pdf](http://www.heartlandntbc.org/assets/products/mental_health_screening_tool.pdf)

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*Inventory of Depressive Symptomatology (IDS) and Quick Inventory of Depressive Symptomatology (QIDS)*  
<http://www.ids-qids.org/>

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*Nursing protocol for preventing psychiatric adverse events associated with cycloserine*—Utah Department of Health (2010)  
[http://health.utah.gov/epi/diseases/TB/guidelines/nursing\\_protocol.pdf](http://health.utah.gov/epi/diseases/TB/guidelines/nursing_protocol.pdf)

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## PATIENT-CENTERED CARE AND ENSURING ADHERENCE TO TREATMENT

### Providing the injectable agent

*Administration of Amikacin Injection*, Heartland National TB Center  
[http://www.heartlandntbc.org/assets/products/administration\\_of\\_amikacin\\_injection.pdf](http://www.heartlandntbc.org/assets/products/administration_of_amikacin_injection.pdf)

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*Administration of Capreomycin Injection*, Heartland National TB Center  
[http://www.heartlandntbc.org/assets/products/administration\\_of\\_capreomycin\\_injection.pdf](http://www.heartlandntbc.org/assets/products/administration_of_capreomycin_injection.pdf)

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Capreomycin package insert:  
[http://www.akorn.com/documents/catalog/package\\_inserts/17478-080-50.pdf](http://www.akorn.com/documents/catalog/package_inserts/17478-080-50.pdf)

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*Outpatient infusion therapy for MDR-TB: A practical guide* (2004) New Jersey Medical School National Tuberculosis Center.  
<http://globaltb.njms.rutgers.edu/downloads/products/InfusionTherapy.pdf>

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## Patient Education

For patient information sheets in multiple languages on some of the second-line anti-TB medications (CFZ, ETA, PAS, levofloxacin, MFX, pyridoxine) see British Columbia Centre for Disease Control website:

<http://www.bccdc.ca/health-info/diseases-conditions/tuberculosis/more-resources>

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For a patient education flip chart, see:

<https://drtbnetwork.org/mdr-tb-patient-education-flipchart>

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## Patient Disclosure/Consent Examples

*Disclosure and consent for second-line drug therapy for treatment of TB disease:*

Texas Department of State Health Services (2007)

[www.dshs.state.tx.us/idcu/investigation/forms/TB-411.pdf](http://www.dshs.state.tx.us/idcu/investigation/forms/TB-411.pdf)

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*Consent for treatment of TB (2nd-line medications)*

[http://health.utah.gov/epi/diseases/TB/forms/atbd/consent\\_secondline.pdf](http://health.utah.gov/epi/diseases/TB/forms/atbd/consent_secondline.pdf)

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## Economic Support (Health Care Coverage, Incentives and Enablers, Homeless)

National Immigration Law Center: [www.nilc.org](http://www.nilc.org)

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Centers for Disease Control and Prevention. CDC's *Self-Study Module 6: Managing Tuberculosis Patients and Improving Adherence* has section on incentives and enablers.

<http://www.cdc.gov/tb/education/ssmodules/pdfs/module6v2.pdf>

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*Homelessness and TB Toolkit*, Curry International Tuberculosis Center

<http://www.currytbcenter.ucsf.edu/homelessnessandtbtoolkit/index.html>

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## CONTINUITY OF CARE

### Interjurisdictional Transfers

Centers for Disease Control and Prevention: Process for international notification of TB cases

<http://www.cdc.gov/tb/programs/international/default.htm>

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CureTB: 619-542-4013 [http://www.sandiegocounty.gov/hhsa/programs/phs/cure\\_tb/](http://www.sandiegocounty.gov/hhsa/programs/phs/cure_tb/)

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TBNet: 512-327-2017 <http://www.migrantclinician.org/services/network/tbnet.html>

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### Incarcerated Patients

ICE Health Service Corps, Public Health, Safety, and Preparedness Unit: 202-732-4542 or 202-732-3467

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*Tuberculosis Case Management for Undocumented and Deportable Inmates/Prisoners/ Detainees in Federal Custody.* Available at: [http://tbcontrollers.org/docs/corrections/Federal\\_TBCaseMgmt\\_for\\_Undoc-Deport\\_Corrections\\_v3\\_08-12-2014.pdf](http://tbcontrollers.org/docs/corrections/Federal_TBCaseMgmt_for_Undoc-Deport_Corrections_v3_08-12-2014.pdf)

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## INFECTION CONTROL

CDC's *Guidelines for Preventing the Transmission of Mycobacterium tuberculosis in Health-Care Settings*, MMWR 2005; 54 (No. RR-17), available at: [www.cdc.gov/mmwr/preview/mmwrhtml/rr5417a1.htm](http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5417a1.htm)

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Curry International Tuberculosis Center, 2011: *Tuberculosis Infection Control: A Practical Manual for Preventing TB* <http://www.currytbcenter.ucsf.edu/products/view/tuberculosis-infection-control-practical-manual-preventing-tb-printed-book>

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### Transportation – Commercial Airline Flights

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# Adverse Reactions

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# Adverse reactions and toxicity should be anticipated with any treatment course for drug-resistant TB.

## Introduction

Treatment of drug-resistant tuberculosis (TB) requires 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 in anticipation of or because of fear of a reaction. Even some elderly or very ill patients will tolerate complex regimens for drug-resistant TB. By contrast, others may have serious difficulty tolerating relatively simple regimens.

Patients should be well informed about their anti-tuberculosis treatment regimens so that they can be recruited as partners invested in the success of 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 emphasize that having enough effective drugs in the regimen is essential to achieving a cure.** Patients should know that while side effects may be inevitable, they 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.

Quickly recognize and respond to the symptoms a patient expresses. Careful assessment may allow some symptoms to be attributed to causes other than medication toxicity. Most patients will be willing to continue medication despite side effects when: 1) they understand the benefit of the medication; 2) they know that many of these symptoms improve after the first several weeks; and 3) they 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, do not reduce the dose of a drug unless this can be done without compromising the

efficacy of the treatment regimen. In some cases, minor drug reactions and discomfort may persist and will have to be tolerated to ensure the success of the regimen. In some instances, serious adverse events will need to be tolerated in order to cure multidrug-resistant (MDR) or extensively-drug-resistant (XDR) TB. For example, some patients with severe 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 fail treatment or die of TB.

Patients can be counseled that treating drug-resistant TB is more like cancer chemotherapy than treating a typical infection. Treatment of this life-threatening disease is a marathon, not a sprint, and there may be setbacks. Adverse effects are likely on the way toward the goal of a durable cure. Frequent family meetings to clarify goals and address symptom management can strengthen the provider-patient alliance so important to supporting patients through treatment.

## 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 may be equally troubling. Anorexia with or without nausea, vomiting, and/or the metallic taste caused by ethionamide (ETA) can prevent weight gain or even cause worrisome weight loss. Nausea, vomiting, and anorexia are also consistent with possible hepatotoxicity, so if these symptoms develop, liver enzymes and total bilirubin should be checked.

### Common 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**
- **Diabetic gastroparesis**
- **Pregnancy**

## 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 patients 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. Offer ancillary treatment for symptoms.
- **Pregnancy** should be considered as the possible etiology of nausea and vomiting in the appropriate setting, especially if the symptoms occur after a period of initial tolerance.
- If the patient has TB meningitis, nausea and vomiting might be signs of rising intracranial pressure rather than a drug intolerance issue. Obtain urgent imaging to evaluate for hydrocephalus, and neurosurgical consultation if indicated.

**The following are specific interventions that can be attempted, depending on the drug:**

**ETA** tends to cause more upper GI symptoms such as nausea and vomiting, and **para-aminosalicylate (PAS)** more lower GI symptoms, such as abdominal cramping and diarrhea, though there is often overlap. Patients may tolerate one of these two drugs, but many do not tolerate both together. If ETA or PAS is suspected of causing the symptoms, hold the dose for 3 to 4 days to evaluate whether this helps to alleviate the nausea or vomiting. Advise the patient that this is a test to determine which drug is causing side effects and that the drug will be reintroduced at a lower dose and slowly increased to a therapeutic dose.

If the patient improves off of the medication, 1 drug at a time can be restarted at a lower dose (ETA 250 mg, PAS 2 to 4 grams) to identify if the lower dose is 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 ETA better in the evening (ETA 250 mg in a.m., 500 mg at bedtime; or may only tolerate 500 mg at bedtime). The goal should be to increase the ETA dose to at least 500 mg daily and the PAS dose to at least 6 to 8 grams daily. In some situations it may be best to dose ETA at 500 mg daily or PAS at 6 grams daily if the patient tolerates this, rather than to increase to a dose that cannot be tolerated. This will depend on the patient and the patient's weight. Serum drug levels should be obtained to document whether the level is therapeutic.

**Linezolid (LZD)** may also be associated with nausea and vomiting. If the LZD dose is 600 mg/day, reduction of the dose to 300 mg/day may be considered to improve GI tolerance and is not generally associated with loss of efficacy. Most reports noting efficacy at 300 mg daily were in patients who had the dose decreased after a period of time on the 600 mg dose. A therapeutic level should be documented if the dose is decreased. Some patients require a 400-450 mg daily dose to achieve a therapeutic level. These doses are only available with the liquid formulation of the drug.

**Fluoroquinolones, clofazimine (CFZ), and bedaquiline (BDQ)** may also cause nausea or vomiting. The dose of fluoroquinolones such as **levofloxacin (LFX)** or **moxifloxacin (MXF)** should not be decreased because of nausea. The fluoroquinolones are crucial drugs in the treatment regimen and the bactericidal effects are dose-dependent. If GI toxicity is present and the dose of **CFZ** is more than 100 mg daily, it should be reduced to 100 mg daily. **BDQ** may also be associated with nausea and vomiting. There is no information currently about the impact of BDQ dose reduction on the severity of GI side effects or the efficacy of the drug. The dose of BDQ should not be changed.



**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 for GI symptom management (adult doses):**

- **Promethazine** (Phenergan) 12.5 to 25 mg PO, IV, or PRN 30 minutes before the dose and every 6 hours as needed.
- **Ondansetron** (Zofran) 8 mg PO 30 minutes before the dose. The dose can be repeated after 8 hours.
- **Metoclopramide** (Reglan) 10 mg PO or IV every 6 hours as needed.
- **Lorazepam** (Ativan) 0.5 mg sublingual 30 minutes before the dose; it can be helpful for patients who have developed anticipatory nausea because of its anxiolytic and anterograde amnesia effects.
- A number of other antiemetics are also available. Trying another agent may be helpful in some patients when the previously listed options do not work or are not available in your pharmacy.
- Try giving the responsible medication at **bedtime**; some symptoms from adverse effects may be more tolerable during sleep.
  - This is relatively easy when 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. Video DOT can be considered to monitor adherence, because even the most adherent patients may have difficulty taking a medication that predictably makes them feel bad.
- **Give a light snack** (crackers or toast, tea, a ginger drink, or soda) before medications.
- **Space the medications** during the day to lessen the pill burden. This can easily be done during hospitalization, but may represent a challenge in the community setting.
- **Treat gastritis or acid reflux.** Proton pump inhibitors or H<sub>2</sub>-receptor blockers may be helpful. Avoid using antacids or sucralfate within 2 hours of the dose of fluoroquinolones because these agents may interfere with fluoroquinolone absorption.
- **Minimize use of nonsteroidal anti-inflammatory drugs (NSAIDs).** This may be difficult if the patient also has arthralgia and myalgia from other medications. Try acetaminophen with caution as it may increase the risk of hepatotoxicity from other antituberculous medications.
- Diagnose and treat co-existing *Helicobacter pylori* infections.
- **Encourage hydration.** Sports drinks with electrolytes may be helpful (but note that the glucose content of these drinks is 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 before a regimen is abandoned.
- In refractory cases, as a last resort, a percutaneous endoscopic gastrostomy (PEG) tube may be effective and allow treatment to continue despite persistent symptoms.
- For patients who have developed a psychological aversion to swallowing pills, cognitive behavioral therapy may be helpful.
- In most instances, treatment should include at least 4 active drugs likely to be effective.
- **Consultation with an expert is especially important when regimen changes are considered.**

*Eliminate (or at least try to minimize) alcohol consumption to lessen GI irritation and the risk of hepatotoxicity.*

## 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 3, “Dose Escalation (Drug Ramping)” in **Chapter 4, Treatment**.

- Fluoroquinolones and LZD may also cause loose stools or diarrhea, along with increased flatulence. This usually improves after the first several weeks, 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 to 4 mg PO can be used initially and then 1 to 2 mg after each loose stool to a maximum of 8 to 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 and LZD are key drugs in the treatment regimen.
- Diarrhea is one of the most common side effects of LZD, and as with nausea and vomiting, may be ameliorated with LZD dosage reduction from 600 mg/day to 300-450 mg/day.

### If the diarrhea is severe, other etiologies may include:

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

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

## 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 alanine aminotransferase (ALT) 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.
- The ALT is more specific for hepatocellular injury than the aspartate aminotransferase (AST). Elevations in the AST may also indicate injury to the muscle, heart, or kidney. However, elevation of either the AST or ALT should raise concerns about drug-induced hepatotoxicity. Once that possibility is excluded, other causes of the elevated hepatic enzymes, such as alcohol use, should be pursued.
- **If elevated liver enzymes and/or bilirubin are detected, in addition to drug-induced hepatotoxicity, consider other causes such as gallstones or viral hepatitis. 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 and there is no evidence of jaundice (total bilirubin < 3.0 mg/dl), continue the medications using strategies for managing nausea and vomiting and observe carefully. If symptoms continue, repeat liver enzymes again to exclude hepatotoxicity. If the bilirubin is increased but the hepatocellular enzymes are only mildly elevated, this may indicate hepatobiliary obstruction rather than drug-induced liver injury. An evaluation for causes of direct and indirect hyperbilirubinemia should be done. If the bilirubin is greater than 3.0 mg/dl, generally, hepatotoxic medications should be stopped.
- If both bilirubin and alkaline phosphatase are elevated (cholestatic pattern), rifampin (RIF) is the most likely etiology of the liver injury. If the liver injury is predominately transaminitis (elevated AST/ALT), PZA and isoniazid (INH) are the most likely causes of liver injury. However, there is overlap in the pattern of liver injury caused by these drugs, and all individually or in combination may contribute to hepatotoxicity.
- If the enzymes are more than 3 times the upper limit of normal in the presence of symptoms consistent with hepatotoxicity or more than 5 times the upper limit of normal even in the absence of any symptoms, 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, LFX, or cycloserine [CS]), then these can be continued. If not, then all anti-tuberculosis medications

should be held. Fluoroquinolones are rarely hepatotoxic, but MFX has occasionally been implicated.

- Monitor the liver enzymes and bilirubin weekly.
  - If all TB medications have been held, when liver enzymes fall to less than twice normal (some experts prefer to wait until the enzyme levels normalize or return to baseline), one potentially hepatotoxic drug (along with other medications that are not hepatotoxic) can be restarted.
  - If the first potentially hepatotoxic drug is successfully re-introduced, then the remaining potentially hepatotoxic medications should be reintroduced one at a time.
  - Carefully observe for clinical reactions and repeat liver enzymes and bilirubin at least twice weekly until the medication has been taken for at least a week and liver enzymes and bilirubin 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 one medication may be responsible for the hepatotoxicity.
- Monitor liver enzymes at least monthly for the remainder of the treatment course.

Patients with underlying liver disease are at increased risk of drug-induced liver injury. HIV-positive individuals, especially those receiving concomitant antiretroviral therapy (ART), have had an increased incidence of hepatitis in some studies. Several reports of HIV-positive persons with hepatitis C noted hepatotoxicity in over 20% of cases.

ART may be associated with drug-induced hepatitis, with the incidence depending on the individual drugs utilized. Immune reconstitution syndrome with granulomatous hepatitis from disseminated TB may be seen in patients with AIDS after starting ART. Hepatitis C, an elevated baseline serum bilirubin, low CD4 cell count and fluconazole therapy have all been associated with hepatitis. The risk of liver injury from anti-tuberculosis drugs in patients with hepatitis B is variable. It appears to be increased in those with chronic active infection compared to those who are only seropositive.

**If at least 3 medications remain in the treatment regimen that are not hepatotoxic, then these can be continued in the face of elevated liver function tests.**

# Dermatologic reactions

## Maculopapular rash and pruritus

Maculopapular rash and pruritus are common early side effects of essentially all anti-tuberculosis drugs. 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.

**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.**

Under these circumstances, seek consultation with a TB expert, a dermatologist, and possibly an allergist for desensitization (based on availability) prior to rechallenge with any of the anti-tuberculosis medications.

- 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 to 50 mg PO, IV, or IM given before the medication, and then every 4 to 6 hours as needed, 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 to 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 to 20 mg/day) for several weeks can be tried if other measures are not helpful.

### 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 newly-added 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 common problem with CFZ.
- Hypothyroidism.
- Acneiform lesions may flare with the use of INH, ETA, CFZ, and corticosteroids. This will usually resolve after several months. Standard topical acne treatment may be helpful in the meantime.
- Unusual skin lesions may be associated with HIV infection.

## Flushing reactions

Flushing and/or itching reactions of the skin without a rash usually involve the face and scalp, and occur 2 to 3 hours after medications. Redness and watering of the eyes may also occur. This is usually due to RIF or PZA and is usually mild and resolves 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, as well as possible hot flashes, palpitations, or headache 2 to 3 hours after consuming tyramine-containing foods (cheese, cured meats, soy sauce, fermented foods, red wine), certain fish (tuna), and soy products. **Advise patients not to ingest foods that precipitate the reaction while they are receiving INH.**

## Photosensitivity and hyperpigmentation

Warn patients about the potential for photosensitivity if they are taking PZA, CFZ, or fluoroquinolones. Caution patients to limit sun exposure and to use sunscreens. Photosensitivity may persist for prolonged periods even after the causative drug is stopped.

Pseudojaundice (brownish discoloration of the skin) may occur with rifabutin (RFB). The sclera is clear and the bilirubin and other liver enzymes are normal.

Hyperpigmentation, often worse in dark-skinned individuals, can also occur with CFZ and may markedly increase with sun exposure. The hyperpigmentation improves after discontinuation of the drug.

*Caution patients to limit sun exposure and to use sunscreen.*

## Lichenoid 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 can 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 (SM), and CS have all been identified as causing these lesions.

## Hives and urticaria

Hives and urticaria may be caused by essentially any drug in an anti-tuberculosis treatment regimen. They are more commonly due to INH, RIF, PZA, ETA, fluoroquinolones, and EMB but can also be due to newer agents such as LZD and BDQ.

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 in the regimen one at a time (Table 1).** 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, consider a desensitization attempt (Table 2).

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.**

**The patient can be premedicated with Benadryl 25 mg with or without a small dose of prednisone (10–20mg) 30 minutes prior to the first dose when using either the rechallenge approach or the desensitization process. If the initial dose is well tolerated, give 25 mg of Benadryl (but not prednisone) 30 minutes prior to the second dose. If the medication is well tolerated, the third dose should be given without premedication. The dose can be increased while using the premedication following the tables below. The use of premedication makes rechallenge a bit easier for the patient and the health department when this needs to be done in the outpatient setting.**

**Premedication does not prevent a rash but typically makes the reaction less severe and may blunt associated systemic effects, especially the most serious ones. Some patients may benefit from a short course of low-dose steroids if the resulting clinical reaction is only a mildly pruritic rash.**

TABLE 1.

### Suggested Drug Rechallenge Doses Following Non-anaphylactic Allergic Reaction\*

Drug	Dose – Day 1	Dose – Day 2	Dose – Day 3
INH	50 mg	300 mg	
RIF	75 mg	300 mg	600 mg
PZA	250 mg	1 gram	full dose
ETA	125 mg	375 mg	500–750 mg
CS	125 mg	250 mg	500–750 mg
EMB	100 mg	500 mg	full dose
PAS	1 gram	4 gram	6–8 grams
SM	125 mg	500 mg	full dose

\* 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:			
Amikacin (AK)	125 mg	500 mg	full dose
Capreomycin (CM)	125 mg	500 mg	full dose
Fluoroquinolone	50 mg	200–250 mg	full dose

**If the initial reaction was severe, rechallenge should be done using a smaller dose of medication (1/10th) of the Day 1 dose listed in Table 1, and subsequent doses increased carefully. Rechallenge should always be accomplished in a setting where a healthcare provider can respond to the reaction.**

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 (Table 2).

TABLE 2.

### Oral desensitization for INH, RIF, and EMB

Time from start (hour:minute)	Dose of INH* (mg)	Time from start (hour:minute)	Dose of RIF** (mg)	Dose of EMB** (mg)
0:00	0.1	0:00	0.1	0.1
0:15	0.5	0:45	0.5	0.5
0:30	1	1:30	1	1
0:45	2	2:15	2	2
1:00	4	3:00	4	4
1:30	8	3:45	8	8
2:00	16	4:30	16	16
2:30	32	5:15	32	32
3:30	50	6:00	50	50
5:30	100	6:45	100	100
7:30	150	7:30	150	200
8:30	150	11:00	300	400
17:30	150			
Early next a.m.	150 bid x 3 days		300 bid x 3 days	400 tid x 3 days

\* Holland 1990

\*\* Matz 1994

Oral desensitization protocols should only be implemented in a hospital or in a clinical area with the ability to monitor and respond to possible anaphylaxis, and in clinical situations when the drug is determined essential to success of therapy. Because INH and RIF are such important drugs, desensitization is most commonly attempted with these two medications.

Steroid therapy is often used with desensitization and then tapered off over 2 to 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 such as fever and/or mucous membranes, as occurs with Stevens-Johnson syndrome or toxic epidermal necrolysis.**

## Severe drug reactions

### Systemic reactions

Fortunately, anaphylaxis is rare with anti-tuberculosis medications, but does occur. Anaphylaxis typically 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 signs and 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 and ideally with the assistance of an allergist/immunologist. Once an agent is identified as causing anaphylaxis, **do not include this drug in the treatment regimen. Also, do not attempt desensitization to these agents.**

Reactions associated with systemic toxicity—high fever, widely distributed urticaria, and bulla, along with mucous membrane involvement—are characteristic of Stevens-Johnson syndrome. When there is extensive sloughing of skin, toxic epidermal necrolysis is likely. These should be distinguished from staphylococcal scalded skin 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 about the diagnosis. INH, RIF, EMB, SM, ofloxacin, LZD and CS have been reported as causative agents. **If a drug is identified as responsible for one of these reactions, it should never be used again.**

*Anaphylaxis typically presents within minutes of medication dosing.*

### Hypersensitivity syndrome (DRESS)

The drug-induced hypersensitivity syndrome has been described with several of the anti-tuberculosis medications. Recently many of the patients with this group of reactions are identified as having “drug reaction with eosinophilia and systemic symptoms” (DRESS).

- The TB medications most commonly associated with DRESS are **RIF, INH** and **EMB**.
- Some persons experiencing DRESS may be receiving treatment with both allopurinol and first-line antituberculous medications. Allopurinol has been used to decrease the elevated uric acid which is characteristically seen in persons taking **PZA**. Although most patients with elevated uric acid do not need treatment other than adequate hydration, if there is a need to address elevated uric acid levels, allopurinol should not be used.
- A variety of other drugs has also been implicated, including sulfonamides, dapsone, minocycline, and many of the antiepileptic agents. Skin biopsy and liver biopsy may help to establish the diagnosis.

DRESS is rare and can be life-threatening. The syndrome includes a dramatic drug rash along with hematologic abnormalities (eosinophilia, atypical lymphocytosis), lymph node enlargement, involvement of organ systems (liver, kidney, lung) and significant systemic symptoms. DRESS usually begins **2 to 8 weeks after the drug exposure**. Fever, often the first manifestation, may be as high as 40 degrees centigrade and is accompanied by malaise, lymph node enlargement, and rash. The rash begins as a morbilliform eruption, but progresses to a diffuse, confluent eruption with infiltrative erythema. Rash usually starts on the trunk, upper extremities, and face. The face may become edematous, facial involvement is symmetrical and associated with erythema that is persistent. The mucous membranes are involved in up to one-third of patients. The rash usually progresses to involve the lower extremities and often involves more than half of the body. The erythema may progress to vesicles, pustules, diffuse dermal edema and eventual exfoliative dermatitis.

Lymphadenopathy is a prominent finding and is present in up to 50% of patients. Biopsy usually shows benign lymphoid hyperplasia. Organ involvement most frequently includes the liver but may less frequently involve the kidneys or lungs. Liver involvement may manifest as liver enlargement with jaundice but most often is asymptomatic. If the offending drug is discontinued, the abnormalities are usually mild and resolve quickly. Severe involvement may occur and progress to liver failure. Renal involvement is manifested as interstitial nephritis and has been associated with co-administration of the drug allopurinol. Pulmonary involvement may include cough, fever, and dyspnea with hypoxemia. Interstitial pneumonitis along with pleural effusion may be seen on the chest radiograph. Rare cases of multiple additional organ involvement have been noted.

Laboratory abnormalities include mildly elevated ALT and/or alkaline phosphatase in over 80 percent of patients, leukocytosis with eosinophil counts > 700 in most, and atypical lymphocytosis in 30 to 70 percent of patients. If the kidney is involved, there may be an increase in the creatinine, low-grade proteinuria, and eosinophils in the urine.

The skin eruption and other abnormalities generally resolve slowly once the drug is withdrawn. It may take more than 2 months before the patient experiences complete resolution; remissions and relapses not related to drug therapy may occur. DRESS has been associated with reactivation of human herpes virus 6 (HHV-6) and cutaneous eruptions may coincide with reactivation of the virus.

Management of DRESS is based on stopping potential offending drugs and avoiding the addition of new medications until the reaction has resolved. This may not be possible with TB patients because they need to be treated for TB, especially if infectious and if steroid therapy is required to control DRESS. It is sometimes not possible to distinguish a reaction as due to the addition of a new drug or due to a flare of the underlying reaction. Stopping and starting medications or treating with a weak regimen can lead to drug resistance and treatment failure, so the balance of preventing harm and providing treatment requires significant clinical skill and experience. **Most experts would not recommend rechallenge once a drug is identified as the causative agent.**

An experienced TB clinician should be consulted in addition to a dermatologist. High potency topical corticosteroids applied 2 to 3 times daily are preferred to systemic steroids, but can be used for only 1 to 2 weeks. Systemic steroids, sometimes in high dose, may be needed for an extended period of time.

## RIF hypersensitivity reactions

A variety of reactions have been reported with RIF therapy. One of these is a **flu-like syndrome** that is characterized by fever, chills, headache, and bone pain. Symptoms begin 1 to 2 hours after the dose of medication and resolve spontaneously after 6 to 8 hours. Typically the syndrome develops after several months of therapy and is more common with intermittent therapy. Many patients are able to tolerate RIF if the dosing interval is changed from intermittent to daily.

For most other hypersensitivity reactions, 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**

## Hematologic abnormalities

Hematologic abnormalities may represent underlying disease, either a comorbid condition such as chronic renal failure, HIV, alcoholism with nutritional deficiencies leading to anemia or a malignancy. *M. tuberculosis* can be directly responsible for hematological abnormalities such as seen with disseminated TB involving the bone marrow directly or related to decreased bone marrow production due to chronic illness from *M. tuberculosis*. Gastrointestinal TB may result in anemia due to blood loss from the GI tract, and pulmonary disease associated with hemoptysis may also be associated with a significant anemia.

Hematological abnormalities due to drug toxicity can involve any cell line and can be related to most of the medications. However, the most common causes of hematological abnormalities are related to INH, RIF and LZD, any of which may cause abnormalities in all cell lines. Most TB medications can occasionally be associated with hematologic abnormalities. See Table 3.

TABLE 3.

**Hematologic Abnormalities Associated with Anti-Tuberculosis Drugs**

Drug	WBC ↓	WBC ↑	PMN ↓	Pit ↓	Pit ↑	Pan ↓	Red cell aplasia	DIC or Coag abnl	Hgb ↓	Hemolytic anemia	Eos ↑	Aplastic anemia
Amikacin											X	
Amox/clav	X		X	X	X				X	X	X	
Capreomycin	X	X									X	
Clofazimine	X						X		X		X	
Cycloserine									X			
Ethambutol	X		X	X							X	
Ethionamide	X			X								
Imipenem	X	X	X	X	X	X		X	X	X	X	
Isoniazid	X		X	X		X		X	X	X	X	X
Kanamycin												
Levofloxacin	X	X		X					X	X	X	X
Linezolid	X			X		X			X			
Moxifloxacin	X	X	X	X	X			X	X	X	X	
PAS				X								
Pyrazinamide				X					X			
Rifabutin			X	X								
Rifampin	X	X	X	X				X	X			
Streptomycin	X			X		X		X				

ADVERSE REACTIONS

# 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, loss of sensation, loss of ankle reflexes, and weakness of dorsiflexion of the toes may occur. 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**, **ETA**, **CS**, and **LZD**. Fluoroquinolones and EMB have rarely been associated with the development of neuropathy, although neuropathy has recently been added as a “black box” warning for the fluoroquinolones.

**Neuropathy is more likely to occur in patients with diabetes, alcoholism, HIV infection, hypothyroidism, pregnancy, poor nutrition, 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 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 INH, ETA, CS, or LZD. If symptoms develop or progress, doses of 150 mg may be tried; however, pyridoxine-related neuropathy has been reported with doses greater than 100 mg daily and some experts would not go beyond 100 mg. Doses greater than 200 mg should not be used.

*There are rare reports of neuropathy attributed to pyridoxine in doses of 100 mg or greater.*

Neuropathy associated with LZD usually tends to occur after 4 months of therapy and is likely dose-related. Initial use of the 600 mg once-daily LZD dosing followed by a decreased dose of 300 to 450 mg daily (or alternatively 600 mg 3 or 4 times weekly if toxicity develops) usually allows continuation of LZD in the treatment regimen. Patients must be followed closely once peripheral neuropathy develops, as symptoms may not improve or may even progress when LZD is discontinued. The degree of tolerable neuropathy for an individual patient must be balanced against alternative medications available for treatment, the toxicities of these medications, and the opportunity for a lasting cure of drug-resistant TB.

### Additional interventions should include:

- **Correct vitamin and nutritional deficiencies.**
- **Address additional medical problems.**
- **Evaluate and correct electrolytes.**
- **Identify and stop (if possible) other medications that may cause peripheral neuropathy.**
- **Consider whether the dose of ETA or CS can be reduced without compromising the regimen.** Monitor serum drug concentrations if doses are lowered.

- **Physical therapy may be helpful.**
- **NSAIDs or acetaminophen may be helpful.**
- **Gabapentin** (Neurontin) has been helpful for many patients. 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 in 3 divided doses, 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. The dose should be decreased in patients with renal insufficiency.
- **Pregabalin** (Lyrica) may be tried in patients who do not respond to gabapentin. The starting dose is 50 to 75 mg per day in two divided doses, with escalation to the usual effective dose of 150 to 300 mg twice daily.
- **A low dose of tricyclic antidepressant** (amitriptyline [Elavil] 25 mg PO at bedtime) **can be tried if there are no contraindications.** The dose of amitriptyline may be increased (to 150 mg maximum) if lower doses are not helpful. However, LZD cannot be given with tricyclic drugs or selective serotonin reuptake inhibitors (SSRIs) due to its mild monoamine oxidase (MAO) activity contributing to the risk of the serotonin syndrome.
- **Carbamazepine** (Tegretol), an anticonvulsant, at 100 to 400 mg PO BID, can be tried. Blood dyscrasias and elevated liver function may complicate therapy; a complete blood count (CBC) and liver enzymes should be routinely monitored in patients on this medication.
- **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 relatively mild symptoms should not lead to the discontinuation of a medication unless unusual circumstances are present.

- Give medication at a time of day that minimizes the effects; for example, at bedtime in patients who experience drowsiness. Consult the patient as to timing of drug ingestion.
- Analgesics or NSAIDs may help headache.
- Limiting caffeine intake in the evenings may improve sleep disturbances.
- Exercise may be effective.

**Support from caregivers and family members and acceptance of the patient's mood changes and irritability will make these side effects more tolerable.**

## Psychiatric effects

### Depression

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

Medication-induced depression is especially a problem with CS and ETA. CS-related depression may be severe and is sometimes associated with suicidal ideation. Patients on CFZ who experience hyperpigmentation from the drug have been known to develop a reactive depression due to the changes in skin coloration.

*CS should not usually be part of an initial treatment regimen if significant depression is present.*

- Assess and address underlying psychological/social issues.
- Assess patients for coexisting substance abuse and refer to counseling if appropriate.
- Always be alert to indications of suicidal ideation in patients with depression, especially those on CS or ETA. If depression is significant or suicidal ideation is present, both CS and ETA must be stopped, and the patient observed carefully with psychological support until they are stable.
- When depression is significant, give a trial of antidepressant therapy and/or request psychiatric consultation. **Note: tricyclic antidepressants and SSRIs should not be given to patients on LZD, because of the risk of serotonin syndrome.**
- Obtain CS levels. Reduce the dose if levels are >35 mg/dl. Adjust dosing to achieve levels toward the lower end of the target range (peak level at 2 hours post dose target range is 20–35 mg/dl).
- Reduce the dose of CS and ETA from 750 mg daily to 500 mg daily to see if depression is lessened.
- If depression progresses or is not improved by a trial of antidepressant therapy, discontinue CS and, possibly, ETA as well.
- CS 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 CS and ETA.
- INH has been associated with depression, reported as severe in several case reports. Withdrawal of the drug is associated with rapid recovery.

### Psychosis

- If psychosis is present, hospitalize the patient and put him/her under 24-hour surveillance.
- Obtain psychiatric consultation.
- Hold all medications that possibly contribute until the patient stabilizes.
- **The most likely drugs to cause psychosis are CS and fluoroquinolones; INH can occasionally be implicated.**
- Pyridoxine (100–150 mg) should be given if not already part of the treatment.
- Start antipsychotic therapy (for example, haloperidol [Haldol] PO, IV, or IM 0.5 to 5 mg) at the earliest sign of psychosis.
- If CS is part of the treatment regimen, stop CS and obtain a random CS level.

- When symptoms resolve, the medications least likely to have contributed to the symptoms should be reintroduced first, one at a time, with careful observation.
- If no alternative drug is available, CS may be restarted at low dose. Do not increase to the previous dose without first checking a serum drug concentration. If any recurrence of psychotic behavior occurs, promptly and permanently discontinue CS.
- When the patient has stabilized, all medications have been successfully restarted, and all symptoms have resolved, taper the antipsychotic drugs with careful observation of the patient.
- Consider and address all other etiologies, especially illicit drugs, alcohol, and medical problems (meningitis, hypothyroidism, and depression).
- Some patients may tolerate CS 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 CS 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 CS.
- Obtain psychiatric consultation.
- Initiate antidepressant therapy.
- If the patient is also on INH or ETA, hold these medications and only rechallenge once the patient is stable. INH, if restarted, is given at 300 mg daily. ETA, if restarted, should be given initially at a dose of 250 mg once daily and then increased to 500 mg and finally 750 mg daily if the patient is stable and tolerates the dose escalation.
- If the patient is on a fluoroquinolone, check the serum drug concentration of the fluoroquinolone and lower the dose if the serum concentration is greater than the therapeutic range. Do not decrease the dose if the serum level is therapeutic.
- Keep the patient in the hospital until the risk of suicide has passed.

### Seizures

Immediate steps:

- Hospitalize patient. Ensure adequate ventilation, support cardiac output and protect the airway while treating seizures.
- Hold CS, fluoroquinolones, LZD, INH, imipenem (consider stopping meropenem as well), and initiate anticonvulsant therapy (phenytoin, valproic acid). Monitor anti-epileptic drug levels as drug interactions and synergistic toxicity are possible. If the patient is on CS, obtain a random CS level as seizure activity is closely related to elevated serum CS levels.
- In cases of INH toxicity: If the dose of INH is known, the patient should be treated initially with a slow intravenous bolus of pyridoxine, over 3 to 5 minutes, on a gram per gram basis, equal to the INH dose. If the quantity of INH ingestion is unknown, then consider an initial intravenous bolus of pyridoxine of 5 grams in the adult or 80 mg/kg in the child. If seizures continue, the dosage of pyridoxine may be repeated. It would be rare that more than 10 grams of pyridoxine would need to be given. The maximum safe dose for pyridoxine in INH intoxication is not known. If the patient does not respond to pyridoxine, diazepam may be administered.



- Evaluate for other etiologies of seizures.
- Check serum electrolytes, calcium, and magnesium.

When seizures have resolved, restart medications one at a time, generally with the most effective drug in the regimen first.

- CS should not be restarted unless it is absolutely essential to the regimen. This will not often be the case.
- Continue anticonvulsant therapy during the remainder of therapy for drug-resistant TB.

A history of prior seizures is not an absolute contraindication to the use of CS, fluoroquinolones, LZD, and INH. Do not include CS if an alternative drug is available.

## Serotonin syndrome

**Serotonin syndrome** consists of clinical symptoms and signs that occur in the presence of excess serotonin activity. Three different mechanisms may lead to elevated serotonin levels: 1) inhibition of serotonin metabolism (MAO inhibitor use), 2) blockade of serotonin reuptake at the presynaptic neuron (SSRI and/or tricyclic antidepressant use), or 3) increase in the release of stored serotonin (amphetamine use).

LZD is a weak, reversible, nonselective inhibitor of MAO.

Although LZD alone is not potent enough to cause the serotonin syndrome, it may occur when LZD is given along with medications that increase the serotonin level or when a diet is very high in tyramine (cheese, cured meats, fermented soy products or sauce, red wine). Although this is a rare occurrence, it can be severe and even fatal. Because the syndrome does not resolve unless the offending medications are withdrawn, recognition is imperative.

The clinical picture varies from mild to severe toxicity.

### Serotonin syndrome is characterized by neuromuscular findings.

Recent diagnostic criteria focus on the presence of at least one of the following: clonus, seizure, myoclonus, ataxia, incoordination, jaw-trismus, rigidity, shivering, rigors, nystagmus, tremor or twitching, and hyperreflexia. Additional findings may include tachycardia, fever, mydriasis, diaphoresis, hyperactive bowel sounds, diarrhea, agitation, and delirium.

The syndrome typically develops soon after the introduction of the offending medication or an increase in a dose of a previously used drug.

- A physical exam should focus on assessment for clonus, deep-tendon reflexes, pupil size, mucosal dryness, bowel sounds, and diaphoresis.
- **A good drug history, including the use of any over-the-counter medications, herbal and dietary supplements, and illicit drugs (in addition to any recently prescribed drugs) is an essential part of the evaluation.**
- The differential diagnosis includes anticholinergic poisoning, malignant hyperthermia, and neuroleptic malignant syndrome. The drug history will help to identify the cause.

- Most cases have been associated with the **concomitant use of LZD and an SSRI or tricyclic antidepressant**. The half-lives of these drugs are prolonged, and if LZD therapy is planned, these agents should be withdrawn at least two weeks prior to its use. Observe the patient carefully; there are reports of serotonin syndrome occurring even two weeks after withdrawal of these agents

**If serotonin syndrome is identified, LZD should be discontinued.**

The SSRIs or tricyclics cannot be abruptly stopped and even if discontinued will continue to exert effects due to their long drug half-life. With supportive care and discontinuation of LZD, the syndrome will often resolve within 24 to 48 hours. No controlled trials are available to guide management of more severe forms of serotonin syndrome. Several drugs have been helpful, including the benzodiazepine, lorazepam. Some patients need aggressive management of their cardiorespiratory and thermal abnormalities.

## Ototoxicity (eighth nerve toxicity)

**All of the aminoglycosides and CM are toxic to the eighth cranial nerve and can cause both vestibular and auditory toxicity.**

- Higher doses increase the risk of toxicity. However even patients with serum drug levels that are always in the therapeutic range may develop both auditory and vestibular toxicity.

### Vestibular toxicity

- At least monthly, assess vestibular toxicity. [See **Chapter 8, Monitoring and Case Management** for instructions.]
- Ask the patient about tinnitus and dizziness, and observe the patient closely for unsteadiness.

**Fullness in the ears may be an early symptom of vestibular toxicity. When this is reported, it is sometimes possible to both limit toxicity and continue the injectable agent for another month or more by decreasing the dosing interval to 2 or 3 times a week.**

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 CS, fluoroquinolones, ETA, INH, or LZD. Prior to stopping the injectable agent, evaluate whether these and/or other medications are causing the symptoms. All drugs can be held for several days to see if the symptoms improve. Symptoms of vestibular toxicity generally do not improve rapidly after holding medication, although some improvement may occur after time if the injectable is stopped before significant toxicity occurs. Stopping the injectable should be done only after carefully excluding other causes of the symptoms.

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 often may 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 frequently 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 hearing loss occurs in nearly all patients treated for MDR-TB. High-frequency loss usually occurs first but this rarely has an effect on conversational speech. With continued treatment, 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 to 4 months of treatment, and once the cultures are negative.
- Avoid loop diuretics because they increase eighth nerve toxicity.
- SM has less auditory toxicity than the other injectables, but has more vestibular toxicity.
- One retrospective study suggested that CM might be less toxic than AK.
- Resistance to SM 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 the patient and with an expert in the management of drug-resistant TB.

## 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.
- Check drug levels.
  - The authors have obtained excellent therapeutic benefits while limiting toxicity by adjusting the dose to target peak levels of approximately 25 mcg/mL at 1 hour after intravenous administration or 2 hours after intramuscular injection.
  - Trough levels should be less than 5 mcg/mL or undetectable prior to the next dose.

- For adults over 59 years of age, many experienced clinicians prefer to decrease the dose of the injectable drugs to 10 mg/kg and monitor drug concentrations. Target levels should be the same as for younger individuals.
- For patients with creatinine clearance less than 30 mL/min or those receiving hemodialysis, 12-15 mg/kg 2 to 3 times per week is recommended. Some experts would recommend considering 3 times per week dosing for patients with creatinine clearance of 50-70 mL/min, and twice-weekly dosing if less than 50 mL/min. (See **Chapter 7, Co-Morbidities and Special Situations, Renal Failure, Table 1**, for creatinine clearance calculations.)

- **Monitor serum drug concentrations and adjust the medication dose accordingly.** Trough drug levels are especially helpful when there is evidence of renal insufficiency.

**See Chapter 5, Medication Fact Sheets, and Chapter 3, Laboratory, for more details. A trough concentration before the next dose should be less than 5 mcg/mL. Decreasing the dose to achieve concentrations of less than 20 mcg/mL 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 to 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, CS, all of the aminoglycosides, and CM.
- **For a creatinine clearance between 50 and 70 mL/min, the patient may tolerate 3-times-a-week aminoglycoside dosing at 12 to 15 mg/kg.**
- **For a creatinine clearance between 30 and 50 mL/min, twice-weekly aminoglycoside dosing at 12 mg/kg should be tried.**

- **Monitor peak and trough drug concentrations.** It is especially important that a therapeutic peak be obtained and that trough concentrations be less than 5 mcg/mL before another dose of the drug is given.

- Follow renal function carefully.

## Electrolyte loss

All of the aminoglycosides and CM can cause electrolyte disturbances due to renal tubular wasting of potassium, magnesium, and calcium salts. These effects are most pronounced with CM. 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. Electrolyte disturbances with these medications may precipitate serious, even fatal cardiac arrhythmias.

- 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 an isolated potassium value is low, also check the calcium and magnesium.
- A low serum calcium is most commonly caused by hypoalbuminemia. If the calcium is low, check albumin and free calcium to obtain the corrected value.
- Hypomagnesemia, if present, must be treated in order to correct hypocalcemia and hypokalemia.

For **severe** electrolyte abnormalities, hospitalize and monitor the patient.

- Perform an electrocardiogram.
- Hold medications that may contribute to prolongation of the QT interval (fluoroquinolones, CFZ, BDQ). See **Miscellaneous adverse reactions: QT interval prolongation**.
- Hold medications (digoxin, tricyclic antidepressants) that may precipitate arrhythmias. Consider change of CM to AK, as CM has been associated with more severe electrolyte losses.

## 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 believe that EMB doses of 15 mg/kg given for less than 2 months are rarely associated with toxic changes to the optic nerve. Patients receiving prolonged or high-dose EMB are at greater risk of optic nerve toxicity. High-dose EMB (25 mg/kg) generally should not be used for more than 2 months. The dosing interval of EMB should be adjusted if the creatinine clearance is <50 mL/min to minimize ocular toxicity.

LZD produces a toxic optic neuropathy that is usually reversible. If no other reasonable options exist, restarting LZD at a lower dose (300 mg) has been successfully used without recurrence in one published 2012 study from Korea.

ETA and INH are also rare causes of optic nerve toxicity.

CFZ toxicity produces a bull's-eye pigmentary maculopathy and generalized retinal degeneration.

Visual loss due to RFB is part of a pan-uveitis that is reversible with RFB dosage adjustment.

#### When using any of these drugs:

- Conduct baseline assessment of visual acuity (Snelling chart) and of color discrimination (Ishihara plates) 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.

- Correct nutritional deficiencies; consider a multivitamin for individuals with malnutrition (wait until they are tolerating TB therapy before starting the multivitamin; remember to dose 2 hours before or after fluoroquinolone drugs if the multivitamin contains iron or other divalent cations).
- **Whenever a question about visual toxicity exists, immediately discontinue the likely offending medication and refer the patient to an ophthalmologist.** RFB 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.

## Retrobulbar neuritis

Often presenting as a unilateral process, symptoms of eye pain and/or changes in vision while on EMB should be evaluated by ophthalmology for potential retrobulbar neuritis due to drug-associated inflammation of the optic nerve. If symptoms are present:

- 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 LZD, ETA, INH and CFZ 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. This is more common when toxicity is recognized early and medication discontinued quickly after symptoms develop. However, some series report fairly abrupt vision loss that is permanent.

## Uveitis

**RFB**, especially in doses greater than 300 mg daily (or given along with medications that decrease clearance, i.e., protease inhibitors, antifungal azoles, and macrolides), can cause pan-uveitis. Patients typically present with erythematous, painful eyes, and blurring of vision.

- Hold RFB until symptoms have resolved and then reinstitute at a lower dose. A lower dose is usually needed with some drugs that cause decreased clearance of the RFB, i.e., protease inhibitors, azoles, and macrolides. If the dose is lowered ensure it is still therapeutic if the drug is depended on for treatment.
- Consult an ophthalmologist.
- Consider other etiologies, especially in HIV-positive individuals; exclude bacterial and viral infection.
- Use topical steroid drops if ocular infection is ruled out.

Some patients may improve even when RFB treatment is continued. If recurring uveitis is a problem, stop RFB.

# 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, RFB, INH, ETA, and BDQ**. Electrolyte disturbances associated with the aminoglycosides and CM may also cause muscle pain and cramping. Thyroid dysfunctions may also contribute.

- Do not discontinue medications.
- NSAIDs are usually helpful. Monitor renal function more closely when using higher doses of NSAIDs; use caution in patients with underlying chronic kidney disease.
- If acute swelling, erythema, and warmth are present, evaluate for the presence of infection or inflammatory disease:
  - **Aspirate joint if fluid is present.**
  - **Send fluid for culture for routine, mycobacterial and fungal pathogens, cell count, protein, glucose, and crystals.**
  - **Institute treatment (often ibuprofen) if the diagnosis is gout. Check uric acid level and consider discontinuation of PZA.**
  - **Consult with a rheumatologist if evidence of inflammatory or autoimmune arthritis is present.**
- Evaluate for hypothyroidism or hyperthyroidism.
- Draw serum electrolytes, calcium, and magnesium. Correct deficiencies.

## Tendonitis and tendon rupture

Tendon rupture, mostly commonly involving the Achilles tendon, has been reported with **fluoroquinolone use**. Rupture is more common when new physical activities are undertaken and in older patients, diabetics, and patients on steroids.

When tendon inflammation is **mild**:

- Administer nonsteroidal anti-inflammatory agents.
- Rest the involved joint and avoid any strenuous activity.
- Evaluate the fluoroquinolone dose and reduce if possible. Serum drug concentrations may help to direct fluoroquinolone therapy.

When **significant inflammation** of tendons or tendon sheaths occurs:

- Fluoroquinolones should generally be stopped.
- 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.

# Miscellaneous adverse reactions

## Hypothyroidism

Hypothyroidism may develop with either **PAS** or **ETA**; when both drugs are used the incidence of hypothyroidism may be 40% or greater. **BDQ** guidelines instruct clinicians to monitor for hypothyroidism, but clear causation by the drug has not been documented.

- Assess baseline thyroid function prior to start of these medications and correct if needed. Assess thyroid function every 1 to 2 months unless clinical assessment indicates the need to evaluate sooner. Conduct monthly clinical assessments for hypothyroidism, although these may lag behind laboratory findings.
- When thyroid stimulating hormone (TSH) begins to increase, evaluate for clinical evidence of hypothyroidism. Begin to monitor more frequently.
- When TSH rises to more than 1.5 times the upper limit of normal, begin thyroid hormone replacement:
  - **Most adults will require 100 to 150 mcg of synthroid daily.**
  - **Young healthy adults can be started on 75 to 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 to 2 months of treatment, adjust dose if needed and continue to monitor monthly while on treatment. Hormone treatment can be stopped once treatment with the offending medication is stopped.

- **Adjust thyroid hormone replacement until the patient's TSH is within the normal range.**

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

## QT interval prolongation

During clinical trials, treatment with **BDQ** resulted in prolongation of the QT interval on the electrocardiogram (ECG). QT prolongation was found to develop within the first week of treatment and may persist several months even after drug discontinuation. Despite its association with QT prolongation, there have been no reported cases of *torsade de pointes*.

Monitoring of ECG and serum electrolytes is recommended before and during therapy with **BDQ** (with need for continued ECG monitoring until QT normalizes if prolongation persists after drug discontinuation). Potassium and magnesium should be maintained in the normal range with electrolyte repletion. The fluoroquinolones, especially **MXF**, can also result in prolongation of the QT interval. Guidelines issued by the CDC recommend that ECG be monitored weekly in patients who take **BDQ** along with other medications that may prolong the QT interval. There are no consensus guidelines on the concomitant use of **BDQ**, along with **MXF** and/or **CFZ**.

**Delamanid (DLM)**, although not yet approved in the United States, is also associated with QT prolongation.



## Metallic taste

**Metallic taste** is reported as an adverse reaction in patients taking **ETA** and **clarithromycin (CLR)**. 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 **ETA** 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 **ETA**. 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 with **ETA**, but rare cases have been reported due to **INH**.

## Superficial fungal infection

Vaginal or penile candidiasis may occur. This is most common with **fluoroquinolone** and **LZD** 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; be mindful of the drug interaction between rifamycin drugs and oral antifungal azoles. Exclude other diseases if response to treatment is not prompt.

## Non-specific numbness

Transient numbness, especially around the mouth, occurs with **SM**. Unlike vestibular or auditory toxicity, these symptoms associated with **SM** are not progressive, and **SM** does not always have to be discontinued. If the symptoms are particularly difficult to tolerate and the treatment regimen would not be compromised, consider a reduction in dose to alleviate the symptoms. However, ensure that the serum drug levels remain therapeutic. Another option: if the daily dose has produced therapeutic levels, use this same dose 2 or 3 times a week.

## Hypo-/Hyperglycemia

Several cases of hypoglycemia have been reported due to **LZD**. These were documented by dechallenge and rechallenge. Hypoglycemia was more often associated with diabetes. Later-generation **fluoroquinolones** have been reported to cause both hypo- and hyperglycemia, especially in older persons and diabetic patients. **Gatifloxacin (GFX)** (no longer available in the United States) has been most frequently implicated, but **MFX** and **LFX** may also cause dysglycemia.

## Summary

- Adverse reactions and toxicity should be anticipated with any treatment course 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 crucial to the regimen cannot be permanently discontinued; patients and staff need to understand that the treatment goal to achieve a cure might fail if an aggressive multidrug regimen is not maintained.
- 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** (leukopenia, 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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# Contacts

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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: Limited data and consensus

The Centers for Disease Control and Prevention (CDC) guidelines for treatment of contacts exposed to multidrug-resistant tuberculosis (MDR-TB) were last updated in 1992. The national guidelines for the investigation of contacts to infectious TB cases were last updated in 2005 when limited data were available for newer methods for diagnosing latent TB infection (LTBI). Over the past two decades, several publications on the tolerability and toxicity of regimens used for treatment of LTBI among contacts to MDR-TB cases, and more extensive publications on the application of newer LTBI diagnostics, have appeared. These reports can inform the approach to the identification, evaluation, and treatment of contacts to patients with MDR-TB.

The management and treatment of persons exposed to and presumably infected by patients with MDR-TB pose unique challenges because:

- the evidence base remains of low quality for selecting a safe and effective regimen; and
- the growing body of evidence indicates that the multidrug regimens recommended in 1992 are poorly tolerated and some have unacceptable toxicity.

A systematic review conducted in 2012 reached the same conclusion as the 2006 Cochrane review of the literature that there is insufficient data to address the question of the efficacy of MDR-LTBI treatment. However, a number of studies have documented high rates of discontinuation of treatment, particularly with combination regimens including pyrazinamide (PZA). In addition, patients treated with PZA and rifampin (RIF) for LTBI after exposure to pan-susceptible TB have been reported to have 0.9% fatality and 2.8% hospitalization rates. These observations should lead to avoidance or extreme caution in using combination LTBI regimens containing PZA.

*The management and treatment of persons exposed to and infected by MDR-TB pose unique challenges because of the low quality of the evidence base for therapy and the documented toxicity of combination regimens containing pyrazinamide.*



# Contact investigation

Recent studies have demonstrated a wide variation in the concentration of infectious particles in sputum specimens from patients with smear-positive TB. Transmission to contacts was more strongly associated with concentration of infectious particles than with the grade of the acid-fast bacilli (AFB) smear. These findings may provide an explanation for years of observation that some sputum AFB smear-positive TB patients seem not to transmit at all, and some with the same clinical features are associated with high rates of transmission and secondary TB cases. Until new tools are developed to gauge the risk of infectiousness, public health staff must continue to use the results of the contact investigation to determine if, and how extensively, transmission has occurred. One of the primary responsibilities of the case manager or disease investigator is to identify, locate, and evaluate contacts. **Contact investigation for cases of MDR-TB is important for detection of prevalent TB cases as well as identification of contacts with LTBI who were likely infected by the MDR-TB strain of the index case.**

Results from a number of studies show that zero to 8% of contacts to MDR-TB cases were found to have active TB at the initial evaluation or during follow-up. Half or more of the cases among contacts are prevalent active TB cases detected at the initial evaluation, and the majority of the subsequent incident cases are detected within the first year after the diagnosis of the index case. The majority of culture-confirmed cases among contacts are also due to MDR-TB but some may have isolates with other drug-susceptibility findings.

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 locations where transmission could have occurred
- Interview of the case to identify contacts exposed at one or more locations
- Performance of a field investigation
- Risk assessment for TB transmission
- Prioritization of contacts for evaluation
- Evaluation of initial contacts
- Review of the data on baseline results of initial contacts to assess the likelihood that transmission has occurred and whether expanded contact investigation may be indicated
- Provision of treatment for LTBI and follow-up of contacts
- Evaluation of contact investigation outcomes

This assessment of whether transmission of *Mycobacterium tuberculosis* has occurred due to exposure to MDR-TB is critical to reaching the conclusion that individual contacts have been infected with MDR-TB. Since many of the contacts to infectious TB cases may have been exposed previously, it can be challenging to determine whether TB infection among contacts represents exposure to the recent drug-resistant TB case or exposure to a previous and likely drug-susceptible case. **This assessment should be based on the transmission risk assessment findings, the individual contact's TB exposure and LTBI history, and an evaluation of the results of the contact investigation.**

# TB transmission risk assessment

The risk of TB transmission is contingent on 4 main factors:

- 1. Infectiousness of the TB patient:** Symptoms, sputum smear status, site of TB, presence of cavitory 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, proximity and cumulative duration of the exposure
- 4. Host susceptibility:** Very young children and immunocompromised patients may or may not be at increased risk of infection, but are certainly at increased risk of progression to TB if infected

## Indications of transmission include:

- Identification of a secondary case
- High infection rate among contacts, especially those born in the United States or other TB low-burden countries
- Infection in a young child
- Presence of converters

A “**close contact**” is described by the CDC as, “A person who had prolonged, frequent, or intense contact with a person with TB while he or she was infectious.”

According to the American Thoracic Society and CDC, a skin test “**converter**” is someone who has an increase in reaction size of 10 mm or more within a period of 2 years. An interferon-gamma release assay (IGRA) converter is a person who changes from negative to positive within a 2-year period.

## Contact TB exposure history

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

Include these essential factors in the assessment:

- Prior tuberculin skin test (TST) or IGRA history and baseline TST (or IGRA if done). Taking the time to find documented prior TST history is time well spent in a drug-resistant TB contact investigation. Sources of this information include:
  - **Employment or immigration/refugee health record**
  - **Primary care provider medical record**
  - **School/immunization health record**
  - **Military health/immunization records**



- **History of incarceration** (a situation in which TST or IGRA is often performed)
- **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 prescribed and completed? If so, what medications were used?
- 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

## Latent tuberculosis infection (LTBI)

Traditionally, LTBI is defined as a positive TST without clinical or radiographic evidence of TB disease.

Two commercial IGRAs are now available for the diagnosis of LTBI: the **QuantiferON®-TB Gold In-Tube (QFT-GIT)** and the **T-SPOT.TB (T-SPOT)**. It is important to remember that these blood assays (as well as the TST) are not direct measures of LTBI but are immunologic assays that measure cell-mediated immunity to protein (PPD for the TST) or more specific peptides (ESAT and CFP-10 for both IGRAs, with TB-7 added for QFT-GIT).

The 2010 CDC recommendations stated that IGRAs could be used instead of TST, and noted the specific advantages of these tests among populations likely to have received prior bacille Calmette–Guérin (BCG) vaccination or who were less likely to return for the TST interpretation. At that time, caution was advised for the use of IGRA in young children and individuals with impaired immunity, primarily due to limited data. Since then, numerous studies have been published, including systematic reviews, and the overall conclusions are 1) **IGRAs appear to perform at least as well as TST in adults, children 5 years of age and older, and immunocompromised populations, having equal or better sensitivity for active TB than TST**; and 2) **IGRAs have improved specificity over TST, particularly in BCG-vaccinated persons**. The 2015 American Academy of Pediatrics Redbook® notes that some experts use IGRAs for children as young as 3 years of age.

IGRAs have a lower frequency of positive results compared to TST among individuals with prior BCG vaccination, a finding best interpreted as higher specificity rather than lower sensitivity. Thus, positive IGRA results at baseline testing are less likely than a positive TST to be falsely positive among high-risk foreign-born populations. Repeat TST has the potential for immunological boosting. Although the IGRAs avoid the potential for boosting, false-positive conversions at the 8-week follow-up testing may occur due to test variability. False-positive rates of up to 4% have been reported during repeat IGRA testing in low-risk populations, such as U.S.-born health care workers, and this phenomenon is likely to occur among baseline-negative contacts when retested at 8-10 weeks, at least among adults.

According to the 2010 CDC guidelines, testing for LTBI with more than one test is not recommended in most situations, and one should not do a second test without specific plans for how the results will be used. An IGRA can help to decide whether a positive TST

is due to prior BCG vaccination or true TB infection (but if the IGRA is negative, it should be interpreted with caution in the setting of high-risk exposures, especially to MDR-TB). Among adolescent and young adult contacts likely to have received BCG at birth and previously diagnosed with LTBI based on TST done during routine screening, there is up to a 50% chance that the prior TST was a false-positive. If a patient has been more recently exposed to MDR-TB, IGRA testing is still indicated even if the patient was previously treated for LTBI. This is based on a randomized trial that demonstrated that LTBI treatment does not result in reversion of a positive IGRA to negative. Contacts with a negative baseline IGRA likely represent individuals previously treated for a false-positive TST who require an 8-10 week follow-up IGRA.

Currently, no data exist to determine the optimal timing for performing IGRAs in exposed contacts, but it is reasonable to assume that the tests perform similar to the TST for which the assumption has been accepted that a test **8-10 weeks after the last exposure is adequate for detection of new TB infection.**

**The greatest limitation of IGRAs is the more limited prospective data on the predictive value of a positive IGRA for future TB disease.** This has been established for different-sized TST reactions in many large-scale cohort and experimental studies, which permits the estimation of risk for disease and benefit of therapy.

**As with the TST, a negative IGRA does not rule out early LTBI or even TB disease.**

This fact is particularly important in subgroups at high-risk for progression to TB disease, such as young children, and adults with HIV or other medical conditions associated with defects in cell-mediated immunity. When the risk of progression is high and validity of TST and/or IGRA questionable, clinicians may treat in the face of discordant results or in the absence of positive test results.

## The importance of treating LTBI

- For the population as a whole, there is a **5-10% lifetime risk of developing TB disease** following infection, half of the risk occurring within 1 to 2 years after infection.
- **Treatment of LTBI is widely recommended for individuals at increased risk of developing TB disease**, including, but not limited to, contacts to infectious TB cases, HIV-positive and other immunocompromised hosts, children, and recent immigrants.
- Treatment with **isoniazid (INH)**, either daily or intermittently, has been shown to decrease the risk of progressing to TB disease among contacts, and a more recent study showed similar effectiveness using **12 once-weekly, directly-observed doses of INH plus rifapentine (RPT). RIF for 4 months** and the combination of INH plus RIF for 4 months are also options for treating LTBI based on less extensive data. The combination of PZA and RIF was also shown to be as effective as INH in preventing progression to TB disease among HIV-positive patients, but significant hepatotoxicity led to the withdrawal of this regimen as a recommendation for treatment of LTBI.

- Transmission of MDR-TB is well documented to healthcare workers, immunocompromised persons, children in homes or at school, and other close contacts such as family members and those at work sites. Aggressively pursue a full evaluation of all close contacts, and carefully **consider expanding the contact investigation when high rates of transmission are documented in the initial evaluation.**
- **Given the high morbidity and mortality associated with drug-resistant TB disease, consider treatment of LTBI thought to be due to infection with drug-resistant TB,** but weigh the risks and benefits to lessen the risk of toxicity from unnecessary treatment with toxic medications.

## General principles of evaluating and managing contacts

- Evaluate exposed contacts expeditiously in order to identify any other cases of TB disease and to prevent further transmission.
- IGRAs are the preferred test for exposed contacts who originate from areas where they were likely to have received BCG vaccine, even among adolescents and young adults who were vaccinated only at birth.
- **Rule out TB disease prior to starting any treatment.** Before starting a patient on treatment for LTBI, exclude TB disease to avoid amplification of resistance by use of a LTBI regimen when active MDR-TB is present.
  - Contact screening for active TB in the United States is most often done with a two-stage screening process of testing individuals with a TST or IGRA test and performing chest radiography only among those with either a positive TST or IGRA test or symptoms of TB. This approach is limited by the possibility of false negative TST or IGRA, and radiography of only those with a positive TST or IGRA will miss 10-15% of TB cases. Therefore, it is important to evaluate those contacts with symptoms both clinically and radiographically for TB.
  - Children under 5 years of age and those with HIV infection or significant immunosuppression are routinely evaluated by chest radiography even if the TST or IGRA tests are negative.
  - Some patients with normal chest radiographs should have sputum and other specimens collected if there are clinical signs or symptoms of TB.
- **Some general principles for treating LTBI due to MDR-TB are as follows:**
  - Efficacy of any regimen depends on adherence to and completion of therapy.
  - Educate patients on drug resistance, drug side effects, importance of adherence, and TB symptoms.
  - Select the most effective, best-tolerated regimen to which the presumed source case isolate is susceptible. Despite the emphasis on two-drug regimens in the 1992 CDC guidelines, recent reports indicate that fluoroquinolone single-drug therapy can be used and may be preferable due to fewer side effects and, as a result, greater tolerability.
  - For immunosuppressed contacts with a positive TST or IGRA test, consider treatment with a two-drug MDR-LTBI regimen rather than monotherapy.
  - In children under age 5 and in HIV-positive close contacts with initial negative LTBI tests, **consider window prophylaxis** when exposure was very intimate

and prolonged, and when transmission to other contacts has been documented. See section on **Window prophylaxis** later in this chapter.

- In children under age 6 months and in HIV-positive close contacts, consider treating for presumed MDR-LTBI even in the absence of positive test for LTBI, especially in the setting of documented transmission (converters, secondary cases).
- Take into account the patient's wishes, as there is limited evidence to guide treatment of presumed MDR-LTBI.

## Summary of management options of LTBI in contacts exposed to MDR-TB

- 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 at regular intervals for a minimum of 2 years following exposure;** and **2) Educate patients about the signs and symptoms of TB in case they progress to TB disease.**
- The range of treatment options for contacts to patients with MDR-TB includes:
  - Monotherapy with a fluoroquinolone. This option has increasingly been employed although not included in 1992 CDC guidelines.
  - Treatment with 2 drugs to which the organism is sensitive and the toxicity profile is acceptable. This would most likely be a fluoroquinolone plus ethambutol (EMB).
- The recommended duration of treatment is generally 6 to 12 months.
- Since there are limited observational data supporting specific recommendations for the treatment of MDR-LTBI, treatment recommendations must take into account the well-documented toxicity of PZA-containing regimens, and the poor tolerability of most of the second-line anti-TB drugs. Recommendations are based on expert opinion, and **the risk versus benefit must be considered.**
- A 2014 observational study by Bamrah et al., showed a treatment completion rate of 89% and no secondary MDR-TB cases among contacts treated with a fluoroquinolone as monotherapy or combined with EMB or ethionamide (ETA) in an MDR-TB outbreak in Micronesia and the Marshall Islands. Of 15 contacts not treated, 3 developed TB disease.
- Other regimens such as INH alone, RIF, or INH plus RPT may be considered for patients likely to have been infected by a drug-susceptible case before exposure to the drug-resistant case.
- Consider the BCG vaccine 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. (See **Resources** at the end of this chapter for information on how to obtain and administer the BCG vaccine.)
- No treatment with clinical monitoring may be appropriate. (See section, **No Treatment: Clinical Monitoring.**)

# Selecting a treatment regimen for contacts to drug-resistant TB

## Variables to consider:

- 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 based upon higher than expected prevalence of 8-week conversions by TST or IGRA tests
- 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-susceptible TB, which can be evaluated by:
  - Place of birth and history of foreign residence or travel
  - History of prior exposures to TB disease
  - TST/IGRA history must be interpreted cautiously – prior positive TST during routine screening in younger immigrants may have been false-positive TST due to BCG cross-reaction. IGRA testing of such contacts may be recommended since some may have negative IGRA results at baseline and be candidates for 8-week post-exposure testing. For those with a positive baseline IGRA, one cannot distinguish between those previously infected or more recently infected with MDR-TB.
- Likelihood that the contact will progress to TB disease, including factors such as:
  - **Immunosuppression** (HIV, steroids, tumor necrosis factor [TNF] alpha agents, other immune-suppressing drugs)
  - **Age** (less than 5 years old)
  - **Documented TST or IGRA conversion**
  - **Diabetes, renal failure, and certain other medical conditions**
- Tolerability and toxicity of potential anti-TB drugs for treatment of LTBI

## Drug-resistant LTBI treatment options

Table 1 includes suggestions for regimens that are fluoroquinolone-based, due to the significant activity of levofloxacin (LFX) or moxifloxacin (MFX) for TB disease and lower anticipated toxicity. EMB, if likely to be effective, may be a reasonable second drug. Other second-line drugs for LTBI treatment may be less acceptable due to toxicity. The actual regimen chosen will depend on the individual case; consultation with an expert in drug-resistant TB is recommended.

TABLE 1.

**Specific treatment options dependent on susceptibility of source case isolate**

Resistance pattern	LTBI treatment options
INH (RIF-susceptible)	RIF 4 months (Adults and children)
INH and RIF	Fluoroquinolone or Fluoroquinolone + EMB
INH, RIF, EMB	Fluoroquinolone or Fluoroquinolone + ETA
INH, RIF, PZA	Fluoroquinolone or Fluoroquinolone + EMB
INH, RIF, PZA, EMB, +/-injectable	Fluoroquinolone or Fluoroquinolone + ETA
INH, RIF, PZA, EMB, injectable, ETA	Fluoroquinolone or Fluoroquinolone + cycloserine (CS)
INH, RIF, PZA, EMB, and fluoroquinolone	No treatment, clinical monitoring* (In select cases, CS + para-aminosalicylic acid [PAS] or PAS + ETA* or ETA* + CS may be considered)

\* See section, **No treatment: Clinical monitoring**

**Considerations when choosing MDR-LTBI treatment options**

**LFX or MFX alone**

- Better tolerated than 2-drug combination, and therefore more likely to complete regimen.
- Demonstrated bactericidal activity against *M. tuberculosis*.
- Only limited observational data on efficacy in preventing progression to TB disease.
- Due to the potential risk of tendon rupture (a few case reports), advise patients to avoid vigorous exercise and to report any symptoms of calf pain or tenderness.
- Use of fluoroquinolones for pediatric MDR-LTBI has been well-tolerated, despite concerns for potential arthropathy seen in animal studies. (See **Chapter 6, Pediatrics**).
- Consider the risks versus benefits regarding the use of fluoroquinolones in pregnant or breastfeeding women. (See **Chapter 7, Co-morbidities and Special Situations**, for more information.)

- Consider use in TST or IGRA converters and those with newly documented positive TST or IGRA, but who may have intermediate exposure to index case (exposure to MDR-TB was less certain).

**LFX or MFX and a second drug (EMB preferable) to which isolate is likely to be susceptible (e.g., EMB, ETA, PAS, CS)**

- Follows CDC/ATS 1992 recommendations of using 2 drugs to which isolate is susceptible.
- Consider use in immunocompromised individuals and children under age 5.
- Frequently poorly tolerated due to increased side effect profile.
- Side effects may deter patient from completing this regimen.
- Potential toxicity must be balanced against benefits.
- Due to the potential risk of tendon rupture, advise patients to avoid vigorous exercise and to report any symptoms of calf pain or tenderness.
- Consider the risks versus benefits regarding the use of fluoroquinolones in pregnant or breast-feeding women. See **Chapter 7, Co-morbidities and Special Situations**, for more information.
- Limited observational data on efficacy in preventing progression to TB disease.

Published experience in Texas, New York City, Orange County, California, and Geneva, Switzerland indicates high risk for hepatitis and/or intolerance to a fluoroquinolone and PZA combination, and it should generally be avoided.

*Experience in Texas, New York City, Orange County, California, and Geneva, Switzerland, as well as published data on the 2-month RIF-PZA regimens indicates the **use of PZA should be avoided for LTBI treatment.***

## No treatment: Clinical monitoring

- This may be a reasonable alternative to treatment, particularly when the source resistance pattern limits options to toxic combinations, given the limited data on efficacy of treatment regimens for MDR-LTBI and side effects.
- Evaluate with clinical exam, symptom review every 3 to 6 months for 2 years (with chest radiographs and/or sputum collection as clinically indicated).
- Educate the patient about symptoms of TB disease.

**Clinical monitoring without treatment, especially when there is evidence of significant transmission, is not advised when:**

- Contact is HIV-positive or otherwise significantly immunocompromised.
- Contact is under age 5.
- Contact is someone with a documented recent conversion or otherwise at high risk for progression to TB disease.

## Treatment of children exposed to drug-resistant TB

Many providers treat children for MDR-LTBI, although efficacy data from randomized controlled trials are lacking. In general, MDR-LTBI regimens have been found to be better tolerated in children than adults. Fluoroquinolone monotherapy is sometimes used, especially in older children. See **Chapter 6, Pediatrics**, for more information.

## Duration of therapy

- National guidelines from 1992 suggest treatment of MDR-LTBI for 6 to 12 months.
- Consideration of 12 months of treatment should be made for HIV-positive patients, children, and other individuals with medical risk factors.
- Lower-risk individuals should receive at least 6 months of treatment.

## Adherence and monitoring

- If local resources permit, consider directly observed therapy (DOT) for treatment of contacts with presumed MDR-LTBI 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 treatment options are available.
- Arthralgias and myalgias are common in patients receiving fluoroquinolones for prolonged periods of time. Expert opinion suggests that giving patients short drug holidays may decrease these symptoms and allow for treatment completion.

*Children under age 5 are at increased risk of developing TB if infected and deserve aggressive evaluation and treatment if exposed to an individual with TB.*

## Window prophylaxis

**Window prophylaxis** is the practice of treating a patient who has been exposed to a potentially infectious source case, but has no current evidence of TB disease or infection.

- Since it can take weeks to months for the immune system to recognize a TB infection (and therefore to produce a positive TST or IGRA test), **window prophylaxis** can potentially abort an early infection or prevent rapid progression from early TB infection to TB disease in vulnerable hosts.
- Individuals at very high risk of progressing to TB if infected (very young children, HIV-positive patients and other significantly immunocompromised contacts) are targeted for window prophylaxis.



- Contacts should be screened by history, physical exam, symptom review and chest radiograph to rule out early TB disease before initiating window prophylaxis.
- Contacts are typically treated for 8 to 10 weeks from the end of risk of transmission, and then the TST or IGRA is repeated. If the test has become positive, treatment for LTBI is continued to complete a full course. If the 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). In the case of suspected anergy, a full course of LTBI treatment may be warranted.
- 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 two groups: children under age 5, and HIV-positive individuals or others with significant immunocompromise.** This is especially true if there has been intimate and prolonged contact with individuals likely to be infectious (smear-positive, cavitary disease, coughing source case, and TST/IGRA conversions among other contacts or secondary cases indicating transmission of TB).

## Follow-up of MDR-TB contacts

- It is essential to carefully educate infected 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.
- **Given the limited efficacy data on MDR-LTBI treatment, some experts recommend evaluation/symptom review every 3-6 months for 2 years, even for contacts who have completed treatment.** Chest radiographs and sputum should be done as clinically indicated. Special emphasis should be placed on high-risk contacts: HIV-positive and other immunocompromised individuals; children under age 5; and persons with documented TST/IGRA conversion.

## Summary

- IGRAs may be used instead of TST in contact investigations, and these are preferred in foreign-born persons who have a history of BCG vaccination, even if previously TST-positive. Conversions need to be interpreted cautiously given the boosting with TST and false-positive rate of up to 4% with repeat testing using IGRAs in adults.

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- While it is highly desirable to prevent MDR-TB cases by treatment of LTBI and use of window prophylaxis, there are limited data on efficacy, and more extensive data on poor tolerability, especially for PZA-containing regimens.

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- Treatment of LTBI should be considered in most circumstances, and particularly for patients at highest risk for progression to TB.

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- Careful contact investigation is required to determine likely timing of infection. Patients who were previously TST or IGRA positive are more likely infected with a susceptible strain and may be treated with regimens for drug-susceptible TB. However, when there has been evidence of significant transmission and prolonged exposure, re-infection with a MDR-TB strain may occur and MDR-LTBI treatment warranted.

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- Given the lack of data on efficacy and the documented poor tolerability/toxicity of the previously recommended 2-drugs regimens, most patients should receive fluoroquinolone monotherapy (for contacts to fluoroquinolone-susceptible cases), after active TB is excluded.

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- In children under age 5 and patients who are immunocompromised, consider treatment with 2 drugs to which the presumed source case isolate is susceptible for 12 months.

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- For some patients, clinical monitoring without treatment may be an appropriate option.

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- High-risk contacts with MDR-LTBI should be monitored for 2 years for evidence of progression to active TB disease.

# Resources

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**Contact Investigation:** Guidelines for the Investigation of Contacts of Persons with Infectious Tuberculosis: Recommendations from the National Tuberculosis Controllers Association and CDC. *MMWR* 2005; 54 (No. RR-15, 1-37).

[www.cdc.gov/mmwr/preview/mmwrhtml/rr5415a1.htm](http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5415a1.htm)

Accessibility verified November 1, 2015.

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***Instructions for BCG application.***

[http://www.merck.com/product/usa/pi\\_circulars/b/bcg/bcg\\_pi.pdf](http://www.merck.com/product/usa/pi_circulars/b/bcg/bcg_pi.pdf)

Accessibility verified November 1, 2015.

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***Information about how to obtain BCG.***

BCG can be ordered from any wholesaler that distributes Merck vaccines. You may also contact Merck (800-672-6372) directly to determine if the product is available as short-ages may occur. It is important to clarify your request for BCG vaccine for percutaneous use (not the BCG live for intravesical administration for bladder cancer).

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***The Online TST/IGRA Interpreter.*** An online tool that estimates the risk of active TB for an individual with a TST reaction of  $\geq 5$ mm, based on his/her clinical profile. Intended for adults tested with standard tuberculin (5 TU PPDS, or 2 TU RT-23) and/or a commercial IGRA.

<http://www.tstin3d.com>

Accessibility verified November 1, 2015.

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***The BCG World Atlas.*** An interactive website providing detailed information on current and past BCG policies and practices for over 180 countries. A useful resource to assist clinicians with interpretation of TB diagnostics.

<http://www.bcgatlas.org>

Accessibility verified November 1, 2015.

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# Appendix 1.

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## Expert Resources for Drug-Resistant TB

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### Regional TB Training and Medical Consultation Centers (RTMCCs)

#### **Curry International Tuberculosis Center (CITC)**

**Service area:** Alaska, California, Colorado, Hawaii, Idaho, Nevada, Oregon, Utah, Washington, and the U.S. Affiliated Pacific Islands.

University of California, San Francisco  
300 Frank H. Ogawa Plaza, Suite 520, Oakland, California 94612

**Telephone:** 510-238-5100 main office

**TB Medical Consultation:** 877-390-6682 (toll-free)

**Website:** [www.Currytbcenter.ucsf.edu](http://www.Currytbcenter.ucsf.edu)

**Email:** [CurryTBcenter@ucsf.edu](mailto:CurryTBcenter@ucsf.edu)

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#### **Heartland National Tuberculosis Center (HNTC)**

**Service area:** Arizona, Arkansas, Kansas, Louisiana, Missouri, Nebraska, New Mexico, Oklahoma, and Texas

The University of Texas Health Science Center at Tyler  
2303 SE Military Drive, San Antonio, TX 78223

**Telephone:** 800-TEX-LUNG (800-839-5864) (toll free)

**Website:** [www.heartlandntbc.org](http://www.heartlandntbc.org)

**Email:** [catalina.navarro@uthct.edu](mailto:catalina.navarro@uthct.edu); [debbie.onofre@uthct.edu](mailto:debbie.onofre@uthct.edu)

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#### **Mayo Clinic Center for Tuberculosis**

**Service area:** Illinois, Indiana, Iowa, Michigan, Minnesota, Montana, North Dakota, Ohio, South Dakota, Wisconsin, and Wyoming

200 First Street SW, Rochester, Minnesota 55905

**Telephone:** 855-360-1466 (toll-free)

**Website:** <http://centerfortuberculosis.mayo.edu>

**Email:** [tbcenter@mayo.edu](mailto:tbcenter@mayo.edu)

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#### **New Jersey Medical School Global Tuberculosis Institute at Rutgers (GTBI)**

**Service area:** Connecticut, Delaware, Maine, Maryland, Massachusetts, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, Vermont, and Washington, DC.

225 Warren Street 2nd floor, East Wing, Newark, New Jersey 07103

**Telephone:** 973-972-3270

**TB Medical Consultation:** 800-4TB-DOCS (toll free)

**Website:** <http://globaltb.njms.rutgers.edu/>

**Email:** [globaltbinstitute@njms.rutgers.edu](mailto:globaltbinstitute@njms.rutgers.edu)

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### **Southeastern National Tuberculosis Center (SNTC)**

**Service area:** Alabama, Florida, Georgia, Kentucky, Mississippi, North Carolina, South Carolina, Tennessee, Virginia, West Virginia, Puerto Rico, and U.S. Virgin Islands

2055 Mowry Road, Gainesville, Florida 32611

**Telephone:** 352-273-SNTC; 888-265-SNTC (toll free)

**TB Medical Consultation:** 800-4TB-INFO (toll free)

**Website:** <http://sntc.medicine.ufl.edu>

**Email:** [sntc@medicine.ufl.edu](mailto:sntc@medicine.ufl.edu)

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### **California Department of Public Health, Center for Infectious Diseases, Division of Communicable Disease Control, TB Control Branch, MDR-TB Service**

The TB Control Branch offers telephone and e-mail consultations for providers within California. Consultation can continue throughout treatment and includes assistance with clinical and public health management of MDR-TB patients.

850 Marina Bay Parkway, Richmond, California 94804

**Telephone:** 510-620-3000

**Website:** <https://www.cdph.ca.gov/programs/tb/>

**E-mail:** [lisa.true@cdph.ca.gov](mailto:lisa.true@cdph.ca.gov)

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### **Centers for Disease Control and Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, Division of Tuberculosis Elimination (DTBE)**

CDC/DTBE provides programmatic consultation to local and state health departments including onsite assistance for outbreaks and medical consultation for management of individual patients. CDC/DTBE also provides information on current guidelines and their interpretation.

CDC/DTBE, Mailstop E-10

1600 Clifton Road, NE, Atlanta, Georgia 30333

**Telephone:** 800-CDC-INFO (toll free)

**Website:** [www.cdc.gov/tb/](http://www.cdc.gov/tb/)

**E-mail:** [cdcinfo@cdc.gov](mailto:cdcinfo@cdc.gov)

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## National Jewish Health Mycobacterial Diseases Consult Line

The Mycobacterial Consult Service at National Jewish Health helps practitioners manage drug-resistant tuberculosis and other refractory mycobacterial and respiratory infections. The consult line provides telephone, email, and web-based consultations for health care professionals only.

1400 Jackson Street, Denver, Colorado 80206

**Telephone:** 800-652-9555 (toll free)

**Website:** <https://my.njhealth.org/PatientPortal/Users/Common/Forms/MycobacterialConsultation.aspx>

**E-mail:** [physicianline@njhealth.org](mailto:physicianline@njhealth.org)

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## New York City Department of Health and Mental Hygiene, Bureau of TB Control

The New York City Bureau of TB Control provides telephone and e-mail consultations, and can provide advice for drug-resistant TB cases outside the New York City area. Patients can be sent to New York City outpatient clinics, which provide free evaluation and treatment.

42-09 28th Street, Queens, NY 11101

**Telephone:** 347-396-7486

**Website:** <http://www.nyc.gov/health/tb>

**Contact:** Diana Nilsen, MD, RN

**E-mail:** [dnilsen@health.nyc.gov](mailto:dnilsen@health.nyc.gov)

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For contact information for laboratories that conduct molecular testing for drug resistance and therapeutic drug monitoring, see **Chapter 3, Laboratory**.

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# Appendix 2.

## Selected Organizations Working to Control and Prevent TB in the International Arena

### World Health Organization Global TB Programme

[www.who.int/en](http://www.who.int/en)  
+ 41-22-791-2111

#### Stop TB Partnership

[www.stoptb.org](http://www.stoptb.org)  
+ 41-22-791-4650

#### Global Drug-resistant TB Initiative (GDI)

<http://www.stoptb.org/wg/mdrtb>  
[gdi\\_secretariat@who.int](mailto:gdi_secretariat@who.int)

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### INTERNATIONAL NON-GOVERNMENTAL ORGANIZATIONS (NGOS)

#### American Thoracic Society (ATS)

[www.thoracic.org/](http://www.thoracic.org/)  
212-315-8600

#### FHI 360

[www.fhi360.org/expertise/tuberculosis](http://www.fhi360.org/expertise/tuberculosis)

United States headquarters:  
Durham, North Carolina  
919-544-7040

#### International Union Against Tuberculosis and Lung Disease (IUATLD)

[www.theunion.org](http://www.theunion.org)  
+33-1-44-32-0360

#### KNCV Tuberculosis Foundation

[www.tuberculose.nl](http://www.tuberculose.nl)  
+31-70-416-7222

#### Management Sciences for Health (MSH)

[www.msh.org/our-work/health-area/tuberculosis](http://www.msh.org/our-work/health-area/tuberculosis)

United States headquarters:  
Medford, Massachusetts  
617-250-9500

#### Médecins Sans Frontières (Doctors Without Borders)

International headquarters: Geneva, Switzerland  
[www.msf.org](http://www.msf.org); +41-22-849-8484

United States headquarters:  
New York City, New York

[www.doctorswithoutborders.org](http://www.doctorswithoutborders.org); 212-679-6800

#### Partners in Health

[www.pih.org](http://www.pih.org)  
617-998-8922

#### Program for Appropriate Technology in Health (PATH)

[www.path.org](http://www.path.org)  
206-285-3500

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## DIAGNOSTIC AND DRUG DEVELOPMENT

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### **Foundation for Innovative New Diagnostics (FIND)**

[www.finddiagnostics.org](http://www.finddiagnostics.org)

+ 41-22-710-0590

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### **Global Alliance for TB Drug Development**

[www.tballiance.org](http://www.tballiance.org)

212-227-7540

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## ADVOCACY AND RESOURCES

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### **Sentinel Project on Pediatric Drug-Resistant TB**

<http://sentinel-project.org>

[sentinel\\_project@hms.harvard.edu](mailto:sentinel_project@hms.harvard.edu)

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### **Treatment Action Group**

[www.treatmentactiongroup.org/tb](http://www.treatmentactiongroup.org/tb)

[tag@treatmentactiongroup.org](mailto:tag@treatmentactiongroup.org)

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## PATIENT REFERRAL AND CONTINUITY OF CARE PROGRAMS

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### **CureTB: Binational TB Referral Program**

[www.sandiegocounty.gov/hhsa/programs/phs/cure\\_tb/](http://www.sandiegocounty.gov/hhsa/programs/phs/cure_tb/)

619-542-4013

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### **TBNet (Migrant Clinicians Network)**

[www.migrantclinician.org/network/tbnet](http://www.migrantclinician.org/network/tbnet)

512-327-2017

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Contact information verified December 30, 2015.

# Appendix 3.

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## International Resources for TB Treatment and Policies

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The following websites are potential sources of information about the various TB protocols practiced in countries with high rates of immigration to the United States:

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**World Health Organization (WHO) *Global Tuberculosis Report*** compiles data from 200 countries, monitoring the scale and direction of TB epidemics, implementation and impact of the Stop TB Strategy, and progress towards the Millennium Development Goals: [www.who.int/tb/publications/global\\_report/en/](http://www.who.int/tb/publications/global_report/en/)

A special supplement to the ***Global Tuberculosis Report*** (2014) titled, ***Drug-resistant TB—Surveillance & Response***, marks the 20th anniversary of the Global Project on Anti-Tuberculosis Drug Resistance Surveillance and its TB Supranational Reference Laboratory Network:

[http://apps.who.int/iris/bitstream/10665/137095/1/WHO\\_HQ\\_TB\\_2014.12\\_eng.pdf?ua=1](http://apps.who.int/iris/bitstream/10665/137095/1/WHO_HQ_TB_2014.12_eng.pdf?ua=1)

Two additional key resources from WHO are:

- ***Guidelines for the programmatic management of drug-resistant tuberculosis, 2011 update***  
[www.who.int/tb/publications/tb-drugresistant-guidelines/en/](http://www.who.int/tb/publications/tb-drugresistant-guidelines/en/)
- ***Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis, 2014***  
[www.who.int/tb/publications/pmdt\\_companionhandbook/en/](http://www.who.int/tb/publications/pmdt_companionhandbook/en/)

The WHO website provides links to, and contact information for TB programs located throughout the world:  
[www.who.int/topics/tuberculosis/en/](http://www.who.int/topics/tuberculosis/en/)

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## Centers for Disease Control and Prevention (CDC)

- **Division of Tuberculosis Elimination**  
[www.cdc.gov/tb/](http://www.cdc.gov/tb/)
  - **Global Tuberculosis Branch, Division of Global HIV/AIDS**  
[www.cdc.gov/globalaids/](http://www.cdc.gov/globalaids/)
  - **Division of Global Migration and Quarantine**  
[www.cdc.gov/ncezid/dgmaq/](http://www.cdc.gov/ncezid/dgmaq/)
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**GHDonline** is a platform for online communities for health care professionals to connect and discuss challenges in care delivery, part of the Global Health Delivery Project at Harvard University.

- **MDR-TB Treatment and Prevention:**  
[www.ghdonline.org/drtb/](http://www.ghdonline.org/drtb/)
- **TB Infection Control:**  
[www.ghdonline.org/ic/](http://www.ghdonline.org/ic/)

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**USAID** is working in 26 countries to improve TB services

[www.usaid.gov/what-we-do/global-health/tuberculosis](http://www.usaid.gov/what-we-do/global-health/tuberculosis)

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The ***International Standards for Tuberculosis Care (ISTC)***; the ***Patients' Charter for Tuberculosis Care; ISTC Handbook***; and ***ISTC Training Materials*** (includes translated materials)

[www.currytbcenter.ucsf.edu/international-research#guidelines](http://www.currytbcenter.ucsf.edu/international-research#guidelines)

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**BCG Atlas** provides detailed information on current and past bacille Calmette-Guérin (BCG) vaccination policies and practices for over 180 countries.

[www.bcgatlas.org](http://www.bcgatlas.org)

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### **International Medication Identifier**

[www.drugs.com/pill\\_identification.html](http://www.drugs.com/pill_identification.html)

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### **Global TB Community Advisory Board: TB Guidelines from Countries and International Organizations**

[www.tbonline.info/guidelines/](http://www.tbonline.info/guidelines/)

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### **Geneva Foundation for Medical Education and Research (GFMER) Guidelines Clearinghouse, TB**

[www.gfmer.ch/Guidelines/Tuberculosis/Tuberculosis\\_mt.htm](http://www.gfmer.ch/Guidelines/Tuberculosis/Tuberculosis_mt.htm)

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Websites accessed December 30, 2015.

# Appendix 4.

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## Multicultural Resources

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### HEALTH-RELATED CULTURAL INFORMATION AND CROSS-CULTURAL TRAINING

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#### **The Cross Cultural Health Care Program**

[www.xculture.org/](http://www.xculture.org/)

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#### **Culture Clues**

[depts.washington.edu/pfes/CultureClues.htm](http://depts.washington.edu/pfes/CultureClues.htm)

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#### **DiversityRX**

[www.diversityrx.org/](http://www.diversityrx.org/)

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#### **EthnoMed**

[ethnomed.org/](http://ethnomed.org/)

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#### **Management Sciences for Health, Providers Guide to Quality & Culture**

<http://erc.msh.org/mainpage.cfm?file=1.0.htm&module=provider&language=English>

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#### **National Center for Cultural Competence (NCCC)**

<http://nccc.georgetown.edu/>

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### TB-SPECIFIC CULTURAL INFORMATION

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**Country Guides** — Brazil, Cambodia, China, Colombia, Dominican Republic, Ecuador, El Salvador, Guatemala, Haiti, Honduras, India, Indonesia, Mexico, Myanmar (Burma), Peru, Philippines, Somalia, South Korea, Vietnam

Produced by Southeastern National Tuberculosis Center

<http://sntc.medicine.ufl.edu/Products.aspx>

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#### ***Cultural Competency and Tuberculosis Care: A guide for self-study and self-assessment***

Produced by Rutgers Global Tuberculosis Institute

<http://globaltb.njms.rutgers.edu/>

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#### ***Ethnographic Guides — Burma, China, Laos, Mexico, Somalia, Vietnam***

Produced by CDC — Division of TB Elimination

[www.cdc.gov/tb/publications/guidestoolkits/EthnographicGuides/default.htm](http://www.cdc.gov/tb/publications/guidestoolkits/EthnographicGuides/default.htm)

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#### **TB & Cultural Competency Newsletters**

Produced by Rutgers Global Tuberculosis Institute

<http://globaltb.njms.rutgers.edu/educationalmaterials/tbandculturalcompetency.html>

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## TRANSLATED PATIENT EDUCATION TB RESOURCES

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### **British Columbia Centre for Disease Control**

[www.bccdc.ca/health-info/diseases-conditions/tuberculosis](http://www.bccdc.ca/health-info/diseases-conditions/tuberculosis)

Includes videos about TB in many languages:

[www.bccdc.ca/health-info/diseases-conditions/tuberculosis/videos](http://www.bccdc.ca/health-info/diseases-conditions/tuberculosis/videos)

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### **EthnoMed**

<http://ethnomed.org/patient-education/tuberculosis>

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### **Georgia Department of Public Health**

<https://dph.georgia.gov/tb-public-health-clinic-forms>

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### **Harborview Medical Center, Seattle**

[https://healthonline.washington.edu/health\\_online/translations.asp](https://healthonline.washington.edu/health_online/translations.asp)

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### **Massachusetts Health and Human Services Department**

[www.mass.gov/eohhs/gov/departments/dph/programs/id/tb/public-health-cdc-tb-prevention.html](http://www.mass.gov/eohhs/gov/departments/dph/programs/id/tb/public-health-cdc-tb-prevention.html)

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### **Minnesota Department of Health**

[www.health.state.mn.us/divs/idepc/diseases/tb/ed/index.html#language](http://www.health.state.mn.us/divs/idepc/diseases/tb/ed/index.html#language)

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### **National Library of Medicine, National Institutes of Health**

[www.nlm.nih.gov/medlineplus/languages/tuberculosis.html](http://www.nlm.nih.gov/medlineplus/languages/tuberculosis.html)

Refugee Health Information Network: <https://healthreach.nlm.nih.gov/> (searchable database)

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### **National Prevention Information Network (NPIN) Educational Materials Database**

<https://npin.cdc.gov/>

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### **New South Wales Health**

[www.mhcs.health.nsw.gov.au](http://www.mhcs.health.nsw.gov.au)

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### **TB Control — India**

[www.tbcindia.nic.in/](http://www.tbcindia.nic.in/)

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### **TB Education and Training Resources (CDC)**

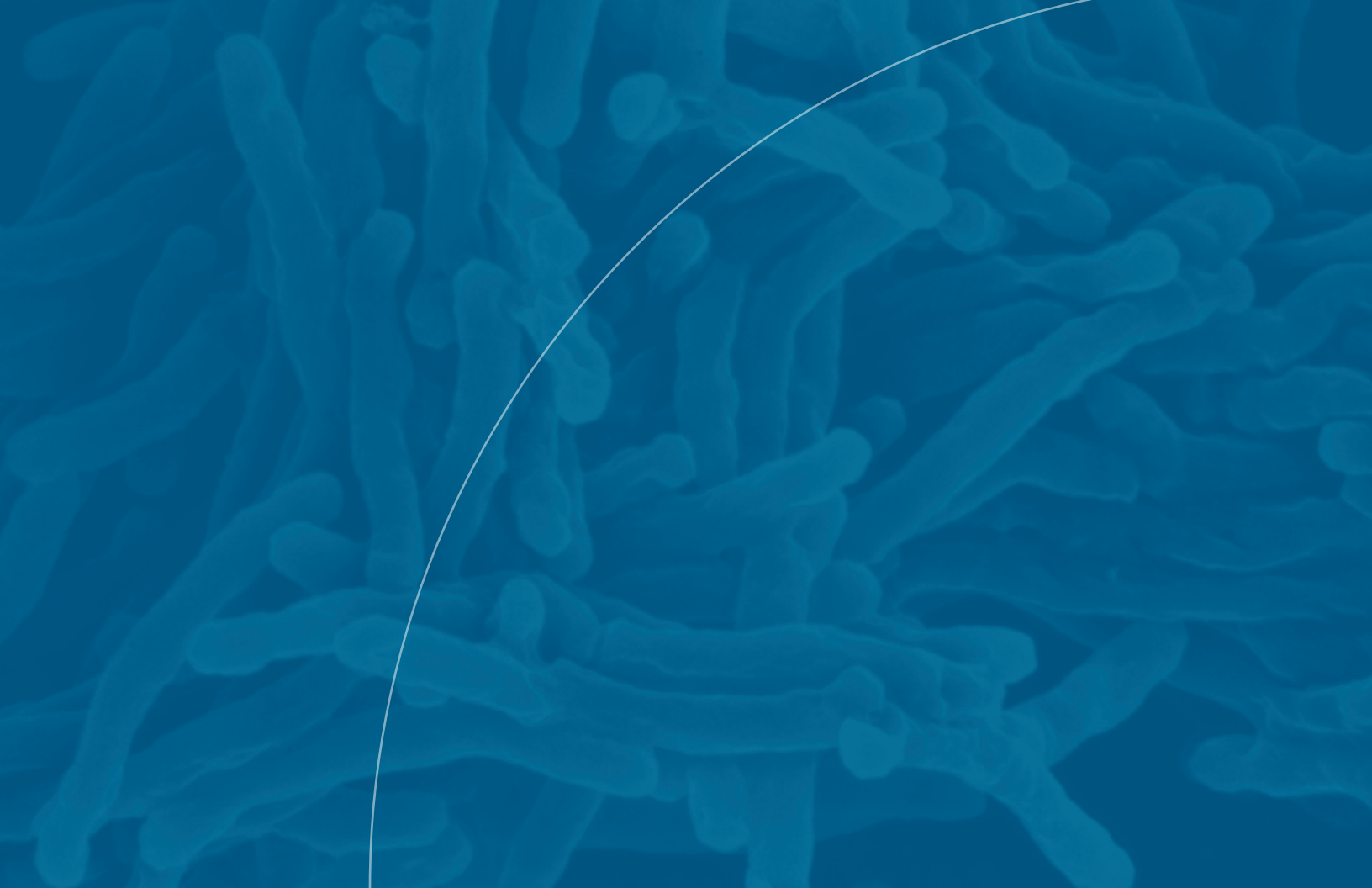
<https://findtbresources.cdc.gov/>

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Websites accessed December 30, 2015.







CURRY  
INTERNATIONAL  
TUBERCULOSIS  
CENTER

[www.currytbcenter.ucsf.edu](http://www.currytbcenter.ucsf.edu)

The Curry International Tuberculosis Center is a project of the University of California, San Francisco, funded by the Centers for Disease Control and Prevention