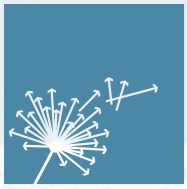

FRANCIS J. CURRY
NATIONAL
TUBERCULOSIS
CENTER

Drug-Resistant Tuberculosis

A SURVIVAL GUIDE FOR CLINICIANS 2ND EDITION

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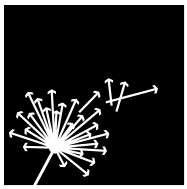

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Introduction to this *Survival Guide*

The Problem of Drug-Resistant Tuberculosis

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

1. Monoresistant: Resistant to only one anti-tuberculosis drug
2. Multidrug-resistant (MDR): Resistant to at least isoniazid (INH) and rifampin (RIF), considered to be the two most effective anti-tuberculosis drugs
3. Polyresistant: Resistant to more than one anti-tuberculosis drug, but not the combination of INH and RIF
4. Extensively drug-resistant (XDR): Resistant to at least INH and RIF, any fluoroquinolone, and at least one of three injectable second-line drugs (amikacin, kanamycin, or capreomycin)

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

The Need for Expertise

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

The Tuberculosis Control Branch of the California Department of Public Health (CDPH) has developed a systematic approach to consultation on cases of drug-resistant TB in California. The CDPH model builds on the experience and shared expertise of two successful programs: the Texas Department of State Health Services and the Los Angeles County MDR-TB Unit. To complement its service, CDPH collaborated with the Francis J. Curry National Tuberculosis Center (CNTC) in San Francisco to develop the first edition (2004) of *Drug-Resistant Tuberculosis: A Survival Guide for Clinicians*. Recognizing the national need for such a resource, CDPH and CNTC disseminated the *Guide* to jurisdictions and providers across the country. This second printing of the second edition of the *Guide* presents the best practice strategies available in late 2008.

What's New in the Second Edition of the *Guide*

- Updated epidemiology of TB and MDR-TB (Chapter 1)
- Emergence of XDR-TB (Chapter 1)
- Treatment for XDR-TB (Chapter 3)
- Information about interferon gamma release assays (IGRAs), new blood tests for LTBI (Chapter 10)
- Updated Medication Fact Sheets (Chapter 4)
  Gamma-interferon and gatifloxacin are no longer included. Gamma-interferon was shown to not be useful in treatment of MDR-TB in a clinical trial, and gatifloxacin is no longer available in the United States.
- Updated information about Patient Assistance Programs for TB medications and infection control guidelines (Chapter 8)
- Updated listings of Expert Resources, Lab Resources, International Resources, and Multicultural Resources (Appendices)

Description of the *Guide* and Target Audience

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

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

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

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

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

- **Duration of daily aminoglycoside/capreomycin therapy:** Assuming good clinical and microbiologic response, some experts feel comfortable using daily injectable therapy for as little as a month or 2 before changing to 3-times-weekly therapy. Others use 6 months of daily therapy (barring toxicity or renal impairment) before changing to intermittent therapy.
- **Total duration of injectable drug therapy:** The most quoted guideline recommends 4 to 6 months of aminoglycoside/capreomycin therapy. All experts would use longer injectable therapy if there was delayed response to therapy, or if there were fewer than 3 to 4 oral drugs remaining in the regimen. Some experts routinely use the injectable drug 12 months from the time of culture conversion.
- **Dose of aminoglycoside/capreomycin:** The standard daily/intermittent dose for the aminoglycosides is 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.
- **Number of drugs in the regimen:** Older recommendations suggested that a regimen of 2 to 3 drugs to which the isolate is susceptible was acceptable. Newer series suggest that better outcomes are associated with more drugs. Expert opinion varies: some begin with 4 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.
- **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 other diarrheal processes). Some experts use TDM routinely and serially, especially for monitoring the levels of injectable drugs.

- **Duration of therapy:** Some experts recommend 18 to 24 months of therapy total, and some treat 18 to 24 months from the time of culture conversion. Pediatric series have used shorter durations of therapy.
- **Treatment of MDR-LTBI and use of window prophylaxis for MDR-TB contacts:** Some providers use fluoroquinolone monotherapy for MDR-LTBI, some use 2-drug therapy, and some experts and jurisdictions would never use window prophylaxis for contacts to MDR-TB, while others would treat the most at-risk individuals with 2 drugs to which the isolate is susceptible.

Managing drug-resistant TB is extremely challenging. National guidelines call for treatment of drug-resistant TB to be provided by or in close consultation with experts. Regardless of their individual styles, the experts in treatment of drug-resistant TB have developed insight from treating many different patients in different situations. This *Guide* should be considered a supplemental resource to expert consultation. Contact information for expert resources can be found in Appendix 1.

List of Acronyms and Abbreviations

ad	right ear
AFB	acid-fast bacilli
AIDS	acquired immunodeficiency syndrome
AK	amikacin
ALT	alanine aminotransferase
ANA	antinuclear antibodies
ART	antiretroviral therapy
as	left ear
AST	aspartate aminotransferase
ATS	American Thoracic Society
BAL	bronchoalveolar lavage
BCG	bacille Calmette-Guérin
BID	twice a day
BUN	blood urea nitrogen
Ca	calcium
CAPD	continuous ambulatory peritoneal dialysis
CBC	complete blood count
CDC	Centers for Disease Control and Prevention
CDPH	California Department of Public Health
CM	capreomycin
CNS	central nervous system
CNTC	Francis J. Curry National Tuberculosis Center
CS	cycloserine
CSF	cerebrospinal fluid
CXR	chest x-ray
DOT	directly observed therapy
EMB	ethambutol
ETA	ethionamide
FDA	Food and Drug Administration
FQN	fluoroquinolone
GI	gastrointestinal
HEPA	high efficiency particulate air
Hgb	hemoglobin
HIV	human immunodeficiency virus
IGRA	interferon gamma release assay
IM	intramuscular
INH	isoniazid
IUATLD	International Union Against Tuberculosis and Lung Disease
IV	intravenous
KM	kanamycin
LFT	liver function test
LFX	levofloxacin
LTBI	latent tuberculosis infection
MAC	*Mycobacterium avium* complex
MAO	monoamine oxidase
M. bovis	*Mycobacterium bovis*
M. tuberculosis	*Mycobacterium tuberculosis*
MDR-TB	multidrug-resistant tuberculosis (resistant to at least isoniazid and rifampin)

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Mg	magnesium
MIC	minimum inhibitory concentration
MIRU	mycobacterial interspersed repetitive units
NAAT	nucleic acid amplification test
NIOSH	National Institute for Occupational Safety and Health
NJMRC	National Jewish Medical and Research Center
NPO	nothing by mouth
NSAID	nonsteroidal anti-inflammatory drug
NTM	nontuberculous mycobacteria
OB	obstetrics
od	right eye
os	left eye
PAP	patient assistance program
PAS	para-aminosalicylate
PCR	polymerase chain reaction
Plt	platelet
PO	by mouth
PPD	purified protein derivative
PR	per rectum
PRN	as needed
PRUCOL	Permanent Residence Under Color of Law
PZA	pyrazinamide
qam	every morning
qd	once a day
qhs	every evening
qid	four times a day
QFT-G	QuantiFERON®-TB Gold
QFT-GIT	QuantiFERON®-TB Gold In Tube
QT	the interval from the beginning of the QRS complex to the end of the T wave on an electrocardiogram
RFB	rifabutin
RIF	rifampin
SGPT	serum glutamic-pyruvic transaminase
SIRE	streptomycin, isoniazid, rifampin, ethambutol
SJS	Stevens Johnson Syndrome
SM	streptomycin
SSRI	selective serotonin reuptake inhibitor
TB	tuberculosis
TEN	toxic epidermal necrolysis
TID	three times a day
TSH	thyroid stimulating hormone
TST	tuberculin skin test
WBC	white blood cell
WHO	World Health Organization
XDR-TB	extensively drug-resistant tuberculosis

1 Epidemiology & Background

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

Pathologic evidence of tuberculosis (TB) has been found in Egyptian mummies, and Hippocrates described phthisis (consumption) as the most widespread disease of the times. Some of TB's more famous casualties include Anton Chekov, Frederick Chopin, Robert Louis Stevenson, George Orwell, and Charlotte and Emily Brontë. It is little wonder that the discovery of effective anti-tuberculosis drugs in the 1940s was hailed as a medical milestone. Tragically, in the last 25 years, the misuse of these "miracle" drugs has resulted in a new public health problem: drug-resistant TB. For various reasons, elimination of tuberculosis has not been achieved, despite the availability of effective chemotherapy.

*Multidrug-resistant tuberculosis (**MDR-TB**): A TB isolate resistant to at least isoniazid (INH) and rifampin (RIF)*

Global Response

Fortunately, there is renewed energy for control of TB and for treatment of drug-susceptible and drug-resistant TB worldwide.

- With the goal of unifying the approach to diagnosis and treatment of TB globally, a collaboration of international organizations has recently endorsed and published a set of standards of care for tuberculosis. The ***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, tuberculosis. These international standards differ from existing guidelines in that standards present what should be done, whereas guidelines describe how the action is to be accomplished. Two of the 17 standards specifically address drug-resistant disease.
  - Standard 14 advises an assessment of the likelihood of drug resistance for TB patients and culture and susceptibility testing for patients at risk of resistance.
  - Standard 15 recommends use of specialized regimens for MDR-TB, including at least 4 drugs to which the organism is known or presumed to be susceptible for at least 18 months.
- The ***Patients' Charter for Tuberculosis Care*** was developed by the World Care Council in tandem with the ISTC to promote a "patient-centered" approach to tuberculosis care. Initiated and developed by patients from around the world, this document outlines the rights and responsibilities of people with tuberculosis defining what the patient should expect from the provider and what the provider should expect from the patient.
- Around the world, many international organizations are working to control and prevent TB; for a partial list, see Appendix 2, "Contact Information for Selected Organizations Working to Control and Prevent TB in the International Arena."
- Along the United States–Mexico border, a number of organizations and collaborations exist to address TB control:

- **CureTB** (operated from the San Diego TB Control Program) and **TBNet** (operated by the Migrant Clinicians Network in Austin, Texas) are designed to improve continuity of care and access to health care for TB patients who move between Mexico and the United States.
- **Puentes de Esperanza** is a binational program created to diagnose, treat, and prevent drug-resistant TB in Baja California.
- Many of the **state health department TB control programs** along the border collaborate with these programs to provide care and continuity for TB patients.

Long-term control and prevention of TB, including drug-resistant TB, will require:

- Prioritization of TB by policy makers; political will
- Resources for TB control activities
- Effective, well-organized TB control programs
- Widespread surveillance and accurate reporting systems
- Adequate and accessible laboratory services for timely TB diagnosis and susceptibility testing
- Supervision of therapy—directly observed therapy (DOT) in context of patient-centered management
- Adherence to published protocols and standards, including sound infection control measures (especially in high HIV-prevalence settings)
- Adequate supply of anti-tuberculosis first- and second-line drugs
- Research and development into new diagnostics, drugs, and vaccines
- Access to specialized centers with expertise in use of second-line drugs and alternate therapies

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

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

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

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

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

Extremely drug-resistant (XDR)-TB is a strain that is resistant to isoniazid, rifampin, a fluoroquinolone, and at least one of three injectable second-line drugs (amikacin, kanamycin, or capreomycin).

XDR-TB: The Latest Chapter in the Evolution of Drug-Resistant TB

In 2006, details about an outbreak of HIV-associated XDR-TB emerged from Tugela Ferry, KwaZulu-Natal Province in South Africa. Of 221 MDR-TB cases identified during a 14-month period in this isolated community, 53 (23%) were also resistant to kanamycin and ciprofloxacin. Half of the patients were new cases of TB. Among the 53 patients, 44 were tested for HIV, and all 44 were HIV-positive. The mortality rate among the 53 patients was shocking: 52 (98%) of the patents died within weeks of initial sputum collection. The rapid spread of disease was attributed to inadequate infection control in the crowded rural hospital.

The Tugela Ferry outbreak tragically demonstrated both the emergence and dire consequences of XDR-TB. **Worldwide health experts mobilized to respond to the crisis, and WHO issued a revised definition of XDR-TB in its 2006 global alert: "TB that is resistant to isoniazid, rifampin, a fluoroquinolone, and at least one of three injectable second-line drugs (amikacin, kanamycin, or capreomycin).**

Not all XDR patients die, but high mortality is associated with **HIV coinfection,** as seen in South Africa. For all XDR patients, the risk of mortality is increased because treatment options are extremely limited and rely on regimens that are less effective, highly toxic, lengthy, and expensive.

In March 2007 a single case of suspected XDR-TB gained worldwide notoriety when an American lawyer disregarded warnings not to travel and boarded several international flights to and within Europe, exposing hundreds of passengers from multiple countries to a TB isolate subsequently diagnosed as XDR (but later confirmed to be MDR.) The case raised urgent issues regarding not only drug-resistant TB and its transmission, but the strength of governmental quarantine and isolation authority.

As of early 2008, XDR-TB was reported from 45 countries.

In the United States, from 1993-2006, 49 cases of XDR-TB were identified, involving 9 states and New York City. During the same period in California, among 425 MDR-TB with complete drug susceptibility reporting, 19 (4.5%) were XDR and 77 (18%) were pre-XDR.*

*When considering the burden of MDR and XDR in a given population, a significant but often overlooked category is "**pre-XDR,**" described as MDR-TB isolates with **resistance to a fluoroquinolone or an injectable, but not both.** Because pre-XDR is merely one drug away from developing into XDR, some researchers now include this transitional category of resistance in their analyses.

TB Epidemiology Overview

- The World Health Organization (WHO) estimates that each year there are **9 million new TB cases.** Annually, **TB kills approximately 1.5 millon people,** making it second only to HIV/AIDS as the leading cause of death from infectious disease.
- **Approximately 2 billion people (1 in 3 individuals worldwide) are infected with *Mycobacterium tuberculosis*.** Among those infected with *M. tuberculosis,* approximately **50 million are infected with drug-resistant strains.**
- Worldwide, an estimated **490,000 cases of MDR-TB** emerge each year, (5.3% of all new and previously treated TB cases), resulting in 110,000 deaths.
- In the United States, drug resistance in foreign-born persons with TB is much more common than in persons born in the United States, corresponding to the higher rates of drug resistance in the countries of origin. In 2006, **80% of multidrug-resistant TB (MDR-TB) cases in the United States were among foreign-born persons.**
- Fortunately, in the United States, drug-resistant TB has been declining in all categories (U.S.-born, foreign-born, previously treated and no previous history of TB) since the early to mid 1990s. For example, among foreign-born individuals not previously treated for TB, resistance to isoniazid (INH) peaked in 1998 at 640 cases (11.3%) and in 2006 was down to 577 cases (10.2%). MDR-TB in previously untreated foreign-born individuals declined from 110 (2.1%) in 1994 to 73 (1.3%) in 2006.

Global Burden of Drug Resistance

Accurate data regarding rates of drug resistance are not universally available. Prior to 1994, rates of drug resistance were mostly based on non-standardized, non-representative samples. Starting in 1994, WHO began to systematically sample countries or regions in order to better assess rates of drug-resistant TB, and new statistical models have recently been developed to approximate the data missing from over 100 countries. The latest estimates portray a sobering snapshot of MDR's worldwide presence:

- In 2004, there were an estimated 424,203 cases of MDR-TB worldwide, of which 181,408 occurred from previously treated cases. There were 116,000 deaths from MDR-TB.
- With a total of 261,362 cases, China, India, and the Russian Federation accounted for nearly two-thirds of the estimated global MDR-TB burden.

In its 2007-2008 global response plan, WHO identified the top 25 priority MDR-TB and XDR-TB countries, based on their estimated MDR-TB burden and their proportion of MDR-TB among new and previously treated cases combined (see Table 1). The selected countries constitute 85% of the global burden of MDR-TB.

- The five countries with the highest **number** of MDR cases are China, India, the Russian Federation, South Africa, and Indonesia.
- In the list of countries with the highest **proportions** of MDR-TB cases among all new and previously treated cases, nations within the Eastern European region – such as Kazakhstan, Estonia, Georgia, Azerbaijan, Uzbekistan, and the Republic of Moldova—dominate the entire first half of the list:

Unfortunately, the latest and most deadly form of drug resistance, XDR-TB, is now found in 45 countries throughout the world, including the United States.

Note: Laboratory capacity in Africa is severely limited, and only 6 African countries were able to provide drug resistance data for WHO's 2008 report.

TABLE 1: **The 25 priority MDR-TB and XDR-TB countries, 2007–2008**

Country	Estimated proportion of MDR-TB among combined* cases (%)	Estimated total number of MDR-TB cases
Kazakhstan	23.4	6,718
Estonia	20.1	147
Georgia	19.5	980
Republic of Moldova	18.9	1,459
Azerbaijan	18.8	1,579
Uzbekistan	18.5	7,043
Russian Federation	16.8	34,055
Lithuania	16.4	422
Ukraine	13.6	7,854
Latvia	11.5	208
Tajikistan	10.9	1,394
Kyrgyzstan	10.6	766
Belarus	10.4	707
China	8.9	139,894
Myanmar	5.2	4,756
India	4.1	87,413
Pakistan	3.2	9,306
Vietnam	3.2	5,033
South Africa	2.6	10,348
Democratic Republic of the Congo	2.3	4,941
Bangladesh	2.2	7,216
Nigeria	2.0	7,969
Ethiopia	1.9	5,102
Indonesia	1.8	10,024
Philippines	1.8	4,469
TOTAL		**359,803**

*New MDR-TB cases plus previously treated MDR-TB patients.
MDR-TB: multidrug-resistant tuberculosis
XDR-TB: extensively drug-resistant tuberculosis
Source: World Health Organization: The Global MDR-TB & XDR-TB Response Plan, 2007-2008

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

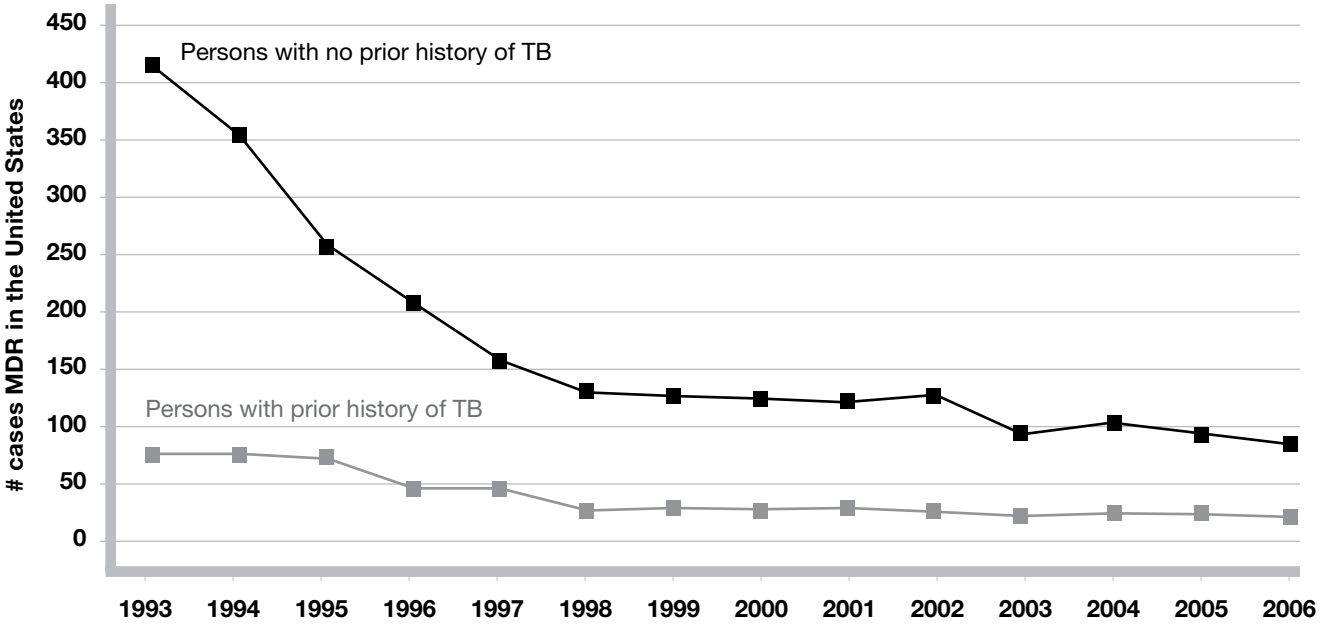
In the year 2004, there were an estimated 424,203 new and previously treated cases of MDR-TB in the world (representing just over 4% of all new and previously treated cases). This figure is in contrast to the 1960s, when rifampin was introduced and not a single MDR case had yet been documented. Appropriate care of these MDR-TB patients would cost more than the care of all drug-susceptible cases **combined**. A recent survey of local XDR-TB cases in Southern California estimated the cost of inpatient treatment for a single XDR-TB case to be $600,000 in 2006 dollars.

Drug-Resistant TB in the United States

- In 2006: 13,779 TB cases (4.6 per 100,000) were reported in the United States. There were 646 deaths from TB in 2005 (the latest year for which complete data are available).
- In 2006, among the cases reported that were **new cases** (no previous history of TB): 7.7% were INH-resistant and 0.9% were caused by MDR-TB strains.
- Among the cases reported with **previously treated** TB: 13.6% were INH-resistant and 4.2% were caused by MDR-TB strains.
- The number of MDR-TB cases in the United States has declined steadily since 1993 (see Figure 1) after aggressive public health intervention in the early 1990s. Completion of therapy by DOT and effective infection control measures have helped to control the spread of MDR-TB in immunocompromised and hospitalized individuals.
- **In 2006, 45 states reported INH-resistant TB cases; 25 states reported MDR-TB.**
- California, New York, and Texas contribute the highest number of drug-resistant TB cases to the U.S. total, accounting for just over one-half of the MDR-TB cases reported in 2006.
- California, with nearly 3000 cases of TB annually, has reported the largest number of MDR-TB cases in the nation since 2002. California's MDR-TB cases decreased from 42 in 2005 to 31 in 2006. Given the lengthy period of treatment, the prevalence of MDR-TB cases can be more than twice the number of new cases reported in a given year.
- In 2006, 73 of 91 (80%) new cases of MDR in the United States were foreign-born. In California, more than 85% of MDR cases were foreign-born. In 1993, 25% of patients with MDR-TB in the United States were foreign-born, and the percentage has gradually increased to the current level.

FIGURE 1.

MDR-TB in the United States, 1993-2006



Source: Centers for Disease Control and Prevention

Of the foreign-born patients diagnosed with MDR-TB in the United States from 2005 to 2006, 81% were born in only 14 countries. Table 2 shows the drug resistance pattern for the top 14 countries of origin for United States cases of drug-resistant TB. Younger patients, patients who have recently immigrated, and patients previously treated for TB will have higher rates of resistance. In addition, the true measure of MDR and XDR remains underestimated due to continuing surveillance gaps in many regions of the world.

TABLE 2.

Drug Resistance Among Foreign-Born Persons in the United States, 2005–2006 Combined

Country of origin	Total TB cases*	MDR		Any resistance		INH resistance	
		No.	%	No.	%	No.	%
Mexico	2969	26	0.9	508	17.1	244	8.2
Philippines	1350	20	1.5	242	17.9	192	14.2
Vietnam	985	19	1.9	280	28.4	185	18.8
India	878	22	2.5	134	15.3	101	11.5
China	612	18	2.9	102	16.7	81	13.2
Guatemala	342	7	2.0	54	15.8	25	7.3
Haiti	334	5	1.5	43	12.9	36	10.8
Republic of Korea	312	7	2.2	46	14.7	37	11.9
Ethiopia	276	5	1.8	56	20.3	40	14.5
Peru	253	10	4.0	57	22.5	36	14.2
Somalia	237	4	1.7	50	21.1	26	11.0
Ecuador	203	3	1.5	29	14.3	18	8.9
Laos	122	9	7.4	29	23.8	19	15.6
Russia	68	6	8.8	14	20.6	11	16.2

* Total cases with positive cultures and initial susceptibilities performed
Source: Centers for Disease Control and Prevention, National Tuberculosis Surveillance System

TB Drugs and the Development of Resistance

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

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

Clinical Use of Anti-Tuberculosis Drugs in the United States	
1945	Streptomycin
1946	Para-aminosalicylic Acid
1952	Isoniazid / Pyrazinamide
1962	Ethambutol
1967	Rifampin

Evolution and Genetic Basis of Drug-Resistant TB

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

- **Selection of the naturally occurring drug-resistant mutants by inadequate TB treatment will cause the population of *M. tuberculosis* bacteria to become increasingly drug-resistant. As the drug-susceptible organisms are killed during sub-optimal treatment, the drug-resistant mutants become an increasing proportion of the disease burden.**

- A large body of knowledge has been accumulated regarding the molecular basis for drug resistance in *M. tuberculosis.*
- Known mutations account for most resistance of strains of *M. tuberculosis* to INH, RIF, pyrazinamide (PZA), SM, EMB, and fluoroquinolones (see Table 3).
- Some strains are drug resistant and do not have any of the known mutations.

TABLE 3.

Mutations

Anti-tuberculosis drug	Gene mutated	% of mutations	Product of that gene
Isoniazid	*katG*	40–60%	Catalase-peroxidase *(activates INH)*
Isoniazid – ethionamide	*inhA*	15–43%	Reductase analog *(Mycolic acid synthesis)*
Isoniazid	*ahpC*	10%	Hydroperoxidase reductase
Isoniazid	*kasA*	unknown	Carrier protein synthase
Rifampin	*rpoB*	>96%	Subunit of RNA polymerase
Pyrazinamide	*pncA*	72–97%	Pyrazinamidase
Ethambutol	*embB*	47–65%	Arabinosyltransferase
Streptomycin	*rpsL or rrs*	50–75%	Ribosomal protein S12 / 16S rRNA
Fluoroquinolones	*gyrA*	75–94%	DNA gyrase A subunit

Factors that Create Resistance

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

- The patient may not take all the drugs prescribed, due to any of the following factors:
  - **Lack of resources**
  - **Intolerance/toxicity**
  - **Misunderstanding**
  - **Interrupted drug supply**
  - **Disbelief 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 a large enough dose to be effective.
- The patient may not absorb the full dose of medication and/or have disease in areas where the penetration of 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, 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; repeated courses of a fluoroquinolone for community-acquired pneumonia).
- The patient may take TB medicines available without a prescription.
- The TB medicines may interact with other drugs being taken by the patient.

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

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

Summary

- **Worldwide, there is renewed energy for control of TB and for treatment of drug-susceptible and drug-resistant TB.**
- **Sustained political will, significant resources, and efficient TB control programs are required to reverse the trend of TB drug resistance.**
- **There are 2 types of drug-resistant TB cases: "new cases"** (infected by an already drug-resistant strain) **and "previously treated" TB cases.**
- The latest evolution of drug-resistance, **XDR-TB,** is found in 45 countries, including the United States. **High mortality is associated with HIV coinfection.**
- **Drug-resistant TB in all its variations** (monoresistant, polyresistant, MDR, and XDR) **is found throughout the world.** High-burden areas of the world include China, India, and the Eastern European region.
- Although MDR-TB in the United States has declined over the last decade, 45 states reported drug-resistant cases in 2006. **California, New York, and Texas have the highest numbers of MDR-TB cases. Between 2000 and 2006, 17 cases of XDR-TB were reported in the United States.**
- **The incidence of drug-resistant TB in the United States is highest among foreign-born cases.**
- **Mutations leading to drug-resistant *M. tuberculosis* occur spontaneously and independently.** The tiny populations of inherently resistant mutants are easily treated during appropriate multidrug TB regimens. Inadequate TB treatment or inadvertent mono-drug therapy allows for the proliferation and eventual clinical significance of drug-resistant populations.

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2 Diagnosis

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

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

Risk Assessment for Drug Resistance

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

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

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

The most important predictors of drug-resistant TB are:

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

Risk Factors in Persons <u>with</u> a History of TB

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

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

Risk Factors in Persons <u>without</u> Prior TB History

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

- **Exposure** to a person with documented drug-resistant TB
- **Residence in or travel to a region** with high rates of drug-resistant TB
- Residence or work in an **institution** or setting in which drug-resistant TB is documented
- **Treatment of pulmonary problems with a prolonged course of multiple medicines or an injectable agent for more than a few weeks in a foreign country;** i.e., the patient may not realize that he/she was treated for TB
- Treatment of a pulmonary problem with a **fluoroquinolone**
- **Previous treatment for latent TB infection (LTBI)** when signs of TB disease were not recognized

Questions to Ask Your Patient

Soliciting history of previous TB treatment requires a great deal of patience and attention to detail. In a culturally sensitive and confidential setting, allow plenty of time, utilize an accurate and unbiased medical interpreter (if necessary), and be willing to repeat or rephrase a question to obtain the information. Give the patient encouragement to reveal accurate information by asking and responding in a 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 for a lung problem?**
- **Have you purchased and used medicated cough syrups in a foreign country?**

If your patient answers **"yes"** to any question(s) that indicate he or she may have been previously treated for TB:

- Where were you treated?
- What drugs did you receive?
- How many different drugs? How many pills each day? What size and colors were the pills/capsules?
- Did you receive injections?
- How long were you on treatment?
- When did you start?
- When did you stop? Why did you stop (completed treatment, adverse reaction)?
- It's hard to remember to take medicine everyday. Did you take medications daily? Every pill?
- TB medicine is expensive. Were you ever without medication?
- Did you miss medication sometimes? How often?
- Did healthcare workers observe you taking your medications?
- Did your urine turn orange?
- Did you feel better?
- Did you ever have a sputum examined? What was the result?
- If positive, did your subsequent sputa test negative?
- Did your doctor ever tell you: That you had to be treated for TB longer? That you had a return of TB? That you had drug resistance?
- Did your TB symptoms return after finishing treatment?

If the patient was previously treated for TB in the United States or Mexico, records detailing his/her treatment should be obtained from the local jurisdiction or CureTB (see Appendix 2, "Contact Information for Selected Organizations Working to Control and Prevent TB in the International Arena"). If the patient was treated in Western Europe or by a private provider in a developed country, records may be available and should be sought. Appendix 3, "International Resources for TB Treatment and Policies," lists Websites that may be helpful in identifying TB policies in selected countries.

If your patient answers **"no"** to the questions that indicate he or she may have been previously treated for TB:

- Have you been exposed to or had contact with anyone with TB?
- If yes, when was that?
- What is that patient's name and birthdate? Where was he/she treated? How long was he/she treated? Was he/she cured?
- Did you have a skin test? Do you know the results?
- Did you have a chest X-ray? Do you know the results?
- Did you receive medications to prevent TB? If so, what drugs and for how long? Did you come to a clinic for the medications where a 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?

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

Multidrug-resistant TB (MDR-TB) refers to an isolate which is resistant to at least isoniazid and rifampin. Extensively drug-resistant TB (XDR-TB) refers to an MDR-TB isolate which is also resistant to a fluoroquinolone and at least one of the following injectable drugs: amikacin, kanamycin or capreomycin.

Testing for TB Infection

Suspicion or evaluation of TB sometimes begins with the use of the tuberculin skin test (TST) or an interferon gamma release assay (IGRA) such as QuantiFERON®-TB Gold (QFT-G) or T-SPOT.*TB*. Neither the IGRAs nor the TST have 100% sensitivity nor specificity for diagnosis of TB infection, and their ability to detect TB disease may be even less. Studies suggest that among newly diagnosed, culture-positive TB cases, the TST and QFT-G may be positive in as few as 80% and 70% of cases respectively. A negative TST or IGRA test does not rule out TB disease.

Laboratory Diagnosis

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 TB requires that *M. tuberculosis* be isolated and drug susceptibility results be completed and conveyed to the clinician. Prompt turnaround time for laboratory results is of paramount importance in rapid diagnosis and appropriate treatment of drug-resistant TB, including multidrug-resistant TB and extensively drug-resistant TB.

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

The laboratory's results are essential for TB patient management, infection control, and public health. This dual charge, serving patient care and public health, must be viewed within the context of the social, political, economic, scientific, and technical changes that are occurring in industrialized countries. All the stakeholders should form a synergistic network, making the whole of the virtual organization more effective than the sum of its parts.

The laboratory diagnosis of TB begins with the requisition form. The healthcare provider, TB control, and TB laboratory need to design forms that serve all parties involved, benefiting patient care and control of tuberculosis. The following information is needed in order to optimize scarce resources in the current healthcare environment and to optimize the laboratory's contribution:

- Diagnostic versus follow-up specimen?
- Date when anti-TB treatment was started and drug regimen?
- In congregate setting?
- In respiratory isolation?
- Is drug resistance suspected?

The laboratory is charged with informing its partners of the conditions for optimum testing, such as sample volume requirements, transit conditions, and test limitations. While public health laboratories can fine-tune their operations with careful communication with local TB control programs, this may pose a challenge for commercial laboratories serving the entire country.

Laboratory Turnaround Times

Growth detection and identification of *M. tuberculosis* complex may take a few weeks. Drug susceptibility testing of a TB isolate 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 susceptibility testing. Delays in the return of reports of culture confirmation and susceptibility results will delay the diagnosis of drug-resistant TB and initiation of appropriate treatment.

Fortunately, newer laboratory strategies and technologies are impacting TB care. One of the *Healthy People 2010* goals for TB care is to reduce the average time for a laboratory to confirm and report TB cases from 21 days in 1996 to 2 days for 75% of cases. To overcome the poor sensitivity and specificity of smear microscopy, the use of nucleic acid amplification in facilities such as the Orange County Public Health Laboratory in California has demonstrated the ability to nearly reach this goal (75% of cases detected within 4 days). Novel technologies, such as line probe assays and molecular beacon assays, have been studied or implemented, enabling rapid screening for MDR-TB by direct testing of sputum sediment without waiting for growth from cultures.

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

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

Because drug susceptibility results are essential for prescribing appropriate regimens for treating drug-resistant TB, **second-line susceptibility tests should be requested as soon as drug resistance is suspected or identified.** Consult with the laboratory about which second-line susceptibility tests (if any) are performed and which reference laboratory it is using. See Appendix 4, "Laboratory Resources," for tests performed by some of the public health and reference laboratories. Clinicians should contact their state or local TB programs or an expert in MDR-TB for assistance in identifying a qualified public health/reference laboratory, if necessary. In some jurisdictions, molecular methods are available to rapidly detect some drug resistance.

If drug resistance is strongly suspected based on the patient's prior treatment history or exposure to drug-resistant disease, concerns should be discussed immediately with the laboratory director.

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

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

False-Positive Results

False-positive results for isolation of *M. tuberculosis* complex or detection of drug resistance may occur. When there is a question regarding laboratory results, it is important to discuss the situation with the laboratory.

- **When would a clinician suspect a false-positive result?**
  - When the patient's clinical manifestations do not seem to be compatible with the laboratory finding
  - When only 1 culture is positive among several specimens collected or there are discrepant results among different cultures from the same patient
- **When would the laboratory suspect a false-positive result?**
  - When a culture is late to turn positive (at 5 or 6 weeks), especially if there is close proximity to another strongly positive culture (suggesting possible cross-contamination)
  - When unusual drug resistance patterns are found in unrelated patients suggesting possible misinoculation or mislabeling of specimens

Possible causes of discrepant results, pseudo-outbreaks and misdiagnosis of drug-resistant TB include:

- **Errors may occur at the specimen collection site:**
  - Mislabeling of specimens at the clinic, ward, or bronchoscopy suite
  - Contamination of medical devices used for collecting specimens, such as inadequate sterilization of bronchoscopy tubing
- **Errors may occur 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 drug susceptibility testing
  - Malfunctioning biosafety cabinet
  - Malfunction of laboratory test systems
  - Cross-contamination due to poor technique or using a common vessel to add reagents among specimens.

- Failure to check for contamination with bacteria
- Failure to check for mixed infection with nontuberculous mycobacteria (NTM)
- Result-entry errors

- **When investigating discrepant results, check all possible sources of errors.**
  - If possible, test another isolate from the same patient.
  - Repeat testing on original sample (if still available).
  - Repeat susceptibility testing by using another method or another laboratory.
  - Consult with experts. It may take a team effort, with candid communication between the healthcare provider and laboratory personnel, to find a solution.

Susceptibility Testing

Susceptibility Interpretations

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

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

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

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

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

Susceptibility Methods

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

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

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

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

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

BACTEC 460 TB method: *M. tuberculosis* is grown in bottles of broth containing $^{14}CO_2$-labeled substrate. The BACTEC 460 TB system is well standardized and very reliable; however, it is a radioactive test system and requires the use of needles/syringes and is not fully automated. (See Appendix 10, "BACTEC 460 TB Method.")

Newer broth methods: Other broth systems have been developed to detect mycobacterial growth in a fully automated system. In addition, these systems can be used for drug susceptibility testing. These include the following:

- **BACTEC MGIT 960** is a nonradiometric antimicrobial susceptibility system for testing *M. tuberculosis* complex from broth culture. It has been validated to provide results for SM, INH, RIF, EMB (SIRE) and PZA in a time frame close to the BACTEC 460 TB system. MGIT 960 has been Food and Drug Administration (FDA) approved.
- **VersaTREK** is an automated method that was first developed for blood cultures and later adapted for the recovery and drug susceptibility of mycobacteria. It has been validated for performing qualitative susceptibility testing with INH, RIF, EMB and PZA with *M. tuberculosis* complex isolates.
- **MB/BacT ALERT 3D** is a nonradiometric antimicrobial susceptibility system for testing *M. tuberculosis* complex isolates. It was developed to provide susceptibility results for SM, INH, RIF, and EMB, but recently, critical concentrations of the drugs listed were modified and a new acidified vial for standardized PZA testing was introduced. However, no antimycobacterial drugs have been cleared for susceptibility testing with this system by the FDA.

Molecular methods: DNA is extracted from the bacteria and amplified. Certain mutations associated with drug resistance can be detected. (See Appendix 7, "Molecular Methods.")

Variation in Results

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

- Although new methods are validated against the standard method, perfect agreement cannot 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. Long experience has shown that the reproducibility for testing of these strains can be poor.
- The different laboratories may not have actually used the same specimen.
- Errors can occur during drug-susceptibility testing:
  - **Failure to use a standardized inoculum** (well-dispersed suspension)
  - **Failure to add a drug to the 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 another organism,** which is more difficult to recognize in broth systems
- Changes in drug activity or support of mycobacterial metabolism can occur between different lots of culture media. Ideally, laboratories should check new batches of medium ingredients to verify that the medium they produce has the same drug activity as previous, validated lots of medium.
- If a subculture is tested, it may not represent the entire initial population.

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

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

Use of Strain Typing

Molecular genotyping of *M. tuberculosis* complex can be useful in:

- Detecting unrecognized outbreaks or confirming outbreaks under investigation
- Investigating or identifying possible false-positive culture results
- Distinguishing between relapse or reinfection (if a previous isolate is still available for genotyping)
- Documenting the amplification of initial monoresistance to MDR-TB versus reinfection with a more resistant strain

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

Overview of the CDC Tuberculosis Genotyping Program

Two public health genotyping laboratories, one in Michigan and one in California, are under contract with CDC to provide genotyping services to TB programs in the United States. TB programs, through their state public health laboratories, may submit one isolate from each culture-positive TB patient to a genotyping laboratory.

The genotyping laboratories will use three genotyping methods:

- **Spoligotyping**
- Mycobacterial interspersed repetitive units (**MIRU**) analysis
- IS*6110*-based restriction fragment length polymorphism (**RFLP**) analysis

Spoligotyping and MIRU analysis are polymerase chain reaction (**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. The genotyping services are free to TB programs, but neither CDC nor the genotyping laboratories will pay the packaging and shipping costs.

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

Therefore, it is particularly important that all drug-resistant TB isolates are genotyped.

Summary

- **Patients at highest risk of drug-resistant TB are those who:**
  - Previously have been treated for TB
  - Came from or traveled to regions/countries with high rates of drug resistance
  - Have been exposed to individuals with drug-resistant TB
  - Are failing TB treatment
- **Each TB patient should be assessed for risk of drug resistance.**
- **The laboratory is crucial in the diagnosis and management of drug-resistant TB.**
- **Communication to the laboratory that drug resistance is suspected is essential for rapid susceptibility testing and optimal patient care.**
- **Drug-resistant TB should be confirmed by a public health laboratory or experienced reference laboratory.**
- **Proper control of TB transmission requires timely performance of all laboratory testing and close communication between the clinician and the laboratory.**
- **All drug-resistant TB isolates should be genotyped.**

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Treatment

3

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

Introduction

Ideally, a treatment regimen for drug-resistant TB would be designed and initiated based on *in-vitro* drug-susceptibility test results for each patient's *M. tuberculosis* isolate. The choice of drugs would be based on:

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

Unfortunately, first-line susceptibility results are not available for several weeks and second-line results are frequently not available for 2 or more months. In several situations, the risk of drug resistance is anticipated and treatment for drug-resistant TB may be initiated even before susceptibility data returns:

- 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

The treatment regimen can be changed once the results of drug-susceptibility tests are available. More information regarding when and how to initiate an empiric regimen for drug-resistant TB prior to susceptibility results can be found later in this chapter.

Once drug resistance has been documented by *in vitro* drug susceptibility testing, the following treatment regimens are recommended:

Individualized Treatment Regimens

Monoresistant *Mycobacterium Tuberculosis*

Isolated Resistance to ISONIAZID (INH)

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

Option 1: Patients can be treated with daily rifampin (RIF), ethambutol (EMB), and pyrazinimide (PZA), 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.

Option 2: For patients with extensive disease, a fluoroquinolone may be added to the regimen. Treatment should continue daily for at least 6 months.

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

Isolated Resistance to RIFAMPIN (RIF)

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

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

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

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

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

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

Given the importance of having drug susceptibility results, every effort should be made to obtain high-quality specimens for culture and drug-susceptibility testing. Repeat 2 to 3 sputum cultures when changing regimens.

Polyresistant *Mycobacterium Tuberculosis*

TB due to organisms that demonstrate *in vitro* drug resistance to more than one anti-TB drug (but not INH and RIF) is referred to as polyresistant TB. Any number of combinations of resistance can occur, but the outcome of treatment is usually good. Treatment should include the addition 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 Monoresistant and Polyresistant TB

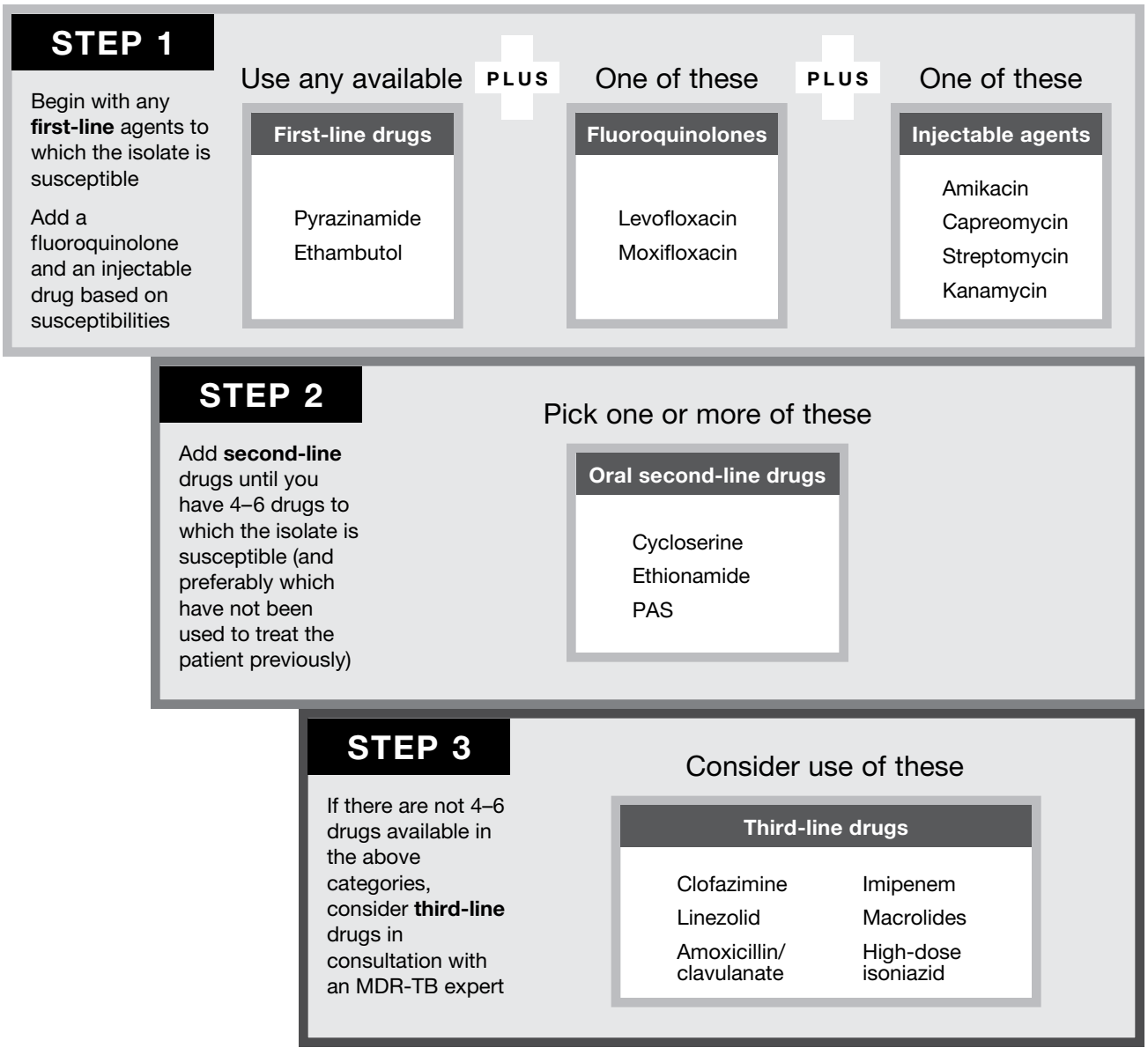
Pattern of Drug Resistance	**Suggested Regimen**	**Minimum Duration of Treatment** (mos)	**Comments**
INH (± SM)	RIF, PZA, and EMB	6–9 months	A fluoroquinolone (FQN) may strengthen the regimen for patients with extensive disease.
INH and PZA	RIF, EMB, and FQN	9–12 months	A longer duration of treatment should be used for patients with extensive disease
INH and EMB	RIF, PZA, and FQN	9–12 months	A longer duration of treatment should be used for patients with extensive disease.
RIF	INH, EMB, FQN, plus at least 2 months of PZA	12–18 months	An injectable drug may strengthen the regimen for patients with extensive disease
RIF and EMB (± SM)	INH, PZA, FQN, plus an injectable agent for at least the first 2–3 months	18 months	A longer course (6 mo) of the injectable may strengthen the regimen for patients with extensive disease.
RIF and PZA (± SM)	INH, EMB, FQN, plus an injectable agent for at least the first 2–3 months	18 months	A longer course (6 mo) of the injectable may strengthen the regimen for patients with extensive disease.
INH, EMB, PZA (± SM)	RIF, FQN, plus an oral second-line agent, plus an injectable agent for the first 2–3 months	18 months	A longer course (6 mo) of the injectable may strengthen the regimen for patients with extensive disease.
PZA	INH, RIF plus at least 2 months of EMB	9 months	Most commonly seen in *M. bovis* infections.

Multidrug-Resistant *Mycobacterium Tuberculosis* (MDR-TB)

Patients with MDR-TB, defined as resistance to at least INH and RIF, should always be treated with a minimum of 4 or more drugs to which the isolate is susceptible. In choosing drugs, begin with the available first-line drugs, and then add a fluoroquinolone and an injectable agent. Additional oral second-line drugs should be added to have a total of 4 to 6 drugs in the regimen. In patients with highly resistant organisms, alternative third-line drugs (in vitro activity against *M. tuberculosis*, limited clinical experience) may be needed. These should be chosen in consultation with someone who has experience using these drugs to treat MDR-TB (Figure 1).

FIGURE 1.

Building a Treatment Regimen for MDR-TB



Guidelines for Management of Multidrug-Resistant TB

- A single new drug should never be added to a failing regimen.
- When initiating or revising therapy, always attempt to employ at least 3 previously unused drugs to which there is demonstrated *in vitro* susceptibility. One of these should be an injectable agent.
- Sufficient numbers of oral drugs should be started at the onset of therapy to make sure there is an adequate regimen once the injectable agent is discontinued.
- Do not limit the regimen to 4 agents if other previously unused drugs that are likely to be active are available.
- Patients should receive either hospital-based or domiciliary directly observed therapy (DOT).
- Intermittent therapy should not be used in treating TB caused by multidrug-resistant organisms, except perhaps for injectable agents after an initial period (usually 2 to 3 months) of daily therapy.
- The use of drugs to which there is demonstrated *in vitro* resistance is not encouraged because there is little or no efficacy of these drugs (assuming the test results are accurate). In the case of low-level resistance to INH, high doses are sometimes given intermittently to complement the regimen.
- Resistance to RIF is associated in most cases with cross-resistance to rifabutin and in all cases to rifapentine.
- Cross-resistance between amikacin and kanamycin is nearly universal. There is emerging data that certain mutations may confer cross-resistance between amikacin, kanamycin and capreomycin .
- Determination of resistance to PZA is technically problematic and thus, is not determined in all laboratories. However, resistance to PZA is uncommon in the absence of resistance to other first-line drugs. PZA monoresistance *in vitro* is essentially universal for *Mycobacterium bovis* isolates.

Source: American Thoracic Society, Centers for Disease Control and Prevention, 2003.

Individual Regimens for Specific MDR-TB Resistance Patterns

Resistance to INH and RIF

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

Resistance to INH, RIF, and EMB

A regimen consisting of PZA, a fluoroquinolone, and 2 second-line oral agents (cycloserine, ethionamide, or PAS) for 18 to 24 months beyond culture conversion is recommended. Give an injectable agent for at least the first 6 months of therapy (longer may be considered in cases of extensive disease and delayed culture conversion). In patients with extensive or cavitary disease, consider an additional oral drug. Consider surgery if there is focal cavitary disease. (See "Role of Surgery in the Treatment of Drug-Resistant Tuberculosis" later in this chapter.)

Resistance to INH, RIF, and PZA

A regimen consisting of EMB, a fluoroquinolone, and 2 second-line oral agents (cycloserine, ethionamide, or PAS) for 18 to 24 months beyond culture conversion is recommended. Give an injectable agent for at least the first 6 months of therapy. Administer EMB at a higher dose of 25 mg/kg/day until culture conversion has occurred (at which point the dose should be decreased to 15 mg/kg/day). Monitor the patient monthly for evidence of optic neuritis while receiving EMB. In patients with extensive or cavitary disease, consider an additional oral drug. Consider surgery if there is focal cavitary disease.

Resistance to INH, RIF, PZA, and EMB

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

Treatment must be more aggressive in situations where the patient has long-standing disease (years), extensive disease, or multiple previous failed treatment efforts.

The duration of therapy will depend on the anti-tuberculosis drugs used and the extent of the disease.

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

Resistance to All First-Line Drugs and Fluoroquinolones

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

Resistance to All First-Line Drugs and Injectables

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

NOTE:

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

Extensively Drug-Resistant *Mycobacterium Tuberculosis* (XDR-TB)

XDR-TB is defined as resistance to at least INH, RIF, a fluoroquinolone, and one of three injectables (amikacin, kanamycin, or capreomycin). Treatment of patients with XDR-TB is challenging because of the lack of potent anti-TB drugs. However, the approach to designing a treatment regimen is the same as with MDR-TB. First, begin with any first-line drugs that demonstrate *in vitro* activity, followed by second- and third-line drugs (Figure 2). Surgery should be a strong consideration in patients with XDR-TB.

Table 2 presents recommended regimens for the treatment of XDR-TB.

FIGURE 2.

Building a Treatment Regimen for XDR-TB

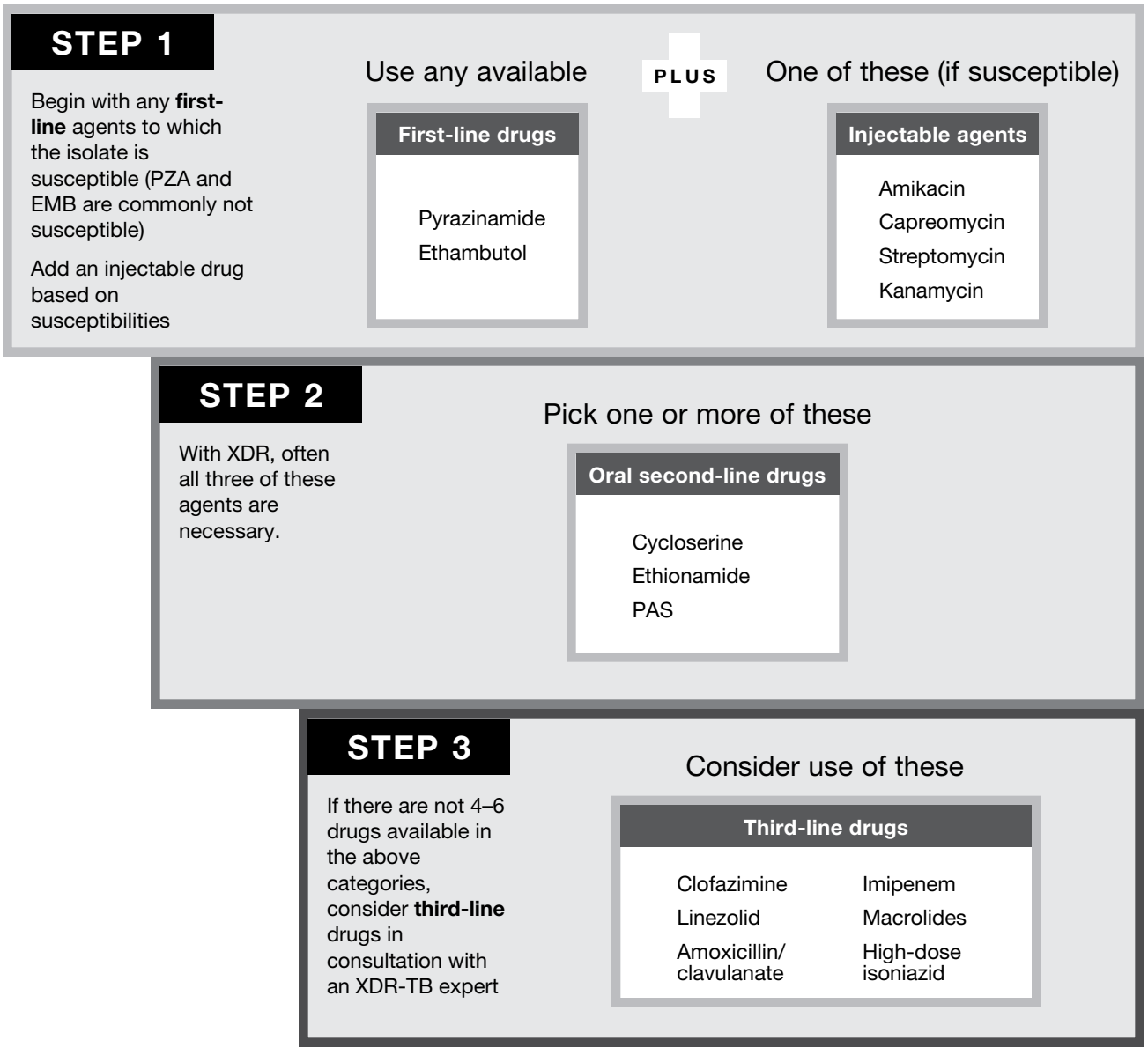


TABLE 2.

Treatment regimens for the management of patients with multidrug-resistant TB

Pattern of Drug Resistance	Suggested Regimen	Minimum Duration of Treatment	Comments
INH and RIF (± SM)	PZA, EMB, FQN, injectable agent ± another second-line agent.	18–24 months beyond culture conversion	Extended treatment is necessary to lessen the risk of relapse.
INH, RIF (± SM), and EMB or PZA	FQN, (EMB or PZA if available), injectable agent, plus 2 other second-line agents.	18–24 months beyond culture conversion	Consider surgery. Consider high-dose INH treatment if low-level resistance is documented.
INH, RIF, EMB, PZA (± SM)	FQN, injectable agent, 3 other second-line drugs	24 months beyond culture conversion	Consider surgery. Consider high-dose INH treatment if low-level resistance is documented.
INH, RIF, EMB, PZA, FQN	3 second-line drugs, an injectable agent, plus consider third-line agent.	24 months beyond culture conversion	Consider surgery. Consider high-dose INH treatment if low-level resistance is documented.
INH, RIF, EMB, PZA, injectables	FQN, 3 other second-line drugs, ± additional third-line agents. Include an injectable drug if there is one available to which the isolate is susceptible.	24 months beyond culture conversion	Surgery should be performed if possible. Consider high-dose INH treatment if low-level resistance is documented.
INH, RIF, FQN injectable	EMB, PZA, 3 second-line drugs ± additional third-line agent. Include an injectable drug if there is one available to which the isolate is susceptible.	24 months beyond culture conversion	Surgery should be performed if possible. Consider high-dose INH treatment if low-level resistance is documented
INH, RIF, EMB, FQN, injectable	PZA, 3 second-line drugs, plus a third-line agent. Include an injectable drug if there is one available to which the isolate is susceptible.	24 months beyond culture conversion	Surgery should be performed if possible. Consider high-dose INH treatment if low-level resistance is documented
INH, RIF, PZA, FQN, injectable	EMB, 3 second-line drugs, plus a third-line agent. Include an injectable drug if there is one available to which the isolate is susceptible.	24 months beyond culture conversion	Surgery should be performed if possible. Consider high-dose INH treatment if low-level resistance is documented
INH, RIF, EMB, PZA, FQN, injectable	3 second-line drugs, plus 2-3 third-line agents. Include an injectable drug if there is one available to which the isolate is susceptible.	24 months beyond culture conversion	Surgery should be performed if possible. Consider high-dose INH treatment if low-level resistance is documented

Selection and Dosing of Individual Drugs—Building the Regimen

The number of drugs required to cure MDR-TB is not known. Most studies that have been published have used 4- to 6-drug regimens. Table 3 lists most published series of MDR-TB treatment and outcomes. These regimens have resulted in cure in 56% to 83% of patients. The outcome of treatment is likely to vary depending on the number of drugs to which the isolate is resistant, the drugs used, the duration of therapy, the extent of disease, and the presence of other medical conditions, such as HIV infection.

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

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

Predictors of a good outcome include:

- Susceptibility to and use of PZA and/or EMB
- Susceptibility to and use of a fluoroquinolone
- Use of > 5 drugs for treatment
- Sputum culture conversion by 2 months of treatment
- Surgical resection

Predictors of failure include:

- History of previous therapy
- Greater number of drugs to which the organism is resistant
- Presence of cavitation on the chest radiograph
- Positive cultures after 2 to 3 months of treatment
- HIV infection

TABLE 3. **Selected Series of MDR-TB, Variables, and Outcomes** [PAGE 1 OF 2]

Study site, study dates, study design, and citation	Number of patients and comments	Mean number of drugs to which the isolate was resistant	Mean number of drugs given
NJMRC Denver, CO** (1973–1983) Retrospective chart review Goble 1993	N = 171 (134 eligible for outcome analysis) Mean inpatient stay >7 months	6 drug resistance	6 drugs
Bellevue Hospital, New York (1983–1994) Retrospective chart review Park 1996	N = 173	37% 2 drugs 26% 3 drugs 37% ≥ 4 drugs	Not reported
New York City (1990–1993) Outbreak investigation Frieden 1996	N = 357 "Strain W" 96% likely nosocomially acquired	6–7 drug resistance	Not reported
Istanbul, Turkey (1992–1999) Retrospective chart review Tahaoglu 2001	N = 158 Mean inpatient stay 200 days	4.4 drug resistance	5.5 drugs 4.4 effective drugs
Florida (1994–1997) Retrospective chart review Narita 2001	N = 81 39 patients managed at specialized TB hospital; 42 managed in the community Outpatients who survived > 2 mo included in outcome analysis	4.8 drug resistance Community management: 3.2 drugs Hospital management: 6.6 drugs	Effective drugs: Community management: 2.9 drugs Hospital management: 5.5 drugs
Lima, Peru (1996–1999) Retrospective chart review Mitnick 2003	N = 75 Community-based therapy	6 drug resistance	6 drugs
NJMRC Denver, CO** (1983–1998) Retrospective chart review Chan 2004	N = 205 Mean inpatient stay 93 days	6 drug resistance	6 drugs
Riga, Latvia (2000) Retrospective cohort study Leimane 2005	N = 204	Median of 4	Median of 6

* Statistically significant on multivariate analysis ** National Jewish Medical and Research Center *** Treatment with 2 or more drugs to which the isolate was susceptible

TABLE 3. **Selected Series of MDR-TB, Variables, and Outcomes** [PAGE 2 OF 2]

	HIV status	Outcomes	Variables associated with good outcome*
	Not reported	37% mortality (all causes) 21% mortality (TB) 65% initial culture conversion (56% cure; 9% relapse)	History of exposure to fewer drugs Female gender
	52% HIV+ 24% unknown	58% mortality (all causes) 20% mortality (TB)	HIV seronegative status Appropriate therapy*** Isolated pulmonary involvement Cavitary disease at diagnosis (HIV-)
	86% HIV+ 7% unknown	83% mortality (all causes) 20% mortality (TB)	Capreomycin use CD4 lymphocyte > 200 Fluoroquinolone use INH use
	0% HIV+	4% mortality 77% overall success 49% cure	Lack of previous fluoroquinolone use Younger age Resistance to more than 5 drugs
	Community management: 48% HIV+ 32% unknown Hospital management: 41% HIV+ 5% unknown	32% mortality (all causes, all patients) Community management: 45% mortality 48% cure Hospital management: 18% mortality 79% cure	Treatment at specialized TB hospital
	1.3% HIV+ 13% unknown	23% mortality (all causes) Of n=66 completing > 4 mo treatment, 83% probable cure	Pyrazinamide use, if susceptible Ethambutol use, if susceptible
	Not reported	25% mortality (all causes) 12% mortality (TB) 75% long-term favorable outcome	Surgical resection Fluoroquinolone use
	96% HIV negative, 1% HIV positive, 3% unknown	135 (66%) cured or competed therapy 14 (7%) died. 26 (13% defaulted. 29 (14%) failed treatment Of 178 adherent patients, 135 (76%) achieved cure	No previous treatment for MDR Treatment with over 5 drugs Susceptibility to ofloxacin Body mass index of ≥18.5 at start of treatment

Specific Drugs

Fluoroquinolones

There are few clinical data to help decide which fluoroquinolone to choose. Levofloxacin has been used extensively for the treatment of drug-resistant TB. Limited data suggest that levofloxacin may be more efficacious than ofloxacin when treating drug-resistant TB. Ciprofloxacin is the least potent of the available fluoroquinolones and should not be used to treat drug-resistant TB. Moxifloxacin has better *in vitro* activity against *M. tuberculosis* compared with levofloxacin, ofloxacin, and ciprofloxacin. In addition, recent studies have demonstrated excellent early bactericidal and sterilizing activity with moxifloxacin.

The dose of levofloxacin has been successfully increased to 1 gram/day or more on a case-by-case basis and tolerated well. The dose of **moxifloxacin** should not be increased beyond the Food and Drug Administration (FDA) recommended dose without measuring serum for concentration because of the possibility of more drug-related toxicity.

Aminoglycosides and Polypeptides

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

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

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

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

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

Additional Oral Second-Line Drugs

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

When INH resistance occurs at low concentrations, the organism may also be resistant to ethionamide. Mutations in the inhA region of *M. tuberculosis* can confer resistance to ethionamide as well as to isoniazid at low concentrations. In this situation, ethionamide

may not be the best choice of a second-line drug unless the organism has been shown to be susceptible with *in vitro* testing.

Alternative or Third-Line Drugs

In this *Guide*, we refer to third-line anti-tuberculosis drugs (e.g., imipenem, clofazimine, amoxicillin/clavulanate potassium, clarithromycin, azithromycin, and linezolid) as those that have demonstrated *in vitro* activity against *M. tuberculosis*, but for which there are little clinical data supporting their use. Most of these drugs are expensive, and in some cases require intravenous administration. At least one study demonstrated activity of imipenem *in vitro* and in patients with MDR-TB. Linezolid has been reported to be an active agent in several reports, but this drug is associated with a high rate of peripheral neuropathy that is usually not completely reversible and optic neuritis that usually is reversible. In one small study, decreasing the dose of linezolid from 600 mg twice daily to 600 mg once daily did not appear to decrease the frequency of neuropathy. Third-line drugs should only be used in consultation with an expert in the treatment of drug-resistant TB.

Several novel agents are currently being studied and have promise for treatment of drug-resistant TB. PA-824 is a nitroimidazole that has both bactericidal and sterilizing activity in mice. TMC-207, a diarylquinoline, is a novel anti-tuberculosis agent that targets ATP synthase. Because of its mechanisms of action, the drug has significant activity against both drug-susceptible and drug-resistant strains of *M. tuberculosis*. OPC-67683 is a nitroimidazo-oxazole that also has bactericidal and sterilizing activity against *M. tuberculosis*. These compounds are currently undergoing Phase I and II tests in patients with tuberculosis and MDR-TB.

Be aware of potential cross-resistance that can occur between certain drug classes (Table 4).

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TABLE 4.

Cross-resistance for anti-tuberculosis drugs

Drug	Cross-Resistance	Comments
Isoniazid	Ethionamide	Cross-resistance to ethionamide may occur when there is low-level resistance to isoniazid.
Rifampin	Rifamycins	Cross-resistance among the rifamycin class of drugs is typical. In a few strains that are resistant to rifampin, rifabutin may retain susceptibility *in vitro*.
Ethambutol	None	
Pyrazinamide	None	
Streptomcyin	None	
Amikacin	Kanamycin	High likelihood of cross-resistance since it is associated with the same mutation.
Kanamycin	Amikacin	High likelihood of cross-resistance since it is associated with the same mutation.
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 *in vitro*. However, data suggest that moxifloxacin may continue to demonstrate some activity despite *in vitro* resistance to ofloxacin.
Cycloserine	None	
PAS	None	
Ethionamide	Isoniazid	Cross-resistance to isoniazid may occur when there is low-level resistance to ethionamide.
Clofazimine	None	

Avoid Drugs that Have Been Used Previously fo Treat The Patient's TB

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

Consider Side Effects When Choosing Drugs

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

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

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

Administration of the Treatment Regimen

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

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

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

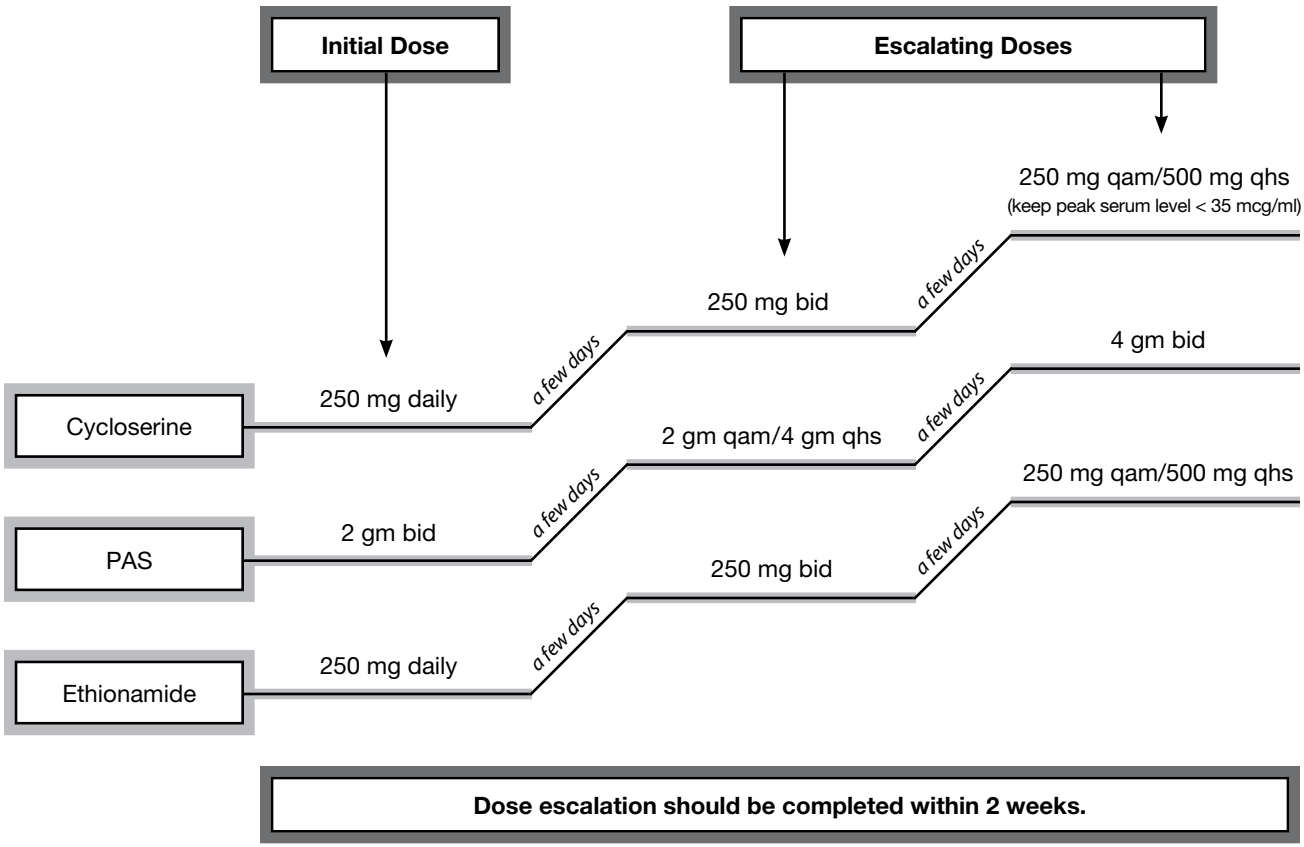
Escalation of Dosages (Drug Ramping)

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

In some patients, beginning with a low dose and gradually increasing the dose is more acceptable and allows the clinician time to manage drug-related adverse effects. This approach of slowly escalating drug dosage is referred to as "drug ramping" and is most often used with the drugs PAS, ethionamide, and cycloserine. Examples of drug ramping can be seen in Figure 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 cycloserine to once daily dosing which can enhance adherence.

Role of Surgery in the Treatment of Drug-Resistant TB

Surgery is sometimes necessary to cure patients with MDR-TB. The decision to perform resectional surgery should be made in consultation with an expert in treating drug-resistant TB and should be based on the degree of underlying drug resistance, the presence of focal cavitary disease, and the patient's ability to tolerate surgery. Most patients who undergo resectional surgery have evidence of focal cavitary disease. However, if the clinical situation is such that the treatment options are severely limited, resection of a primary site of focal non-cavitary disease has been used with good outcomes.

Surgery should be considered:

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

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

To maximize the potential success of surgery:

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

Groups at High-Risk of Having Drug-Resistant Tuberculosis

Treatment Failures

Recognition of a Failing Regimen

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

A treatment regimen has failed when sputum cultures remain positive after 4 months of treatment or become positive again after a period of negative cultures. However, the possibility of a failing treatment regimen should be considered well before 4 months of

treatment. Patients who are not clinically improving and/or remain smear-positive during the first months of treatment should be considered for the possibility of drug resistance.

There are several potential reasons for treatment failure:

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

The Clinician's Response to Treatment Failure

Determine the cause of treatment failure:

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

Consider a Treatment Regimen Change

If treatment failure is presumed to be due to underlying drug resistance and the patient does not have severe TB, either initiate an empiric regimen (see "Starting an Expanded Empiric Treatment Regimen" later in this chapter) or wait for the results of drug-susceptibility testing. In most cases, the first-line drug regimen should be continued pending second-line susceptibility test results. If the patient is seriously ill or has a positive sputum acid-fast bacilli (AFB) smear, start and continue an empiric regimen until drug-susceptibility test results are available.

Never add a single drug to a failing regimen.

Persons Who Have Relapsed After Prior Treatment

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

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

Acquired drug resistance is more likely in persons who were not treated initially with DOT.

In patients who received DOT and were adherent to therapy, the risk of developing acquired resistance is small unless the patient has advanced HIV infection and received highly intermittent therapy (e.g., weekly or twice weekly).

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

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

Re-Treatment Options

In patients who relapse after initial treatment with a regimen that included INH, RIF, PZA, and EMB administered under well-documented DOT, initiate re-treatment with the same 4-drug regimen pending the results of drug-susceptibility tests.

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

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

TB Disease in a Contact of a Drug-Resistant Case

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

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

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

Persons Who Come from Regions Where Drug-Resistant TB Is Prevalent

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

Starting an Expanded Empiric Treatment Regimen

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

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

An Expanded Treatment Regimen*

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

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

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

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

* When extensive disease is present, extensive resistance is suspected, or the patient is seriously ill, do not limit the empiric regimen to 2 to 3 additional drugs.

Consultation with Experts

Treatment of TB caused by drug-resistant organisms should be done by or in close consultation with an expert in the management of these difficult cases. Second-line regimens often present the patient's best hope for cure, and thus, inappropriate management of a drug-resistant case can have life-threatening consequences.

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

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

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

Expert Consultation

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

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

Summary

- Each patient should be assessed for risks of drug resistance: previous TB treatment, exposure to a drug-resistant case, or travel to or immigration from an area of high resistance.
- An empiric expanded TB regimen is appropriate for patients at high risk for drug resistance, especially if they are seriously ill or have extensive disease.
- An empiric expanded regimen should be customized based on suspected resistance patterns and the patient's previous TB treatment. In general, an expanded empiric regimen should contain the 4 first-line TB drugs, a fluoroquinolone, and an injectable drug.
- Never add a single drug to a failing regimen.
- In treatment of MDR-TB, the number of drugs in the regimen depends on the susceptibility pattern, availability of first-line agents, and extent of disease.
- The minimum duration of treatment for pulmonary MDR-TB is 18 months beyond culture conversion.

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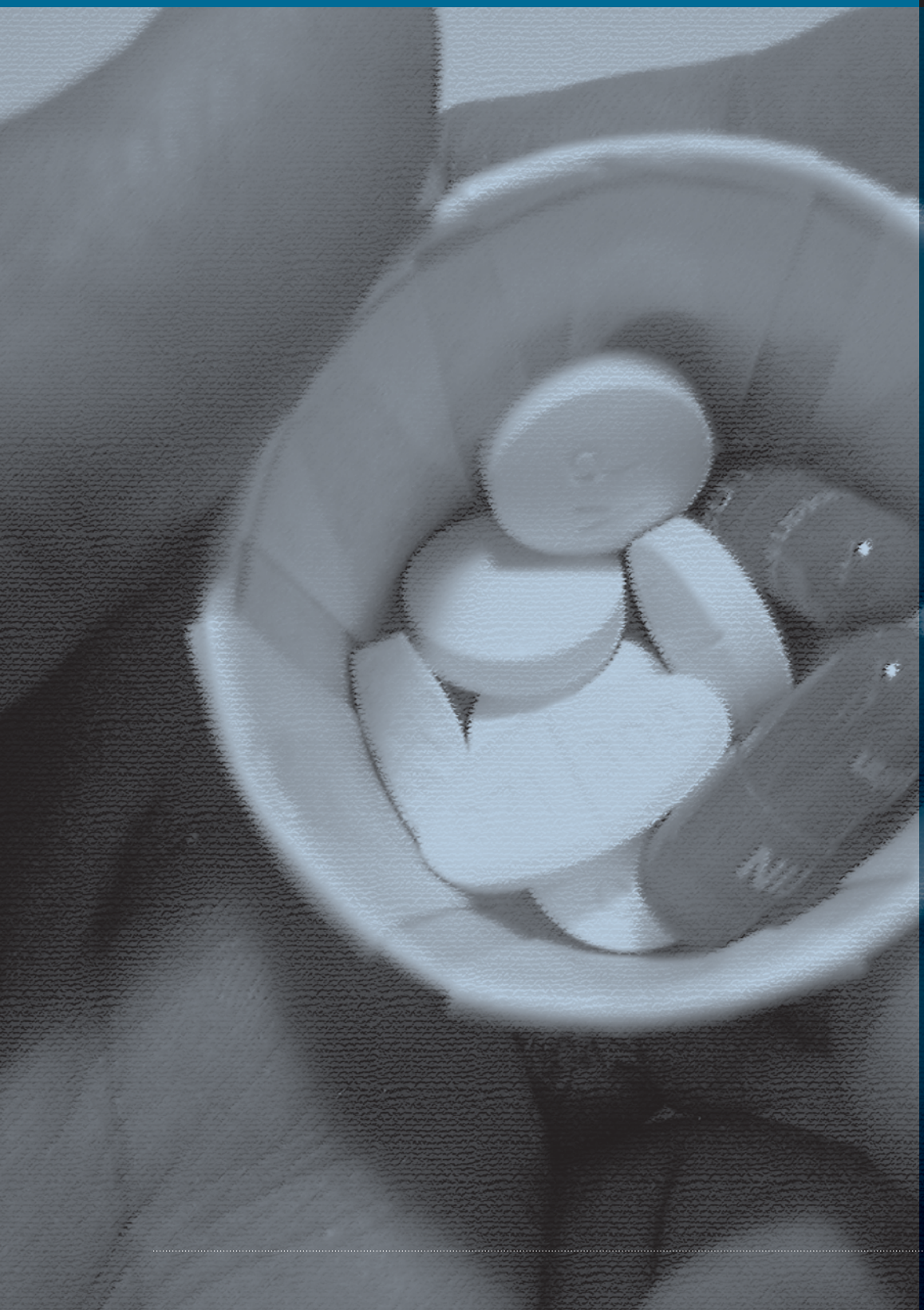
4 Medication Fact Sheets



AMIKACIN [1 of 2]

Drug class	Aminoglycoside
Trade name	Amikacin/Amikin
Activity against TB	**Bactericidal;** has strong anti-TB activity. Cross-resistance with kanamycin and some data suggesting cross-resistance with capreomycin.
Dose (all once daily)	**Adults:** 15 mg/kg/day, 5–7 days per week (maximum dose is generally 1 gram, but a large, muscular person could receive more and should have 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). **> 59 yrs of age:** 10 mg/kg/dose (max 750 mg) 5–7 times per week or 2–3 times per week after initial period. **Children:** 15–30 mg/kg/day (max 1 gram) 5–7 days per week. 15–30 mg/kg/day (max 1 gram) 2–3 days per week after initial period daily. **Renal failure/dialysis:** 12–15 mg/kg/dose 2–3 times weekly (not daily). **Markedly obese individuals** should have an adjusted dose due to the decreased distribution of extracellular fluids in adipose tissues. Dosing based on actual weight will give supratherapeutic concentrations. The suggested adjusted weight is ideal body weight plus 40% of the excess weight. Ideal body weight (men): 50 kg plus 2.3 kg/inch over 5 ft Ideal body weight (women): 45 kg plus 2.3 kg/inch over 5 ft *Concentrations should be followed closely.*
Route of administration	IV or IM (intraperitoneal and intrathecal have been reported—penetrates meninges only with inflammation). Some report that it is more painful than IM streptomycin. Not absorbed orally.
Preparation	Colorless solution; 250 mg/ml (2, 3, or 4 ml vials) and 50 mg/ml (2 ml vial). For intravenous solution, mix with D5W or other solutions (in at least 100 ml of fluid for adults or 5 mg/ml for children).
Storage	Solution is stable at room temperature; diluted solution is stable at room temperature at least 3 weeks or in the refrigerator at least 60 days.
Pharmacokinetics	For intravenous administration, infuse over 60 minutes for adults; 1–2 hours for children; intramuscular absorption is complete within 4 hours and peak 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 peak to be extrapolated. **Peak concentrations** for a 15 mg/kg dose are between 35 and 45 mcg/ml. **Peak concentrations** of 25–35 mcg/ml are acceptable if you anticipate using amikacin for more than 6 months. **Peak concentrations** of 65–80 mcg/ml are obtained after a 25 mg/kg dose. Trough concentrations are generally < 5 mcg/ml in patients with normal renal function. See Appendix 12, "Therapeutic Drug Monitoring."

AMIKACIN [2 of 2]

Oral absorption	There is no significant oral absorption. Intramuscular absorption might be delayed if the same site is used consistently.
CSF penetration	Variable penetration; appears to penetrate inflamed meninges better.
Special circumstances	**Use in pregnancy/breastfeeding:** Generally avoided in pregnancy due to congenital deafness seen with streptomycin and kanamycin. Can be used while breastfeeding. **Use in renal disease:** 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 5, "Special Situations – Renal Failure." **Use in hepatic disease:** 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. **Diuretic use:** Coadministration of loop diuretics and aminoglycoside antibiotics carries an increased risk of ototoxicity.
Adverse reactions	Nephrotoxicity: 9% for general population (may be lower for once-daily use, higher for prolonged use). Ototoxicity (hearing loss): Increased with advanced age and prolonged use. Local pain with IM injections. Vestibular toxicity. Electrolyte abnormalities, including hypokalemia and hypomagnesemia.
Contraindications	**Pregnancy** — relative contraindication (congenital deafness seen with streptomycin and kanamycin use in pregnancy. See Chapter 5, "Special Situations"). **Hypersensitivity to aminoglycosides.** **Caution with renal, hepatic, vestibular, or auditory impairment.**
Monitoring	Monitor renal function by documenting creatinine at least monthly (more frequently if renal or hepatic impairment); document creatinine clearance if there is baseline renal impairment or any concerns; document baseline and monthly audiology exam; 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.
2007 wholesale cost 30-day supply, 75-kg person	$59 (TB clinic) $138 (community hospital)
Patient instructions	**Call your doctor right away if you have:** • Problems with hearing, dizziness, or balance • Rash or swelling of your face • Trouble breathing • Decreased urination • Swelling, pain, or redness at your IV site • Muscle twitching or weakness

AMOXICILLIN/CLAVULANATE [1 of 2]

Drug class	Penicillin/beta-lactam inhibitor
Trade name	Augmentin XR or Augmentin ES-600 suspension
Activity against TB	Conflicting and limited reports, but possible early bactericidal activity.
Dose	**Adults:** 2000 mg as amoxicillin/125 mg clavulanate twice daily. **Children:** 80 mg/kg/day divided twice daily of the amoxicillin component. **Renal failure/dialysis:** For creatinine clearance 10–30 ml/min dose 1000 mg as amoxicillin twice daily; for creatinine clearance < 10 ml/min dose 1000 mg as amoxicillin once daily. **Hemodialysis:** Single dose every 24 hours and after each dialysis session.
Route of administration	Oral. Imipenem/cilastatin should be used if a parenteral beta-lactam drug is desired.
Preparation	For 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: 2000 mg amoxicillin and 250 mg clavulanate).
Storage	Tablets are stable at room temperature; reconstituted suspension should be stored in the refrigerator and discarded after 10 days.
Pharmacokinetics	Time to peak oral concentration is 60–90 minutes. **Serum concentrations** of 17 mcg/ml of amoxicillin were reported following a 2000 mg (as amoxicillin) dose.
Oral absorption	Good oral absorption, best tolerated and well absorbed when taken at the start of a standard meal.
CSF penetration	Approximately 5% of the plasma concentration reaches the CSF.
Special circumstances	**Use in pregnancy/breastfeeding:** Probably safe in pregnancy (no known risk); can be used while breastfeeding. **Use in renal disease:** Amoxicillin is renally excreted and the dose should be adjusted for renal failure. It is cleared by dialysis, so should be dosed after dialysis (see above). **Use in hepatic disease:** Clavulanate is cleared by the liver, so care should be used when using in patients with liver failure.
Adverse reactions	Diarrhea and abdominal discomfort are most common. Hypersensitivity. Nausea, vomiting, and rash are also common. Rare side effects have been reported in all other organ systems.
Contraindications	Penicillin allergy; use with caution with cephalosporin allergies.
Monitoring	No specific monitoring is required.

AMOXICILLIN/CLAVULANATE [2 of 2]

2007 wholesale cost 30-day supply, 75-kg person	$241 (TB clinic) $343 (community hospital)
Patient instructions	Take at the beginning of a meal. Store tablets at room temperature; store suspension in the refrigerator—throw away after 10 days and refill the prescription. **Call your doctor right away if you have:** • Rash or swelling • Trouble breathing • Severe diarrhea

CAPREOMYCIN [1 of 2]

Drug class	Cyclic polypeptide
Trade name	Capastat
Activity against TB	**Bactericidal;** has strong anti-TB activity; inhibits protein synthesis. Some data suggesting cross-resistance with amikacin and kanamycin.
Dose (all once daily)	**Adults:** 15 mg/kg/day, 5–7 days per week (maximum dose is generally 1 gram, but a large, muscular person could receive more and should have 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). **> 59 yrs of age:** 10 mg/kg/dose (max 750 mg) 5–7 times per week or 2–3 times per week after initial period. **Children:** 15–30 mg/kg/day (max 1 gram) 5–7 days per week. 15–30 mg/kg/day (max 1 gram) 2–3 days per week after initial period daily. **Renal failure/dialysis:** 12–15 mg/kg/dose 2–3 times weekly (not daily). **Markedly obese individuals** should have an adjusted dose due to the decreased distribution of extracellular fluids in adipose tissues. Dosing based on actual weight will give supratherapeutic concentrations. The suggested adjusted weight is ideal body weight plus 40% of the excess weight. Ideal body weight (men): 50 kg plus 2.3 kg/inch over 5 ft Ideal body weight (women): 45 kg plus 2.3 kg/inch over 5 ft *Concentrations should be followed closely.*
Route of administration	IV or IM.
Preparation	Capreomycin is available in vials of 1 gm for either IM or IV administration. The contents of the vial should be reconstituted with 2 ml or more of NS or sterile water.
Storage	Package insert indicates that reconstituted capreomycin can be stored in the refrigerator up to 24 hours prior to use. Other data suggest that it may be held for 14 days in the refrigerator or 2 days at room temperature.
Pharmacokinetics	Intramuscular peak 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 peak to be extrapolated. **Peak concentrations** for a 15 mg/kg dose are between 35 and 45 mcg/ml. **Peak concentrations** of 25–35 mcg/ml are acceptable if you anticipate using capreomycin for more than 6 months. **Peak concentrations** of 65–80 mcg/ml are obtained after a 25 mg/kg dose. Trough concentrations should be < 5 mcg/ml in .patients with normal renal function. See Appendix 12, “Therapeutic Drug Monitoring.”
Oral absorption	There is no significant oral absorption. Intramuscular absorption might be delayed if the same site is used consistently.

CAPREOMYCIN [2 of 2]

CSF penetration	There is a paucity of data regarding capreomycin's penetration of the meninges.
Special circumstances	**Use in pregnancy/breastfeeding:** Generally avoided in pregnancy due to congenital deafness seen with streptomycin and kanamycin. There are case reports of its safe use in pregnancy (unaffected newborns). Can be used while breastfeeding. **Use in renal disease:** Use with caution. 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 5, "Special Situations – Renal Failure." **Use in hepatic disease:** 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.
Adverse reactions	Similar to the aminoglycosides. Nephrotoxicity: 20%–25% including proteinuria, reduced creatinine clearance, and depletion of potassium and magnesium. Ototoxicity (hearing loss): Occurs more often in elderly persons or those with pre-existing renal impairment; vestibular toxicity. Local pain with IM injections. Electrolyte abnormalities, including hypokalemia, hypocalemia, and hypomagnesemia. Liver function test abnormalities when used with other TB drugs.
Contraindications	**Hypersensitivity to capreomycin.** Most experts would not use capreomycin if vestibular side effects resulted from aminoglycoside use. **Generally avoided in pregnancy** due to congenital deafness seen with aminoglycoses. There are case reports of its safe use in pregnancy (unaffected newborns).
Monitoring	Monitor renal function by documenting creatinine at least monthly (more frequently if renal or hepatic impairment); document creatinine clearance if there is baseline renal impairment or any concerns; document baseline and monthly 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.
2007 wholesale cost 30-day supply, 75-kg person	$352 (TB clinic) $413 (community hospital)
Patient instructions	**Call your doctor right away if you have:** • Rash • Fever or chills • Bleeding or bruising • Problems with hearing, dizziness, or balance • Bleeding or a lump where the shot is given • Decreased urination • Trouble breathing • Muscle weakness

CLOFAZIMINE [1 of 2]

Drug class	Iminophenazine
Trade name	Lamprene
Activity against TB	*In vitro* activity against *M. tuberculosis* without much *in vivo* data. Generally reserved for cases with few other options.
Dose (all once daily)	**Adults:** 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. **Children:** Limited data, but doses of 1 mg/kg/day have been given. **Renal failure/dialysis:** No adjustment required.
Route of administration	Oral; not available parenterally.
Preparation	50 and 100 mg capsules.
Storage	Room temperature.
Pharmacokinetics	Tissue half-life estimated to be around 70 days. **Peak concentrations** 2–3 hours after a dose are expected to be 0.5–2.0 mcg/ml. Peak concentrations occur at 4–8 hours when given with food. See Appendix 12, "Therapeutic Drug Monitoring."
Oral absorption	70% absorption after an oral dose.
CSF penetration	Limited data are available regarding CNS penetration.
Special circumstances	**Use in pregnancy/breastfeeding:** 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. **Use in renal disease:** No dosage adjustment required. **Use in hepatic disease:** Metabolized by the liver; use caution and/or adjust the dose for severe hepatic insufficiency.
Adverse reactions	Pink or red discoloration of skin, conjunctiva, cornea, and body fluids. Gastrointestinal intolerance. Photosensitivity. Other side effects include retinopathy, dry skin, pruritus, rash and severe abdominal symptoms, bleeding, and bowel obstruction.
Contraindications	**Allergy to clofazimine.**
Monitoring	Symptomatic monitoring.

CLOFAZIMINE [2 of 2]

2007 wholesale cost
30-day supply, 75-kg person

Clofazimine is not commercially available within the United States. Clinicians should contact the FDA's Office of Emergency Operations (301-443-1240) in order to apply for a single patient Investigational New Drug (IND).

Patient instructions

Take with food to avoid stomach upset and improve absorption.

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

Call your doctor right away if you have:

- Bloody or black stools or diarrhea
- Yellowing of your skin or eyes
- Severe nausea, vomiting, abdominal pain, cramps, or burning
- Depression or thoughts of hurting yourself

CYCLOSERINE [1 of 2]

Drug class	Analog of D-alanine
Trade name	Seromycin
Activity against TB	**Bacteriostatic;** inhibits cell wall synthesis.
Dose	**Adults:** 10–15 mg/kg/day usually; 250 mg PO twice a day; can increase to 250 mg PO 3 times a day or 250 mg qam and 500 mg PO qhs if peak concentrations are kept below 35 mcg/ml. **Children:** 10–20 mg/kg/day divided every 12 hours (daily maximum 1 gram). **Vitamin B6:** All patients should receive vitamin B6 while taking cycloserine. Adults need 100 mg or more (or 50 mg per 250 mg of cycloserine) and children should receive a dose proportionate to their weight. **Renal failure/dialysis:** 250 mg once daily or 500 mg 3 times per week (see Chapter 5, "Special Situations – Renal Failure"); monitor drug concentrations to keep peak concentrations < 35 mcg/ml.
Route of administration	Oral; not available parenterally.
Preparation	250 mg capsule.
Storage	Room temperature in airtight containers.
Pharmacokinetics	**Peak oral absorption** usually occurs by 2 hours (may be up to 4 hours). **Peak concentration** 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. **Peak concentrations** 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. See Appendix 12, "Therapeutic Drug Monitoring."
Oral absorption	Modestly decreased by food (best to take on an empty stomach); not significantly affected by antacids and orange juice.
CSF penetration	Concentrations approach those in serum.
Special circumstances	**Use in pregnancy/breastfeeding:** Not well studied, but no teratogenicity documented. Use if there are not better choices. Can be used while breastfeeding (dose the infant with vitamin B6 if breastfed). **Use in renal disease:** Cycloserine is cleared by the kidney and requires dose adjustment for renal failure (see above). Use with caution. **Use in hepatic disease:** Not associated with hepatotoxicity. **Ethionamide use:** May have increased toxicity when ethionamide also used.

CYCLOSERINE [2 of 2]

Adverse reactions	CNS toxicity, including inability to concentrate and lethargy. More serious CNS side effects, including seizure, depression, psychosis, and suicidal ideation, *usually* occur at peak 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.
Contraindications	**Significant CNS disease,** including seizure disorder, psychotic disease, or alcohol abuse.
Monitoring	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. The dose is generally increased if the peak is less than 15 mcg/ml, and the dose is decreased if the peak is above 40 mcg/ml. If the dose is adjusted, repeat the peak concentration after at least 3–4 days.
2007 wholesale cost 30-day supply, 75-kg person	$375; cycloserine is available through the Chao Center at Purdue University (877-930-CHAO).
Patient instructions	Best taken on an empty stomach, with juice, or antacids. If food is taken, avoid a large fatty meal. Avoid alcohol. You must also take a high-dose vitamin B6 supplement while on this drug. **Call your doctor right away if you have:** • Seizures • Shakiness or trouble talking • Depression or thoughts of hurting yourself • Anxiety, confusion, or loss of memory • Personality changes, such as aggressive behavior • Rash or hives • Headache

ETHAMBUTOL [1 of 2]

Drug class	Unspecified
Trade name	Myambutol
Activity against TB	**Bacteriostatic** 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.
Dose (all once daily)	**Adults:** 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. **Children:** 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. **Renal failure/dialysis:** 15–25 mg/kg/dose 3 times weekly (not daily). **Obesity:** Ethambutol should be dosed on lean body weight. Ideal body weight (men): 50 kg plus 2.3 kg/inch over 5 ft Ideal body weight (women): 45 kg plus 2.3 kg/inch over 5 ft
Route of administration	Oral; not available parenterally.
Preparation	100 mg tablets; scored 400 mg tablets; coated 100 mg tablets; coated, scored 400 mg tablets.
Storage	Room temperature.
Pharmacokinetics	**Peak oral absorption** occurs 2–4 hours after the dose. Draw a peak serum 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. **Peak concentrations** of 2–6 mcg/ml are expected. See Appendix 12, "Therapeutic Drug Monitoring."
Oral absorption	80% bioavailability independent of food.
CSF penetration	Ethambutol penetrates meninges poorly.
Special circumstances	**Use in pregnancy/breastfeeding:** Safe in pregnancy; can be used while breastfeeding. **Use in renal disease:** Use with caution—cleared by the kidneys; dose adjustment required for renal failure. Increased risk of toxicity with renal failure. If needed for use in the regimen, consider therapeutic drug monitoring; see Chapter 5, "Special Situations – Renal Failure." **Use in hepatic disease:** Safe in liver disease.
Adverse reactions	Retrobulbar neuritis (dose-related—exacerbated during renal failure).
Contraindications	**Pre-existing optic neuritis; visual changes on ethambutol.**

ETHAMBUTOL [2 of 2]

Monitoring	Patients should be counseled to report any visual changes. Baseline and monthly visual acuity and color discrimination monitoring should be performed (particular attention should be given to individuals on higher doses or with renal impairment).
2007 wholesale cost 30-day supply, 75-kg person	$64 (TB clinic) $77 (community hospital)
Patient instructions	Can be taken with food or on an empty stomach. **Call your doctor right away if you have:** • Any problems with your eyes: vision changes, blurring, color blindness, trouble seeing, or eye pain • Swelling of face • Rash, hives, or trouble breathing • Numbness, pain, or tingling in hands or feet • Joint pain • Fever or chills • Nausea, vomiting, poor appetite, or abdominal pain • Headache or dizziness

ETHIONAMIDE [1 of 2]

Drug class	Derivative of isonicotinic acid
Trade name	Trecator-SC
Activity against TB	Weakly bactericidal; blocks mycolic acid synthesis.
Dose	**Adults:** 15–20 mg/kg/day frequently divided (max dose 1 gm per day); usually 500–750 mg per day in 2 divided doses or a single daily dose. **Children:** 15–20 mg/kg/day usually divided into 2–3 doses (max dose 1 gm per day). A single daily dose can sometimes be given at bedtime or with the main meal. Many individuals require gradual ramping up of the dose and treatment for GI upset. **Vitamin B6:** All patients should receive vitamin B6 while taking ethionamide. Adults need 100 mg (more if also taking cycloserine) and children should receive a dose proportionate to their weight. **Renal failure/dialysis:** No change.
Route of administration	Oral; not available parenterally.
Preparation	Coated 250 mg tablet.
Storage	Store at room temperature.
Pharmacokinetics	**Peak oral absorption** is usually reached in 2–3 hours, but delayed absorption is common; peak concentrations should be drawn at 2 hours. **Peak concentrations** are typically 1–5 mcg/ml. See Appendix 12, "Therapeutic Drug Monitoring."
Oral absorption	Erratic absorption, possibly due to GI disturbances associated with the medication.
CSF penetration	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.
Special circumstances	**Use in pregnancy/breastfeeding:** Generally avoided during pregnancy due to reports of teratogenicity; little data during breastfeeding—an estimated 20% of a usual therapeutic dose is thought be received (dose the infant with vitamin B6 if breastfed). **Use in renal disease:** No precautions are required for renal impairment. **Use in hepatic disease:** Can cause hepatotoxicity similar to that of INH—use with caution in liver disease.
Adverse reactions	Gastrointestinal upset and anorexia: Sometimes intolerable (symptoms are moderated by food or taking at bedtime). Metallic taste. Hepatotoxicity. Endocrine effects: Gynecomastia, hair loss, acne, impotence, menstrual irregularity, and reversible hypothyroidism—treat with thyroid replacement. Neurotoxicity (patients taking ethionamide should take high doses of vitamin B6). Side effects may be exaggerated in patients also taking cycloserine.

ETHIONAMIDE [2 of 2]

Contraindications	**Sensitivity to ethionamide.**
Monitoring	Monitor TSH for evidence of hypothyroidism requiring replacement; therapeutic drug monitoring if malabsorption suspected. Monitor liver function tests.
2007 wholesale cost 30-day supply, 75-kg person	$188 (TB clinic) $264 (community hospital)
Patient instructions	Take this medicine with food. You must also take a high-dose vitamin B6 supplement while on this drug. **Call your doctor right away if you have:** • Any problems with your eyes: eye pain, blurred vision, color blindness, or trouble seeing • Numbness, tingling, or pain in your hands or feet • Unusual bruising or bleeding • Personality changes such as depression, confusion, or aggression • Yellowing of your skin or eyes • Dark-colored urine • Nausea and vomiting • Dizziness • Swollen breasts (in men)

IMIPENEM/CILASTATIN [1 of 2]

Drug class	Beta-lactam – carbapenem
Trade name	Primaxin
Activity against TB	*In vitro* activity—very limited clinical experience.
Dose	**Adults:** 1000 mg IV every 12 hours. **Children:** Meropenem preferred: 20–40 mg/kg/dose IV every 8 hours up to 2 grams per dose. **Renal failure/dialysis:** Adjustment in dose and interval based on severity of renal failure and body weight—for example, 500 mg every 8 hours for creatinine clearance 20–40 ml/min, 500 mg every 12 hours for creatinine clearance < 20 ml/min.
Route of administration	IV or IM (total IM doses are not recommended more than 1.5 gm/day and are therefore not very practical for treatment of drug-resistant TB). No oral preparation.
Preparation	Lypholized powder 1:1 ratio of imipenem and cilastatin. Vials are available 250, 500, 750 mg, or 1 gram.
Storage	Powder should be kept at room temperature; suspended product should be kept no more than 4 hours at room temperature or no more than 24 hours refrigerated.
Pharmacokinetics	**Peak concentrations** occur immediately after IV infusion and 1 hour after IM infusion. **Peak concentrations** of 35-60 mcg/ml occur after infusion of 1 gm.
Oral absorption	No oral absorption.
CSF penetration	Good CSF penetration, but children with meningitis treated with imipenem had high rates of seizures (meropenem preferred for meningitis and for children).
Special circumstances	**Use in pregnancy/breastfeeding:** Little information known regarding use in pregnancy; unknown safety during breastfeeding. **Use in renal disease:** Dose adjustment required (see above); dose after dialysis. **Use in hepatic disease:** Elevated liver function tests have been noted in up to 6% of patients, but no definite liver damage has been documented.
Adverse reactions	Diarrhea, nausea, or vomiting. Seizure (noted with CNS infection).
Contraindications	**Carbapenem intolerance; meningitis** (use meropenem rather than imipenem).
Monitoring	Symptomatic monitoring.
2007 wholesale cost 30-day supply, 75-kg person	$1655 (TB clinic) $3795 (community hospital)

IMIPENEM/CILASTATIN [2 of 2]

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 in the face, throat, or lips
- Wheezing or trouble breathing

ISONIAZID [1 of 2]

Drug class	Isonicotinic acid hydrazide (INH)
Trade name	INH/Isoniazid/Laniazid/Nydrazid
Activity against TB	**Bactericidal,** especially for rapidly dividing cells. Affects mycolic acid (cell wall) synthesis.
Dose (all once daily)	**Adults:** 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. **Children:** 10–15 mg/kg/day up to 300 mg (PO or IV); 20–30 mg/kg/dose twice or thrice weekly. **Renal failure/dialysis:** 300 mg once daily or 900 mg thrice weekly. **Vitamin B6** should be used when high-dose INH employed and in patients with diabetes, uremia, HIV infection, alcohol abuse, malnutrition, or peripheral neuropathy. Additionally, pregnant and post-partum women and exclusively breastfeeding infants should receive vitamin B6 while taking INH.
Route of administration	Oral, intravenous, or intramuscular.
Preparation	50 mg, 100 mg, or 300 mg scored or unscored tablets; 50 mg/5 ml oral suspension in sorbitol; solution for injection 100 mg/ml.
Storage	Suspension must be kept at room temperature.
Pharmacokinetics	**Peak serum concentrations** are achieved at 1–2 hours after the oral dose. **Peak concentrations** should be drawn at 1 and 4 hours; if other drug concentrations are being submitted, 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). **Peak concentration** is expected to be 3–5 mcg/ml after daily dose and 9–15 mcg/ml after twice weekly dose. See Appendix 12, "Therapeutic Drug Monitoring."
Oral absorption	Well absorbed orally or intramuscularly; best absorbed on an empty stomach; up to 50% reduction in peak concentration with a fatty meal.
CSF penetration	Concentration equivalent to plasma in inflamed meninges. 20% of concentrations in plasma in non-inflamed meninges.
Special circumstances	**Use in pregnancy/breastfeeding:** Safe during pregnancy; safe during breastfeeding (both baby and mother should receive pyridoxine supplementation). Up to 20% of the infant therapeutic dose will be passed to the baby in the breast milk. **Use in renal disease:** No dose adjustment for renal failure, but pyridoxine supplementation should be used. **Use in hepatic disease:** May exacerbate liver failure. Use with caution. **Seizure medication:** Serum concentrations of phenytoin may be increased in persons taking INH. Inclusion of INH in the regimen of patients with strain W MDR-TB was also associated with improved outcomes.

ISONIAZID [2 of 2]

Adverse reactions	Hepatitis (age-related). Peripheral neuropathy. Hypersensitivity reactions. Other reactions, including optic neuritis, arthralgias, CNS changes, drug-induced lupus, diarrhea, and cramping with liquid product.
Contraindications	**Patients with high-level INH resistance** who have failed an INH-containing regimen should not receive INH.
Monitoring	Clinical monitoring of all patients on INH is essential. Routine laboratory monitoring is not recommended for patients receiving INH monotherapy. For patients receiving multiple TB drugs or other hepatotoxic drugs, or with underlying liver disease (including viral hepatitis), baseline liver function testing is recommended. Follow-up liver function testing is determined by baseline concerns and symptoms of hepatotoxicity. Therapeutic drug monitoring is recommended only for patients suspected of having malabsorption or treatment failure. Monitor 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.
2007 wholesale cost 30-day supply, 75-kg person	$1 (TB clinic) $3 (community hospital)
Patient instructions	Do not take this medication with a large fatty meal. If you have an upset stomach, take the medicine with a snack. If you (or your child) are taking the liquid suspension—do not put it in the refrigerator. Avoid alcohol while taking this medicine. If you need an antacid, don't take it within an hour of this medicine. Make sure your doctor knows if you are also taking medicine for seizures. Let your doctor know if you get flushing, sweating, or headaches when eating certain cheeses or fish. Ask your doctor if you should be taking a vitamin B6 (pyridoxine supplement). **Call your doctor right away if you have any of these side effects:** • Loss of appetite for a few days that is not going away • Tiredness, weakness • Moderate stomach pain, nausea, or vomiting • Numbness or tingling of your fingers or toes • Blurred vision, eye pain • Yellow skin or eyes or dark-colored urine

KANAMYCIN [1 of 2]

Drug class	Aminoglycoside
Trade name	Kantrex
Activity against TB	**Bactericidal;** has strong anti-TB activity. Cross-resistance with amikacin and some data suggesting cross-resistance with capreomycin; inhibits protein synthesis.
Dose (all once daily)	**Adults:** 15 mg/kg/day, 5–7 days per week (maximum dose is generally 1 gram, but a large, muscular person could receive more and should have 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). **> 59 yrs of age:** 10 mg/kg/dose (max 750 mg) 5–7 times per week or 2–3 times per week after initial period. **Children:** 15–30 mg/kg/day (max 1 gram) 5–7 days per week. 15–30 mg/kg/day (max 1 gram) 2–3 days per week after initial period daily. **Renal failure/dialysis:** 12–15 mg/kg/dose 2–3 times weekly (not daily). **Markedly obese individuals** should have an adjusted dose due to the decreased distribution of extracellular fluids in adipose tissues. Dosing based on actual weight will give supratherapeutic concentrations. The suggested adjusted weight is ideal body weight plus 40% of the excess weight. Ideal body weight (men): 50 kg plus 2.3 kg/inch over 5 ft Ideal body weight (women): 45 kg plus 2.3 kg/inch over 5 ft Concentrations should be followed closely.
Route of administration	Intravenous or intramuscular; not absorbed orally.
Preparation	Clear colorless solution stable at room temperature; 250 mg/ml in vials of 500 mg or 1 gram; 1 gram in 3 ml vial; or 75 mg/vial for infants. Can be mixed with D5W or normal saline for intravenous infusion. Adult doses should be mixed in at least 100 ml of fluid, and pediatric doses should be mixed to a concentration of at least 5 mg/ml.
Storage	Store in the refrigerator.
Pharmacokinetics	For intravenous administration, infuse over 60 minutes for adults; 1–2 hours for children; intramuscular absorption is complete within 4 hours and peak 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 peak to be extrapolated. **Peak concentrations** for a 15 mg/kg dose are between 35 and 45 mcg/ml. **Peak concentrations** of 25–35 mcg/ml are acceptable if you anticipate using kanamycin for more than 6 months. **Peak concentrations** of 65–80 mcg/ml are obtained after a 25 mg/kg dose. Trough concentrations should be undetectable after a 24-hour dose. See Appendix 12, “Therapeutic Drug Monitoring.”
Oral absorption	Not absorbed orally; 40–80% of the dose is absorbed intramuscularly.

KANAMYCIN [2 of 2]

CSF penetration	Minimal and variable CSF penetration—slightly better with inflamed meninges.
Special circumstances	**Use in pregnancy/breastfeeding:** Generally avoided in pregnancy due to documented congenital deafness. Can be used while breastfeeding. **Use in renal disease:** 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 5, "Special Situations – Renal Failure." **Use in hepatic disease:** 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. **Diuretic use:** Coadministration of loop diuretics and aminoglycoside antibiotics carries an increased risk of ototoxicity.
Adverse reactions	Nephrotoxicity: Appears to be more nephrotoxic than streptomycin. 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.
Contraindications	**Pregnancy** (congenital deafness seen with streptomycin and kanamycin use in pregnancy); **hypersensitivity to aminoglycosides;** caution with renal, vestibular, or auditory impairment; patients with intestinal obstructions.
Monitoring	Monitor renal function by documenting creatinine at least monthly (more frequently if renal or hepatic impairment); document creatinine clearance if there is baseline renal impairment or any concerns; document baseline and monthly audiology exam. Question patient regularly about vestibular complaints and perform serial vestibular exams. Document peak and trough 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.
2007 wholesale cost 30-day supply, 75-kg person	$129 (TB clinic) $151 (community hospital)
Patient instructions	**Call your doctor right away if you have:** • Problems with hearing, dizziness, or balance • Rash or swelling of your face • Trouble breathing • Decreased urination • Watery or bloody diarrhea • Swelling, pain, or redness at your IV site • Muscle twitching or weakness

LEVOFLOXACIN [1 of 2]

Drug class	Fluoroquinolone
Trade name	Levaquin
Activity against TB	**Bactericidal;** has strong anti-TB activity. Cross-resistance with other fluoroquinolones, but data suggests greater activity than ciprofloxacin or ofloxacin. Inhibits DNA gyrase.
Dose (all once daily)	**Adults:** 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 > 45.5 kg (100 lbs). **Children:** 10 mg/kg/day for older children and 15–20 mg/kg/day divided bid for younger children (PO or IV) bsed on limited data and extrapolation from adult data (see discussion of fluoroquinolones in children in Chapter 5, "Special Situations – Pediatrics"). **Renal failure/dialysis:** 750–1000 mg/dose 3 times weekly (not daily).
Route of administration	Oral or intravenous.
Preparation	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.
Storage	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.
Pharmacokinetics	**Peak oral absorption** occurs at 1–2 hours. **Peak concentrations** should be drawn at 2 hours after the dose, and a trough 6–10 hours after the dose allows for calculation of the half-life. **Peak concentrations** of 8–12 mcg/ml are expected. See Appendix 12, "Therapeutic Drug Monitoring."
Oral absorption	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).
CSF penetration	Concentrations are 16–20% of that in the serum.
Special circumstances	**Use in pregnancy/breastfeeding:** 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 (see Chapter 5, "Special Situations"). **Use in renal disease:** Dosage adjustment is recommended if creatinine clearance is < 50 ml/min. The drug is not cleared by hemodialysis; supplemental doses after dialysis are not necessary. (See Chapter 5, "Special Situations – Renal Failure.") **Use in hepatic disease:** Drug concentrations not affected by hepatic disease. Presumed to be safe in severe liver disease.

LEVOFLOXACIN [2 of 2]

Adverse reactions	Nausea and bloating. Headache, dizziness, insomnia, or tremulousness. **Rare** tendon rupture, arthralgias (can usually be treated symptomatically). QTc prolongation.
Contraindications	**Fluoroquinolone intolerance, prolonged QTc, pregnancy (relative contraindication)**
Monitoring	Side effect monitoring, but no specific laboratory monitoring required.
2007 wholesale cost 30-day supply, 75-kg person	$144 (TB clinic) $598 (community hospital)
Patient instructions	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), or multivitamins within 2 hours of this medication. This medicine may cause sun sensitivity; use sunscreens. Do not undertake new strenuous activities. **Call your doctor and stop the medicine right away if you have:** • Pain, swelling or tearing of a tendon (such as the back of your ankle, elbow, etc.), or muscle or joint pain • Rashes, hives, bruising or blistering, trouble breathing, or tightness in your chest • Diarrhea • Yellow skin or eyes • Anxiety, confusion, or dizziness

LINEZOLID [1 of 2]

Drug class	Oxazolidinones
Trade name	Zyvox
Activity against TB	Has *in vitro* bactericidal activity—little clinical experience; inhibits protein synthesis.
Dose	**Adults:** 600 mg once daily. **Children:** 10 mg/kg/dose every 8 hours. **Vitamin B6:** All patients should receive Vitamin B6 while receiving linezolid. **Renal failure/dialysis:** No dose adjustment required.
Route of administration	Oral or intravenous.
Preparation	Coated tablets: 400 and 600 mg; intravenous solution: 2 mg/ml: 100, 200, or 300 mg bags. Oral powder for suspension: 100 mg/5 ml 240 ml bottle.
Storage	Store tablet at room temperature. Reconstituted oral suspension may be stored at room temperature for 21 days. Parenteral preparation should be stored at room temperature (protect from light and do not freeze).
Pharmacokinetics	Intravenous doses are administered over 30–120 minutes. **Peak concentrations** are achieved 1–1.5 hours after an oral dose and ½ hour after an IV dose. **Peak concentrations** 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. **Peak concentrations** are expected to be 12–24 mcg/ml. See Appendix 12, "Therapeutic Drug Monitoring."
Oral absorption	Nearly complete oral absorption.
CSF penetration	CSF concentrations are about 1/3 of those in serum in animal models and has been used to treat meningitis in humans.
Special circumstances	**Use in pregnancy/breastfeeding:** Not recommended during pregnancy or breastfeeding due to limited data. **Use in renal disease:** No dose adjustment is recommended, but metabolites may accumulate. **Use in hepatic disease:** Rarely associated with increased transaminases.
Adverse reactions	Myelosuppression. Diarrhea and nausea. Optic and peripheral neuropathy.
Contraindications	**Hypersensitivity to oxazolidinones.** **Symptoms of neuropathy** (pain, numbness, tingling or weakness in the extremities)

LINEZOLID [2 of 2]

Monitoring	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.
2007 wholesale cost 30-day supply, 75-kg person	$1183 (TB clinic) $1909 (community hospital)
Patient instructions	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. **Call your doctor right away if you have any of these side effects:** • Pain, numbness, tingling or weakness in the extremities • Black, tarry stools or severe diarrhea • Unusual bleeding or bruising • Unusual tiredness or weakness • Headache, nausea, or vomiting

MOXIFLOXACIN [1 of 2]

Drug class	Fluoroquinolone
Trade name	Avelox
Activity against TB	**Bactericidal;** inhibits DNA gyrase; cross-resistance with other fluoroquinolones, but may be more active based on *in vitro* data.
Dose (all once daily)	**Adults:** 400 mg daily (PO or IV). **Children:** No established dose (see discussion of fluoroquinolones in children in Chapter 5, "Special Situations – Pediatrics"). **Renal failure/dialysis:** No dose adjustment required.
Route of administration	Oral or IV.
Preparation	Tablets (400 mg); aqueous solution (400 mg/250 ml) for IV injection.
Storage	Store oral and IV products at room temperature (do not refrigerate).
Pharmacokinetics	**Peak absorption** after an oral dose is noted in 1–3 hours. **Peak concentrations** should be drawn at 2 hours. A 6-hour concentration can be drawn to calculate half-life. **Peak concentrations** are expected to be 3-4 mcg/ml after a 10-day course. Trough concentrations of 0.3–0.5 mcg/ml were noted. See Appendix 12, "Therapeutic Drug Monitoring."
Oral absorption	Good oral absorption (90% bioavailable). Should not be administered within 2 hours of ingestion of milk-based products, antacids, or other medications containing divalent cations (iron, magnesium, calcium, zinc, vitamins, didanosine, sucralfate).
CSF penetration	Good penetration in animal model studies.
Special circumstances	**Use in pregnancy/breastfeeding:** Fluoroquinolones are generally avoided in pregnancy and breastfeeding due to observation of arthropathy in puppy models. However, there are a few case reports of fluoroquinolones being used safely in pregnancy (see Chapter 5, "Special Situations"). **Use in renal disease:** Excretion unchanged in the face of renal failure; no data on effect of dialysis. **Use in hepatic disease:** Rarely associated with hepatotoxicity; use with caution. No dose adjustment required for mild or moderate liver disease.
Adverse reactions	Nausea and diarrhea. Headache and dizziness. **Rare** tendon rupture; arthralgias. Rare hepatotoxicity. QTc prolongation.
Contraindications	Fluoroquinolone intolerance, prolonged QTc, pregnancy (relative contraindication)

MOXIFLOXACIN [2 of 2]

Monitoring	Symptomatic monitoring.
2007 wholesale cost 30-day supply, 75-kg person	$127 (TB clinic) $76 (community hospital)
Patient instructions	Keep moxifloxacin at room temperature. Moxifloxacin can be taken with food, but do not take milk-based products, antacid (especially aluminum-coating), vitamin supplements, or sucralfate within 2 hours of this medication. Do not undertake new strenuous activities. **Call your doctor and stop the medicine right away if you have:** • Pain, swelling or tearing of a tendon (such as the back of your ankle, elbow, etc.), or muscle or joint pain • Rashes, hives, bruising or blistering, trouble breathing, or tightness in your chest • Diarrhea • Yellow skin or eyes • Anxiety, confusion, or dizziness

PARA-AMINOSALICYLATE (PAS) [1 of 2]

Drug class	Salicylic acid – anti-folate
Trade name	PASER
Activity against TB	**Bacteriostatic.**
Dose	**Adults:** 8–12 grams per day divided 2–3 times per day. **Children:** 200–300 mg/kg/day divided 2–4 times per day. **Renal failure/dialysis:** No change.
Route of administration	Oral; not available parenterally in the U.S.
Preparation	4 grams per packet.
Storage	Packets should be kept in the refrigerator or freezer.
Pharmacokinetics	Delayed peak concentration with the PASER formulation (the only product available in the United States) due to its enteric coating and sustained release (1–6 hours). **Peak concentrations** should be collected at 6 hours. **Peak concentrations** are expected to be 20–60 mcg/ml. See Appendix 12, "Therapeutic Drug Monitoring."
Oral absorption	Incomplete absorption—sometimes requires increased doses to achieve therapeutic concentrations.
CSF penetration	Poorly penetrates the meninges (somewhat better with inflammation).
Special circumstances	**Use in pregnancy/breastfeeding:** Not studied, but no teratogenicity known. There is little data regarding breastfeeding. In one patient, the milk concentration was 1 mcg/ml compared to a serum concentration of 70 mcg/ml. **Use in renal disease:** Inactive metabolite is cleared by the kidneys. The package insert says to avoid with severe renal failure. Other authorities believe it can be used with caution (no toxicity of metabolite known). See Chapter 5, "Special Situations–Renal Failure." **Use in hepatic disease:** Use with caution; 0.5% incidence of hepatotoxicity.
Adverse reactions	Gastrointestinal distress (less with the PASER formulation than with older preparations). Rare hepatotoxicity and coagulopathy. Reversible hypothyroidism (increased risk with concomitant use of ethionamide)—treat with thyroid replacement.
Contraindications	**pregnancy (relative)**
Monitoring	Monitor TSH, electrolytes, blood counts, and liver function tests.

PARA-AMINOSALICYLATE (PAS) [2 of 2]

2007 wholesale cost 30-day supply, 75-kg person	$262 (TB clinic) $581 (community hospital)

Patient instructions

Keep the product in the refrigerator or freezer. Sprinkle granules over applesauce or yogurt or swirl in acidic juices (tomato, grape, grapefruit, cranberry, apple, or orange). Do not chew the granules. Take with food if desired. Do not use the packet if swollen or if the granules are discolored. Gastrointestinal discomfort and diarrhea usually improve over time. The shells of the granules may be seen in the stool – 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 [1 of 2]

Drug class	Synthetic derivative of nicotinamide
Trade name	Pyrazinamide
Activity against TB	**Bactericidal** for semi-dormant *M. tuberculosis*. Mechanism unclear.
Dose (all once daily)	**Adults:** 25 mg/kg/day (max dose 2 grams). **Children:** 20–40 mg/kg/dose. **Renal failure/dialysis:** 25 mg/kg/dose 3 times per week (not daily). **Obesity:** Pyrazinamide should be dosed on lean body weight. Ideal body weight (men): 50 kg plus 2.3 kg/inch over 5 ft Ideal body weight (women): 45 kg plus 2.3 kg/inch over 5 ft
Route of administration	Oral; not available parenterally.
Preparation	500 mg scored or unscored tablet.
Storage	Store the tablets at room temperature.
Pharmacokinetics	**Peak concentration** is 1–4 hours after an oral dose. **Peak concentrations** should be drawn at 2 and 6 hours for therapeutic drug monitoring. **Peak concentrations** of 20–40 mcg/ml are expected after a daily dose. Pyrazinamide can be found in the urine all day long and can be an indication of adherence to therapy. See Appendix 12, "Therapeutic Drug Monitoring."
Oral absorption	Well absorbed from the GI tract.
CSF penetration	Concentrations equivalent to serum.
Special circumstances	**Use in pregnancy/breastfeeding:** 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 sensitive to pyrazinamide (no known teratogenicity). Can be used while breastfeeding. **Use in renal disease:** Cleared by the kidneys; dose 3 times a week and after dialysis. **Use in hepatic disease:** Use with caution; pyrazinamide is associated with hepatotoxicity in about 1% of patients. It can be quite severe and worsen off treatment.
Adverse reactions	Gout (hyperuricemia) and arthralgias. Hepatotoxicity. Rash. Photosensitivity. Gastrointestinal upset.
Contraindications	**Allergy to pyrazinamide; severe gout.**

PYRAZINAMIDE [2 of 2]

Monitoring	Monitor transaminases; check uric acid if the patient develops arthralgias.
2007 wholesale cost 30-day supply, 75-kg person	$42 (TB clinic) $85 (community hospital)
Patient instructions	May be taken with or without food; this medicine may cause a rash after sun exposure: limit your sun exposure. **Call your doctor right away if you have any of these side effects:** • Skin rash, severe itching, or hives • Pain or swelling in the joints • Yellowing of the skin or eyes or dark urine • Nausea or vomiting • Unusual tiredness or loss of appetite

RIFABUTIN [1 of 2]

Drug class	Rifamycin
Trade name	Mycobutin
Activity against TB	**Bactericidal;** same mechanism of activity as rifampin (inhibits RNA polymerase). Less than 20% of rifampin-resistant strains are susceptible to rifabutin.
Dose (all once daily)	**Adults:** 5 mg/kg/dose (max dose 300 mg, though doses up to 450 mg are sometimes used). Dose adjustments sometimes required when dosing with interacting drugs. **Children:** The pediatric dose is not established, but doses of 5–10 mg/kg/day have been used (higher doses have been recommended for children < 1 year of age). Caution should be used in very young children in whom visual changes might not be obvious. **Renal failure/dialysis:** Reduce dose by 50% for creatinine clearance less than 30 ml/minute and monitor concentrations to avoid under-dosing. **Concomitant medications:** Dosage adjustment may be required, particularly with anti-retroviral therapy use. See www.cdc.gov/TB/TB_HIV_Drugs/default.htm.
Route of administration	Oral; not available parenterally.
Preparation	150 mg capsule.
Storage	Capsules should be kept at room temperature.
Pharmacokinetics	Peak concentration is reached 3–4 hours after a dose. Peak serum concentration should be drawn 3 hours after the dose; a second sample 7 hours post-dose is desirable in order to estimate the serum half-life and assess absorption. The peak concentration should be between 0.3 and 0.9 mcg/ml. Dose adjustments should be considered for patients with concentrations < 0.3 or > 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. See Appendix 12, "Therapeutic Drug Monitoring."
Oral absorption	Well absorbed from the GI tract.
CSF penetration	Penetrates inflamed meninges.
Special circumstances	**Use in pregnancy/breastfeeding:** Insufficient data in pregnancy. Unknown effects from breastfeeding. **Use in renal disease:** Used without dose adjustment in mild renal insufficiency. Reduce dose by 50% for creatinine clearance less than 30 ml/minute and monitor concentrations to avoid under-dosing. **Use in hepatic disease:** Use with caution and additional monitoring in liver disease. Dose adjustments necessary for drug interactions—especially HIV drugs. See www.cdc.gov/TB/TB_HIV_Drugs/default.htm.

RIFABUTIN [2 of 2]

Adverse reactions	Leukopenia (dose dependent); thrombocytopenia. Rashes and skin discoloration (bronzing or pseudojaundice). Anterior uveitis and other eye toxicities. Hepatotoxicity similar to that of rifampin. Drug interactions with many other drugs—but only 40% of that seen with rifampin. Rifabutin concentrations may be affected by other drugs. Arthralgias.
Contraindications	**Rifamycin hypersensitivity.** 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.
Monitoring	Increased liver function monitoring; monitor drug concentrations of interacting medications; blood counts and vision screening.
2007 wholesale cost 30-day supply, 75-kg person	$168 (TB clinic) $426 (community hospital)
Patient instructions	May be taken with or without food; if it bothers your stomach, try taking it with food. It is normal for your urine, tears, and other secretions to turn a brownish-orange color when taking this medicine. Sometimes skin even becomes discolored. Soft contact lenses may become discolored while you are on this medicine. Make sure your doctor knows all the medicines you take, as there are many drugs that interfere with this one. Avoid the use of oral hormone-based birth control methods because rifabutin may decrease their effectiveness. **Call your doctor right away if you have any of these side effects:** • Any eye pain, change in vision, or sensitivity to light • Fever, chills, or sore throat • Pain or swelling in the joints • Yellowing of the skin or eyes or dark urine • Nausea or vomiting • Unusual tiredness or loss of appetite

RIFAMPIN [1 of 2]

Drug class	Rifamycin
Trade name	Rifadin (also known as rifampicin)
Activity against TB	**Bactericidal;** inhibits protein synthesis; cross-resistance with other rifamycins.
Dose (all once daily)	**Adults:** 10 mg/kg/dose up to 600 mg (PO or IV). **Children:** 10–20 mg/kg/dose up to 600 mg (PO or IV). **Renal failure/dialysis:** No adjustment required. **Concomitant medications:** Dosage adjustment may be required, particularly with anti-retroviral therapy use. See www.cdc.gov/TB/TB_HIV_Drugs/default.htm.
Route of administration	Oral or intravenous.
Preparation	150 and 300 mg capsules; lyophilized powder for injection: 600 mg/vial; contents of capsules can be mixed with liquid or semi-soft vehicles. Extemporaneously prepared oral solutions have unproven homogeneity and shelf life. Immediate administration of the dose after mixing capsular contents in a vehicle is ideal.
Storage	Capsules and powder should be kept at room temperature; powder suspended in saline is stable for 24 hours; powder suspended in dextrose solutions is stable for 4 hours.
Pharmacokinetics	**Peak time to concentration** after an oral dose is 1–4 hours. **Peak concentrations** should be obtained 2 hours after a dose, and if delayed absorption is considered, a concentration at 6 hours should also be collected. **Peak concentrations** 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. See Appendix 12, "Therapeutic Drug Monitoring."
Oral absorption	Usually rapid absorption, may be delayed or decreased by high-fat meals.
CSF penetration	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.
Special circumstances	**Use in pregnancy/breastfeeding:** Recommended for use in pregnancy; can be used while breastfeeding. **Use in renal disease:** Can be used without dose adjustment. **Use in hepatic disease:** Use with caution, can be associated with hepatotoxicity. Dose adjustments necessary for drug interactions—especially HIV drugs. See www.cdc.gov/TB/TB_HIV_Drugs/default.htm.

RIFAMPIN [2 of 2]

Adverse reactions	**Many drug interactions.** Orange staining of body fluids. Rash and pruritus. GI upset, flu-like syndrome (usually only with intermittent administration). Hepatotoxicity. Hematologic abnormalities (thrombocytopenia, hemolytic anemia).
Contraindications	**Rifamycin allergy;** due to **drug interactions**, may be contraindicated with concurrent use of certain drugs.
Monitoring	Liver function monitoring if appropriate (if given with other hepatotoxic medications or if there are symptoms of hepatotoxicity); monitor drug concentrations of interacting medications.
2007 wholesale cost 30-day supply, 75-kg person	$29 (TB clinic) $78 (community hospital)
Patient instructions	Best taken without food; if it bothers your stomach, try taking it with a small amount of food. It is normal for your urine, tears, and other secretions to turn an orange color when taking this medicine. Soft contact lenses may become discolored while you are on this medicine. Make sure your doctor knows all the medicines you take because many drugs can interfere with this one. Avoid the use of oral hormone-based birth control methods because rifampin may decrease their effectiveness. **Call your doctor right away if you have any of these side effects:** • Unusual tiredness or loss of appetite • Severe abdominal upset • Fever or chills

STREPTOMYCIN [1 of 2]

Drug class	Aminoglycoside
Trade name	Streptomycin sulfate
Activity against TB	**Bactericidal;** inhibits protein synthesis; no significant cross-resistance with other aminoglycosides.
Dose (all once daily)	**Adults:** 15 mg/kg/day, 5–7 days per week (maximum dose is generally 1 gram, but a large, muscular person could receive more and should have 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). **> 59 yrs of age:** 10 mg/kg/dose (max 750 mg) 5–7 times per week or 2–3 times per week after initial period. **Children:** 20–40 mg/kg/day (max 1 gram) 5–7 days per week. 20–40 mg/kg/day (max 1 gram) 2–3 days per week after initial period daily. **Renal failure/dialysis:** 12–15 mg/kg/dose 2–3 times weekly (not daily). **Markedly obese individuals** should have an adjusted dose due to the decreased distribution of extracellular fluids in adipose tissues. Dosing based on actual weight will give supratherapeutic concentrations. The suggested adjusted weight is ideal body weight plus 40% of the excess weight. Ideal body weight (men): 50 kg plus 2.3 kg/inch over 5 ft Ideal body weight (women): 45 kg plus 2.3 kg/inch over 5 ft *Concentrations should be followed closely.*
Route of administration	Intravenous or intramuscular (has been used intrathecally and intraperitoneally). Not absorbed orally.
Preparation	1 gram vial for injection.
Storage	Store in the refrigerator.
Pharmacokinetics	For intravenous administration, infuse over 60 minutes for adults; 1–2 hours for children; intramuscular absorption is complete within 4 hours and peak 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 peak to be extrapolated. **Peak concentrations** for a 15 mg/kg dose are between 35 and 45 mcg/ml. **Peak concentrations** of 25–35 mcg/ml are acceptable if you anticipate using streptomycin for more than 6 months. **Peak concentrations** of 65–80 mcg/ml are obtained after a 25 mg/kg dose. Trough concentrations should be < 5 mcg/ml in patients with normal renal fucntion. See Appendix 12, “Therapeutic Drug Monitoring.”
Oral absorption	There is no significant oral absorption. Intramuscular absorption might be delayed if the same site is used consistently.

STREPTOMYCIN [2 of 2]

CSF penetration	Variable penetration; appears to penetrate inflamed meninges better.
Special circumstances	**Use in pregnancy/breastfeeding:** Avoided in pregnancy due to documented cases of congenital deafness. Can be used while breastfeeding. **Use in renal disease:** Use with caution. 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 5, "Special Situations – Renal Failure." **Use in hepatic disease:** 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. **Diuretic use:** Coadministration of loop diuretics and aminoglycoside antibiotics carries an increased risk of ototoxicity.
Adverse reactions	Nephrotoxicity: Less nephrotoxic than amikacin. Ototoxicity (hearing loss): Increased with advanced age and prolonged use. Local pain with IM injections. Vestibular toxicity. Electrolyte abnormalities, including hypokalemia and hypomagnesemia.
Contraindications	**Pregnancy** (congenital deafness seen with streptomycin and kanamycin use in pregnancy); **hypersensitivity to aminoglycosides;** caution with renal, vestibular, or auditory impairment.
Monitoring	Monitor renal function by documenting creatinine at least monthly (more frequently if renal or hepatic impairment); document creatinine clearance if there is baseline renal impairment or any concerns; document baseline and monthly audiology exam. Question patient regularly about vestibular complaints and perform serial vestibular exams. Document peak and trough 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.
2007 wholesale cost 30-day supply, 75-kg person	$108 (TB clinic) $124 (community hospital)
Patient instructions	Store streptomycin in the refrigerator. **Call your doctor right away if you have:** • Problems with hearing, dizziness, or balance • Rash or swelling of your face • Trouble breathing • Decreased urination • Watery or bloody diarrhea • Swelling, pain, or redness at your IV site • Muscle twitching or weakness

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5 Special Situations

Managing drug-resistant TB, never a simple endeavor, requires additional considerations in the following special situations: extrapulmonary TB, HIV, liver disease, renal failure, pregnancy, and pediatric TB.

Extrapulmonary TB

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

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

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

- **Several forms of extrapulmonary TB (meningitis/pericarditis) are treated with adjunctive corticosteroid treatment in conjunction with an optimal anti-tuberculosis regimen.** Use of corticosteroids for patients not receiving adequate anti-mycobacterial therapy could be problematic. Studies showing efficacy of corticosteroid therapy are reported for drug-susceptible cases. The indication for corticosteroids in patients with drug-resistant TB remains unclear.
- **Some forms of TB** (particularly scrofula and intrathoracic adenopathy) **are known to worsen as the TB is being successfully treated.** This is due to immune reconstitution as the organism is being eliminated and is particularly common in HIV-infected individuals. This phenomenon is known as a "paradoxical reaction" or the immune reconstitution inflammatory syndrome (IRIS). However, if the clinical worsening is actually due to microbiologic failure associated with unrecognized (or not yet diagnosed) drug resistance, it may inappropriately be attributed to a paradoxical reaction. In this case, the correct diagnosis (drug resistance and treatment failure) will be delayed.
- **Drug regimens and durations of treatment for drug-susceptible extrapulmonary TB are based on known penetration of first-line anti-tuberculosis drugs into tissues, years of experience, and some clinical trials.** Unfortunately, much less is known regarding the penetration of second-line drugs into tissues. This is compounded by the increased rates of malabsorption and drug interactions experienced by individuals at risk for drug-resistant TB.
- **Serial cultures are often not available.** Clinical and radiographic assessments should be used to determine duration of therapy. Computed tomography is often useful in following treatment progress in these patients.

Role of Surgery

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

Drug-Resistant Central Nervous System TB

Several reports detail poor outcomes of drug-resistant TB meningitis. Most of the patients in these series were HIV-infected and many developed meningitis while already receiving treatment for MDR-TB. Mortality in 2 series from South Africa, 1 in adults and 1 in children, ranged from 57% to 88%. The majority of patients were HIV-infected. Any degree of drug resistance will hinder the treatment of TB meningitis or other central nervous system (CNS) TB because isoniazid (INH) is the most important drug in the treatment of TB meningitis. Interestingly, one series showed no increased risk of in-hospital mortality with INH resistance.

TB Drugs and their CNS Penetration

INH is the most important drug in the treatment of TB meningitis. INH readily diffuses into the cerebrospinal fluid (CSF), independent of meningeal inflammation due to its small size and lipophilic nature. Levels approach those in serum. Because of this, some experts recommend the use of INH in MDR-TB meningitis, especially in the setting of low-level INH resistance.

Rifampin (RIF), rifabutin, ethambutol (EMB), para-aminosalicylate (PAS), and the **aminoglycosides** penetrate poorly into the CSF with non-inflamed meninges, but better with inflamed meninges. For RIF, 10% to 20% of the serum level reaches the CSF in the setting of inflamed meninges (still exceeding the minimum inhibitory concentration [MIC] of sensitive isolates). One study of RIF CSF with uninflamed meninges showed similar results, with penetration of 13% to 42% (median = 22%).

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

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

The **fluoroquinolones** have variable CSF penetration. Levofloxacin levels in the CSF are about 15% to 30% that of serum (level around 2 mcg/ml for a normal dose). Since higher doses are generally used to treat MDR-TB, CSF levels may be adequate to treat TB meningitis (MIC 0.5–1.0). Moxifloxacin has shown good CSF penetration in several animal studies (CSF levels approximately 50% of serum). Human data will be required to determine which fluoroquinolone will have best efficacy in the treatment of TB meningitis. There is no clinical data yet available on MDR-TB meningitis outcomes with the use of moxifloxacin.

Route of Administration

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

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

Summary **EXTRAPULMONARY TB**

- **Data regarding treatment of extrapulmonary drug-resistant TB are limited.** A few cases are described within larger series of MDR-TB cases.
- **Patients with extrapulmonary TB are at risk of treatment failure due to poor drug penetration to the affected tissue and the lack of accessibility of tissue for serial cultures.**
- **Surgical resection** (scrofula) **and drainage** (empyema, abscesses, and arthritis) **may decrease bacterial burden and improve outcome.** Full medical treatment is still indicated.
- **Drug-resistant TB meningitis is challenging to treat due to the incomplete CSF penetration of many second-line drugs.** Intrathecal administration of medications and the use of newer fluoroquinolones may improve outcome and should be evaluated prospectively.

HIV

Patients with HIV/AIDS are at increased risk of developing tuberculosis (TB) once infected compared to immunocompetent individuals. Additionally, TB increases HIV replication, promoting a vicious cycle of viral and mycobacterial proliferation. Patients with HIV are more likely to have atypical presentations of TB, such as extrapulmonary TB (including lymphadenopathy, miliary TB, and meningitis), sputum smear-negative TB, and sputum culture-positive TB in the absence of an abnormal chest radiograph. These individuals are less likely to have cavitary disease and more likely to have mid- and lower-lung disease than are individuals without HIV infection.

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

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

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

Unfortunately, HIV-infected individuals have higher mortality rates than non-infected, multidrug-resistant TB (MDR-TB) patients, 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 recent large series of HIV-infected 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 HIV-TB coinfected patients.

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

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

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

To maximize care of HIV-infected patients:

- Identify all HIV-infected patients by screening all patients with TB disease for HIV.
- Work closely with the patient's HIV provider. If that provider does not have extensive HIV/TB expertise, consult such an expert throughout the course of therapy.
- Consider the best HIV regimen for immune reconstitution as well as the timing of initiation of ART treatment for antiretroviral-naive patients. Initiation of ART therapy is associated with increased drug toxicity as well as the phenomenon of immune reconstitution. Immune reconstitution may exacerbate clinical symptoms of TB by stimulating an inflammatory response. In patients with CD4 lymphocyte counts over 200, it is reasonable to delay ART therapy for several months. In patients with CD4 less than 100 (or patients with extrapulmonary TB and CD4 less than 200), it is advisable to begin ART therapy as soon as TB therapy is well tolerated (usually within 1 to 2 months).

Consider alternate drugs when interactions between TB and HIV drugs are present (e.g., rifabutin in place of rifampin).

- **Rifamycins are inducers of cytochrome P-450 and interact with many drugs.** Rifampin (RIF) in particular leads to lower levels of protease inhibitors and non-nucleoside reverse transcriptase inhibitors (NNRTIs). Current recommendations about concomitant use of rifamycins (RIF and rifabutin) and ART therapy should be consulted. For the updated guidelines published in 2008, see: www.cdc.gov/TB/TB_HIV_Drugs/default.htm
- **The rifamycins and other TB drugs interact with a number of the anti-infectious agents that may be taken by HIV-infected patients,** including the macrolide drugs, cidofovir, anti-fungal drugs, and others.

- **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.
- Intervene to avoid or treat symptomatic toxicity. Peripheral neuropathy, cutaneous reactions, gastrointestinal (GI) side effects, renal impairment, and neuropsychiatric effects may all be worse in HIV/TB patients.
- Use daily directly observed therapy (DOT).
- Closely monitor signs and symptoms of malabsorption: diarrhea, abnormal stools, abnormal nutritional studies, evidence of vitamin deficiencies, weight loss, etc.
- Consider therapeutic drug monitoring to detect malabsorption, drug-drug interactions for MDR-TB, or clinical suspicion of malabsorption.
- Involve a nutritionist and pay close attention to weight and nutrition. Consider use of appetite stimulants in situations of extreme malnutrition.
- Involve ancillary services such as social workers, substance abuse clinics, and mental health facilities.
- Involve the patient's social support system, as appropriate.

Summary **HIV**

- **MDR-TB patients coinfected with HIV have higher mortality rates,** particularly when they are profoundly immunocompromised (CD4 lymphocyte count less than 100) and an optimal TB regimen is not initiated early in the course of disease.
- **HIV-infected patients can be cured of their drug-resistant TB disease,** but require special monitoring and concurrent care of their HIV disease. Initiation of ART prolongs survival.
- **Malabsorption and drug interactions increase risk of drug-resistant TB** as well as complicate its treatment.
- **Rifamycins can be used in HIV-infected patients on ART,** but dose adjustments may be required. Rifabutin generally has fewer drug interactions than does rifampin.

Liver Disease

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

Drug	Effect on Liver
Isoniazid (INH)	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.
Rifampin (RIF)	RIF more commonly causes a cholestatic jaundice, but can potentiate the hepatocyte damage caused by INH.
Pyrazinamide (PZA)	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.
Ethionamide **PAS**	Ethionamide and para-aminosalicylate (PAS) have also been implicated in hepatotoxic drug reactions.
Fluoroquinolones	Some of the fluoroquinolone drugs **(ciprofloxacin and moxifloxacin)** have been associated with occasional cases of liver damage. **Travafloxacin** has been associated with severe liver toxicity in rare cases.
Levofloxacin **Ethambutol (EMB)** **Aminoglycosides** **Cycloserine**	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 1 patient has successfully undergone liver transplantation for toxicity of multidrug-resistant TB (MDR-TB) treatment.

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

Summary LIVER DISEASE

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

  See Chapter 7, "Adverse Reactions," for more information regarding response to hepatotoxicity encountered on 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 tuberculosis (TB) 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 drug interactions). Table 1 describes dosing changes for patients with renal insufficiency.

For TB drugs that are cleared by the kidney, the general strategy is to increase the interval between dosing rather than to decrease the dose.

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

Specific TB Drugs

Ethambutol (EMB)

- Up to 80% cleared by the kidney
- Incompletely dialyzed
- Dose should be adjusted as per Table 1, but there may be an increased risk of accumulation of the drug and eye toxicity in the setting of renal failure
- Drug levels may be helpful in cases where EMB is important for the regimen
- In some circumstances (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 calculator at bottom of Table 1)
- Monitor carefully for red-green color discrimination and visual changes

Aminoglycosides (Streptomycin, Kanamycin, Amikacin) and Capreomycin

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

Levofloxacin

- Cleared more extensively by the kidney than is moxifloxacin.
- 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 levofloxacin for non-tuberculosis infections suggests using smaller doses that may not be adequate. Again, drug concentration monitoring might be beneficial and general toxicity monitoring is imperative.

Moxifloxacin

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

Cycloserine

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

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	No change	300 mg once daily, or 900 mg 3 times/week
Rifampin	No change	600 mg once daily, or 600 mg 3 times/week
Pyrazinamide	Yes	25–35 mg/kg/dose 3 times/week (not daily)
Ethambutol	Yes	15–25 mg/kg/dose 3 times/week (not daily)
Levofloxacin	Yes	750–1000 mg/dose 3 times/week (not daily)
Moxifloxacin	No change	400 mg daily
Cycloserine	Yes	250 mg once daily, or 500 mg/dose 3 times/week*
Ethionamide	No change	15-20 mg/kg/day (can be in divided doses)
PAS	No change	4 gm/dose twice daily
Streptomycin	Yes	12–15 mg/kg/dose 2–3 times/week (not daily)
Capreomycin	Yes	12–15 mg/kg/dose 2–3 times/week (not daily)
Kanamycin	Yes	12–15 mg/kg/dose 2–3 times/week (not daily)
Amikacin	Yes	12–15 mg/kg/dose 2–3 times/week (not daily)

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

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

Estimated creatinine clearance calculations

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

Table adapted from the American Thoracic Society Treatment Guidelines.

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

Summary RENAL FAILURE

- **Isoniazid (INH), rifampin (RIF), ethionamide, and PAS are not cleared by the kidney, and their dosing does not require adjustment for renal failure.** Most other anti-tuberculosis drugs require dose adjustment for significant renal insufficiency.
- **Dosing guidelines are well established for patients with creatinine clearance less than 30 ml/minute or undergoing hemodialysis.** Adjustment for patients with more mild renal impairment or undergoing peritoneal dialysis is not as well described.
- **Therapeutic drug monitoring is always indicated for patients with impaired renal function receiving an injectable drug, EMB, or cycloserine,** and may be helpful for other medications as well.

Pregnancy

Treatment of drug-resistant tuberculosis (TB) during pregnancy is very challenging. All female patients of childbearing age with multidrug-resistant TB (MDR-TB) should be strongly advised to avoid pregnancy. 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 and since 2003, several small series and case reports (totaling 14 patients) have been published in which treatment for MDR-TB using second- and third-line drugs was given to pregnant women with extensive, progressive disease. One woman elected to terminate her pregnancy. Of 13 live-born infants, none had congenital anomalies. Long-term follow-up of six of these children (average age 3.7 years) 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, we generally avoid use of pyrazinamide (PZA) in the United States. In the case of drug-resistant TB, PZA should be used when the isolate is susceptible. Treatment of monodrug-resistant TB for pregnant women is the same as for nonpregnant individuals:

Resistance	Medications	Duration
INH monoresistance	RIF + EMB + PZA	6–9 months
PZA monoresistance (*M. bovis*)	INH + RIF + EMB Followed by INH and RIF	2 months At least 7 more months
RIF monoresistance *Consider addition of a fluoroquinolone or injectable drug after delivery to shorten course.*	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. The regimen can be strengthened after the baby delivers. A potential regimen might include cycloserine, 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** and **kanamycin** have been implicated as the cause of mild to severe bilateral congenital deafness (eighth nerve toxicity) in up to 17% of pregnancies. For that reason, **amikacin** and **capreomycin** are also not recommended during pregnancy, but have been used safely in some reports.
- **Ethionamide** use has been associated with congenital defects in several children. In general, there are not enough data to determine its safety during pregnancy.
- **Fluoroquinolones** are generally avoided during pregnancy due to the observation of arthropathy in puppy models and adverse events in monkeys receiving norfloxacin. **Levofloxacin** has not been found to be teratogenic in animals, but large doses have led to decreased fetal weight and increased fetal mortality in rats. One series reported 200 women exposed to fluoroquinolones in the first trimester and none of the babies suffered musculoskeletal abnormalities. Fluoroquinolone drugs have been used in the treatment of MDR-TB in pregnancy and have not been associated with identified teratogenicity.
- **PZA** is not included in the TB regimens of most pregnant 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 with HIV coinfection or drug-resistant 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**, **cycloserine**, and **PAS** have not been extensively studied, but animal models and anecdotal human reports have not shown toxicity.

Infection Control

Infection control is particularly challenging during pregnancy and childbirth.

- Consult with experts in infection control and TB treatment to ensure that appropriate measures are in place in settings where these women will receive obstetrics (OB) care.
- If the patient is still contagious at the time of delivery, make plans for delivery well in advance. Arrange for a negative pressure birthing room and appropriately fit test personnel for N-95 or more efficient masks. It will not be realistic to expect that a laboring mother will be able to keep a mask on herself.

Management of the Newborn

Management of the infant born to a mother with 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, cycloserine and ethionamide 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, the 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.
- Examination of the placenta by a pathologist is sometimes helpful. Granulomata in the placenta increases the likelihood that the baby is infected. Fortunately, the placenta is an efficient organ and most babies born to mothers with granulomatous placenta will not themselves be infected.
- If the baby has physical findings or radiographic abnormalities to suggest congenital TB, the baby should immediately undergo gastric aspirate collection, a procedure that has a very high yield for both smear and culture (around 90% each) in cases of congenital TB. **For a video demonstration and complete instructions for gastric aspirate collection, refer to: www.nationaltbcenter.edu/pediatric_tb.** Click on the "Resources" button on the left-hand side. For young babies, gastric aspirates can be collected after the baby is NPO after a long sleep several times in 1 day, and do not necessarily need to be collected in the early morning. Lumbar puncture for cell count, protein, glucose, bacterial and acid-fast bacilli (AFB) smear and culture 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.

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 contagious with drug-resistant TB, mother and baby should be separated until the mother is not contagious.
- If an infant whose mother has known contagious or suspected TB disease is vigorous, afebrile, and has a **completely** normal physical exam and chest radiograph, consideration should be given to treating the infant prophylactically, in case the baby has been infected during the birth process and does not yet have 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, the advice of a pediatric TB expert should be sought.
- If the baby is treated with INH and is breastfeeding, the baby should also receive 6.25 mg or one-fourth of a 25-mg tablet of pyridoxine. If the mother is receiving INH, ethionamide, or cycloserine, the breastfed baby should also receive pyridoxine.
- **Because it is possible for an infant to have early, subclinical congenital TB, the infant should be followed closely (weekly) by an experienced pediatric provider and observed for development of the aforementioned findings.**
- If separation of the mother and infant is not possible and no practical prophylactic regimen is available, the bacille Calmette-Guérin (BCG) vaccine is sometimes administered. BCG 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.

- If the baby is asymptomatic and the mother has been receiving effective TB therapy and is deemed to be noncontagious, and there are no other potentially contagious source cases in the infant's home, close monitoring without chest radiograph or prophylactic treatment is appropriate.

TST

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

Summary **PREGNANCY**

- **Treatment of drug-resistant TB during pregnancy is challenging due to:**
  - Risk of teratogenicity of anti-tuberculosis drugs
  - Infection control risks during OB care
  - Risk of transmission to the infant
- **While PZA is avoided in drug-susceptible TB, it is recommended for use in drug-resistant TB during pregnancy.**

Pediatrics

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

Easier Elements	More Difficult Elements
• Children with drug-resistant TB have almost always acquired it from a contagious teen or adult rather than evolving it over years of failed therapy. This means that their bodies tend to be strong and healthy when the treatment is started. • Children have few *M. tuberculosis* organisms in their diseased tissues compared to adolescents and adults, making amplification of resistance on treatment much less likely. • Some TB disease diagnosed in children is actually already being controlled by their own immune system. • Children tend to tolerate the second-line medications required for drug-resistant treatment better than do adults.	• Young children are more likely to develop TB meningitis. • It is difficult to obtain good clinical specimens for culture confirmation, susceptibility testing, and clinical monitoring. • Anti-tuberculosis drugs are not sold in child-friendly formulations. • It is more difficult to monitor children for drug toxicity. • It is difficult to entice a child to take a few doses of medicines, much less 2 or more years of multiple, bad-tasting tablets crushed into sticky, sweet vehicles.

Cultures

- **Fewer than 25% of children are treated for TB based on positive cultures.**
- **If drug-resistant TB is suspected, aggressively evaluate and culture the child,** as well as all possible source cases to whom the child is exposed.
- **Older children** (older than 5 years) **can sometimes produce sputum by induction with hypertonic nebulized saline and careful coaching.** Sputum induction combined with suctioning the posterior oropharynx can be used in even young children.
- **For very young children with pulmonary TB, aspiration of gastric contents, first thing in the morning, sometimes yields mucous for acid-fast bacilli (AFB) culture.** (See www.nationaltbcenter.ucsf.edu/pediatric_tb. Click on the "Resources" button on the left-hand side for complete instructions for gastric aspiration.) Three specimens are usually considered to give the maximum culture yield for sputum or for gastric aspirates. **The first gastric aspirate collected gives the very highest yield and should be undertaken very carefully and seriously.** Unfortunately, even the best collection techniques yield less than 50% positive cultures (higher in young infants). Therefore, the culture results are only helpful if they are positive. Gastric aspirates are occasionally positive in children with TB meningitis.
- **Bronchoalveolar lavage (BAL) specimens have a slightly lower yield than gastric aspirate specimens.** In sick children, especially those in whom the diagnosis of TB is not certain or in whom the concern for drug resistance is very high, a BAL is frequently useful.

Note:
A negative culture never rules out tuberculosis.

An older child can and should be monitored during treatment with serial sputum specimens, but serial gastric aspirates are rarely valuable due to their low yield. If the patient is sedated for another procedure, such as deep line placement or auditory brainstem response, collect a gastric aspirate at that time to avoid some discomfort.

Other specimens that can be analyzed (particularly for children suspected of having extrapulmonary TB):

- **Excisional biopsies of lymph node, bone, and other tissue are more likely to grow *M. tuberculosis* than are needle aspiration specimens.** Surgeons and operating room personnel need to be reminded to send specimen for culture in a sterile cup without formalin.
- **Cerebrospinal fluid should be collected if meningitis is suspected.** Larger volumes should be submitted in order to increase the yield of smears and cultures.
- **Blood and urine cultures for mycobacterial cultures are sometimes positive in children with disseminated TB disease** (contact your lab to obtain the proper bottles for processing the blood).

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

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

Treatment

There are no controlled trials for treatment of drug-resistant TB in children. Given the paucity of clinical data and the inability to fully characterize children's TB disease, the most prudent course to treat children with drug-resistant TB is: Use the same principles as for adults and seek expert consultation.

Based on small series and experience in adult patients, the following regimens are recommended:

Isoniazid (INH) Mono-Resistant TB in Children

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

PZA Mono-Resistant TB in Children

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

Multidrug-Resistant TB in Children

There are several series published, mostly from New York and South Africa, and more recently from Peru. South African children were treated with 4 to 5 drugs (at least 2 to 3 drugs to which the presumed source case isolate was susceptible) for 9 to 12 months. No cases of disseminated disease were identified. All children were well after 30 months of follow-up. The authors from New York recommend 1 year of treatment for non-serious or non-life-threatening forms of TB, and a minimum of 18 months for serious or life-threatening forms of TB. Among the 38 Peruvian children treated for multidrug-resistant TB

(MDR-TB), 29% had severe radiographic findings. All were treated with at least five drugs including an injectable drug for a minimum of 6 months after culture conversion and a fluoroquinolone for the duration of therapy. The total duration of therapy was 18 to 24 months. Many children experienced some side effects (42%), but all could be managed without treatment interruption for more than five days. No joint or musculoskeletal complaints were observed. Cure or probable cure was achieved in 95% of these children.

In the absence of efficacy data derived from randomized, controlled trials, the following are generally accepted principles for treatment of MDR-TB in children:

- **For MDR-TB, at least 4 drugs to which the organism is susceptible should be employed,** including the fluoroquinolones and injectable agents.
- **At least 3 drugs should be utilized in the continuation phase, and the total duration of therapy should be at least 18 months.**
- **In the case of symptomatic children or children with extensive radiographic disease, treatment should be continued at least 18 months after clinical or radiographic improvement begins.**

Drug Administration

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. Any small discrepancy in dosing will even out over time.
- **Cut tablets into approximate fragments** (freeze ethionamide in a small plastic bag before dividing into fragments); **crush fragments for smaller children.**
- **Jiggle capsules open and approximate fractions for serial doses.**
- **Mix crushed tablets or capsule contents into a small amount of vehicle.**
  - 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 preventing drug taste in the vehicle itself).
- **Immediately after the medication is given, give good untainted food or drink to clear the palate.**
- **Give lots of praise and incentives.**
- **Some drugs can be mixed in a small amount of liquid and given to babies via a special medicine-dispensing pacifier or bottle.** Some babies will reflexively suck the medication from a bottle while they sleep. Give water in a clean bottle afterwards to rinse the medicine out of the mouth.
- **Be flexible, but firm.** The child should get a few choices, but not whether or not to take the medicine.
- **The method of delivery may need to be changed throughout the course of treatment.**

Specific TB Drugs

(See Tables 1 to 8, "Pediatric Drug Dosing.")

Ethambutol (EMB)

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

Ethionamide

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

Cycloserine

- Generally well tolerated in children, though there have been reports of central nervous system (CNS) side effects.
- Drug levels have not been as consistent as those seen in adults, but should still be monitored in order to minimize the risk of toxicity.

Fluoroquinolones

- Fluoroquinolones have generally been avoided in children because arthropathy has been observed in animal models. Many thousands of children have received courses of fluoroquinolones (generally for short periods of time) and none have been found to have arthropathy or bone abnormalities. Selected patients have been monitored for fluoroquinolone toxicity by histopathologic examination, MRI, and ultra-

sound without any detection of bone or joint damage. Case reports of more than 50 children treated with fluoroquinolones for more than 6 months have been reported without arthropathy. Rates of reversible arthralgia have been similar to those in adults.

- **National guidelines endorse the use of fluoroquinolones in the treatment of children with MDR-TB if the drug is vital to the regimen. Close observation by parents and care providers for musculoskeletal complaints is advised.**
- **Levofloxacin** has significantly better activity against TB than ciprofloxacin (which is licensed for treatment of complicated urinary tract infection in children). Levofloxacin has been studied for otitis media and community-acquired pneumonia in children. Doses of 10 mg/kg in a single daily dose for children over 5 years of age, and 15 to 20 mg/kg/day, divided twice daily for less than 5 years of age, have been proposed based on early pharmacokinetic data in children and extrapolating from the drug-resistant TB experience in adults. There are no data establishing the safety or efficacy of the fluoroquinolones in treatment of TB in children. Levofloxacin comes as unscored 250 and 500 mg tablets. An oral suspension of 25 mg/ml is available (approved based on bioequivalence data generated in adults).
- There are no published pharmacokinetic or safety data for **moxifloxacin** in children.
- Long-term use of fluoroquinolones may promote development of quinolone-resistant *Streptococcus pneumoniae* carriage. While children are not usually treated with fluoroquinolones for presumed pneumococcal disease, their older family members might be. Therefore, the possibility of fluoroquinolone-resistant pneumococcal disease must be considered.

Fluoroquinolones are not licensed for use in very young children due to arthropathy seen in animal models. 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.
- 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.
- **Flatten out the packet of granules so that they are spread evenly in the packet. The packet can then be cut in order to approximate the dose needed—i.e., cut into 4 quadrants for 1 gram doses.** The granules can be sprinkled on top of or mixed into a small amount of soft food and are best tolerated when taken with food. Some experts dose PAS with acidic food to enhance absorption.

Injectable Drugs

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

Tables 1 to 8. **Pediatric Drug Dosing**

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

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

TABLE 1. **ISONIAZID**

Child's weight		**Daily isoniazid dose** 10-15 mg/kg		
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 2. **RIFAMPIN**

Child's weight		**Daily rifampin dose** generally 12-17 mg/kg/dose		
KILOGRAMS	POUNDS	MILLIGRAMS	150 mg CAP	300 mg CAP
4–7.5	9–16	75 mg	1/2	0
7.5–12.5	17–27	150 mg	1	0
12.5–17.5	28–38	225 mg	1 1/2	0
17.5–25	39–55	300 mg	0	1
25–35	55–77	450 mg	1	1
Over 35	Over 77	600 mg	0	2
Maximum daily rifampin dose is 600 mg				

Pediatric Drug Dosing

TABLE 3. **PYRAZINAMIDE**

Child's weight		**Daily pyrazinamide dose** 20-40 mg/kg/dose	
KILOGRAMS	POUNDS	MILLIGRAMS	500 mg TABS
3–6.25	6.6–13	125 mg	1/4
6.25–12.5	14–27	250 mg	1/2
12.5–20	27–44	500 mg	1
20–27	44–59	750 mg	1 1/2
27–35	59–77	1000 mg	2
35–46	77–101	1250 mg	2 1/2
46–54	102–119	1500 mg	3
54–62	119–136	1750 mg	3 1/2
Over 62	Over 136	2000 mg	4
Dose obese children on lean body weight			
Maximum daily pyrazinamide dose is 2 grams			

TABLE 4. **ETHAMBUTOL**

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 is 2.5 grams				

Pediatric Drug Dosing

TABLE 5. **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		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	
Maximum daily cycloserine dose is 1 gram			

TABLE 6. **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
Maximum daily ethionamide dose is 1 gram				

TABLE 7. **CAPREOMYCIN / AMIKACIN / KANAMYCIN / STREPTOMYCIN**

Drug	**Daily dose**
Capreomycin/Amikacin/Kanamycin	15–30 mg/kg/day up to 1 gram IV or IM
Streptomycin	20–40 mg/kg/day up to 1 gram IV or IM
Maximum daily dose is generally 1 gram, but a large muscular adolescent should be treated like an adult	

Pediatric Drug Dosing

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
Maximum daily PAS dose is 10 grams			

Summary **PEDIATRICS**

- **Children with drug-resistant TB generally suffer fewer side effects with second-line anti-tuberculosis drugs than do adults.**
- **Dosing children with tablets and capsules requires patience and creativity.**
- **Fluoroquinolones should be used with care in young children.**
- **Children have a smaller bacillary load compared to adults.** While some series report shorter courses of MDR-TB treatment, duration of treatment should generally approximate that of adults (at least 18 months).
- **Drug-resistant TB in children should be treated by the most experienced clinician or clinic available.** Consult with a pediatric TB expert throughout the course of care.

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EXTRAPULMONARY TB

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6 Monitoring Patients

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

Initial Evaluation

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

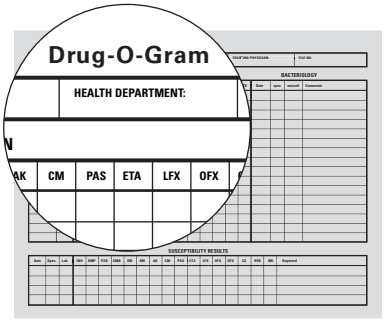
- Demographic information (name, address, date of birth, race and ethnicity, etc.)
- Full TB history (including medications, surgeries, and complications)
- Past medical history (including medications, allergies, psychiatric history, HIV status, diabetes, and other complicating conditions)
- Social history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

Use a systematic approach to monitoring.

Documentation

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

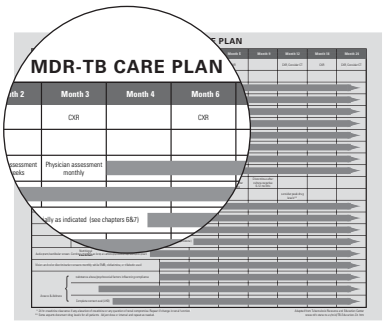
A Drug-O-Gram



- Documents previous and current drug treatment, weights, microbiology and radiology results, and other notable information in an easy-to-read, tabular form
- See Monitoring Tool 1 (monitoring tools are found at the end of this chapter and at www.nationaltbcenter.ucsf.edu/drtb)

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

A Care Plan



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

Monitoring flow sheets can track progression of blood work, bacteriology results, and hearing, vision, and vestibular exams. See Monitoring Tools 3, 4, and 5 for examples of these flow sheets. Additional monitoring tools are available at www.nationaltbcenter.ucsf.edu/drtb in both PDF and Excel (can be modified and typed into) formats.

General Monitoring

General monitoring and relationship building occur with each patient encounter:

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

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

No detail regarding medication administration should be assumed or left to chance.

Specific Monitoring

Drug Administration

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

Routinely ask patients:

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

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

Drug Absorption and Drug Interactions

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

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

Weight and Nutrition

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

- Monitor patients' weight throughout the course of treatment.
- Maximize the nutrition of undernourished patients.
- Offer hospitalized patients flexible meals of their choice, solicit dietary consultation, and offer dietary supplementation.
- Some patients feel best and gain the most nutritional benefit from small, frequent meals throughout the day (mini-meals).
- Occasionally, tube feedings for supplementation are required, and rarely, parenteral nutrition is used (especially prior to surgery for best postoperative healing).

- Customize outpatient management to the nutritional status of the patient. Some patients will only need to have their weight monitored, and others will require food diaries, regular nutritional labs, and ongoing nutrition consultation.
- Some food supplements (such as Ensure) interfere with absorption of fluoroquinolones and should be offered more than 2 hours before or after the drug.

Substance Abuse and Mental Health

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

- Closely monitor a patient's success and/or relapse with substance abuse issues during TB treatment in order to anticipate toxicity (such as alcohol with isoniazid [INH] and cycloserine, and methadone with rifamycins) and to avoid adherence complications.
- Closely monitor mental health symptoms—especially for patients receiving cycloserine. Cycloserine's most common toxicities are depression, psychosis, and suicidal ideation. The use of standardized tools for assessing and documenting mental health symptoms are very helpful. Two such tools are the *Beck Depression Inventory* (available in English and in Spanish; Harcourt Assessment, San Antonio, TX; http://harcourtassessment.com) and the tools from the Latino Family Institute (Oak Park, IL; telephone: (708) 445-0480).
- 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. Monitor patients for these symptoms and provide support as needed.

Ongoing TB education is essential…

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

Respiratory Symptoms

- Routinely monitor the patient's cough, respiratory status, and sputum production. Most TB patients' respiratory symptoms improve in the first few weeks of effective treatment. Even most patients on appropriate MDR-TB treatment will improve symptomatically by 3 to 6 weeks on treatment.

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

- **Some patients will have another respiratory infection or process** (malignancy among others)
- **Some patients will be nonadherent with therapy or not achieving therapeutic concentrations**
- **Some patients will be experiencing TB treatment failure:**
  - Repeat cultures and susceptibilities
  - Consider a regimen change (never add a single drug to a failing regimen)
  - Interpret respiratory symptoms in the context of the entire clinical picture: fever curve, weight gain, other systemic symptoms, intercurrent illness, and microbiologic response to treatment

Systemic Symptoms

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

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

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

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

Drug Toxicity (See Table 1)

- Warn **every** patient beginning any TB therapy to expect toxicity.
  - Even patients taking INH monotherapy frequently feel lousy in the first couple of weeks of therapy. If patients do not anticipate this reaction and are not reassured that it will improve, they will frequently stop the therapy.
  - Monitor patients for general toxicities and drug-specific toxicity at every healthcare visit (including during DOT encounters).

- Patients with drug-resistant TB will experience much more toxicity than patients treated for drug-susceptible disease. Most of the second-line TB therapies give significant toxicity.

Help the patient to understand:

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

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

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

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

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

TABLE 1.

Common Side Effects of Anti-Tuberculosis Drugs

Side Effect	Drug
GI side effects	■ **Ethionamide** ■ Fluoroquinolones ■ **Para-aminosalicylate (PAS)** ■ Clofazimine ■ Rifabutin ■ Aminoglycosides
Headache	■ Fluoroquinolones ■ INH ■ Cycloserine ■ Ethambutol (EMB) ■ Ethionamide
Skin problems	■ **Clofazimine** ■ Cycloserine ■ INH ■ Rifabutin ■ PAS ■ Ethionamide ■ EMB
Photosensitivity	■ **Clofazimine** ■ Fluoroquinolones
Hepatotoxicity (early symptoms are anorexia and malaise, then abdominal pain, vomiting, jaundice)	■ **INH** ■ Rifabutin ■ Ethionamide ■ PZA ■ PAS ■ Fluoroquinolones ■ Rifampin (RIF)
Behavioral changes	■ INH ■ **Cycloserine** ■ Ethionamide ■ Fluoroquinolones
Musculoskeletal / joint / tendons	■ Fluoroquinolones ■ **PZA** ■ Rifabutin ■ RIF ■ INH (positive antinuclear antibody [ANA])
Visual changes, eye pain, change in color vision	■ **EMB** ■ Rifabutin ■ Clofazimine ■ high-dose INH ■ Linezolid
Hearing loss, ringing in the ears, vestibular toxicity	■ **Aminoglycosides** ■ Capreomycin
Dizziness	■ Cycloserine ■ Fluoroquinolones ■ **Aminoglycosides** / capreomycin (as manifestation of vestibular toxicity)
Peripheral neuropathy	■ **INH** ■ Ethionamide ■ Cycloserine ■ **Linezolid**
Hypothyroidism	■ Ethionamide ■ PAS
Hypokalemia / hypomagnesemia	■ Aminoglycosides ■ Capreomycin

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

For specific drug toxicities, see Chapter 4, "Medication Fact Sheets."

Microbiology

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

Some experts determine duration of drug therapy and use of injectable drugs based on time to sterilization.

- Monitor serially in the early phases of treatment until the patient has 3 negative sputum smears.
- National guidelines suggest monthly monitoring (after smear conversion) of sputum for acid-fast bacilli (AFB) smear and culture throughout the entire duration of treatment of MDR-TB, at completion of therapy, and several times in the 2 years after treatment. Collecting 2 sputum specimens 8 to 24 hours apart will markedly reduce the chance of false-negative sputum culture results. In the second year of treatment, some programs feel comfortable with somewhat less frequent sputum collection.
- Most MDR-TB patients whose disease will eventually be cured convert their sputum cultures to negative within 3 to 4 months. Patients whose sputa are still culture-positive after 3 months of treatment should be reevaluated fully, including repeat susceptibility testing for the possibility of further development of resistance. Patients are considered to have failed therapy when their sputum cultures are still positive after four months of treatment.

Whenever sputum is being collected, appropriate attention should be given to infection control. Sputum should be collected in a secure isolation area or an outdoor environment. **If the patient cannot spontaneously expectorate sputum, perform induction with hypertonic saline in an appropriately engineered environment.**

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

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

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

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

Serial culture collection in children is also difficult.

- Gastric aspirates are the primary source of AFB culture in children with pulmonary disease. These are only positive in 40% of children even before treatment begins.
- Consider repeat cultures in the context of clinical response to therapy vs. yield of the specimen.
- If the child is sedated for any other reason (indwelling catheter placement or removal, auditory brainstem response screening, etc.), collect a gastric aspirate specimen. If there is ever question of amplified drug resistance or treatment failure, the results may be helpful.

Drug Concentrations

The exact role of therapeutic drug monitoring (TDM) in management of drug-resistant TB has not been extensively studied. One recent trial evaluating the efficacy of once-weekly isoniazid (INH)/rifapentine in the continuation phase of treatment for TB found an association with low INH concentrations and failure/relapse. Many experts feel strongly about routine use of TDM. Experts who routinely use drug concentrations to manage their patients cite the following:

- Second- and third-line anti-tuberculosis therapies have much narrower therapeutic windows. The therapeutic serum concentration above the minimum inhibitory concentration (MIC) is very close to the concentration that causes toxicity.
- A drug dose can sometimes be increased if you see that the serum concentration is well below that which causes toxicity.
- An elevated drug concentration can sometimes be noted before the patient suffers significant or discernible clinical toxicity—allowing the dose to be modified and avoiding dangerous toxicity.
- In cases where few drugs are available, use of drug monitoring may allow you to maximize drug doses to avoid amplification of drug resistance and optimize chance of cure.

Situations in which drug concentrations are routinely used:

- Aminoglycoside concentrations, especially in patients who have known renal dysfunction. The patient should have trough drug concentrations below the nephrotoxic concentration. 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 concentrations on all patients.
- Monitoring cycloserine concentrations can help the provider to predict and minimize CNS adverse reactions and prevent seizure activity.
- EMB concentrations may be useful for patients with reduced renal function.

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

Radiographs

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

Obtain routine chest radiographs:

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

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

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

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

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

Summary

- **The monitoring of patients with drug-resistant TB requires a systematic, organized approach. Helpful tools are the "Drug-O-Gram" and "Care Plan," which should be developed and customized for each patient.**
- **Elements which require monitoring include:**
  - Drug administration
  - Weight and nutrition
  - Drug absorption and drug interactions
  - Substance abuse and mental health
  - Respiratory and systemic symptoms
  - Symptoms of drug toxicity
  - Blood tests, visual screens, audiology and vestibular testing
  - Bacteriology
  - Therapeutic drug monitoring
  - Radiology

Drug-O-Gram

SUMMARY DATE:	NAME:	DOB:	HEALTH DEPARTMENT:	TREATING PHYSICIAN:	FILE NO:

TREATMENT REGIMEN

BACTERIOLOGY

Date	Wt.	INH	RIF	PZA	EMB	SM	KM	AK	CM	PAS	ETA	LFX	CS			Date	spec	sm/cult	Comments

SUSCEPTIBILITY RESULTS

Date	Spec.	Lab	INH	RIF	PZA	EMB	SM	KM	AK	CM	PAS	ETA	LFX	CS	RFB				Reported

Treatment Key: ● = DOT; ▲ = SAT

Adapted from LA County TB Control Program Drug-O-Gram

Monitoring Tool 2: **Care Plan**

Baseline	Initiation of Treatment	Month 1	Month 2	Month 3	Month 4	Month 6	Month 9	Month 12	Month 18	Month 24
CXR – PA & lateral; Compare to old films	Consider CT and alternate views	CXR		CXR		CXR		CXR, Consider CT	CXR	CXR, Consider CT
TST Report case to LHD										
Request/review old records	Physician assessment	Physician assessment q 1-2 weeks	Physician assessment q 1-2 weeks	Physician assessment monthly	→	→	→	→	→	→
Create drug-o-gram	Update drug-o-gram	Update drug-o-gram	→	→	→	→	→	→	→	→
CBC, metabolic panel, 24° creatinine clearance*; review prior abnormal labs		CBC, LFTs, K+, Ca++, Mg++, Creat Clearance serially as indicated (see chapters 6&7)	→	→	→	→	→	→	→	→
HIV serology with pre/post test counseling		If HIV+: CD4, viral load	Evaluate for treatment	→	→	→	→	→	→	→
Baseline TSH (cycloserine / ethionamide)				TSH q 3 mo - Synthroid if elevated TSH	→	→	→	→	→	→
Review prior sputum results. Repeat sputum	Sputum q a.m. x3 days	Sputum x3 q 2 weeks until smear-negative	Sputum x2-3 q 1 mo until culture-negative	Sputum x2-3 q 1 mo until culture-negative	Sputum x1-2 q 1 mo	→	→	→	→	→
Review susceptibilities; request extended susceptibility tests	Follow-up pending susceptibilities			Repeat susceptibility if sputum culture-positive	Repeat serially for persistently positive cultures	→	→	→	→	→
Infection control/isolation	Continue until culture negative x3 (see chapter 8)	→	→	→	→	→	→	→	→	→
Consider insertion of indwelling catheter	Aminoglycoside and/or Capreomycin IV (IM) 5-7 days/wk	Consider peak/trough drug levels**	Consider peak/trough drug levels**		Consider peak/trough drug levels**	Δ to 3x/wk after 2-6 months	Discontinue after culture-negative 6-12 months			
	4-6 oral drugs	Consider peak drug levels**		Consider peak drug levels**				Consider peak drug levels**		
	DOT initiated/pt educated	Educate as needed	→	→	→	→	→	→	→	→
	Pyridoxine 100-150 mg (or more)	As long as ethionamide or cycloserine given	→	→	→	→	→	→	→	→
	Baseline weight	Weigh 2x/week	Weigh monthly	→	→	→	→	→	→	→
	Nutritional assessment	Nutritional supplement as needed (Not within 2 hours of fluoroquinolone)	→	→	→	→	→	→	→	→
Audiogram/vestibular screen. Continue monthly as long as aminoglycoside/capreomycin given		→	→	→	→	→	→	→	→	→
Vision and color discrimination screens monthly while EMB, clofazimine, or rifabutin used				→	→	→	→	→	→	→
Assess & Address: Substance abuse/psychosocial factors influencing compliance				→	→	→	→	→	→	→
Assess & Address: Education needs		→	→	→	→	→	→	→	→	→
Assess & Address: Complete contact eval (LHD)		→	→	→	→	→	→	→	→	→

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

Adapted from Tuberculosis Resource and Education Center
www.tdh.state.tx.us/tcid/TB-Education-Ctr.htm

Monitoring Tool 3: **Lab Flow Sheet**

	DATE:								
HEME	WBC								
	Hbg								
	Hct								
	Platelets								
	ESR								
Chemistry	Na+								
	K+								
	Ca++								
	Cl-								
	Mg++								
	Total Bili								
	Glucose								
	CO2								
	BUN								
	Creatinine								
	Uric Acid								
	Alk Phos								
	AST (SGOT)								
	ALT (SGPT)								
	T. Protein								
	Albumin								
	Cholesterol								
	LDH								
	CPK								
	Amylase								
	GGTP								
ABG	PH								
	PCO_2								
	PO_2								
	HCO_2								
	FIO_2								
Urine	Spec. gravity								
	Ph								
	Ketone								
	Glucose								
	Protein								
	Heme								
	Cr Clearance								
Other	TSH								
	PT								
	PTT								
Drug Levels									

Adapted from Los Angeles County TB Control Program Lab Flow Sheet

Monitoring Tool 4: **Bacteriology Flow Sheet**

bacteriology: **file #:**

Date collected	Report date	Spec #	Source	Smear	Culture	Lab	Susceptibilities & Comments

A more detailed bacteriology flow sheet is available at www.nationaltbcenter.ucsf.edu/drtb

Monitoring Tool 5: **Hearing, Vision, & Vestibular Exams**

Eye Exams					Neurological Exams				
	SNELLEN		Color (Ishihara)		Vestibular Exam			Audiogram	
Date	O.S.	O.D.	O.S	O.D.	Romberg	Heel-to-Toe	Finger-Nose-Finger	A.S.	A.D.

Adapted from the Los Angeles County TB Program Eye/Ear Exam Flow Sheet

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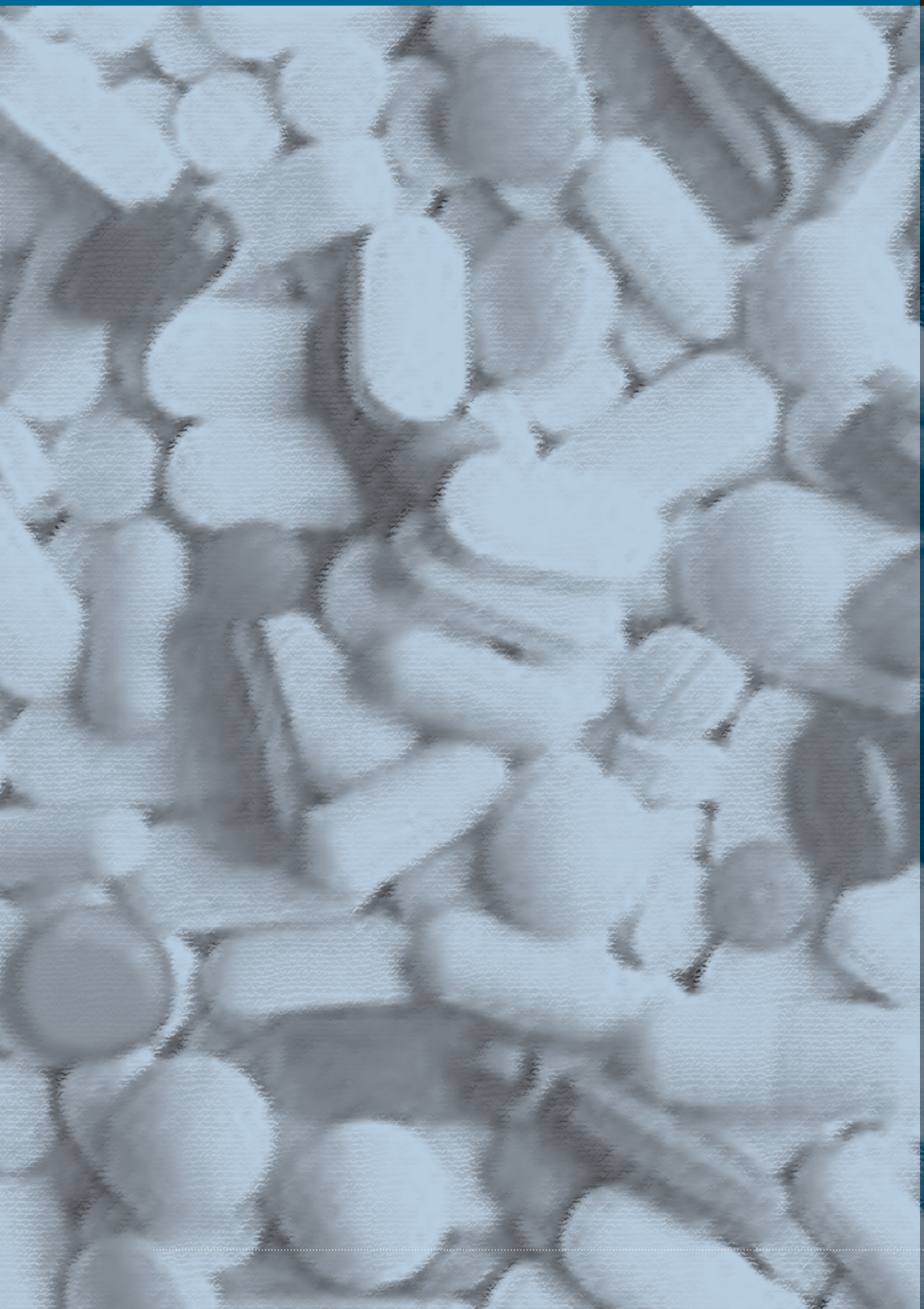
7 Adverse Reactions



Adverse reactions and toxicity accompany essentially all treatment courses for drug-resistant TB.

Introduction

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

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

- **Prior to initiating a treatment regimen, it is essential to discuss the benefits and risks of therapy.** The patient should understand the need for treatment, the importance of each medication in the treatment regimen, and the possible side effects and toxicities.
- **Assure patients that every possible attempt to make their treatment as easy as possible will be made, but stress that having enough effective drugs in the treatment is essential to achieving a cure.** While side effects will be addressed and treated as aggressively as possible, patients should be mentally prepared for likely discomfort and should brace themselves for the long road ahead.
- **Help patients realize that this may be their last opportunity for cure, and future treatment regimens could be more toxic and less effective.**
- **Breaks in therapy should be avoided whenever possible to maximize the effectiveness of treatment.**

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

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

Gastrointestinal

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

Pregnancy should be considered as the possible etiology of nausea and vomiting, especially if the symptoms occur after a period of initial tolerance.

Causes of GI symptoms include:

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

Nausea and Vomiting

Treatment of nausea and vomiting:

- **First, ask the patient; patients may have strong ideas about which medication is causing them problems. Their opinions must be addressed and respected (even if no change can be made).**
- Encourage the patient to continue to take the medication and assure them that for most patients many adverse reactions lessen over the first several weeks and may become tolerable or resolve entirely.

The following are specific interventions that can be attempted, depending on the drug:

- If the drug suspected of causing the symptoms is ethionamide or para-aminosalicylate (PAS), decrease the dose (ethionamide 250 mg, PAS 2 to 4 grams) to see if the lower dose is better tolerated. Advise the patient that this is a test to determine which drug is causing side effects and that the drug dose will be increased back to therapeutic dose in a manner that will be better tolerated. The dose of medication can be gradually increased over the next 2 weeks. Both medications can be given in 2 or 3 doses over the day, which may improve tolerance. Many patients tolerate the higher dose of ethionamide better in the evening (ethionamide 250 mg in a.m., 500 mg at bedtime; or may only tolerate 500 mg at bedtime). The goal should be to increase the ethionamide dose to at least 500 mg daily and the PAS dose to at least 6 to 8 grams daily.

Eliminate (or at least try to minimize) alcohol consumption to lessen GI irritation and the risk of hepatotoxicity.

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

  The following are some specific options (adult doses):

  - **Promethazine** (Phenergen) 12.5 to 25 mg PO, IV, or PRN 30 minutes before the dose and every 6 hours as needed
  - **Metoclopramide** (Reglan) 10 to 20 mg PO or IV every 4 to 6 hours as needed
  - **Ondansetron** (Zofran) 8 mg PO 30 minutes before the dose and again 8 hours after the dose; for refractory nausea 24 mg 30 minutes before the dose can be tried
  - A number of other antiemitics 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 to separate the responsible medication from other drugs by several hours or give it before bedtime to allow most of the adverse effects to occur during sleep.
  - This is relatively easy if the patient is hospitalized, but in the outpatient setting, directly observed therapy (DOT) may only be available once daily. It may be necessary to allow the patient to self-administer the evening dose of medications or a dose later in the day. This can be problematic either way. If the medication is taken along with others and all medications are vomited, nothing is gained; alternatively, if the medication is essential to the regimen, even the most compliant patients may have difficulty taking a medication that predictably makes them feel bad.
- Give a light snack (crackers or toast, tea or soda) before medications.
- Space the medications out during the day to lessen the pill burden.
- Treat gastritis or acid reflux. Proton pump inhibitors or H2-receptor blockers may be helpful in many patients. Use of a drug such as sucralfate interferes with absorption of fluoroquinolones if used within 2 hours of the dose.
- Minimize use of nonsteroidal anti-inflammatory drugs (NSAIDs). This may be difficult if the patient also has arthralgias and myalgias from medications. Try acetaminophen, although it has been reported to increase isoniazid (INH) hepatotoxicity.
- Diagnose and treat co-existing *Helicobacter pylori* infections.
- Encourage hydration. Sports drinks such as Gatorade or PowerAde may be helpful as they also replace electrolytes. However, the glucose content of these drinks would be unacceptable for most diabetics.
- If the odor of a medication is contributing, try concealing the odor by putting the drug into a gelatin capsule that can be purchased at a pharmacy.
- Electrolytes, BUN, and creatinine should be evaluated and corrected if significant vomiting or diarrhea occurs.

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

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

Diarrhea

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

- PAS often causes diarrhea with the initiation of medication. Inform patients that diarrhea usually resolves or improves considerably after several weeks.
- **Always start PAS at a low dose and then increase gradually over the next 2 weeks to minimize this problem as much as possible.** See Figure 3, "Dose Escalation (Drug Ramping)" in Chapter 3, "Treatment."
- Fluoroquinolones can also cause loose stools or diarrhea, along with increased flatulence. This can improve, but may persist in part for the duration of therapy. Lactobacillus or foods such as yogurt (not given within 2 hours of the fluoroquinolone dose) with active cultures may improve symptoms by replacing normal flora. Loperamide (Imodium) 2 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 is a key drug in the treatment regimen.

If the diarrhea is severe, other etiologies may include:

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

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

Hepatotoxicity

- Any GI complaint may represent hepatotoxicity. **If hepatotoxicity is suspected, hold all anti-tuberculosis medications that are potentially hepatotoxic until laboratory results are available.** The ALT or SGPT is the hepatocellular enzyme most directly associated with hepatocellular damage. If the enzymes are normal, continue medications using the strategies previously noted to lessen nausea and vomiting.
- The ALT (SGPT) is more specific for hepatocellular injury than the AST (SGOT). Elevations in the AST may indicate abnormalities in the muscle, heart, or kidney. If the ALT is elevated more than the AST, this is consistent with liver inflammation. When the AST is elevated more than the ALT, the possibility of alcohol-related elevation of the transaminase should be considered.

- **If elevated liver function tests (LFTs) are detected, in addition to 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, consider repeating liver enzymes again to exclude hepatotoxicity. If the bilirubin is increased but the hepatocellular enzymes are only mildly elevated, this could still represent significant drug-induced liver injury. An evaluation for causes of direct and indirect hyperbilirubinemia should be done, and if the bilirubin is > 3.0 mg/dl, generally, hepatotoxic medications should be stopped.
- If the enzymes are more than 3 times the upper limit of normal, hold all potentially hepatotoxic medications. If at least 3 medications remain in the treatment regimen that are not hepatotoxic (for example, ethambutol [EMB], the aminoglycosides, levofloxacin, or cycloserine), then these can be continued. If not, then all anti-tuberculosis medications should be held.
  - Monitor the LFTs weekly.
  - When liver enzymes fall to less than twice normal (some experts prefer to wait until the enzyme levels normalize or return to baseline), the remaining potentially hepatotoxic medications should be reintroduced one at a time. If other **non**-hepatotoxic medications were also held, they should be restarted along with the first possibly hepatotoxic drug. Carefully observe for clinical reactions and repeat liver enzymes twice weekly until the medication has been taken for at least a week and enzymes are stable. The next medication can then be added to the regimen and monitored. All remaining medications should be reintroduced in this manner.
  - If reintroduction of a medication leads to clinical symptoms of hepatotoxicity and enzymes increase, stop that medication and eliminate it from the regimen.
  - Even if a medication is identified as causing hepatotoxicity, reintroduce each additional medication one at a time, because in some instances, more than 1 medication may be responsible for the hepatotoxicity.
- Monitor liver enzymes at least monthly for the remainder of the treatment course.

If at least 3 medications remain in the treatment regimen that are not hepatotoxic, then these can be continued.

Patients with underlying liver disease are at increased risk of drug-induced liver injury. HIV-infected individuals treated with first-line anti-tuberculosis drugs have had an increased incidence of hepatitis in some studies. Several reports of HIV-infected persons with hepatitis C noted hepatotoxicity in over 20% of cases. Antiretroviral therapy (ART)

may be associated with drug-induced hepatitis, with the incidence depending on the individual drugs utilized. 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.

Dermatologic and Hypersensitivity Reactions

Maculopapular Rash and Pruritus

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

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.

- 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 new agents, should be evaluated as possible etiologies.
- Other dermatologic causes; psoriasis, pityriasis, atopic dermatitis, etc.
- Dry skin, especially in diabetic patients, may be the cause of pruritus. Consider liberal use of lotions, such as petroleum jelly and lanolin (may be purchased in a feed supply store where it is less expensive). Dry skin is a serious problem with clofazimine.

- Hypothyroidism.
- Acneiform lesions may flare with the use of INH, ethionamide, and clofazimine. This will usually resolve after several months, often with improvement in the patient's acne. Standard topical antibiotic 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 rifampin (RIF) or pyrazinamide (PZA). It is usually mild and resolves in time without therapy. If it is bothersome to the patient, an antihistamine may be administered to treat or to prevent the reaction.

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

Caution patients to limit sun exposure and to use sunscreens.

Phototoxicity

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

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

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 may be made by a biopsy showing eosinophilic infiltration. Lesions may resolve while medication continues. Topical hydrocortisone or antihistamines may be helpful to control pruritus. Medication should not be discontinued unless an equally effective drug is available for substitution. Identifying the medication responsible in a multidrug regimen may be difficult because lesions resolve slowly and EMB, INH, streptomycin, and cycloserine have all been identified as causing these lesions.

Hives, Urticaria

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

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

TABLE 1.

Suggested Drug Rechallenge Doses Following Non-anaphylactic Allergic Reaction*

Drug	Dose – Day 1	Dose – Day 2	Dose – Day 3
Isoniazid	50 mg	300 mg	
Rifampin	75 mg	300 mg	600 mg
PZA	250 mg	1 gram	full dose
Ethionamide	125 mg	375 mg	500–750 mg
Cycloserine	125 mg	250 mg	500–750 mg
Ethambutol	100 mg	500 mg	full dose
PAS	1 gram	4 gram	6–8 grams
Streptomycin	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	125 mg	500 mg	full dose
Capreomycin	125 mg	500 mg	full dose
Fluoroquinolone	50 mg	200–250 mg	full dose

If a test dose of any drug causes a reaction, that drug should be discontinued, unless it is deemed essential to the regimen. If that is the case, desensitization can be considered.

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

TABLE 2.

Oral Desensitization for Isoniazid, Rifampin, and Ethambutol

Time from start (hour:minute)	Dose of INH* (mg)
0:00	0.1
0:15	0.5
0:30	1
0:45	2
1:00	4
1:30	8
2:00	16
2:30	32
3:30	50
5:30	100
7:30	150
8:30	150
17:30	150
Early next a.m.	150 bid x 3 days

Time from start (hour:minute)	Dose of RIF** (mg)	Dose of EMB** (mg)
0:00	0.1	0.1
0:45	0.5	0.5
1:30	1	1
2:15	2	2
3:00	4	4
3:45	8	8
4:30	16	16
5:15	32	32
6:00	50	50
6:45	100	100
7:30	150	200
11:00	300	400
	300 bid x 3 days	400 tid x 3 days

* Holland 1990
** Matz 1994

Implement these protocols only in a hospital or in a clinical area with the ability to monitor and respond to possible anaphylaxis, and when the drug is determined essential to success of therapy. Because isoniazid and rifampin are such important drugs, desensitization is most commonly attempted with these 2 medications.

Steroid therapy may be used with desensitization and then tapered 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 and/or mucous membranes as occurs with Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN).

Hematologic Abnormalities

Table 3 summarizes potential hematologic abnormalities associated with TB medications.

TABLE 3.

Hematologic Abnormalities Associated with Anti-Tuberculosis Drugs

Drug	WBC ↓	WBC ↑	PMN ↓	Plt ↓	Plt ↑	Pan ↓	Red cell aplasia	DIC or Coag abnl	Hgb ↓	Hemolytic anemia	Eos ↑	Aplastic anemia
Amikacin											X	
Amox/clav	X		X		X						X	
Capreomycin	X	X		X							X	
Clofazimine	X							X	X		X	
Cycloserine									X			
Ethambutol			X	X							X	
Ethionamide				X								
Imipenem	X			X	X	X		X	X		X	
INH			X	X			X	X	X	X	X	X
Kanamycin												
Levofloxacin	X			X					X	X	X	
Linezolid	X			X		X	X		X			
Moxifloxacin	X			X				X		X	X	
PAS			X	X								
Pyrazinamide				X					X			
Rifabutin			X	X								
Rifampin	X		X	X			X	X		X		
Streptomycin	X			X		X		X		X	X	

Other etiologies of hematologic abnormalities should be concurrently sought.

Severe Drug Reactions

Anaphylaxis presents within minutes of medication dosing.

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

Severe drug reactions may occur with any medication. Reactions associated with systemic toxicity—high fever, widely distributed urticaria, and bulla, along with mucous membrane involvement—are characteristic of SJS. When there is extensive sloughing of skin, TEN 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 of the diagnosis. INH, RIF, EMB, streptomycin, ofloxacin, and cycloserine have been reported as causative agents. **If a drug is identified as responsible for one of these reactions, it should never be used again.**

Hypersensitivity Syndrome

The drug-induced hypersensitivity syndrome has been described with several of the antituberculosis medications. A dramatic drug rash is present along with significant systemic symptoms. **This syndrome is an idiosyncratic reaction characterized by the development of fever, rash, and internal organ involvement which develops within the first 1–2 months of therapy.** Fever, often the first manifestation, may be as high as 40 degrees centigrade. A variety of types of rashes have been noted, but a morbilliform rash is most common. This can become indurated after several days, with development of bullae and purpura. Facial swelling may occur, and some patients have mucosal lesions, but these are not as prominent as with SJS or TEN. Lymphadenopathy is a prominent finding and is present in up to 75% of patients. Biopsy usually shows benign lymphoid hyperplasia. Hepatitis is seen in more than half and is severe when the offending agent is not withdrawn. The overall mortality of this syndrome is 10%, but when hepatitis is present, mortality can be as high as 40%, with acute liver failure the most common cause of death. Eosinophilia is a prominent feature, and some patients have an atypical lymphocytosis.

Although first described with phenytoin use, hypersensitivity syndrome has been attributed to ethambutol, isoniazid, and rifampin.

A variety of other drugs has also been implicated, including sulfonamides, dapsone, minocycline, many of the antiepileptic agents, and allopurinol. Skin biopsy and liver biopsy may help to establish the diagnosis. The reaction occurs later than SJS or TEN, and these reactions are not characterized by significant organ involvement.

Steroid therapy is life-saving, and tapering may need to be slow and guided by recurrence of clinical and laboratory abnormalities. The presumed offending agent is usually withdrawn, and rechallenge can be associated with rapid recurrence of severe hepatitis. When the offending agent is unknown, careful reintroduction of medications thought not likely to be involved should be considered only when alternative therapy is not possible. High-dose steroids may be required if the responsible drug is re-introduced. **Most experts would not recommend rechallenge once a drug is identified as the causative agent.**

Rifampin Hypersensitivity Reactions

A variety of reactions have been reported with RIF therapy. One of these is a flu-like syndrome which 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 rifampin if they are changed back to daily therapy.

For most of the 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**

Neurotoxicity

Peripheral Neuropathy

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

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 to 150 mg daily.

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

There are rare reports of neuropathy attributed to pyridoxine in doses of 200 mg or greater.

There are rare reports of neuropathy attributed to pyridoxine in doses of 200 mg or greater. Neuropathy associated with linezolid usually tends to occur after 4 months of therapy and is probably dose-related. Use of the 600 mg once-daily linezolid dosing may prolong the ability to use the drug compared to other infections that require a 600 mg twice-daily dose. Patients may have further progression of symptoms even when linezolid is discontinued. Limited information about the toxicity of long-term linezolid is available and patients should be watched carefully.

Additional interventions include:

- **Correct vitamin and nutritional deficiencies.**
- **Address additional medical problems.**
- **Evaluate and correct electrolytes.**
- **Identify and change other medications that may cause peripheral neuropathy, if possible.**
- **Consider whether the dose of ethionamide or cycloserine can be reduced without compromising the regimen.** Doses of aminoglycosides or fluoroquinolones should be reduced only if adequate serum concentrations will still be present. Monitor serum drug concentrations if doses are lowered.
- **Physical therapy may be helpful but is often not available.**
- **NSAIDs or acetaminophen may be helpful.**

- **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. Linezolid 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, and a complete blood count (CBC) and liver function should be routinely monitored in patients on this medication.
- **Patients who fail to respond to a tricyclic may respond to gabapentin** (Neurontin). Adults should be treated initially with a single dose of 300 mg PO on Day 1, increased to 300 mg twice a day on Day 2, and 300 mg 3 times a day on Day 3. The dose may be titrated up to 1800 mg as needed for relief. Gabapentin is also associated with a wide range of adverse effects, including nausea and vomiting, as well as arthralgias and CNS symptoms. Decrease dosage with renal insufficiency.
- **Rarely, medication may be discontinued, but only if an alternative drug is available or the regimen is not compromised.**

Central Nervous System Toxicity

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

- Give medication at a time of day to minimize the effects. Consult the patient as to timing of drugs.
- Analgesics or NSAIDs may help headache.
- Limiting caffeine intake in the evenings may improve sleep disturbances.
- Exercise may also 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.

Depression

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

- Assess and address underlying psycho/social issues.
- Assess patients for coexisting substance abuse and refer to counseling if appropriate.
- When depression is more significant, give a trial of antidepressant therapy. Consider psychiatric consultation. Tricyclic antidepressants and SSRIs should not be given to patients on linezolid.
- Question the patient regarding suicidal ideation any time depression is judged to be more than mild.
- Reduce the dose of cycloserine and ethionamide to 500 mg daily to see if depression is lessened.

Cycloserine should not usually be part of an initial treatment regimen if significant depression is present.

- If depression progresses or is not improved by a trial of antidepressant therapy, discontinue cycloserine and, possibly, ethionamide as well.
- Cycloserine should not usually be part of an initial treatment regimen if significant depression is present. When no alternative drugs are available and depression is controlled on therapy, some patients may tolerate cycloserine and ethionamide.
- INH has been associated with depression, which has been reported as severe in several case reports. Withdrawal of the drug is associated with rapid recovery.

Psychosis

- If severe psychosis is present, hospitalize patient and put under 24-hour surveillance.
- Consider psychiatric consultation.
- Hold all medications that possibly contribute until the patient stabilizes.
- **The most likely drugs to cause psychosis are cycloserine and fluoroquinolones; INH can occasionally be implicated.**
- Pyridoxine (150 mg) should be given if not already part of the treatment.
- Start antipsychotic therapy (haloperidol [Haldol] PO, IV, or IM 0.5 to 5 mg) at the earliest sign of psychosis.
- When symptoms resolve, the least likely medications that contributed to the symptoms should be reintroduced first, one at a time, with careful observation. If no alternative drug is available, cycloserine may be tried at low dose. Do not increase the dose to previous quantities without first checking a serum drug concentration. If any recurrence of psychotic behavior occurs, promptly and permanently discontinue cycloserine.
- When the patient has stabilized, all medications have been successfully restarted, and all symptoms have resolved, the antipsychotic drugs can be tapered with careful observation of the patient.
- Consider and address all other etiologies, especially illicit drugs, alcohol, and medical problems (meningitis, hypothyroidism, and depression).
- Some patients may tolerate cycloserine with an antipsychotic drug if no other treatment options are available. These patients require special observation. Utilize this therapy only after consultation with an expert in the management of drug-resistant TB, and when the cycloserine is determined to be essential to the regimen and no alternative is available.

Suicidal Ideation

- **Hospitalize the patient and put under 24-hour surveillance**
- Discontinue cycloserine
- Request psychiatric consultation
- Initiate antidepressant therapy
- Lower the dose of ethionamide to 500 mg daily until the patient is stable
- Check the serum drug concentration of the fluoroquinolone and lower the dose if the serum concentration is high
- Keep the patient in the hospital until the risk of suicide has passed
- If no improvement occurs after holding cycloserine, hold INH and/or ethionamide

Seizures

- Hospitalize patient.
- **Intravenous pyridoxine will stop seizures due to pyridoxine deficiency.**
- Hold cycloserine, fluoroquinolones, and INH and initiate anticonvulsant therapy (phenytonin, valproic acid). Monitor anti-epileptic drug levels as drug interactions and synergistic toxicity are possible.
- Increase pyridoxine to 150 to 200 mg daily.
- When seizures have resolved, restart medications one at a time. Cycloserine 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.
- Evaluate for other etiologies of seizures.
- Check serum electrolytes, calcium, and magnesium.
- A history of prior seizures is not an absolute contraindication to the use of cycloserine, fluoroquinolones, and INH. Do not include cycloserine if an alternative drug is available.

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).

Linezolid is a weak, reversible, nonselective inhibitor of MAO.

Although linezolid alone is not potent enough to cause it, serotonin syndrome may occur when linezolid is given along with other medications that increase the serotonin level. This may be especially important in patients with MDR-TB because many require antidepressant medication or other psychotropic drugs. 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.

The 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 linezolid and an SSRI or tricyclic antidepressant. The half-lives of these drugs are prolonged, and if linezolid therapy is planned, these agents should be withdrawn at least two weeks prior to its use. The patient should be observed carefully; there are reports of serotonin syndrome occurring even two weeks after withdrawal of these agents.

Once serotonin syndrome is identified, linezolid 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 stopping linezolid, 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 benzodiazepines, lorazepam and cyproheptadine. Some patients need aggressive correction of their cardiorespiratory and thermal abnormalities.

Ototoxicity

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

Vestibular Toxicity

- Observe the patient closely for tinnitus and unsteadiness.
- At least monthly, assess vestibular toxicity.
- **Fullness in the ears and intermittent ringing in the ears are early symptoms of vestibular toxicity. When these are reported, it is sometimes possible to change the dosing to 2 or 3 times a week and continue the injectable agent for another month or more.**
- Watch the patient carefully. Toxicity is related to the total dose and is cumulative. It is impossible to predict for an individual patient what dose is tolerated.
- A degree of disequilibrium can be caused by cycloserine, fluoroquinolones, ethionamide, INH, or linezolid. Prior to stopping the injectable agent, evaluate whether these and/or other medications are causing the symptoms. Stopping the injectable should be done after carefully excluding other causes of the symptoms. Other drugs or all drugs can be held for several days to see if the symptoms improve. Symptoms of vestibular toxicity generally do not improve with holding medication.

- If tinnitus and unsteadiness develop and these are attributed to vestibular toxicity, stop the injectable agent. This is one of the few adverse reactions that cause permanent intolerable toxicity and necessitate discontinuation of a class of agents. If the injectable agent is continued or an attempt is made to substitute one injectable for another, persistent vertigo, unsteadiness, tinnitus, and ataxia will develop. **Drug-induced vestibular toxicity is not reversible.**

Auditory Toxicity

Prevention and Monitoring

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

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

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

Ophthalmic Toxicity

Prevention and Monitoring

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

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

Linezolid produces a toxic optic neuropathy that is sometimes reversible.

Visual loss due to rifabutin is part of a pan-uveitis that is reversible.

When using any of these drugs:

- Conduct baseline visual assessment with acuity testing (Snellen chart) and testing of color discrimination (Ishihara tests) at the start of treatment.
- Conduct monthly testing of visual acuity and color discrimination during treatment.
- Educate patients to report any change in visual acuity or red-green color discrimination, scotomata, change in visual fields, erythema, or eye pain.
- Improve diabetic control.
- **Avoid or adjust the EMB dose and dosing interval, and monitor concentrations when the creatinine clearance is less than 30 ml/minute.**
- Correct nutritional deficiencies; consider a multivitamin for individuals with malnutrition along with TB therapy (wait until they are tolerating TB therapy before starting the multivitamin; remember to dose 2 hours before or after fluoroquinolone drugs).

Retrobulbar Neuritis

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

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

Uveitis

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

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

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

Nephrotoxicity

Prevention and Monitoring

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

- Perform a 24-hour creatinine clearance at baseline if there are any concerns about renal function abnormality and monitor the serum creatinine weekly for the first several weeks, and then at least monthly.
- Encourage adequate hydration.
- For adults over 59 years of age, decrease the dose of the injectable drugs to 10 mg/kg (max dose 750 mg) and monitor drug concentrations.
- If baseline creatinine clearance is less than 70 ml/min, begin injectable therapy with a 3-times-a-week dosing regimen; if creatinine clearance is less than 50 ml/min, start twice weekly.
- Monitor serum drug concentrations and adjust the medication dose accordingly. See Chapter 4, "Medication Fact Sheets," and Appendix 12, "Therapeutic Drug Monitoring," 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 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, cycloserine, all of the aminoglycosides, and capreomycin.
- **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 35 and 50 ml/min, 2-times-a-week aminoglycoside dosing at 12 mg/kg should be tried.**
- Monitor peak and trough drug concentrations. It is especially important that trough concentrations be less than the critical value before another dose of the drug is given.
- Follow renal function carefully.

Electrolyte Loss

All of the aminoglycosides and capreomycin can cause electrolyte disturbances due to renal tubular wasting of potassium, magnesium, and calcium salts. These effects are most pronounced with capreomycin. Chloride and hydrogen losses may also occur with resulting alkalosis. A defect in renal tubular resorption of chloride may be caused by these drugs. Nausea, vomiting, and diarrhea may also contribute to electrolyte abnormalities.

- Conduct baseline assessment and at least monthly follow-up of potassium, calcium, and magnesium during injectable drug treatment.

- Replace electrolytes as needed.
- Assess renal function when replacing electrolytes.
- If the potassium is low, also check the calcium and magnesium.
- Hypocalcemia is most commonly caused by hypoalbuminemia. If the calcium is low, check albumin and free calcium.
- Hypomagnesemia, if present, must be treated in order to correct hypocalcemia.

For **severe** electrolyte abnormalities, hospitalize and monitor the patient.

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

Musculoskeletal Adverse Effects

Myalgias and Arthralgias

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

- Do not discontinue medications.
- NSAIDs are usually helpful.
- If acute swelling, erythema, and warmth are present, evaluate for the presence of inflammatory diseases:
  - **Aspirate joint for diagnosis if fluid is present**
  - **Evaluate for infection, gout, or autoimmune disease**
  - **Institute treatment (often indomethacin) if the diagnosis is gout**
  - **Consult with a rheumatologist**
- Evaluate for hypothyroidism or hyperthyroidism.
- Draw serum electrolytes, calcium, and magnesium. Correct deficiencies.

Tendonitis and Tendon Rupture

Tendon rupture has been reported with fluoroquinolone use and is more likely when new physical activities are undertaken and is more common in older patients and diabetics.

When **significant inflammation** of tendons or tendon sheaths occurs:

- Fluoroquinolones should generally be stopped.
- Administer nonsteroidal anti-inflammatory agents.
- Rest the joint.

- If the treatment regimen is likely to fail without the fluoroquinolone, inform the patient of the risk of tendon rupture and the risk of treatment failure. Carefully try to continue the fluoroquinolone.
    - **Evaluate the fluoroquinolone dose and reduce if possible.** Serum drug concentrations may help to direct therapy with the fluoroquinolone.
    - **Rest the involved joint and avoid any strenuous activity.**

When tendon inflammation is **mild**:

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

Miscellaneous Adverse Reactions

Hypothyroidism

Hypothyroidism may develop with either PAS or ethionamide; when both drugs are used, the incidence of hypothyroidism may be 40% or greater.

- Assess baseline thyroid function prior to start of these medications and correct if needed. Assess thyroid function every 3 months unless clinical assessment indicates the need to evaluate sooner. Conduct monthly clinical assessments for hypothyroidism. Clinical assessments may be a better indicator of thyroid function than laboratory values.
- When thyroid stimulating hormone (TSH) begins to increase, evaluate for clinical evidence of hypothyroidism. Begin to monitor more frequently.
- When TSH rises to 1.5 to 2 times above 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 thyroid hormone replacement until the patient's TSH is within the normal range.**
    - Increase thyroid hormone slowly in patients with significant cardiovascular disease
- When TB treatment is complete, stop thyroid hormone replacement; the thyroid gland will now be able to respond to endocrine stimulation with release of thyroid hormone.

Metallic Taste

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

Gynecomastia

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

Alopecia

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

Superficial Fungal Infection

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

Summary

- **Adverse reactions and toxicity accompany essentially all treatment courses for drug-resistant TB.** Patients must be well-informed so that they will know what to expect and can be partners in their therapy.
- **Close attention to toxicity and reports of discomfort are essential in maintaining the patient's good will and cooperation with the regimen.**
- **In many cases, some toxicity will have to be tolerated** (although it should be treated and minimized). In many cases, offending drugs cannot be permanently discontinued; patients and staff need to understand that the treatment regimen would be compromised without the inclusion of many medications.
- **Common side effects include:**
  - **Gastrointestinal** (nausea, vomiting, diarrhea, abdominal pain, anorexia, taste perturbation, and hepatotoxicity)
  - **Dermatologic reactions** (rashes, flushing, phototoxicity, alopecia, superficial fungal infections, and hypersensitivity)
  - **Systemic hypersensitivity reactions**
  - **Hematologic abnormalities** (leukopenia, thrombocytopenia, anemia, red cell aplastia, 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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8 Case Management

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

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

Assigning primary responsibility for coordination of patient care to ensure that the patient's medical and psycho/social needs are met through appropriate utilization of resources. The case manager ensures that the patient is adherent with and completes an appropriate course of therapy until cure, and coordinates a regular, systematic review of the patient's progress in therapy.

Roles and Responsibilities

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

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

The case manager has primary responsibility for ensuring that:

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

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

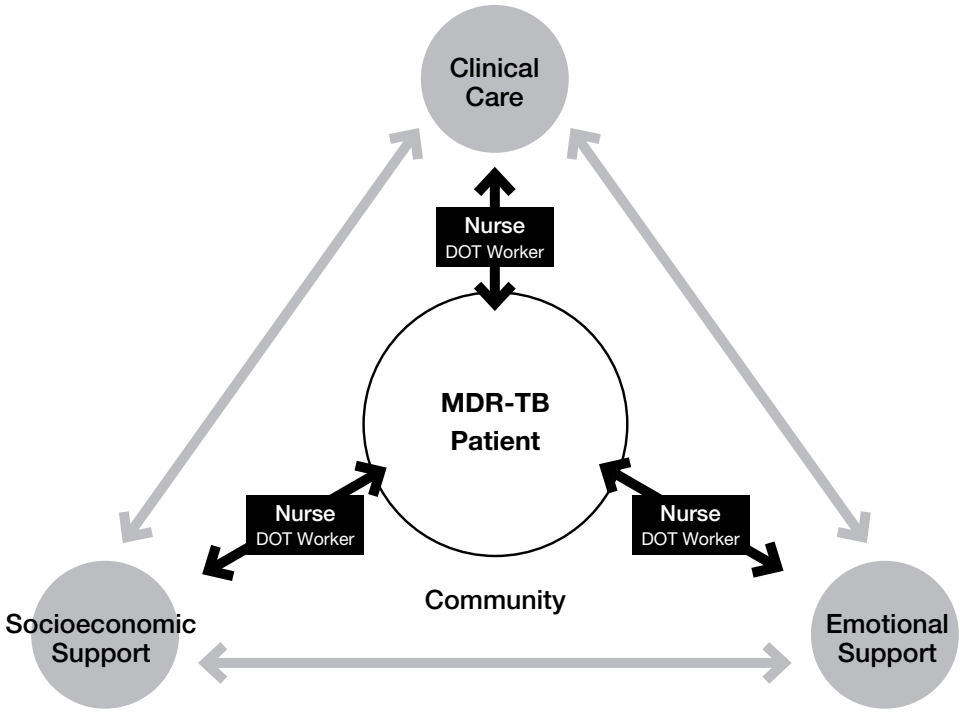
- Facilitates exchange of information between the family, medical providers, laboratories, pharmacies, insurance companies, and the public health infrastructure
- Builds relationships within all these systems to achieve the best results for the patient
- Ensures expert consultation has been sought and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

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

This chapter highlights some of the challenges surrounding the care of drug-resistant TB patients in the United States and the role of case management in addressing them.

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

Ensuring Adherence to Treatment

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

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

Directly Observed Therapy (DOT)

DOT is so important to the treatment of drug-resistant TB that experts in the field of TB control around the world consider it a vital strategy.

The consequences of treatment failure and further acquired drug resistance make DOT a high priority for cases of drug-resistant TB. DOT is so important to the treatment of drug-resistant TB that experts in the field of TB control around the world consider it a vital strategy. Achieving this standard of care, however, requires far greater time and commitment in the treatment of drug-resistant TB than for drug-susceptible disease:

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

The case manager must keep an open line of communication with the individual providing DOT and ensure that he/she can assess which signs and symptoms indicate potential medication toxicity. Any toxicity must be quickly identified, reported, and acted upon (see Chapter 6, "Monitoring Patients" and Chapter 7, "Adverse Reactions"). Use of standardized forms to record DOT doses and toxicities is crucial for these complicated patients. See examples of monitoring tools in Chapter 6 and on-line (www.nationaltbcenter.ucsf.edu/drtb).

Addressing Psycho/Social Needs

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

Many patients experience a period of prolonged unemployment associated with the period of contagiousness and due to employment discrimination. There is often a need for the case manager to intervene and educate employers and find alternative sources of income and other assistance for the patient and his/her family while he/she cannot work.

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

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

- Social services and programs for the medically indigent
  - Medicaid and any other third-party payer eligibility
  - In California, legal residents may be eligible for TB-MediCal, which may provide more outpatient benefits than other payer sources
  - In some jurisdictions, all TB care can be provided free of charge in the public health setting
- Immigration law counsel—National Immigration Law Center: www.nilc.org
- Drug and alcohol counseling
- Mental health programs
- Other community-based outreach services

Your key to successfully assisting patients with these challenges is to develop a trusting relationship with the patient and to be familiar with resources in your community. Ideally, case managers will have familiarity with and ongoing relations with valuable community resources prior to their first cases of drug-resistant TB.

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

Bridging Cultural Barriers

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

Barriers to diagnosis and treatment may include:

- Cultural stigma about TB
- Fear of the cost of TB care and lack of eligibility for programs
- Concern that the illness might interfere with the immigration process
- Fear of deportation
- Hindered access to health care because of language or cultural barriers as well as the general difficulty of navigating complex health care systems in the United States
- Patient's preference to seek traditional healing when ill
- Patient's preference to seek out a physician from his/her own culture, who may not be familiar with diagnosis and treatment of drug-resistant TB

- Fear of loss of employment and financial stress
- For women: Loss of importance to her family if she cannot continue her usual activities or if she experiences disapproval from her spouse
- Fear of the diagnosis itself if the individual has lost a friend or family member due to drug-resistant TB

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

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

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

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

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

Patient Education

In many respects, facing a diagnosis of drug-resistant TB can be likened to preparing for a marathon—the goal being to complete treatment with the fewest interruptions.

The case manager can play a key role in coaching the patient through the various phases of treatment by assisting the patient to set achievable interim goals. A standardized form can help the case manager document the many elements of patient education.

The following phases may not fit the treatment course for all drug-resistant TB cases, but hopefully will provide a context for case managers to anticipate their patients' educational capacities and needs.

1. Initial Phase

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

- **Keep information simple** with a focus on the following: minimizing transmission; achieving commitment from the patient to comply with the treatment plan; and sharing information about contacts and legal requirements.
- If the case manager is not the individual actually providing the DOT, **regular contact with the DOT provider and weekly contact with the patient will be important during this phase** to ensure that the patient is tolerating the medication and that side effects are quickly addressed. While most patients will experience mild complaints that can be managed without a change in the drug regimen (e.g., initiating adjuvant therapy, changing dosing time), some side effects warrant at least temporary discontinuation of the offending drug. Address all complaints, even if no change can be made. Make sure that the patient does not feel isolated during this phase.
- **If the patient is hospitalized, the case manager will need to provide support to the patient as well as 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. If the patient's medical needs are not given careful attention during this initial phase, the patient is at higher risk for becoming demoralized and discouraged. Hospital staff should be encouraged to seek expert consultation when necessary. Frequent and timely communication with the patient's hospital-based treatment team regarding discharge planning should include: procuring second-line medications prior to discharge, coordinating infusion therapy services if the health department cannot provide them, and dealing with psychosocial issues (such as homelessness) prior to discharge.
- **Prepare the patient to expect some side effects** so that when they occur, the patient does not fear that the treatment is doing more harm than good. Close monitoring is needed to ensure side effects are responded to promptly, particularly when treatment is initiated in an outpatient setting.
- **Assist the patient in coordinating ongoing care of co-morbid conditions,** such as HIV, diabetes mellitus, and renal disease.

In many respects, facing a diagnosis of drug-resistant TB can be likened to preparing for a marathon – the goal being to complete treatment with the fewest interruptions.

Information to reinforce during the initial phase:

- **Simple infection control practices,** such as covering the mouth when coughing and disposing of tissues properly. Discuss the patient's plans regarding work, travel, or moving.
- **Strategies for keeping the home well-ventilated** with fresh air and adhering to visitor restrictions if isolated at home.
- **Expected side effects** and plan for addressing minor complaints should they occur.
- **Potential consequences of nonadherence to treatment** and respiratory isolation.
- **Maximizing nutritional intake.**
- **Sharing information** to assist in the identification and evaluation of contacts.
- **Emphasizing the importance of keeping scheduled clinical appointments.**
- **Understanding the criteria for noninfectiousness** (i.e., when home isolation can be discontinued and the patient will be allowed to return to work or school).

2. Second Phase

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

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

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 well have to take oral medications for another year or more before reaching the finish line.**

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

4. Final Phase

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

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

Use of Incentives and Enablers

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

- Centers for Disease Control and Prevention. *Improving Patient Adherence to Tuberculosis Treatment.* 1994. Available from the CDC, Division of TB Elimination website: www.cdc.gov/tb/

Use of Legal Orders

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

Legal measures are sometimes required when a patient with infectious, drug-resistant TB remains nonadherent despite interventions to overcome barriers and gain the patient's cooperation.

Clinical Response Monitoring

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

- Scheduling regular visits with the patient, initially weekly and then monthly, to perform a thorough nursing assessment until completion of therapy
- The **"Care Plan"** and the **"Drug-O-Gram"** are documents that can be customized for the case manager's own needs and patient's circumstances (see Chapter 6, "Monitoring Patients", and Monitoring Tools 1 and 2)
- Monitoring flow sheets to track progression of bacteriology results, blood work, audiograms, and vision/vestibular screening (see Chapter 6, "Monitoring Patients," and Monitoring Tools 3, 4, and 5)
- Real-time reminders on the computer or "Palm," a tickler system, Post-it notes on the desk, highlighted messages on the desk calendar, a hanging file system, etc.
- 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.

The case manager will be instrumental in assessing:

1. Conversion of sputum smear and culture
2. Resolution of symptoms
3. Weight gain and stabilization
4. The need to adjust medication as weight changes or as renal function changes

Bacteriology

- Obtain 3 sputa for AFB smear every 2 weeks until smears become negative.
  - Sputum specimens should be collected at least eight hours apart.
  - At least 1 specimen should be an early morning specimen. Some patients will be able to collect higher quality specimens if all of them are collected first thing in the morning.
  - Consider supervision of collections and/or sputum induction.
- Collect 2 to 3 sputum samples monthly until cultures become negative.
- Repeat susceptibility testing if cultures remain positive after 3 months of treatment
- Once the culture has consistently converted to negative, obtain **at least 1** specimen of sputum for AFB smear and culture **monthly** if clinically improving, and more frequently if indicated. Once the patient is no longer able to spontaneously produce sputum, sputum induction may be required.
- Obtain sputum for AFB smear and culture at the end of treatment.
- A critical activity of the case manager is coordination of microbiologic evaluation for the patient's cultures. Specimens should be of good quality and at least 5 to 10 ml

in volume. Specimens need to be routed to the appropriate reference labs, specific detection of drug resistance tests need to be requested, and results communicated as quickly as possible to the treating physician.

Therapeutic Drug Monitoring

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

Symptoms

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

Weight

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

A Word about Nutritional Supplements

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

Continuity of Care

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

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

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. The patient should be provided with only enough medications to last through the travel period until they can reestablish 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 moving prior to completion of therapy.

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

Interface With Private Providers

If the patient is managed by a private provider:

- Make an appointment to meet the provider and the office staff as soon as possible.
- Make it clear through your actions and words that you are an ally and will be very helpful in the complicated management of the patient.
- Explain your legal responsibility to monitor the patient throughout the course of treatment.
- **Explain the regulations** in your state or jurisdiction regarding the provider's responsibility to provide information to the health department.
- Explain the absolute **necessity of DOT** and that it is not in any way punitive. Patients frequently take their cues from their physicians; enlist the provider's support in encouraging the patient to accept DOT.
- Relay the benefits of case management and DOT in the efficient treatment of drug-resistant TB.

- Explain the **infection control** practices required to keep office staff and other patients safe.
- Ensure that the office staff has been appropriately evaluated if unprotected exposure to the patient has occurred.
- Offer resources to help manage the patient's co-morbid conditions, such as diabetes, malnutrition, and HIV.
- **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, "List of Expert Resources for Drug-Resistant TB").
- If the provider and staff have the infrastructure and resourcefulness to problem-solve for the patient (i.e., interfacing with insurance companies; seeking supplies of hard-to-get medications; making sure that the patient follows through on all monitoring; ordering and following through on detection of drug resistance testing, blood levels, etc.), stay actively involved in order to ensure that **everything** gets done and is followed up on appropriately.
- Touch base with the office staff regularly. Continue to offer yourself as a resource, problem-solver, and advocate. Anticipate staff needs, such as an audiologist who takes the patient's insurance or an interpreter who the patient trusts.

Reach an agreement about how and when important information (sputum results, laboratory results, and radiographic results) will be shared between the private provider and public health agency.

Infection Control

In order to halt the transmission of *M. tuberculosis*, the correct diagnosis must first be considered, the appropriate treatment must be initiated, and appropriate infection control measures must be instituted. Contagious or potentially contagious TB patients should be housed within a negative pressure room in the hospital setting or separated from family or friends in the outpatient setting.

When dealing with suspected or confirmed infectious drug-resistant TB, even greater emphasis should be placed on strict adherence to infection control standards, as there are limited options and scant data defining effective measures for preventing drug-resistant TB in exposed contacts. 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. 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 utilization of resources required to isolate a patient beyond the necessary and appropriate time frame.

Infection Control Guidelines

The following resources reflect current standard practices regarding TB and infection control:

- CDC's *Guidelines for Preventing the Transmission of Mycobacterium tuberculosis in Health-Care Settings*, MMWR 2005; 54 (No. RR-17), available online at: www.cdc.gov/mmwr/preview/mmwrhtml/rr5417a1.htm
- Francis J. Curry National *Tuberculosis Center's 2007 Tuberculosis Infection Control: A Practical Manual for Preventing TB*, available online at: www.nationaltbcenter.ucsf.edu/TB_IC/
- Your local health jurisdiction is an important resource and may have specific guidelines

Discontinuation of Isolation

When is it safe to discontinue isolation for multidrug-resistant TB patients? There are several times during the treatment regimen when this issue will need to be addressed:

- In the hospital environment, when discontinuation of negative-pressure isolation is contemplated
- When travel or transport to another facility is desired
- When discharge to the home environment is considered
- When transfer to a high-risk environment such as a congregate setting is the only option
- When home isolation may be discontinued

While there are no clear-cut guidelines for these decisions, the following information may be helpful:

- Studies have shown that most transmission of TB occurs before drug treatment has been initiated and that smear-positive cases transmit more efficiently than smear-negative cases. A recent molecular epidemiology study concluded that 17% of secondary cases of TB in San Francisco were transmitted from smear-negative TB cases.
- For drug-susceptible TB, a patient receiving TB treatment is deemed to be non-contagious when he/she has produced 3 consecutive smear-negative sputa, has started an appropriate treatment regimen, and is clinically improved.
- Outbreaks of MDR-TB have been reported in hospitals, jails, and congregate settings. Transmission has been documented in households and in communities. The dramatic decline in MDR-TB cases in the U.S. since 1993 is attributable both to improved awareness and better drug regimens, but also to more aggressive infection control measures.
- MDR-TB takes a terrible toll on individuals and their families, and secondary cases should certainly be avoided whenever possible. Unfortunately, the aforementioned transmission studies primarily included drug-susceptible cases. The current guidelines reduce risk to contacts, but do not eliminate it. Patients with smear-negative, culture-positive sputum on treatment certainly could still transmit TB.
- Because the consequences of MDR-TB are so much more dire, and there are no proven regimens for window prophylaxis or treatment of LTBI, **it is appropriate to be more cautious about returning MDR-TB patients back to their homes, schools, work sites, and congregate settings.**
    - **Particular care should be taken when considering if patients can return to settings where there are young children, immunocompromised individuals, and people who have not previously been exposed to the patient.**
    - Some experts would consider MDR-TB patients **potentially** contagious as long as their sputum cultures remain positive. These experts recommend isolation while hospitalized and would not release MDR-TB patients to congregate settings until their sputum cultures become negative.
    - World Health Organization guidelines consider patients with MDR-TB to be contagious until their sputa are culture-negative, and forbids travel in public airplanes or other public transportation until their sputa are culture- negative.

Discontinuation of Isolation—Management at Home

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

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

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

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

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

Healthcare and other service providers entering the home to deliver DOT and/or other healthcare services (e.g., patient interviews) must comply with current infection control measures to prevent occupational exposure when caring for drug-resistant TB patients who are considered potentially infectious. 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 Regional TB Training and Medical Consultation Center (RTMCC).

Long-term hospitalization in negative-pressure isolation is exceedingly expensive. Safe options should be explored once the patient is medically stable and tolerating the full drug-resistant TB regimen. In some cases, management at home will not be possible while a patient is still potentially contagious because of young children or previously unexposed individuals living in the home, or the physical layout or small space prevents the patient from having a private space for home isolation. In these cases, 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-contagious.

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 negative pressure and high efficiency particulate air (HEPA) filtration. Patient should still wear surgical masks, and providers and drivers should wear N-95 masks.
- **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 contagious tuberculosis patients by airline (see "References.")

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

Contact Investigation

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

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

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

To determine whether the TB infection you find among contacts represents exposure to the recent drug-resistant TB case or exposure to a previous and possibly drug-sensitive case, consider the transmission risk assessment findings and the individual contact's TB exposure history.

TB Transmission Risk Assessment

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

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

1. **Infectiousness of the TB patient:**
   Symptoms, sputum smear status, site of TB, presence of cavitary disease
2. **Environment where transmission likely occurred:**
   Size of room, amount of ventilation, presence of air cleaning systems
3. **Characteristics of the contact's exposure:**
   Frequency of contact and duration of the exposure

Indications of transmission include:

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

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

Contact TB Exposure History

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

Include these essential factors in your assessment:

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

For detailed information, see: **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); available on-line: www.cdc.gov/mmwr/preview/mmwrhtml/rr5415a1.htm

"It costs 100 times more to cure MDR-TB than drug-susceptible TB."

—World Health Organization

Drug Supply

Drug Availability

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

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

Drug Shortages

Some second-line drugs have pre-established production quotas that make access to the drug difficult when demand suddenly increases. If your state does not have a central pharmacy that stocks and distributes drugs used to treat drug-resistant TB, order and keep on hand a several-month supply of drugs to prevent treatment interruption due to supply shortages. If you are told a required drug is on back order, unavailable, or out of stock, report this immediately to your state TB control program. The Food and Drug Administration (FDA) is also a potential resource and can be contacted at: www.fda.gov/cder/drug/shortages; drugshortages@cder.fda.gov; telephone: 301-796-4570

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. Ask the pharmacy to help you anticipate any such restrictions on the patient's prescription plan. A simple treatment authorization request (TAR) letter explaining the medical condition, duration of anticipated use of the drug, and need for that particular drug over another formulary drug will usually suffice. 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, some require refrigeration.

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

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

Patient Assistance Programs (PAPs)

The distribution of drugs used to treat drug-resistant TB varies throughout the country, with some states maintaining central purchasing and distribution. The cost of these drugs is also variable, but in general, they are expensive, particularly when you factor in the length of treatment. Patient assistance programs (PAPs) may be helpful in offsetting costs. Table 1 displays some drugs used to treat drug-resistant TB that are known to be included in PAPs.

TABLE 1.

TB Medications and Patient Assistance Programs (PAPs)

Brand name	Generic name	Manufacturer	Eligibility criteria	PAP telephone
Treactor-SC	Ethionamide	Wyeth Pharmaceuticals	U.S. resident, without resources	800-568-9938
Levaquin	Levofloxacin	Ortho-McNeil Pharmaceuticals	Without resources	800-652-6227
Avelox	Moxifloxacin	Schering Plough	Without resources	SPCares: 800-656-9485
Zyvox	Linezolid	Pfizer	Without resources	888-327-7787
Augmentin	Amoxicillin/ clavulanate	GlaxoSmithKline	U.S. resident, without resources	866-PATIENT 866-728-4368 www.bridgestoaccess.com
Lamprene	Clofazimine	Novartis	MDR-TB	301-443-1240 FDA, single patient Investigational New Drug (IND)

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: Moxifloxicin, capreomycin, ethionamide, cycloserine, para-aminosalicylate, imipenem/cilastin, linezolid, and levofloxin. The ADAP formulary now includes most if not all of the drugs used to treat pan-sensitive MDR- and XDR-TB. Providers who wish to inquire about their patients' eligibility for this program should contact the local ADAP coordinator at their state's health department.

Summary

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

The case manager:

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

The case manager might be the first team member to detect "red flags" that might suggest increased risk of treatment failure. The case manager should alert the treating physician and team if the following are observed:

- **Nonadherence with treatment**
- **Nonadherence with infection control**
- **Missed clinical appointments**
- **Failure to gain weight**
- **Failure to convert cultures, etc.**

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9 Ethical & Legal Issues

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

Suboptimal ethical and legal attention to the issues surrounding drug-resistant TB has implications for both the patient and for the public.

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

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

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

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

All states have laws specific to the control of TB. The federal government is also authorized, through the Public Health Service Act (PHSA), to take measures to prevent the entry and spread of communicable diseases from foreign countries into the United States and between states (Title 42, United States Code Section 264; Section 361 of the PHSA). The Centers for Disease Control and Prevention (CDC), through its Division of Global Migration and Quarantine, is empowered to detain, medically examine, or conditionally release persons suspected of carrying a communicable disease. These include “Do Not Board” (travel by flight) and “Border Look-out” (crossing borders, not by flight) provisions defined by the U.S. Department of Homeland Security. These provisions restrict travel for those identified as having an infectious disease of public health significance or quarantinable disease.

The exercise of powers granted by statute to control the behavior of persons with TB must always be tempered not just by the question “Is it legal?” but also “Is it ethical?”

Inherent in the use of public health authority is a struggle to balance two important principles: individual autonomy and protection of the public’s health.

Conflict in Ethical Principles

Individual Autonomy	vs.	Risks to the Public Health
• Rights to privacy • Right to liberty and self-determination		• Transmission of TB • Development and spread of drug-resistant TB

The Ethical Framework

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

Examples of potential risks to the patient include:

Loss of privacy

- Reporting
- Contact identification

Loss of liberty and self-determination

- Court-ordered diagnostic procedures, evaluations, and directly observed therapy (DOT)
- Long-term isolation, possibly even indefinite, in some cases of MDR-TB
- Detention

Loss of legal rights

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

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

- Are substantiated by individualized assessments based on science (sometimes lacking in the case of treatment and transmission of drug-resistant TB)
- Identify and minimize burdens to the patient using a range of interventions from least to most restrictive
- Are implemented fairly and minimize social injustice or discrimination

Legal Issues for Practitioners

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

Legal Priorities

Priorities for TB control programs include ensuring that:

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

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

Reporting Requirements

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

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

Health care providers caring for TB patients should be familiar with the reporting requirements in their jurisdictions.

Reporting requirements are designed to provide the public health authorities with information necessary to ensure that persons with TB obtain timely, adequate, and appropriate treatment and are not lost to follow-up.

Orders to Appear and Comply

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

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

Orders to Isolate or Detain

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

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

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

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

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

Least restrictive alternatives that should be pursued prior to detention:

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

Summary

- **Many physicians are uncomfortable with discussions of the use of legal powers to "force" patients to adhere to treatment regimens.**
- **MDR-TB patients may have more difficulty adhering to prolonged, complex TB regimens than do drug-susceptible patients.**
- **TB patients, and drug-resistant patients in particular, present a risk to others in the community with whom they may come into contact.**
- **While the physician's primary focus is the individual patient, the public health department must also consider its legally mandated responsibility to protect the public's health. Fortunately, the two are rarely in conflict.**
- **Public health authorities rely heavily on healthcare providers to notify them of TB cases and to provide appropriate evaluation and treatment of persons with or exposed to TB.**
- **Physicians often do not have the same resources as the health department to fully address a patient's psycho/social needs and barriers to adherence to TB care. By working together, the physician and health department can meet the needs of most patients.**
- **For those few patients who, for whatever reasons, continue to pose a risk to the public despite all efforts to address their barriers, ethical and legal options are needed to ensure that these patients do not continue to put others in the community at risk.**

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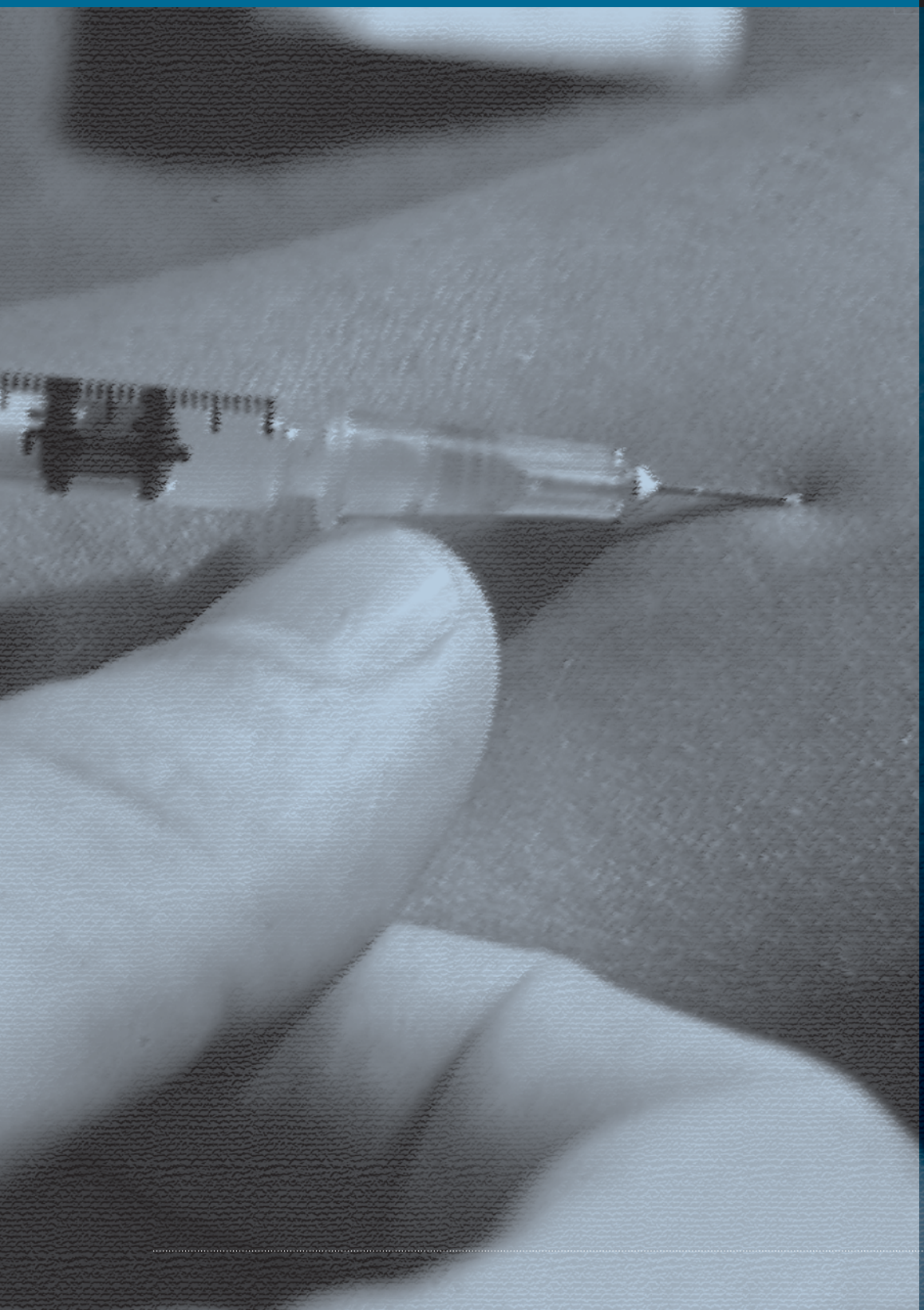
10 Managing Contacts



The rise in tuberculosis resistance rates worldwide and outbreaks of MDR-TB have brought attention to the treatment of contacts to drug-resistant TB cases.

Challenges: A Lack of Data and Consensus

The management and treatment of persons exposed to and infected by patients with MDR-TB pose unique challenges because of the absence of evidence-based therapy and the lack of significant experience in these situations.

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

The management and treatment of persons exposed to and infected by patients with MDR-TB pose unique challenges because of the absence of evidence-based therapy and the lack of significant experience in these situations.

A 2006 systematic Cochrane review of the literature showed that there still have been no randomized controlled trials to address the question of the efficacy of treatment for MDR latent tuberculosis infection (LTBI) treatment. Two observational studies did meet inclusion criteria. A prospective cohort study found individualized tailored treatment to be effective for preventing TB in children, while a retrospective cohort study found isoniazid (INH) not to be effective. The authors concluded that evidence of the effects of treatment of LTBI in people exposed to MDR-TB is extremely limited in both quantity and quality.

Latent Tuberculosis Infection (LTBI)

Traditionally, LTBI is defined as a positive tuberculin skin test (TST) without clinical or radiographic evidence of tuberculosis. The TST has limitations, including false positive results in patients previously infected with nontuberculous mycobacteria (NTM) or vaccinated with bacille Calmette-Guérin (BCG), and false negatives associated with early infection or due to anergy. **New blood tests called interferon gamma release assays (IGRAs) are now available which measure interferon-gamma (IFN-γ) released from a patient's T cells after stimulation with specific TB antigens.** Two commercial IGRA kits are available now in the United States: the QuantiFERON®-TB Gold (QFT-G), approved by the U.S. Food and Drug Administration (FDA) in 2005, and the QuantiFERON®-TB Gold In-Tube (QFT-GIT), a simplified variant of the QFT-G test (FDA approved in 2007). The T-SPOT.*TB* test is available outside the United States and was licensed by the FDA in August 2008.

As reviewed elsewhere, IGRAs have high specificity and are not affected by prior BCG vaccination. Thus, false positive results are highly unlikely. In low-incidence settings, the results of IGRAs correlate well with surrogate markers of exposure. In addition, IGRAs have several potential advantages over the TST: testing requires only one patient visit and these assays are *ex vivo* tests, which reduce the risk for adverse effects and eliminate potential boosting when testing is repeated.

However, IGRAs have disadvantages, including higher material cost, need for an equipped laboratory, and a requirement to draw blood with subsequent careful handling to maintain viability of lymphocytes. Although boosting will not occur, the variability of these tests when repeated after months or years, such as in **serial testing of exposed populations, has not been well studied. In fact, serial testing studies show high rates of both conversions and reversions in exposed populations, and the prognosis of conversions and reversions is unknown.** Currently, no data exist to determine the optimal timing for performing IGRAs in exposed contacts. Because a high rate of reversions has been reported in household contacts even over a short period of 3 months, a negative IGRA result does not rule out transient TB infection. Furthermore, IGRAs cannot distinguish between LTBI and TB disease, and unexplained discordances between TST and IGRAs have been reported in a variety of settings.

The greatest limitation of IGRAs is the lack of prospective data regarding the future risk for TB in persons with positive results on IGRAs.
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.

In July 2005, the CDC convened a meeting of consultants and researchers with expertise in the field to review scientific evidence and clinical experience with QFT-G. On the basis of this review and discussion, CDC recommended that QFT-G may be used in all circumstances in which the TST is currently used, including contact investigations, evaluation of recent immigrants, and sequential-testing surveillance programs for infection control (e.g., those for healthcare workers). This recommendation was also reinforced in the 2005 CDC contact investigation guidelines by the National Tuberculosis Controllers Association and the CDC. **According to this guideline, QFT-G can be used in place of and not in addition to the TST while investigating contacts** (adults and children). A positive QFT-G result should prompt the same evaluation and management as a positive TST. No reason typically exists to follow a positive QFT-G with a TST. For persons with recent contact to infectious TB, negative QFT-G results typically should be confirmed with a repeat test performed 8 to10 weeks after the end of exposure. Lastly, the guideline recommends that the timing of QFT-G testing should be similar to that used for the TST.

Given the paucity of published data regarding the sensitivity and specificity of the QFT-G in children, the CDC recommends using caution when interpreting the test in children < 17 years of age. Additionally, the CDC suggests caution in close contacts who are at particularly high risk of progression to TB disease (children < 5 years of age and immunocompromised individuals). **As with the TST, a negative IGRA does not rule out early LTBI or even TB disease,** a fact that is particularly important in these very high-risk subgroups.

With the recent FDA approval of the QFT-GIT test, and the likely impending approval of the T-SPOT.*TB* test, revised guidelines will be issued by CDC, the American Thoracic Society (ATS) and the Infectious Disease Society of American (IDSA). Although the QFT-G test can be used for contact investigation in the United States, some caveats are worth remembering: 1) **There are no data on the use of IGRAs for investigating contacts of MDR-TB cases;** 2) IGRAs provide no information on whether the contacts are likely to be infected with the same *M. tuberculosis* strain as the index case; 3) IGRAs provide no information on whether the contacts are likely to be infected with drug-sensitive or resistant strains (and, therefore, do not help in selecting the LTBI treatment regimen); 4) **IGRAs offer no help in distinguishing between latent infection and TB disease;** and 5) Because of concerns about suboptimal sensitivity, IGRAs should not be used alone to rule out TB disease in contacts. This is particularly relevant for high-risk subgroups such as HIV-infected and child contacts.

The Importance of Treating LTBI

- For the population as a whole, there is a 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, including contacts of TB cases, HIV-infected and other immunocompromised hosts, children, and recent immigrants.
- Treatment with INH, rifampin (RIF), and the combination of pyrazinamide (PZA) and RIF have been shown to decrease the risk of progressing to TB disease. (**Note:** The combination of RIF and PZA is not currently recommended for treatment of LTBI due to increased risk of hepatotoxicity.)
- Although some data suggest that MDR-TB may be less pathogenic than drug-sensitive TB, **transmission of MDR-TB to healthcare workers, children, immunocompromised persons and other close contacts is well documented,** and full evaluation of all contacts should be aggressively pursued.
- Treatment of LTBI with drug-resistant TB or MDR-TB should be considered, given the high morbidity and mortality associated with TB disease.

General Principles of Providing Care to Contacts & Selecting Treatment Regimens

- Evaluate exposed contacts expeditiously in order to identify any other cases of TB disease and to prevent further transmission.
- Consider the use of an IGRA for exposed contacts who are from areas where they were likely to have received BCG vaccine (especially in persons recently vaccinated).
- **Rule out TB disease prior to starting any treatment.** Amplification of resistance by use of a suboptimal regimen must be avoided.
- Immunosuppressed contacts should be treated with a multidrug MDR-LTBI or window prophylaxis regimen rather than monotherapy.
- Efficacy of any regimen depends on adherence and completion of therapy.
- Educate patients on drug side effects, importance of adherence, and TB symptoms.
- Select the most effective, best-tolerated regimen to which the isolate is likely to be sensitive.

- Window prophylaxis of very high-risk close contacts who are TST-negative should be considered when exposure is very intimate and prolonged, and transmission to other contacts has been documented.

Summary of LTBI Treatment Options

- The range of treatment options for contacts to patients with MDR-TB includes:
  - Treatment with 2 or more drugs to which the organism is sensitive
  - Monotherapy with a fluoroquinolone (this option is employed by some experts and is not included in current national guidelines)
  - Clinical monitoring for 2 years without medication if serial evaluation is feasible
  - INH alone (for patients likely to have been infected by a drug-sensitive case before exposure to the drug-resistant case)
- The recommended duration of treatment is generally 6 to 12 months.
- Experts agree that, regardless of the decision to treat or the treatment option selected, it is important to: **1) Follow those with presumed latent MDR-TB infection for a minimum of 2 years following exposure; and 2) Educate patients about the signs and symptoms of TB in case they progress to TB disease.**
- While there are specific recommendations for the treatment of latent infection with drug-resistant TB, these recommendations are also largely empirical, and **all regimens must be individualized.**
- The use of BCG vaccine should be considered for infants and children with a negative TST who are continually exposed to a case of MDR-TB and who cannot be removed from this exposure.

Contacts to a drug-resistant TB patient should be continually reassessed, due to the potential for a prolonged period of infectiousness.

Variables to Consider

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

- Drug-susceptibility pattern of the *M. tuberculosis* isolate of the presumed source case
- Infectiousness of the source MDR-TB case, which can be evaluated by:
  - **Smear and culture status**
  - **The presence or absence of cavitary disease**
  - **The site of TB involvement (pulmonary or laryngeal vs. other sites)**
  - **The evidence of transmission to other contacts**
- Closeness and intensity of MDR-TB exposure, which can be evaluated by documenting hours of cumulative exposure and setting of exposure (i.e., indoor vs. outdoor, ventilation, etc.)

- Contact's likelihood of prior exposure to drug-sensitive TB, which can be evaluated by:
  - **TST/IGRA history**
  - **Place of birth and history of foreign residence**
  - **History of prior exposures to TB disease**
- Likelihood that the contact will progress to TB disease, including factors such as:
  - **Immunosuppression** (HIV, steroids)
  - **Age** (less than 5 years old, elderly)
  - **Documented skin test or IGRA conversion (skin test conversion is defined as increase in reaction size by 10 mm or more within a period of 2 years)**
  - **Diabetes, renal failure, and certain other medical conditions**
- Tolerability and toxicity of potential anti-tuberculosis drugs for treatment of LTBI

Drug-Resistant LTBI: Treatment Options

Treatment of contacts depends on the resistance pattern of the source case's isolate. Current national guidelines advise treatment of MDR-LTBI with 2 drugs to which the isolate is susceptible. The following are suggestions for regimens that may be used in specific situations. The actual regimen chosen will depend on the individual case.

TABLE 1.

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

* Better tolerated in children than in adults.

Duration of Therapy

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

MDR-LTBI Treatment Options

Pyrazinamide and Ethambutol

- Follows CDC/ATS 1992 recommendations of using 2 drugs to which isolate is sensitive
- No data on efficacy in preventing progression to disease
- May be better tolerated than a fluoroquinolone-containing regimen

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

- Follows CDC/ATS 1992 recommendations of using 2 drugs to which isolate is sensitive
- Frequently poorly tolerated due to increased side effect profile
- Side effects may deter patient from completing this regimen
- Potential toxicity in children must be balanced against unproven 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
- Avoid fluoroquinolones in pregnant or breast-feeding women (See Chapter 5: "Special Situations" for more information)
- Levofloxacin/EMB may be better tolerated than Levofloxacin/PZA
- No data on efficacy in preventing progression to TB disease

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

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

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

Levofloxacin or Moxifloxacin Alone

- Better tolerated than 2-drug combination, and therefore more likely to complete regimen
- Demonstrated bactericidal activity against TB
- No evidence of efficacy in preventing progression to TB disease
- Recommended by some TB experts because of the higher likelihood of completion and known *in vitro* anti-tuberculosis activity; this option is not included in current national guidelines

- Some experts are reluctant to use fluoroquinolone monotherapy because of the possibility of developing resistance
- Potential toxicity in children must be balanced against unproven benefits
- Due to the potential risk of tendon rupture, advise patients to avoid vigorous exercise and to report any symptoms of calf pain or tenderness
- Avoid fluoroquinolones in pregnant or breast-feeding women (See Chapter 5, "Special Situations" for more information)
- Consider use in TST/IGRA converters and those with newly documented positive TST/QFT, but who may have intermediate exposure to index case so that likelihood of exposure to MDR-TB is less certain

INH Alone

- Proven to decrease likelihood of progression to TB disease if infected with a drug-susceptible strain
- Use for contacts with history of previously untreated LTBI
- Use for contacts with lower likelihood of infection with MDR-TB
- Consider for contacts to cases with low-level INH resistance. Can be used twice weekly by directly observed therapy (DOT) and/or with a second drug in these cases. Ask the lab what the level of INH resistance is (percent resistance with proportion method, minimum inhibitory concentration [MIC], or concentrations studied).
- No efficacy for treatment of MDR-TB LTBI

Other Possible Regimens Include:

- INH, Levofloxacin or moxifloxacin, and a third drug
- INH and Levofloxacin or moxifloxacin

No Treatment: Clinical Monitoring

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

Consider especially when:

- Contact is **not** HIV-infected
- Contact is over 5 years of age
- Contact is **not** a documented converter or otherwise at risk for progression to TB disease
- An LTBI regimen is not tolerated despite best efforts

Adherence and Monitoring

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

Preschool children and adolescents are at increased risk of developing TB if infected and deserve aggressive evaluation and treatment if exposed to an individual with TB.

Treatment of Children Exposed to Drug-Resistant TB

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

- Children exposed to **INH-resistant, RIF-susceptible** TB should be treated with 6 months of RIF. A study of 157 adolescents receiving RIF for 6 months after exposure to INH-resistant TB reported no cases of TB (at least 56% protection).
- The **2-month regimen of RIF and PZA has not been studied in children,** is associated with **unacceptable hepatotoxicity in adults, and should not be used.**
- In an unpublished series on MDR-LTBI in children, 14 children (age 4 months to 13 years) in New York City were treated with **2 to 3 drugs (without fluoroquinolones)** and none developed TB. Regimens included PZA, EMB, cycloserine, and ethionamide.
- In a South African series, 2 of 41 (5%) children who received 2 to 3 drug treatment (without fluoroquinolones) of MDR-LTBI developed TB, compared to 13 of 64 (20%), who did not receive treatment. The MDR-LTBI regimens consisted of some combination of the following drugs: high-dose INH (probably not effective), EMB, PZA, ofloxacin and ethionamide. The cohort consisted of 125 children contacts to MDR-TB, the median age was 27.5 months and 14 of 125 (12%) had TB disease at time of presentation, suggesting a setting of significant transmission of TB.

Fluoroquinolone Use in Children

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

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

Window Prophylaxis

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

Window prophylaxis typically consists of INH for INH-susceptible or RIF for INH-resistant/ RIF-susceptible TB contacts.

- **Window prophylaxis prevents rapid progression to TB soon after infection.**
- Individuals at very high risk of progressing to TB if infected (very young children, immunocompromised contacts, close contacts to very contagious individuals) are targeted for window prophylaxis.
- Contacts should be screened by history, physical exam, 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 is repeated. If the skin test has become positive, treatment for LTBI is completed. If the skin test remains negative, window prophylaxis is stopped, unless the contact is at risk for anergy (immunosuppressed or an infant younger than 6 months of age).
- Window prophylaxis 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: very young children, and HIV-infected individuals with very intimate and prolonged contact with individuals likely to be contagious (smear-positive, cavitary disease, coughing source case, and TST conversions among other contacts indicating transmission of TB).

Follow-Up of MDR Contacts

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

Summary

- **IGRAs may be used instead of TST in contact investigations,** but the significance of conversions and reversions observed following recent exposure is unknown.
- **While it is highly desirable to prevent MDR-TB cases by treatment of LTBI and use of window prophylaxis, there are limited efficacy data and a lack of expert consensus to guide clinicians.**
- **Treatment of LTBI should be considered particularly for patients at highest risk for progression to TB.**
- **Careful contact investigation is required to determine timing of infection.** Patients who were previously TST positive were more likely infected with a susceptible strain and should be treated with INH.
- **Recommended treatment regimens include 2 drugs to which the source case isolate is susceptible for 6 to 12 months.** Some experts now recommend monotherapy with a fluoroquinolone drug to which the isolate is susceptible for select cases.
- **Young children and patients who are immunocompromised should be treated with 2-drug regimens for at least 12 months.**
- **For some patients, clinical monitoring without treatment can be considered.**
- **All exposed patients should be monitored for symptoms and radiographically for at least 2 years for evidence of TB.**

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Appendices

Appendix 1: List of Expert Resources for Drug-Resistant TB

In 2005, the Centers for Disease Control and Prevention's Division of Tuberculosis Elimination funded four TB Regional Training and Medical Consultation Centers (RTMCCs). The RTMCCs are regionally assigned to cover all 50 states and the U.S. territories. Information about the RTMCC system can be found at: www.cdc.gov/tb/rtmcc.htm.

Contact information for the RTMCCs and other regional and national resources can be found in this appendix.

California Department of Public Health
TB Control Branch, Division of Communicable Disease Control
MDR-TB Service

CONTACT Lisa True, RN, MS, Coordinator
TELEPHONE 510-620-3054
E-MAIL lisa.true@cdph.ca.gov
ADDRESS 850 Marina Bay Parkway, Richmond, CA 94804-6403

- **Types of consultation:** Telephone and e-mail (for callers within California or other state agencies within the United States)
- Can provide on-site presentations related to MDR-TB
- Can provide ongoing consultation during drug-resistant treatment

Centers for Disease Control and Prevention (CDC)
Coordinating Center for Infectious Diseases
National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
Division of Tuberculosis Elimination (DTBE)

CONTACT CDC INFO Contact Center
TELEPHONE 1-800-CDC-INFO
E-MAIL cdcinfo@cdc.gov
INTERNET www.cdc.gov/tb/
ADDRESS Mailstop E-10, 1600 Clifton Road, NE, Atlanta, GA 30333

- **Types of consultation:** Telephone and e-mail
- In general, CDC/DTBE does not provide medical consultation for management of individual patients. CDC/DTBE does provide information on current guidelines and their interpretation. CDC/DTBE also is available for programmatic consultation to local and state health departments including onsite assistance for outbreaks.

Chicago Department of Public Health TB Control Program

CONTACT William Clapp, MD
TELEPHONE 312-746-6003
E-MAIL clapp_william@cdph.org
ADDRESS 2160 W. Ogden Ave., Chicago, IL 60612

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

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

ADULT
University of Illinois Hospitals and Clinics
Dr. Dean Schraufnagel
Department of Medicine
312-996-8039
Division of Pulmonary and Critical Care Medicine

ADULT
University of Illinois Hospitals and Clinics
Dr. James Cook
Department of Medicine
312-996-6732
Division of Infectious Diseases

PEDIATRICS
Rush-Presbyterian St. Lukes Hospital
Dr. James McAuley
Department of Pediatrics
312-942-6396
Division of Infectious Diseases

Francis J. Curry National Tuberculosis Center—TB Warmline

CONTACT Warmline Coordinator
TELEPHONE 877-390-6682 (toll-free) or 415-502-4700
E-MAIL tbcenter@nationaltbcenter.ucsf.edu
INTERNET www.nationaltbcenter.ucsf.edu
ADDRESS 3180 18th Street, Suite 101, San Francisco, CA 94110

- **Types of consultation:** Telephone, email, and bimonthly MDR-TB Expert Network case conferences
- As the Western Regional TB Training and Medical Consultation Center, can provide medical consultation to providers in Alaska, California, Colorado, Hawaii, Idaho, Montana, Nevada, Oregon, Utah, Washington, Wyoming, and the U.S. Pacific Island Territories
- Patients can be sent to our facility—see San Francisco Department of Public Health
- Can provide ongoing consultation during drug-resistant treatment

Heartland National TB Center and Texas Center for Infectious Disease

CONTACT Barbara J. Seaworth, MD
TELEPHONE 210-534-8857, ext. 2489
E-MAIL Barbara.Seaworth@dshs.state.tx.us
INTERNET www.heartlandntbc.org
ADDRESS 23023 SE Military Drive, San Antonio, TX 78218

- **Types of consultation:** Telephone, e-mail, and in-person (clinic)
- Can provide ongoing consultation during drug-resistant treatment
- Provides consultations for all Texas cases of drug-resistant TB, contacts of drug-resistant TB, and use of fluoroquinolones, or other non-formulary drugs (linezolid)
- Provides any needed consultation for the Heartland region and works to support other regions as requested by them
- **Comments:** Enabling legislation has been passed to allow states to contract for the care of patients from other states at the Texas Center for Infectious Disease. There is a fair amount of administrative effort to resolve prior to the first patient.
- We like to use a case management approach for all cases to make sure treatment not only begins correctly but also continues on course, and that problems leading to toxicity and treatment failure are identified and corrected early.

Los Angeles County TB Control Program

CONTACT Jaimin Kim, PHN, MDR-TB Unit
TELEPHONE 213-744-6180
ADDRESS 2615 S. Grand Avenue, Room 507, Los Angeles, CA 90007

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

National Jewish Mycobacterial Diseases Consult Line

CONTACT Bessie Mishra, RN
TELEPHONE 800-423-8891, ext 1279 or 303-398-1279
E-MAIL mycoconsults@njc.org
INTERNET www.nationaljewish.org
ADDRESS National Jewish Medical and Research Center
1400 Jackson Street, Denver, CO 80206

- **Types of consultation:** Telephone, e-mail, and in-person
- Can provide advice for patients not in jurisdiction
- Patients can be sent to our facility
- **Comments:** Contact Bessie Mishra, RN, to discuss referral process or to ask for a clinical consultation (consultations provided by Michael Iseman, MD; Gwen Huitt, MD; Charles Daley, MD; Leonid Heifets, MD; and Charles Peloquin, PharmD).
- Our service provides comprehensive evaluation and treatment programs, including consideration of surgery. If indicated, surgery is performed at our sister institution, the University of Colorado Health Science Center.

New Jersey Medical School Global Tuberculosis Institute Northeastern Regional Training and Medical Consultation Center

CONTACT Reynard J. McDonald, MD or Alfred Lardizabal, MD
TELEPHONE 800-4TB-DOCS or 973-972-3270
INTERNET http://www.umdnj.edu/globaltb
ADDRESS 225 Warren Street, 2nd Floor, East Wing, Newark, NJ 07103

- **Types of consultation:** Telephone, e-mail, and in-person.
- Consultants to the New Jersey DHSS for TB problems, including all cases of MDR-TB.
- Center provides comprehensive diagnostic, treatment, and consultation services for TB patients in the state of New Jersey.
- Can provide advice and consultation for patients not in jurisdiction.
- MDR-TB work is collaborative, utilizing the collective wisdom of the following recognized authorities at the New Jersey Medical School Global Tuberculosis Institute:

ADULTS
Dr. Lee B. Reichman
Dr. Reynard J. McDonald
Dr. Bonita Mangura
Dr. Alfred Lardizabal
Dr. Kevin Fennelly

CHILDREN
Dr. George McSherry
Dr. Helen Aguilla

New York City Department of Health and Mental Hygiene

CONTACT Diana Nilsen, MD
TELEPHONE 212-442-9737
E-MAIL dnilsen@health.nyc.gov
ADDRESS 225 Broadway, 22nd Floor, New York, NY 10007

- **Type of consultation:** Telephone, e-mail, and in-person
- Can provide advice for patients not in jurisdiction
- Patients can be sent to our facility
- **Comments:** Free evaluation and treatment, including CXR, sputa, DOT, and meds in outpatient facilities
- Can provide ongoing consultation during drug-resistant treatment

Partners In Health

TELEPHONE 617-432-5256
E-MAIL info@pih.org
INTERNET www.pih.org
ADDRESS 641 Huntington Ave., Boston, MA 02115

- **Type of consultation:** Telephone, e-mail, and in-person
- Can provide advice for patients not in jurisdiction
- **Comments:** We are a non-profit organization with more than 10 years of experience treating MDR-TB in resource-poor settings
- Can provide ongoing consultation during drug-resistant treatment

San Francisco Department of Public Health—TB Control Section

CONTACT Masae Kawamura, MD
TELEPHONE 415-206-3387
E-MAIL masae.kawamura@sfdph.org
ADDRESS TB Clinic, San Francisco General Hospital, 1001 Potrero Ave., San Francisco, CA 94110

- **Types of consultation:** Telephone (in-person consultation for San Francisco patients only)
- Can provide advice for patients not in jurisdiction
- Can provide ongoing consultation during drug-resistant treatment

Southeastern National Tuberculosis Center / A.G. Holley Hospital TB Hotline

CONTACT Southeastern National TB Center
TELEPHONE 800-4TB-INFO (800-482-4636)
E-MAIL sntc@medicine.ufl.edu
INTERNET http://sntc.medicine.ufl.edu
ADDRESS 1329 SW 16th Street, Room 5174, Gainesville, FL 32608

- **Types of consultation:** Telephone, e-mail, web-based and in-person on all aspects related to TB control and patient care
- Expert medical consultation available 24 hours a day, seven days a week for the 11 southeastern states (Alabama, Arkansas, Florida, Georgia, Kentucky, Mississippi, New Orleans, North Carolina, South Carolina, Tennessee, Virginia) and Puerto Rico and the Virgin Islands. Focus is on providing medical consultation and support to health care providers within the southeast region, supporting the existing resources within each state and working in close partnership with the state TB Control Program.
- Patients requiring complex inpatient support can be sent to our state facility (AG Holley Hospital) on a case-by-case decision once determined appropriate and upon final agreement between the two state programs.
- Provide ongoing medical consultation for drug-resistant TB cases and other complex and challenging TB cases, including use of collaborative case conferences involving multiple providers across the southeast connected by web-based conferencing system.
- Can provide medical consultation for patients not in jurisdiction

Appendix 2: Contact Information for Selected Organizations Working to Control and Prevent TB in the International Arena

CureTB: Binational TB Referral Program
www.curetb.org
619-542-4013

Foundation for Innovative New Diagnostics (FIND)
www.finddiagnostics.org
+ 41-22-710-0590

Global Alliance for TB Drug Development
www.tballiance.org
212-227-7540

Green Light Committee
www.who.int/tb/challenges/mdr/greenlightcommittee/en
+ 41-22-791-2708 or 3224

International Union Against Tuberculosis and Lung Disease (IUATLD)
www.iuatld.org
+33-1-44-32-0360

KNCV Tuberculosis Foundation
www.tuberculose.nl
+31-70-416-7222

Médecins Sans Frontières (Doctors Without Borders)
International headquarters: Geneva, Switzerland
www.msf.org
+41-22-849-8400
United States headquarters: New York
www.doctorswithoutborders.org
212-679-6800

Pan American Health Organization (PAHO)
www.paho.org/english/ad/dpc/cd/tuberculosis.htm
202-974-3000

Partners In Health
www.pih.org
617-432-5256

Program for Appropriate Technology in Health (PATH)
www.path.org
206-285-3500

Stop TB Partnership
(housed by the World Health Organization)
www.stoptb.org
+ 41-22-791-4650

TBNet (Migrant Clinicians Network)
www.migrantclinician.org/network/tbnet
800-825-8205

World Health Organization
www.who.int/en
+ 41-22-791-2111

Appendix3: International Resources for TB Treatment and Policies

The following websites are potential sources of information about the various TB protocols practiced in countries with high rates of immigration to the United States:

Global	The World Health Organization (WHO) Report on Global TB Control compiles data from 200 countries each year, 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/index.html The fourth report by the WHO/International Union Against TB and Lung Disease Global Project on Anti-Tuberculosis Drug Resistance Surveillance presents data from 93 settings or countries: www.who.int/tb/publications/2008/drs_report4_26feb08.pdf The WHO website provides links to, and contact information for TB programs located throughout the world: www.who.int/topics/tuberculosis/en/ The CDC Division of Global Migration and Quarantine is another source of information: www.cdc.gov/ncidod/dq/ E-mail: dqweb@cdc.gov The *International Standards for Tuberculosis Care (ISTC)* (in English, French, and Spanish); the *Patients' Charter for Tuberculosis Care* (in English and Spanish); and a comprehensive list of guidelines, statements, and standards on tuberculosis from agencies around the world are available at: www.nationaltbcenter.ucsf.edu/international/index.cfm
China	www.wpro.who.int/china/sites/stb/
India	www.tbcindia.org www.whoindia.org/EN/Section3/Section123.htm
Mexico	www.salud.gob.mx www.who.int/countries/mex/en/
Philippines	www.doh.gov.ph/programs/tbcontrol www.wpro.who.int/countries/2007/phl.htm www.usaid.gov/our_work/global_health/id/tuberculosis/countries/ane/philippines_profile.html
Russian Federation	www.mednet.ru/main/ www.eurotb.org/index.htm www.who.int/countries/rus/en/
Vietnam	www.moh.gov.vn www.who.int/countries/vnm/en/

Appendix 4: **Laboratory Resources**

The laboratory is the cornerstone of diagnosis and management of drug-resistant tuberculosis (TB) in the United States and other industrialized countries. While initial treatment regimens are designed empirically based on risk of resistance and prior use of antimicrobials, definitive regimens rely on accurate and timely susceptibility results.

There are several types of laboratories that culture mycobacteria:

- **Hospital-based laboratories**
- **Local public health laboratories**
- **State public health laboratories**
- **Commercial laboratories**

Each laboratory performs different services: different types of smears, culture methods, identification methods, rapid tests for early identification (i.e., nucleic acid amplification) or species identification, and susceptibility testing with different panels of drugs for susceptibility testing. Services and protocols may vary based on the source of the specimen (e.g. private provider vs. hospitalized patient), type of specimen (e.g. sputum vs. cerebrospinal fluid [CSF] vs. other specimen type), and third-party payor source.

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

Specific Elements to Know:

Will the laboratory perform nucleic acid amplification tests upon request? On any sputum requested or only smear-positive sputum?

Nucleic acid amplification tests (NAATs) enable rapid detection of DNA of *M. tuberculosis* complex directly on clinical specimens. They are usually used to diagnose TB in sputum from smear-positive patients in order to guide empiric treatment and guide infection control measures. They can be performed on smear-negative specimens as well, but negative results in such a case have a lower predictive value (higher probability of false-negative results) compared to smear-positive specimens. The test can be useful with various biopsy and autopsy specimens and various body fluids, especially with CSF when TB meningitis is suspected (these uses are less well studied). Contact the individual laboratory regarding their policies and protocols for using the NAAT tests.

How and when will smear, nucleic acid amplification, and culture results be reported to me?

Positive acid-fast bacilli (AFB) smear results should be reported to the local public health jurisdiction and the ordering physician or referring laboratory within 24 hours after the arrival of the specimen to the laboratory. Consult with your laboratory on how frequently they perform NAAT testing and when to expect results. Once mycobacterial growth from primary isolation media is confirmed, a DNA probe technique may be used to determine whether the organism is a member of the *M. tuberculosis* complex (in the United States, *M. tuberculosis* and *M. bovis* are the two clinically important species in the complex) or a nontuberculous mycobacterium (NTM). Commercial probes are available for *M. tuberculosis* complex, *M. avium* complex, *M. kansasii* and *M. gordonae*. Identification of *M. tuberculosis* complex should be available in less than 1 week after the culture becomes positive. The positive culture result can be available as early as 14 days from specimen collection on a new patient and is reported to the local public health jurisdiction and the ordering physician or referring laboratory. Communication with the laboratory will ensure that the results are reported to the correct individuals immediately.

How can I keep track of serial cultures being performed at different laboratories?

It is advisable to submit serial cultures to the same laboratory, usually the state or local public health laboratory. Many

public health departments and case managers can access their public health laboratories' computerized results directly, making smear, culture, identification, and susceptibility status available as rapidly as possible. Additionally, most public health laboratories will automatically repeat susceptibilities for patients whose cultures remain positive after 3 months. Having all follow-up cultures at the same laboratory provides the greatest efficiency and optimal communication.

How can I ensure that adequate specimens are being submitted?

It is not possible to be sure of specimen adequacy. It is prudent to submit 2-3 specimens (minimum volume 5-10 ml) biweekly until the sputum is smear-negative. Two specimens should be collected at least monthly until the patient is consistently culture-negative. If there is any concern about the quality of the specimen, arrange sputum induction for the patient, and always submit 2 specimens 8 to 24 hours apart.

Will drug susceptibility tests be performed immediately?

Some mycobacteriology laboratories require an additional request from the ordering physician in order to perform susceptibility tests. Contact your laboratory to expedite this testing.

If the laboratory does not perform susceptibility tests on-site, where will the isolate be sent? Will it be sent automatically? How will that laboratory share results with me?

Contracts between payors and individual hospitals and laboratories determine where susceptibility testing is performed. The reference laboratory reports results to the referring laboratory.

What is the panel of drugs studied initially?

It is fairly routine for laboratories to test for at least isoniazid (INH), rifampin (RIF), pyrazinamide (PZA) and ethambutol (EMB). If a laboratory intends not to test routinely for these drugs, it should seek approval from TB Control. Some laboratories may include streptomycin in the primary drug panel, and some may not test for PZA susceptibility. Request molecular assays, where available, for rapid testing from a sputum sediment or a broth culture if drug-resistance is suspected.

Can I request that second-line susceptibility tests be performed as soon as growth is detected?

In the event of suspected drug-resistance, the laboratory should be informed at the time of specimen submission, in order to set-up second-line drugs simultaneously with first-line drug assays. Request molecular assays, where available, for rapid testing from a sputum sediment or a culture.

How can I arrange to receive results as soon as they are available?

Some laboratories perform confirmatory tests before releasing results. It is valuable to know that an AFB is growing even before identification is performed. It is essential to know if the mycobacteria is *M. tuberculosis* complex (frequently this is the extent of the speciation), even if the laboratory intends to fully speciate the isolate. The laboratory should know that you want to be informed of drug resistance detected by broth methods before confirmation by a reference laboratory or by an alternate method.

How can I arrange for a broader panel of drug susceptibility tests to be performed?

Many laboratories have a regional reference laboratory under contract to perform confirmatory tests or more extensive testing. In the case of many commercial laboratories and some public health laboratories, the list of second-line drugs tested may be quite limited. In the case of extensive drug resistance, many second- and third-line drugs may need to be tested in order to design a curative regimen for your patient. While unnecessary expense should be avoided, expeditious appropriate testing should be performed. Very comprehensive second- and third-line testing is only performed at a few reference laboratories.

An open dialogue with the laboratorian facilitates the prompt communication of results and the most efficient and comprehensive laboratory evaluation of the patient's isolate.

Contact your state/local public health, hospital-based or commercial laboratory for more information.

STATE PUBLIC HEALTH LABORATORIES

Laboratory	Tests performed	Requirements	Cost	Contact information
California Department of Public Health Microbial Disease Laboratory (MDL)	Indirect susceptibility testing: first-line drugs: **INH, RIF, PZA, EMB; second-line (if resistant to RIF or 2 first-line drugs, or by request): SM, capreomycin, ethionamide, amikacin and levofloxacin**	Isolates from solid or broth media	None Full services available only to CA residents	**Edward P. Desmond, PhD, 510-412-3781** **Ed.Desmond@cdph.ca.gov** Chief of Mycobacteriology & Mycology Section Molecular beacons: 510-412-3929 Grace.lin@cdph.ca.gov Genotyping: 510-412-3928 or 3926 Culture identification: 510-412-3924 FAX: 510-412-3927 Microbial Diseases Laboratory c/o Specimen Receiving California Department of Public Health 850 Marina Bay Parkway Richmond, CA 94804 Most specimens come from county public health laboratories **ALL laboratories must submit all MDR-TB isolates from any CA resident**
	Molecular drug resistance assay for INH (*katG, inhA*) or RIF (*rpoB*) by molecular beacons: **by request only – contact Dr. Desmond or Grace Lin**	At least 1+ smear- positive, NALC-NaOH processed sediments Isolates from solid or broth media		
	TB strain typing	Isolates from solid or broth media		
	Identification of mycobacterial species by HPLC or AccuProbes	Isolates from solid or broth media		

EMB ethambutol **INH** isoniazid **PAS** para-aminosalicylate **PZA** pyrazinamide **RIF** rifampin **SM** streptomycin

STATE PUBLIC HEALTH LABORATORIES continued

Laboratory	Tests performed	Requirements	Cost	Contact information
Florida Department of Health **Bureau of Laboratories, Jacksonville** **Mycobacteriology Section**	AFB smear microscopy and growth detection; species ID; nucleic acid amplification of *M. tuberculosis* complex in diagnostic respiratory specimens	Clinical specimens Broth aliquots LJ / Middlebrook agar slants	Full services available only to FL residents For non-FL inquiries, contact David Ashkin, MD, at 1-800-4TB-INFO 1-800-482-4636	**Susan Dean** Medical Laboratory Scientist IV susan_dean@doh.state.fl.us 904-791-1630 FAX: 904-791-1633 1217 Pearl St Jacksonville, FL 32202 For detailed information see: www.doh.state.fl.us/Lab/index.html
	Indirect susceptibility testing; first-line: **INH, RIF, PZA, EMB, SM;** second-line (automatically performed if resistant to 2 first-line drugs, or by request): **kanamycin, clofazimine, capreomycin, rifabutin, ofloxacin, ethionamide**	Broth aliquots LJ / Middlebrook agar slants pure culture required.		
	Molecular drug resistance assays for INH (*katG*, *inhA*), RIF (*rpoB*)	Clinical specimens Broth aliquots LJ / Middlebrook agar slants		

EMB ethambutol **INH** isoniazid **PAS** para-aminosalicylate **PZA** pyrazinamide **RIF** rifampin **SM** streptomycin

STATE PUBLIC HEALTH LABORATORIES continued

Laboratory	Tests performed	Requirements	Cost	Contact information
New York State Department of Health **Wadsworth Center**	Smear and primary culture; species ID using AccuProbe, deletion analysis (final ID within *M. tuberculosis* complex), DNA sequencing for NTM; real-time PCR for NYS FAST TRACK specimens (if suspicion for MDR-TB, molecular assays are performed on strongly smear-positive specimens or upon growth in broth medium), other specimens by request. Several susceptibility testing methods available.	Clinical specimens: can be sent as part of the NYS Fast Track program (eligibility: newly diagnosed, AFB smear-positive, or high likelihood of TB and/or suspicion for drug resistance) Broth samples (at least 3 ml preferred) LJ Slants	Service free for all New York residents	**Vincent E. Escuyer, PhD** Director, Laboratory of Clinical Mycobacteriology 518-474-2196 FAX: 518-408-2264 vee01@health.state.ny.us P.O. Box 509 Albany, NY 12201 Street address: 120 New Scotland Avenue Albany, NY 12208 Laboratory supervisor Phyllis Cunningham: 518-474-7043 www.wadsworth.org
	Indirect susceptibility testing; first-line drugs: **INH, RIF, PZA, EMB, SM;** second-line drugs susceptibility by agar proportion automatically upon detection of any first-line resistance: **INH, RIF, EMB, SM, capreomycin, cycloserine, ethionamide, kanamycin, PAS, amikacin, ofloxacin, rifabutin, cycloserine**	Broth samples (at least 3 ml preferred) LJ Slants		
	Molecular drug resistance assays for INH (*katG*), RIF (*rpoB*), PZA (*pncA*), EMB (*embB*)	Clinical specimens Broth samples (at least 3 ml preferred) LJ Slants		
	TB strain typing	Broth samples (at least 3 ml preferred) LJ Slants		

STATE PUBLIC HEALTH LABORATORIES continued

Laboratory	Tests performed	Requirements	Cost	Contact information
Texas Department of State Health Services Mycobacteriology/ Mycology Group	Smear and primary culture; species ID; HPLC for smear-positive specimens (MTB and common NTMs in smear positive specimens); nucleic acid amplification performed weekly on HPLC inconclusive smear positive specimens and upon request	Clinical specimens	Free for clients of the Texas TB Elimination program; other patients and hospitals will be billed	**Denise Dunbar** Mycobacteriology/Mycology Group Manager 512-458-7342 FAX 512-458-7167 Denise.dunbar@dshs.state.tx.us For overnight shipping to physical address: Denise Dunbar, Mycobacteriology Mycology Laboratory Laboratory Services Section MC 1947 Texas Department of State Health Services 1100 West 49th Street Austin TX 78756-3199 For USPS mailing address: Denise Dunbar Laboratory Services Section MC 1947 Texas Department of State Health Services PO Box 149347 Austin, TX 78714-9347 www.dshs.state.tx.us/lab
	HPLC identification for referred isolates. For *M. tuberculosis* complex: indirect susceptibility testing: First-line **INH, RIF, EMB**. Second-line drugs upon detection of resistance or upon request: **SM, PZA, ofloxacin, capreomycin, kanamycin, ethionamide, rifabutin**	LJ slants or Middlebrook agar slants Broth cultures		

EMB ethambutol **INH** isoniazid **PAS** para-aminosalicylate **PZA** pyrazinamide **RIF** rifampin **SM** streptomycin

LOCAL PUBLIC HEALTH LABORATORIES

Laboratory	Tests performed	Requirements	Cost	Contact information
Los Angeles County Public Health Laboratory	Smear and primary culture; species ID by AccuProbes, HPLC, and biochemicals. Amplified *M. tuberculosis* direct tests for first-time smear-positive patients and by request.	Clinical specimens LJ Slants	Free for LA County patients	**Lorna Eusebio / Elena Ortiz / Hector RIvas** Mycobacteriology Section Supervisors S.F. Sabet, PhD, Dipl (ABMM) Director, Public Health Laboratory 562-658-1380 FAX: 562-401-5992 12750 Erickson Avenue Downey, CA 90242 www.lapublichealth.org/lab/labtb.htm www.lapublichealth.org/lab/tb-1.htm
	Indirect susceptibility testing: **INH, RIF, PZA, EMB, SM;** second-line susceptibilities performed automatically: if RIF, INH/SM; or INH/EMB resistance detected; **or** by request of TB control. Second-line drugs: **ciprofloxacin, ofloxacin, capreomycin, kanamycin, ethionamide, cycloserine, PAS, rifabutin, amikacin, azithromycin and clarithromycin**	LJ Slants MGIT broth (slants preferred)		
	TB strain typing	LJ Slants MGIT broth (slants preferred)		
	Molecular beacons for RIF- and INH-resistance mutation	Sputum sediment; at least 0.5 ml with (+) AFB smear (1+ or greater)		
	Therapeutic drug concentrations are sent to a commercial laboratory after approval by TB Control	Frozen serum		

EMB ethambutol **INH** isoniazid **PAS** para-aminosalicylate **PZA** pyrazinamide **RIF** rifampin **SM** streptomycin

LOCAL PUBLIC HEALTH LABORATORIES continued

Laboratory	Tests performed	Requirements	Cost	Contact information
New York City Department of Health TB Laboratory	Smear and primary culture; species ID by HPLC; nucleic acid amplification for direct specimens for new smear-positive patients and by request	Clinical specimens LJ Slants Broth samples	MTD and drug susceptibilities free for New York City and 5 boroughs residents	**Jafar H. Razeq, PhD** Interim Chief, Mycobacteriology Laboratory 212-447-5155 jrazeq@health.nyc.gov Main laboratory: 212-447-6745 FAX: 212-447-8283 455 1st Avenue New York, New York 10016
	First-line drug indirect susceptibility testing by MGIT: **INH, RIF, PZA, EMB, SM**; second-line drug susceptibility testing by agar proportion automatically if drug resistance detected: **ethionamide, ciprofloxacin, PAS, capreomycin, kanamycin, cycloserine and rifabutin**	LJ Slants Broth samples		
	Therapeutic drug monitoring is processed by the NYC DOH laboratory and performed at a commercial laboratory	Frozen serum		

NATIONAL PUBLIC HEALTH LABORATORY

Laboratory	Tests performed	Requirements	Cost	Contact information
Centers for Disease Control and Prevention	Indirect susceptibility testing: INH, RIF, PZA, EMB, SM, ofloxacin, capreomycin, amikacin, kanamycin, ethionamide, PAS, rifabutin	LJ Slants preferred Will accept plates or broth	None	**Beverly Metchock, DrPH, D(ABMM)** 404-639-2455 All specimens must come from state public health department laboratories
	Other services available upon consultation with laboratory director			

EMB ethambutol **INH** isoniazid **PAS** para-aminosalicylate **PZA** pyrazinamide **RIF** rifampin **SM** streptomycin

COMMERCIAL LABORATORIES

Laboratory	Tests performed	Requirements	Cost	Contact information
Focus Diagnostics, Inc.	Smear and primary culture isolation; ID by HPLC or nucleic acid probe of isolate; nucleic acid amplification of *M. tuberculosis* in raw specimens	Clinical specimens LJ Slants Broth samples Plates if safely packaged	Contracted with each institution – see catalog for base price	Scientific Director of Microbiology 800-445-0185 FAX: 714-484-1296 5785 Corporate Ave. Cypress, CA 90630 www.focusdx.com
	Direct and indirect susceptibility testing: **INH, RIF, PZA, EMB, SM, rifabutin, ciprofloxacin, capreomycin, amikacin, ethionamide, PAS, cycloserine**	LJ Slants Broth samples Plates if safely packaged		
	Therapeutic drug concentrations: **ciprofloxacin, capreomycin, kanamycin, ethionamide, cycloserine, INH, RIF, PZA, SM, rifabutin, ofloxacin**	Frozen serum (See website for methodologies and sample requirements)		
	Rifampin mutation analysis	Frozen smear-positive respiratory secretions OR pure culture growth		
	AMPLICOR™ PCR on clinical specimens	Frozen clinical specimens (sputum/CSF/ tissue, etc.)		

EMB ethambutol **INH** isoniazid **PAS** para-aminosalicylate **PZA** pyrazinamide **RIF** rifampin **SM** streptomycin

COMMERCIAL LABORATORIES continued

Laboratory	Tests performed	Requirements	Cost	Contact information
National Jewish Medical and Research Center	Smear and primary culture isolation; species ID; nucleic acid amplification of *M. tuberculosis* complex in raw specimens; direct and indirect susceptibility testing; several susceptibility testing methods available; TB and NTM genotyping (fingerprinting)	Clinical specimens LJ Slants Broth samples	For cost, download requisition from website National Jewish will bill CO Medicaid, the patient's credit card or the facility from which the specimen came	**Leonid Heifets MD, PhD, Director** Mycobacteriology Reference Laboratory 303-398-1953 FAX: 303-398-1953 www.njc.org/research/clinical-labs Charles Peloquin, PharmD, Director Infectious Diseases Pharmacokinetics Laboratory (IDPL) 303-398-1427 main: 303-398-1422 FAX: 303-270-2124 peloquinlab@njc.org www.njc.org/research/clinical-labs click on the IDPL link to access information and to download a requisition for therapeutic drug concentrations Customer service: 303-398-1422 1400 Jackson St. Denver, CO 80206
	INH, RIF, PZA, EMB, SM, rifabutin, ciprofloxacin, ofloxacin, levofloxacin, gatifloxacin, moxifloxacin, capreomycin, amikacin kanamycin, ethionamide, cycloserine, linezolid, PAS, and experimental drugs (all)	LJ Slants Broth samples		
	Therapeutic drug concentrations: **All**	Frozen serum		

EMB ethambutol **INH** isoniazid **PAS** para-aminosalicylate **PZA** pyrazinamide **RIF** rifampin **SM** streptomycin

The following websites give details for packaging, labeling, and shipping specimens and cultures:

www.cdc.gov/od/ohs/biosfty/shipdir.htm

www.njc.org/pdf/2005%20shipping%20instructions.doc

www.saftpak.com

Appendix 5: **Direct Method**

Note: Given the rapidity of broth methods, this test is very rarely performed in the United States.

- The clinical specimen (usually acid-fast bacilli [AFB] smear-positive sputum) is digested, decontaminated, and diluted. The processed specimen is plated onto agar containing critical concentrations of anti-tuberculosis drugs and a control containing no drugs.
- Results are interpretable if appropriate growth (at least 50 to 150 colonies, identified as *M. tuberculosis*) is found on control agar (no drug). The number of colonies that grow on each drug-containing agar plate (or quadrant) is reported as a percent of the colonies that grow on the control plate. The isolate is resistant if more than 1% of the number of colonies on control agar grow on a given drug agar plate.
- The direct method takes 3 to 5 days longer than indirect method (from the time of plating).
- The direct method is problematic when specimen contains nontuberculous mycobacteria either in pure or mixed culture. The colonies should be scrutinized for the possibility of growth with nontuberculous mycobacteria.
- Currently, only agar methods are well studied; broth methods should not be used.
- Results from the direct method are usually confirmed using the indirect method, especially if the isolate is found to be drug-resistant.
- The direct method may more accurately represent the patient's population of tuberculosis (TB) bacilli. Plates should be read each week for 3 weeks, giving time for slow-growing resistant colonies to be recognized.
- The direct method may be requested if drug-resistant TB is **strongly** suspected, molecular assays are not available, and the sputum is AFB smear-positive.

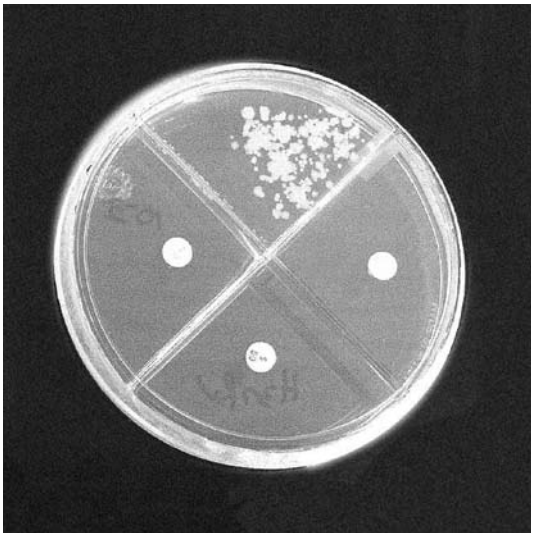


Figure 1. Quad plate – Sputum containing AFB smear-positive organisms is plated onto each of the 4 quadrants. The top quadrant contains no antibiotic and has allowed growth of *M. tuberculosis* colonies. The other 3 quadrants contain antibiotic-containing discs. The antibiotic has diffused into the agar and suppressed growth of the *M. tuberculosis* in the 3 quadrants. This is a pan-susceptible TB isolate.

Appendix 6: **Critical Concentrations**
of Antimycobacterial Agents to Test Against
M. tuberculosis by Broth or Agar Proportion Methods

Antimicrobial Agent	Typical MIC (μg/ml) for susceptible strains	Concentration in serum (μg/ml)	Medium and concentration (μg/ml)				
			7H10 low/high	BACTEC 460TB 12B low/high	MGIT 960 low/high	VersaTREK low/high	MB/BacT ALERT 3D
Primary Agents							
• INH	0.05-0.2	7	0.2/1	0.1/0.4	0.1/0.4	0.1/0.4	1
• RIF	0.5	10	1	2	1	1.0	1
• PZA	20	45	NR*	100	100	300	200
• EMB	1-5	2-5	5/10	2.5/7.5	5	5.0/8.0	2
Secondary Agents							
• SM	8	25-50	2/10	2/6	1/4	8.0	1
• Capreomycin	1-50	30	10	1.25			
• Kanamycin	5	14-29	5	5			
• Cycloserine	5-20	20-40	NR*	NR*			
• Ethionamide	0.6-2.5	2-20	5	1.25			
• PAS	1	7.5	2	4			
Alternative Agents							
• Rifabutin	0.06-8	0.2-0.5	0.5-1	0.5			
• Amikacin	1	16-38	4	1			
• Oflaxacin	0.5-2.5	3-11	2	2			

The critical concentration is the level of drug that inhibits a wild-type TB strain (a strain which has not been exposed to TB drugs), but does not appreciably suppress the growth of a resistant strain.

* NR: no recommendation.

Adapted, by permission, from Inderlied CB, Pfyffer BE. Antibacterial Agents and Susceptibility Test Methods: Susceptibility Test Methods: Mycobacteria. In: Murray PR, Baron EJ, Jorgensen JH, Pfaller MA, Yolden RH, American Society for Microbiology. Manual for Clinical Microbiology. 8th edition. Washington, DC: ASM Press; 2003:1158.

Modified from Francis J. Curry National Tuberculosis Center and California Department of Public Health, 2004: *Drug-Resistant Tuberculosis: A Survival Guide for Clinicians*, [234].

Appendix 7: **Molecular Method**

- Molecular methods are based on detection of specific mutations associated with drug resistance.
- Ideal targets are genes whose mutations account for the vast majority of drug resistance; i.e., *rpoB* for rifampin (RIF) resistance and *pncA* for pyrazinamide (PZA) resistance. Several mutations that cause isoniazid (INH) resistance have been detected; however, 15 to 25% of INH-resistant isolates tested conventionally do not contain known mutations.
- In the laboratory, DNA is released from the mycobacterial cells—either from clinical specimens (if sufficient mycobacteria are present) or from growth on solid medium or in broth.
- Amplified products (amplicons) are detected by:

  DNA sequencing
  Line-probe assays that use PCR and reverse hybridization methods
  Gel analysis (traditional PCR)
  Enzyme-linked immunosorbent assay (ELISA)-based methods
  Fluorescent hybridization with probes or molecular beacons
  Other methods
- Over 96% of resistance to RIF is associated with known mutations within an 81bp region of the *rpoB* gene. Therefore, molecular testing of RIF resistance is highly reliable. Additionally, since RIF monoresistance is rare, detection of RIF resistance is usually diagnostic of MDR-TB.
- A few reference laboratories are routinely using molecular methods to rapidly diagnose drug resistance, and others are studying the practicality of these methods. The methods require specialized instrumentation and expertise, but may become more practical as more applications are found for molecular methods and their use becomes more widespread.
- Line-probe assays are a family of novel DNA strip-based tests that use PCR and reverse hybridization methods for the rapid detection of mutations associated with rifampin and/or rifampin and isoniazid drug resistance. These kits are not currently FDA-approved for use in the United States. Line-probe assays are designed to identify *M. tuberculosis* complex and simultaneously detect mutations associated with drug resistance.
- Advantages of molecular methods include rapid turnaround times and the benefit of knowing the exact location of the point mutation.
- Disadvantages of molecular assays include low sensitivity for some compounds, the potential for false-positive results due to amplicon contamination, and lack of standardization of the assays.

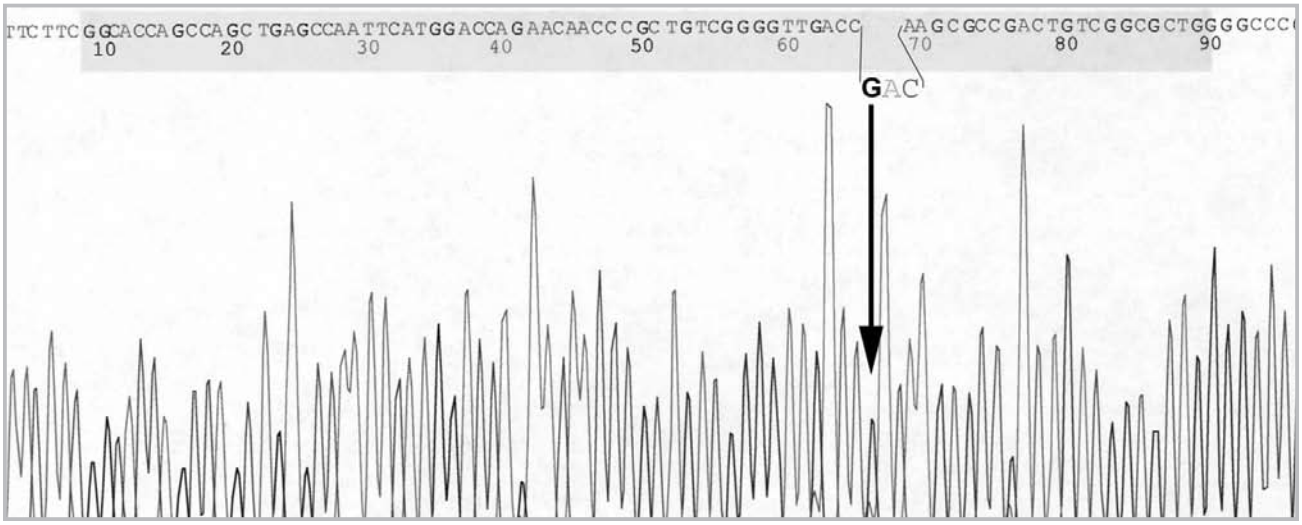


Figure 1. Mutations found in the 81bp of *M. tuberculosis rpoB* gene that are associated with rifampin resistance are located between codons 507 through 533 (highlighted in gray).

This sequence example shows a common mutation seen in rifampin-resistant isolates. Codon 526 (CAC), which encodes amino acid histidine in susceptible isolates, is replaced with amino acid aspartate (GAC, see arrow) in this resistant TB strain.

Appendix 8: **Proportion Method**

- Method of susceptibility testing using agar plates inoculated with either clinical specimen (direct method) or a suspension of mycobacterial growth (indirect method). See Appendix 9, "Indirect Method."
- The proportion method is the gold standard method of drug susceptibility testing in the United States (Middlebrook 7H10 agar medium).
- Anti-tuberculosis drugs are added to the agar media in the form of stock solutions made from reference powders or drug-impregnated discs in order to achieve the critical concentration. Plates are either produced in-house or commercially purchased.
- The isolate is resistant if more than 1% of the number of colonies on the control agar grow on a given drug agar plate.
- Pyrazinamide is difficult to study using solid medium due to the requirements of achieving an acidic environment; therefore, the BACTEC 460TB is considered the gold standard.

Figure 1. Quad plate – Inoculum of *M. tuberculosis* growth from broth has been plated into each of the 4 quadrants with the following results:

Control quadrant:
90 colonies

Isoniazid (INH) quad:
30 colonies

Rifampin (R) quad:
23 colonies

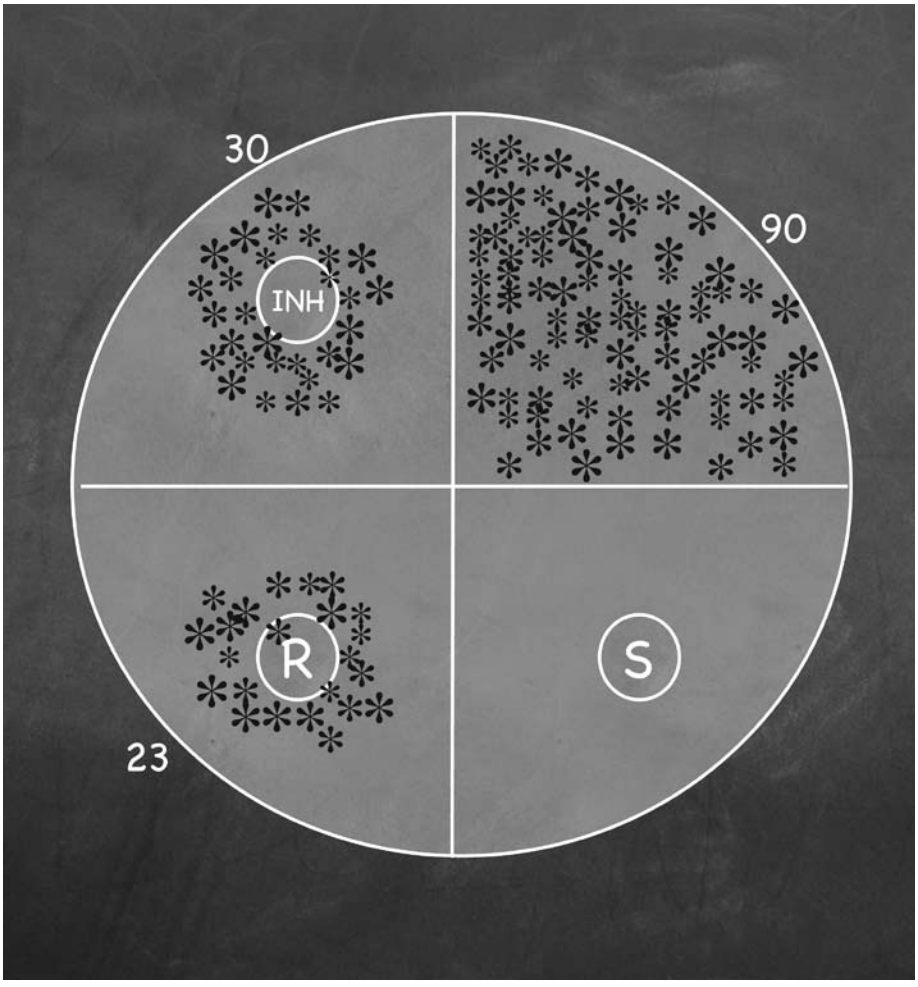
Streptomycin (S) quad:
0 colonies

Isoniazid 30/90 = 33% resistant

Rifampin 23/90 = 25% resistant

Streptomycin 0/90 = susceptible

This is an MDR-TB isolate.



Appendix 9: **Indirect Method**

- The inoculum for indirect susceptibility testing is a suspension of mycobacteria that has already been cultivated on agar or an aliquot from the broth medium, rather than the clinical specimen itself, as for the direct testing.
- Results are interpretable if appropriate growth (at least 50-150 colonies, identified as *M. tuberculosis*) is found on control agar (no drug). The number of colonies that grow on each drug-containing agar plate (or quadrant) is reported as a percent of the colonies that grow on the control plate. The isolate is resistant if more than 1% of number of colonies on control agar grow on a given drug agar plate.
- Several colonies are picked from the solid medium in order to avoid a bias in testing.
- Chocolate plates should be used to ensure that a pure strain is being studied rather than a mixture of different organisms. This is especially important if the source of the inoculum is from a broth system rather than from colonies on a solid medium.
- Egg-based media, such as Löwenstein-Jensen, are not usually used in North America. The preferred agar is Middlebrook 7H10 agar media. If the drug-resistant strain does not grow sufficiently well on this media, 7H11 is sometimes successful (with adjusted critical concentrations of drugs).
- Broth media are used routinely for first-line TB drugs and occasionally for second-line TB drugs.

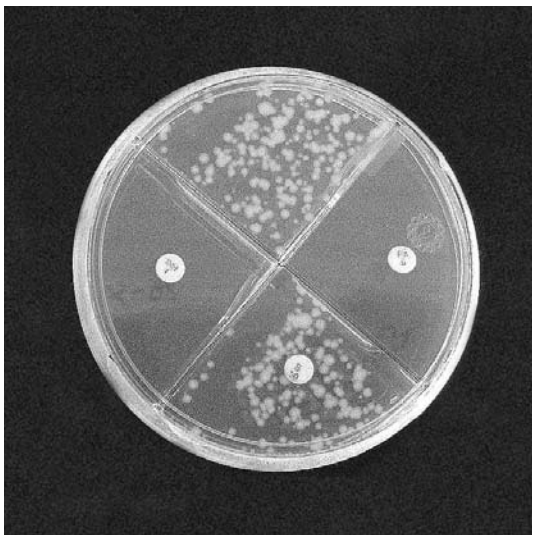


Figure 1. Quad plate – Inoculum of *M. tuberculosis* growth from broth has been plated into each of the 4 quadrants. The organism grows well in the control quadrant (top) and in the quadrant containing streptomycin (diffused into agar from the disc). The other 2 quadrants contain INH and PAS, and the organism has not grown in these quadrants. The isolate is resistant to streptomycin and susceptible to INH and PAS.

Appendix 10: **BACTEC 460TB Method**

This method utilizes a broth system containing ^{14}C-labeled palmitic acid to grow the mycobacteria. If the organism grows in the broth, $^{14}CO_2$ is released into the headspace in the vial and the machine detects the $^{14}CO_2$, indicating growth.

- Drug-containing vials receive 100-fold more inoculum than the drug-free control vials for each strain (corresponding to the 1% resistance rate considered to be clinically significant).
- The method is faster than the proportion method using solid medium, but does not provide an estimate of percentage of resistant bacilli.
- Kits are available for testing the SIRE drugs (streptomycin, isoniazid, rifampin, and ethambutol), and pyrazinamide.
- Second-line drugs can be tested by adding stock solutions from reference powders of individual anti-tuberculosis drugs to the broth vial.
- Resistant strains should be confirmed by the agar proportion method or molecular assays.
- The results are interpreted based on the change in "growth index" in the drug-containing vials compared to the control vial (without drug). If the daily change in the control growth index exceeds that of the drug-containing vial, the isolate is susceptible.

Figure 1. BACTEC bottles containing Middlebrook 7H12 media prior to inoculation.

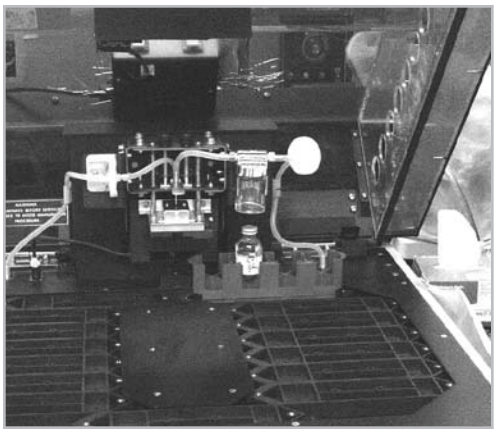


Figure 2. BACTEC machine.

Appendix 11: **Newer Broth Methods**

- Newer broth methods are replacing the radiometric (^{14}C) system (in order to avoid use and disposal of radioactive materials) and, in addition, are fully automated.
- These systems can detect and monitor growth for culture and can also be used to determine susceptibility to isoniazid, rifampin, ethambutol, pyrazinamide, and streptomycin.
- *M. tuberculosis* is grown in vials/tubes of broth containing either the critical concentration of an anti-tuberculosis drug or no drug (control). The growth of the bacteria in the drug-containing bottles is compared to the growth in the control vial/tube.
- The VersaTREK system detects pressure changes due to gas production or consumption due to mycobacterial growth.
- The BACTEC MGIT 960 system (mycobacterial growth indicator tube) uses a fluorescence quenching-based oxygen sensor to detect mycobacterial growth. If mycobacteria are growing in the system, they consume oxygen and fluorescence is increased and detected by the system.
- The MB/BacT ALERT 3D system colorimetrically detects CO_2 production in order to indicate mycobacterial growth.

Figure 1. BACTEC MGIT (mycobacterial growth indicator tube) system – MGIT machine; upper right inset, MGIT tubes; lower right inset, antibiotics solutions for performing susceptibility testing in MGIT.

Appendix 12: **Therapeutic Drug Monitoring**

Therapeutic drug monitoring is routinely used for several circumstances:

- Aminoglycoside/capreomycin serum concentrations in patients with renal impairment
- Cycloserine concentrations in order to minimize risk of CNS toxicity and to safely use optimal dose
- Ethambutol concentrations in patients with significant renal impairment
- Known or suspected malabsorption

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

Most hospital laboratories perform amikacin concentrations. Only a few laboratories perform drug concentrations for other TB drugs (National Jewish Medical Center and Focus Labs performing the most).

Table 1 details the time for blood collection after an injectable drug dose.

Drug name	Blood draw times after completion of IV infusion	Hours after IM dose to "peak"
Amikacin Capreomycin Kanamycin* Streptomycin	1.5 – 2 hours and 6 hours	2 hours

* Kanamycin is determined using a bioassay. **All** other antibiotics must be stopped at least 24 hours prior to sample collection for kanamycin.

To calculate a true peak after an intravenous dose, a level is drawn 90 to 120 minutes and again 6 hours after the infusion is complete. It is important to allow enough time for the dose to be completely distributed before drawing the first level. The exact times of the dose infusion and blood draws must be recorded. The pharmacist can then extrapolate or calculate a peak using a linear regression feature on a computer program or semi-logarithmic graph paper. A trough before the next dose is sometimes necessary for patients with renal failure.

Table 2 details the time for blood collection after an oral drug dose.

Drug name	Hours after oral dose to "peak"	Time after dose for additional concentration if desired *
Azithromycin	2-3 hours	
Ciprofloxacin	2 hours	
Clarithromycin	2-3 hours	
Clofazimine	2-3 hours	
Cycloserine	2-3 hours	6-7 hours
Ethambutol	2-3 hours	6-7 hours
Ethionamide	2 hours	
Isoniazid	1-2 hours	6 hours
Levofloxacin	2 hours	6 hours
Linezolid	2 hours	6 hours
Moxifloxacin	2 hours	
Ofloxacin	2 hours	6 hours
PAS	6 hours	
Pyrazinamide	2 hours	6 hours
Rifabutin	3-4 hours	7 hours
Rifampin	2 hours	6 hours

*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.

Collecting and Processing Samples for Therapeutic Drug Monitoring

One milliliter of serum (about 2 ml of blood) is required per test. It is advisable to provide some excess serum in case there are technical problems.

- The patient should come to clinic with his/her medications.
- No doses of the medication to be tested should have been taken/given since the previously scheduled doses (12 to 24 hours prior).
- Observe the taking or injection of the medications and record the exact time and date.
- Collect the blood by direct venipuncture (timing as described by Tables 1 and 2) and record the exact time of the blood collection.
    - For streptomycin, note if the patient is also receiving ampicillin.
    - Kanamycin is measured using a bioassay. Stop all other antibiotics for at least 24 hours prior to sampling.
- After the blood clots, centrifuge the samples, harvest the serum into labeled polypropylene (or polyethylene) tubes (allow room for expansion of sample inside tube), label, and freeze (-70°C is preferable, if available).
- Label the tubes with the patient's name, date and time of collection, and the drug(s) to be assayed.
- The samples can be stored frozen until ready for shipping.
- Place the samples in a ziplock plastic bag and pack upright in a Styrofoam box (about 10 cubic inches in size) with 3 pounds of dry ice. Fill the empty air space with paper or Styrofoam "peanuts."
- Complete the requisition and provide billing information. Place the requisition and billing page in a plastic bag and tape to the outside of the lid. The foam box is placed inside a cardboard box to prevent damage.
- Ship samples Monday through Wednesday by an overnight delivery service that accepts dry ice packages.

Information excerpted from National Jewish Medical Center website (www.njc.org) and literature.

Appendix 13: **Multicultural Resources**

General Cultural Information Sites

Cross Cultural Health Care Program
www.xculture.org/

Cultural Clues
http://depts.washington.edu/pfes/cultureclues.html

EthnoMed
http://ethnomed.org/

National Center for Cultural Competence (NCCC)
www11.georgetown.edu/research/gucchd/nccc/index.html

University of Michigan Program for Multicultural Health: Cultural Competency Division
www.med.umich.edu/multicultural/ccp/

Translated Patient Education TB Resources

Canadian Lung Association
www.lung.ca/tb/notenglish/

EthnoMed
http://ethnomed.org/ethnomed/patient_ed/index.html#tuberculosis

Minnesota Department of Health
www.health.state.mn.us/divs/idepc/diseases/tb/brochures.html

National Prevention Information Network (NPIN) Educational Materials Database
www.cdcnpin.org/scripts/search/matlSearch.aspx

New South Wales Health
www.mhcs.health.nsw.gov.au

TB Education and Training Resources
www.findtbresources.org/scripts/index.cfm

General Interpreter Resources

CyraCom (customer service number: 800-481-3293)
www.cyracom.net

Appendix 14: **Frequently Asked Questions (FAQs)**

General

1. What is the optimal drug regimen for multidrug-resistant tuberculosis (MDR-TB)?

See Chapter 3, "Treatment."

The optimal drug regimen depends on the susceptibility pattern of the patient's tuberculosis (TB) isolate, the patient's previous TB treatment regimen, underlying health conditions, and other medications the patient currently takes. The patient should generally be initially treated with 4 to 6 drugs to which the isolate is susceptible. Depending on the susceptibility pattern of the isolate, the regimen should include all available first-line drugs, a fluoroquinolone, an aminoglycoside, and appropriate second-line oral drugs.

In general, avoid:

- Drugs the patient has taken previously (associated with a failing regimen)
- Drugs that cause that individual undue toxicity
- Drugs that cause unnecessary drug interactions

2. How many drugs are necessary?

See Chapter 3, "Treatment."

The patient needs to complete therapy with at least 3 drugs to which the isolate is susceptible. In practice, this requires that the patient be initially treated with 4 to 6 drugs that he/she has not previously received. Using this strategy, the injectable drugs can be discontinued after a number of months if appropriate and other drugs that were very poorly tolerated can be trimmed away.

3. How long post–culture conversion should a patient be treated—18 months or 24 months?

See Chapter 3, "Treatment."

There are no randomized controlled studies that have determined optimal length of MDR-TB treatment. The American Thoracic Society (ATS) recommends 18 to 24 months of treatment for MDR-TB. Many experts prefer to choose the duration of therapy based on the time from culture conversion (sputa are consistently culture-negative). In general, the longer regimens are used for patients with more extensive disease and more extensive drug resistance pattern. Shorter regimens might be used for patients with more localized disease who responded promptly to therapy and whose resistance pattern allowed use of more bactericidal drugs in the regimen.

4. The patient's isolate is resistant to all first-line drugs and most second-line drugs. What options exist for treatment?

See Chapter 3, "Treatment."

Use as many/all drugs to which the organism is susceptible. This may include "third-line agents" such as linezolid, gamma-interferon, and β-lactam drugs (imipenem, amoxicillin/clavulanate). Consider use of higher doses of individual drugs (as tolerated by the patient and using therapeutic drug monitoring as appropriate). Consider prolonged use of an injectable drug if tolerated by the patient. Consider surgical intervention if the patient is an appropriate candidate.

5. Can a patient take split doses by self-administered therapy (SAT)?

See Chapter 8, "Case Management."

Some drugs (cycloserine, ethionamide, and para-aminosalicylate [PAS] in particular) may not be tolerated in once-daily doses and must be given more than once a day (split doses). Ideally, all drug-resistant TB treatment will be given fully by directly observed therapy (DOT), even split doses. Patients who have difficulty taking their medications as once-daily doses (amenable to DOT) sometimes are well served by being hospitalized during the initial phase of treatment until they tolerate the regimen well enough at home.

6. Can weekend doses be given by self-administered therapy (SAT)?

See Chapter 8, "Case Management."

Ideally, all drug-resistant TB treatment will be given fully by DOT. Again, hospitalization in the early phase of treatment is sometimes necessary. After documented clinical and microbiologic improvement, some jurisdictions will treat patients with 5-days-per-week therapy by DOT or give SAT on the weekends when local resources do not permit monitored weekend administration.

Use of Specific Drugs

FLUOROQUINOLONES

1. Can I use fluoroquinolones in children? For TB disease? For contacts to MDR-TB?

See Chapter 5, "Special Situations – Pediatrics."

Fluoroquinolones are among the most important agents in MDR-TB treatment when the isolate is susceptible. Most experts feel that fluoroquinolones are indicated in children exposed to or infected with MDR-TB resistant to other first-line drugs.

Fluoroquinolones have been avoided in children because puppy models have suffered irreversible arthropathy. Irreversible joint destruction has not been seen in children who have received fluoroquinolones. Ciprofloxacin has been licensed for use in older children for treatment of complicated urinary tract infection. Levofloxacin and gatifloxacin have been studied for use in children. However, few children have received the very long courses of fluoroquinolones required for TB treatment. If a fluoroquinolone drug is very important for the treatment of an individual child, it can be employed after discussing risks and benefits with the parents and in consultation with a pediatric TB expert. The parents have to be aware of the potential risks and report to the provider and public health workers any signs or symptoms of joint problems (decreased mobility, pain, decreased range of motion, joint swelling, etc.). Additionally, all providers involved in the case should be actively screening for these processes. Finally, many experts avoid these drugs in children too young to show signs and symptoms of musculoskeletal complaints (children too young to sit up, crawl, etc.).

2. What is the optimal dose of levofloxacin for TB disease? For latent tuberculosis infection (LTBI)?

See Chapter 3, "Treatment."

A common strategy for levofloxacin is to initiate therapy at 500 mg daily. If tolerated, the dose can be elevated to 750 mg or even 1000 mg daily (sometimes in divided doses). If the patient weighs more than 100 pounds, a dose of at least 750 mg should be attempted. Fluoroquinolones should not be dosed in close proximity to milk-based products, antacids, or other divalent cations. Currently studied doses of the newer fluoroquinolones (gatifloxacin and moxifloxacin) are limited. At this time, doses should be limited to 400 mg daily to avoid the possibility of more drug-related toxicities (unless serum concentrations are monitored). In the case of patients who are too sick to take enteral doses, the fluoroquinolones are available in IV forms.

AMINOGLYCOSIDES

1. What is the dose when one changes to 2- or 3-times weekly?

See Chapter 4, "Medication Fact Sheets."

When aminoglycoside drugs are administered 2- or 3-times-weekly, the drugs are usually administered at the same dose as daily therapy for that individual (customized based on age, renal function, and sometimes drug concentrations). Some experts use higher doses and monitor concentrations closely.

2. What is the target blood concentration with intermittent dosing?

See Chapter 4, "Medication Fact Sheets."

The target blood concentration depends on dose and planned duration of use.

3. How long do I need to use an aminoglycoside?

See Chapter 3, "Treatment."

Expert opinions vary, as there are no firm data to support a specific length of treatment. At a minimum, use the aminoglycosides for at least 6 months (longer if extensive disease, delayed culture conversion, or limited alternative medications). Some experts continue the aminoglycoside or capreomycin as long as absolutely possible (barring limiting side effects) and use doses to achieve somewhat lower peak concentrations to avoid toxicity.

4. What aminoglycoside is most frequently used?

See Chapter 4, "Medication Fact Sheets."

The injectable drug chosen depends on several factors: susceptibility of the isolate, cost, route of administration, availability of therapeutic drug monitoring tests, and side effects. Many drug-resistant isolates are resistant to streptomycin; amikacin and kanamycin have cross-reactivity and therefore nearly identical resistance. Kanamycin and streptomycin are least expensive; amikacin concentrations are most readily available; streptomycin is less painful if used intramuscularly, but is associated with more vestibular toxicity.

5. A patient on aminoglycoside complains of slight tinnitus. How is this side effect monitored?

See Chapter 7, "Adverse Reactions."

Patients receiving injectable agents should be monitored with hearing tests as well as vestibular monitoring. Patients who suffer tinnitus should be evaluated for the possibility that something other than the injectable agent is causing the problem. Sometimes patients who have isolated tinnitus can be monitored prospectively without change. If change is required, changing to intermittent therapy or lowering the dose of the injectable drug (while remaining in the appropriate therapeutic range) can sometimes lessen the symptoms. If the patient suffers unsteadiness or other vestibular signs or symptoms, the drug should be stopped. Vestibular toxicity is usually irreversible and is generally a contraindication to further use of these drugs.

Use of BCG

1. Is bacille Calmette-Guérin (BCG) indicated for a newborn exposed to a mother with a highly resistant strain of MDR-TB?

See Chapter 5, "Special Situations – Pregnancy."

BCG should be administered to infants and young children who cannot be separated from drug-resistant TB cases and for whom no practical prophylactic regimen is available. There are usually a number of other options before considering BCG use.

Side Effects

1. What do I do when a patient is nauseated but intolerant to compazine?

See Chapter 7, "Adverse Reactions."

Other drug options include phenergen, metoclopramide, lorazepam, and ondansetron. Other options include dosing the drug with a snack, giving at a time of day away from other drugs, splitting the dose, etc.

2. A patient on cycloserine had a high depression score this week. What does this mean?

See Chapter 7, "Adverse Reactions."

Extreme care should be exercised with patients receiving cycloserine and suffering mental health symptoms. Monitoring for suicidal ideation is crucial, and the patient should be evaluated for the need for an antidepressant medication. A cycloserine therapeutic drug concentration should be collected and the dose held until toxicity can be ruled out as a cause.

3. What should be done for a teenage patient on fluoroquinolone with bilateral wrist pain?

See Chapter 7, "Adverse Reactions."

For achiness without significant tendon inflammation, therapy can be continued with use of analgesics and rest. If significant tendon inflammation is present, the fluoroquinolone should be held and measures to reduce inflammation should be undertaken. The patient should not undertake unusual exertion to the area.

Infection Control

1. Can I return a case patient to the home setting if other household members (non-immunocompromised) are tuberculin skin test (TST)-negative after several months of exposure to case?

See Chapter 8, "Case Management."

MDR-TB patients should be considered potentially infectious until they have 3 consecutive culture-negative sputum specimens. Decisions about management at home, and return to school and work, should be undertaken with local health officers and drug-resistant TB experts after considering many factors regarding the patient's disease, treatment, and the household situation.

2. A patient no longer has a productive cough. Are monthly induced sputa necessary?

See Chapter 6, "Monitoring Patients."

National guidelines suggest monthly sputum monitoring. Some experts collect 2 monthly sputa 8 to 24 hours apart to lessen the likelihood of false-negative results. If necessary, sputum induction is indicated both during and after treatment. MDR-TB patients have a higher risk of relapse and delayed sputum sterilization. Persistently positive cultures may be an early indicator for increasing drug resistance and may assist in determining length of treatment.

Payment

See Chapter 8, "Case Management."

1. How can I pay for expensive drugs when a patient is uninsured?

Social workers and financial counselors should work with the family to investigate any third-party payer possible. If the patient is uninsurable, patient assistance programs (PAPs) sponsored by pharmaceutical companies can be explored. Some states and large jurisdictions have programs available to pay for drugs for all TB patients.

2. How can I pay for hospitalization when a patient is uninsured?

Social workers and financial counselors should work with the family to investigate any third-party payer possible. Some states and large jurisdictions have programs available to pay for TB care or have specific TB inpatient facilities. Barring these options, the local "safety net" hospital that is funded to provide indigent care will have to admit the patient.

3. Is an IV injectable agent more costly than IM preparation?

IV therapy is more expensive because, in addition to drug costs, maintenance of the IV requires a home health agency, etc.

Press Release

1. We are doing a highly visible contact investigation at a school. Do we need a press release?

A press release can be very helpful to update the media on results of testing and to educate the public. Some jurisdictions manage the contact investigation successfully without involving the media.

2. Should we reveal in the press release that exposure was to an MDR strain? (If we did, it might create public angst and increase our workload.)

If the media is involved, it is better to be upfront about the nature of the isolate, but also state that medications are available for LTBI treatment. If this is not disclosed upfront, criticism is likely to follow.

Laboratory

1. When do I draw serum drug concentrations?

See Chapter 6, "Monitoring Patients," and Appendix 12, "Therapeutic Drug Monitoring."

Draw cycloserine concentrations before increasing the dose from the initial regimen; draw aminoglycoside concentrations if appropriate after approximately 2 weeks of therapy.

2. To which laboratory do I send samples for serum drug concentrations?

See Appendix 4, "Laboratory Resources."

In many cases, the patient's insurance will mandate which lab will perform the therapeutic drug concentrations. Most large hospital labs will perform amikacin concentrations, and only a few reference labs perform many of the other TB drug concentrations.

3. Are serum drug concentrations (therapeutic drug monitoring [TDM]) useful? Necessary?

See Chapter 6, "Monitoring Patients."

Despite the fact that there are few data proving improved outcomes with TDM, many drug-resistant TB experts monitor drug concentrations routinely. In several circumstances, therapeutic drug monitoring is common: aminoglycoside concentrations in patients who have known renal dysfunction; cycloserine concentrations can help the provider predict and minimize central nervous system (CNS) adverse reactions and prevent seizure activity; and ethambutol (EMB) concentrations may be useful for patients with reduced renal function. Other therapeutic drug monitoring is used depending on the patient's other health issues, concomitant medications, number of drugs in the regimen, preference of the provider, etc.

4. How do I interpret discordant susceptibility results?

See Chapter 2, "Diagnosis."

Discuss results with the laboratorian, repeat the susceptibilities on a second sample, and send a sample to a reference laboratory for confirmation.

5. How do I clarify to my lab that we need a cycloserine blood serum concentration, not a cyclosporine?

Talk to the lab in advance, type or write the request very clearly, and if necessary, write in parentheses: (NOT CYCLOSPORINE). Note: Very few laboratories in the country perform cycloserine concentrations, while most large hospital labs perform cyclosporine concentrations. This may help you discuss this "send-out" test with your lab.

6. Molecular methods: How quick and accurate are the results?

As an example, the "molecular beacon" assay, performed by the California Department of Public Health Microbial Disease Laboratory, uses real-time polymerase chain reaction (real-time PCR) technology with molecular probes for rapid detection of mutations associated with isoniazid (INH) or rifampin (RIF) resistance. Acceptable specimen types are smear-positive (at least 1+) concentrated sediments or growth from solid or broth media. The average turnaround time for results is 1 to 3 days of specimen receipt. The sensitivity of the test is 83% for INH and 97% for RIF. Discuss the results with the laboratory and a drug-resistant TB expert before implementing management plans based on the results.

7. How do I ship/package specimens to send to National Jewish since it's out of state?

See Appendix 4, "Laboratory Resources," www.njc.org and www.saftpak.com.

8. What type of courier do I use to send specimens out of state?

See Appendix 4, "Laboratory Resources," www.njc.org/research/clinical-labs and www.saftpak.com.

9. When sending specimens to the State of California Microbial Diseases Laboratory (MDL) for isolate identification, are susceptibilities automatically performed or is an additional request necessary?

Specific requests are necessary. Susceptibility testing is not automatically performed. Of note: at the time of printing, MDL is performing first-line and second-line drug susceptibility testing by MGIT only, and the second-line drug panel includes levofloxacin, amikacin, capreomycin, and ethionamide. Check with the laboratory (contact information in Appendix 4, "Laboratory Resources") for current testing capabilities.

When dealing with any laboratory performing TB culture, identification, and susceptibilities, you should determine whether susceptibilities will automatically be performed and under which circumstances second-line susceptibilities will be performed. Many commercial laboratories have contracts defining these details for individual clients and third-party payers. Lengthy delays will occur if these details are not defined early on. Sometimes the physician who ordered the initial culture will need to order first- and second-line susceptibility tests.

10. Why does pyrazinamide (PZA) susceptibility testing take longer? Is there a quicker method?

PZA susceptibilities are technically difficult in agar because of the low pH required. Many laboratories do not perform them at all. Testing PZA with the BACTEC TB 460 system is considered the gold standard. However, many laboratories have replaced BACTEC TB 460 with the BACTEC MGIT 960 non-radiometric system. The average turnaround time for PZA testing with the BACTEC MGIT 960 system is 7 to 10 days.

Treatment and Evaluation of Contacts

1. How do I treat contacts?

See Chapter 10, "Managing Contacts."

Each contact is managed on an individual basis. Determinants include extent and intimacy of contact with the source case, susceptibility pattern of the source case isolate, evidence of transmission from the source case, prior TST results, risks for progression to TB, etc. If treatment of drug-resistant LTBI is desired, the regimen is generally based on the susceptibility pattern of the source case.

2. For contacts to an MDR case with positive TST and who refuse treatment, how often should a symptom review or chest radiograph be done?

See Chapter 10, "Managing Contacts."

Untreated contacts should be monitored every 3 to 6 months for at least 2 years.

3. Can a single drug be used to treat MDR-TB infection?

See Chapter 10, "Managing Contacts."

Lower-risk contacts are sometimes treated with fluoroquinolone monotherapy based on *in vitro* drug activity data. No controlled data are available regarding treatment of drug-resistant TB contacts, and current national guidelines recommend 2-drug MDR-LTBI treatment.

4. When should LTBI treatment with levofloxacin/moxifloxacin be discontinued for ambiguous side effects?

See Chapter 7, "Adverse Reactions."

Every effort should be made to safely continue the patient on therapy, including use of rest and analgesics. Significant inflammation of the tendon should be treated with at least temporary cessation of the fluoroquinolone.

5. Can moxifloxacin be used to treat MDR-LTBI?

While programs have less experience with moxifloxacin use, it has excellent *in vitro* activity against many drug-resistant TB strains and has been used in some patients with good success.

Appendix 15: **Case Examples**

CASE EXAMPLE 1

Robert is a 53-year-old Vietnam veteran who is a musician and living in a single-room occupancy hotel in a tough part of town.

11/18/05

Robert is admitted to his local Veterans Administration (VA) hospital with cough and hemoptysis. A chest radiograph shows extensive infiltrates in the right upper lobe, left upper and lower lobes, and cavities in both apices. Acid-fact bacilli (AFB) sputum smears are 4+ positive, and he is started on a regimen of isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB). He slowly begins to clinically improve. He is discharged after 2 weeks to ongoing care through the local health department.

This is an older, American-born man with no previous history of tuberculosis (TB) treatment. A 4-drug regimen such as the one prescribed for him would be a standard treatment.

1/15/06

Because the VA sends all specimens to a central laboratory for AFB cultures, there was a significant delay before the health department received the results of drug susceptibility testing. On 1/15/06, the report arrives and shows that the isolate is resistant to INH, streptomycin (SM), and EMB, and susceptible to RIF and PZA. Two new drugs, capreomycin and moxifloxacin are begun, and INH and EMB are stopped. Additional sputum is collected and sent for smear, culture, and repeat susceptibility testing. The sputum AFB smear is still positive.

Robert had been effectively on RIF and PZA alone for about 2 months. PZA is not considered a good companion drug for RIF, as it does not prevent the emergence of acquired drug resistance. At this point, there was a reasonable chance that resistance to RIF and/or PZA may have developed, especially in a patient with a large bacillary load (cavitary disease and strongly smear positive). Two drugs are not adequate for multidrug-resistant (MDR)TB treatment, and at least 1 additional drug should have been added at this time. Appropriately, repeat susceptibility testing was ordered.

3/4/06

Repeat susceptibility testing show that the isolate is still PZA-susceptible, but that it has now acquired RIF resistance. Robert now has MDR-TB. Second-line susceptibility testing shows sensitivity to ethionamide, capreomycin, and levofloxacin, but resistance to kanamycin. Sputum smears convert to negative by early March, and Robert clinically improves. RIF is discontinued and capreomycin, PZA, and moxifloxacin are continued.

A 3–drug regimen is not optimal for MDR-TB; 4 to 6 drugs are recommended. Because of the slow growth characteristics of M. tuberculosis*, there is a significant delay between obtaining a specimen and finding out the results of the culture. The treating providers believed that the sputum cultures were likely to be negative given the smear-negative results.*

6/8/06

Of 6 sputum specimens obtained between 3/4/06 and 6/8/06, 2 are culture-positive. Second-line susceptibility testing done on 1 of these specimens now shows resistance to levofloxacin. Robert is now diagnosed with extremely drug-resistant (XDR) TB.

The regimen should have been strengthened in March, pending the results of cultures as well as smears. Robert was still culture-positive, and 3 drugs were not enough to prevent additional resistance from developing.

6/18/06

A full evaluation is now repeated with 3 sputum examinations and a chest radiograph. The chest radiograph is improved, but still shows a residual left apical cavity and right apical fibrosis. A follow-up chest CT confirms that the principle site of disease activity is the left apex. Surgery is discussed with Robert, but he adamantly refuses to consider it. A new regimen of linezolid, amikacin, ethionamide, cycloserine, and para-aminosalicylate (PAS) is now begun.

This is a classic situation in which resectional surgery should be considered. Robert has XDR-TB and a residual cavity, which makes the likelihood of treatment failure or relapse much higher. He has predominantly unilateral disease, which increases the potential benefit of surgery. Regardless, he needs the strongest regimen still available to him, and the use of linezolid, which has good in vitro activity against M. tuberculosis *but substantial potential for toxicity, is warranted. Ethionamide, cycloserine, and PAS have overlapping gastrointestinal (GI) toxicities, but there are few other options for this patient.*

12/18/06

Robert is unable to tolerate cycloserine, complaining of severe depression and mood swings, even at relatively low serum concentrations, and it is stopped. The 2 sputa collected each month are now smear- and culture-negative since mid-July 2006. The serum creatinine increases from 1.4 to 1.8 mg/dli. His amikacin, which had been decreased to 3 times a week in October, is now decreased to twice weekly.

Cycloserine has significant central nervous system (CNS) effects and can cause depression and even delusional states. It has been associated with suicide. The drug was appropriately stopped. Because of the Robert's extensive resistance, the goal is to continue the injectable agent for 12 months post-culture, if at all possible, so decreasing the frequency to twice weekly is reasonable..

7/18/07

Robert is now 12 months post-culture conversion and is doing well. The amikacin is stopped and a further 12 months of the remaining oral drugs are planned, to complete 24 months total treatment post culture conversion.

Lessons Learned

- If there is a possibility that MDR-TB has developed, a patient should have a minimum regimen of 3 new drugs, planning on a total of between 4 to 6 drugs to which the isolate is likely to be susceptible. PZA is a poor "companion" drug to prevent the emergence of acquired drug resistance in a functional 2-drug regimen.
- Surgery should be considered if there is extensive resistance, residual cavities, and predominantly unilateral disease. In the California experience, only about half of XDR-TB patients have been cured. Surgery may improve those odds if the patient is a good candidate.
- Once the fluoroquinolones are lost because of resistance, therapy becomes more difficult. Linezolid, despite its cost and potential toxicity, becomes an important mainstay of treatment. Patients must be carefully monitored for bone marrow suppression and peripheral neuropathy.
- Cycloserine has been associated with suicide and severe depression as well as delusional states. Monitoring a patient's mental status is crucial. Vitamin B6 (pyridoxine) is used to prevent seizures, but it does not appear to protect against mood disturbances.
- In the treatment of XDR-TB, if an isolate shows susceptibility to any injectable agent, it should be included in the regimen and continued for 12 months post-culture conversion if at all possible.

CASE EXAMPLE 2

Olga, a 41-year-old female from the Ukraine, is experiencing her second episode of TB.

1986

Olga was first diagnosed with TB in the Ukraine and treated with INH, RIF, and EMB for 6 months and SM daily for 6 to 8 months. Olga was hospitalized during her treatment and claims she was very adherent. After her discharge, she took INH for 2 additional years for "prophylaxis." Drug susceptibilities of this episode are unknown.

What else would you like to know about this episode?

- *Does she have any written documentation or copies of radiographs?*
- *Was she hospitalized the entire time (i.e., all doses observed)?*
- *Were there any interruptions in any of the medications due to drug supply or tolerance?*
- *How extensive was her disease and what kind of clinical and radiographic improvement did she have?*
- *Why did she receive 2 additional years of INH? Had her radiograph not improved; did she still have significant symptoms?*

1994

Olga arrives in the U.S.

3/01

Olga develops a cough, intermittent fever/night sweats, scant blood-tinged yellow sputum, and shortness of breath.

4/14/01

Olga presents to the TB clinic with those symptoms and opacification of the left lung with an air-fluid level. On initial exam, she is a thin, well-appearing female with decreased breath sounds at the left base and bronchial breath sounds at the left apex.

4/17/01

Treatment is started with INH, RIF, PZA, EMB, levofloxacin, and capreomycin. Four out of four sputa return culture-positive for *M. tuberculosis*, with 2 out of 4 smear-positive.

Because she does not have documentation of completely observed therapy and a previously susceptible isolate, Olga is treated with an empiric "expanded" regimen including 3 drugs that she had not previously received.

5/19/01

BACTEC susceptibilities show resistance to all first-line agents, including SM.

6/16/01

Conventional solid agar susceptibilities show borderline resistance to EMB and SM, and full resistance to INH, RIF, and PZA. Second-line drug susceptibilities show additional resistance to capreomycin and ethionamide but susceptibility to amikacin, clarithromycin, linezolid, clofazimine, and levofloxacin.

6/22/01 A 5-French percutaneously-inserted central catheter is placed for IV imipenem and amikacin.

Because of the extent of her disease and extended resistance pattern, Olga receives 7 drugs to which the isolate is susceptible. Unfortunately, 2 of the drugs are "third-line" drugs with limited track records of clinical efficacy in the treatment of MDR-TB.

Olga's revised regimen is as follows: (weight ~110 lbs/50 kg)

Levofloxacin 750 mg qd
Cycloserine 500 mg qd
PAS granules 4 grams bid
Imipenem 1 gram IV bid
Amikacin 750 mg qd
Clarithromycin 500 mg bid
Clofazimine 100 mg qd

Clinically, the patient is doing remarkably well despite the weaknesses of her initial regimen; sputum culture conversion occurs within a month of treatment initiation.

Olga is tolerating a dose of levofloxacin that is common in treatment of MDR-TB (750 mg daily). Some patients will even tolerate 1000 mg per day.

7/01 Negative cultures (final results) are obtained. Monthly sputum smears and cultures are negative. Olga's cough and symptoms have resolved, and from her appearance, one would never guess she has a destroyed left lung and MDR-TB.

A toxic cycloserine level of 40 mg/ml is measured on June 16. A repeat level (29.1 mg/ml) is drawn on July 1 and found to be within therapeutic range of 20 to 35 mg/ml. Olga has not shown any signs of emotional or mental instability.

9/3/01 Screening audiology exam shows significant hearing loss in the right ear compared to baseline.

Many patients experience hearing loss on long-term aminoglycosides. Olga's loss is unilateral and not yet noticeable to her. Since she had already received more than 2 months of daily amikacin, her providers change her to 3 times weekly amikacin and are able to stabilize her hearing loss.

Follow-up chest radiograph shows minimal change. Given Olga's destroyed left lung, she is referred to National Jewish Hospital for surgical and treatment evaluation to improve the chance of a lasting cure.

Contact investigation: Olga has been unemployed for 2 years. She is married and a mother of 2 children (12 and 7 years old). Her husband had a history of a positive tuberculin skin test (TST) prior to meeting the patient. Her older daughter was born in the Ukraine and has a history of bacille Calmette-Guérin (BCG) vaccination and positive TST (11 mm) in 1994. Olga's younger son remains TST negative. Both children are healthy, asymptomatic, and have had recent chest radiographs that are normal. There is no evidence of household transmission from either TB episode to date.

continued

Lessons Learned

- Drug-resistant TB should be suspected in patients from countries with high incidence of drug resistance.
- MDR-TB patients with little or no improvement in chest radiograph after completing treatment are at high risk for reactivation.
- Patients with risk for harboring a drug-resistant TB isolate (incomplete documentation of prior susceptibilities, treatment, and response to treatment) should be considered for an empiric expanded regimen with at least 3 drugs that the patient has not previously received. An aminoglycoside or injectable drug other than SM should be included in the regimen.
- Careful monitoring for toxicities can limit their impact on the viability of the regimen and prevent serious adverse events for the patient.
- Surgical intervention is sometimes considered for patients with localized disease, especially those with extensive resistance patterns or disease that is unlikely to be cured because of significant lung destruction.

CASE EXAMPLE 3

Eva is a 25-year-old Peruvian woman who emigrated to the U.S. to join her American husband. She is healthy and has no symptoms of TB.

6/4/86

Eva has a TST placed for pre-employment screening before employment in a hospital. The TST results in 20 mm induration, and chest radiograph shows right-sided pleural fluid in the right base, which layers on decubitus views. The radiographs show no infiltrates or adenopathy. The pleural fluid is aspirated and pathology shows that the fluid is an effusion only. No malignant cells are seen and cultures grow no bacteria, AFB, or fungus.

TB can cause a pleural effusion due to hypersensitivity reaction to a pleural-based TB lesion. In this case, a pleural biopsy is required to see the granulomatous changes and to grow the AFB. Pleural fluid grows M. tuberculosis *in the event of a pleural-based lesion eroding into the pleural space and causing an empyema with purulent pleural fluid. The diagnosis of pleural TB is often missed because of the failure to obtain a pleural biopsy. In addition, sputum culture can be helpful and is often forgotten when focusing on the effusion. Pulmonary disease may be masked by an effusion or be too subtle to be seen on the radiograph.*

7/30/86

When the AFB cultures are negative at 6 weeks, the employee health provider at Eva's hospital concludes that she has latent tuberculosis infection (LTBI) and treats her with INH.

Monotherapy with INH should never be initiated until the possibility of active TB is ruled out. This practice promotes the development of resistance.

10/20/86

Eva experiences fever and some shortness of breath, which she attributes to a viral process.

12/15/86

Eva reports the symptoms to the employee health provider when she can no longer perform her duties in the hospital. Her provider obtains a chest radiograph that shows enlargement of the pleural fluid and development of extensive infiltrates.

Patients being treated with INH for LTBI should be screened monthly for toxicity, adherence to therapy, and ***symptoms of active TB****. Eva's symptoms of active TB should have been uncovered during active screening.*

12/20/86

Eva's provider concludes that she has active TB and adds RIF and PZA to her regimen. No sputum is collected.

Extensive contact investigation is performed in the hospital and several co-workers have documented skin test conversion. Because Eva does not have direct patient care responsibilities and because transmission is apparently limited, further contact investigation is not performed.

CASE EXAMPLE 3 continued

2/26/87 After initial clinical improvement, Eva reports clinical worsening. Repeat chest radiograph shows continued worsening. Eva's provider calls the county TB controller for advice. The TB controller is quite agitated about the fact that the case was not reported when Eva was considered a TB suspect, and a pleural biopsy and sputum were not obtained for culture and susceptibility testing.

Pulmonary and extrapulmonary TB are reportable diseases in all 50 states. TB should be reported within 1 working day of clinical suspicion of the disease. Reporting should not be delayed while providers are waiting for smear and culture results. Specimens for smear and cultures should be obtained from all practical sources.

3/1/87 Sputum is collected and is smear-positive and eventually grows MDR-TB (resistant to INH and RIF).

Eva should have been presumed to have INH-resistant TB when her disease blossomed on INH alone. A TB expert, who would have treated her with 4-drug therapy, should have been involved. INH-resistant TB is treated with at least RIF, PZA, and EMB, as PZA alone does not "protect" the rifampin from development of resistance.

Lessons Learned

- Pleural TB requires a pleural biopsy for histologic and culture diagnosis unless **purulent** fluid is drained by thoracentesis.
- Monotherapy with INH should not be initiated until active TB is ruled out.
- Individuals inexperienced in TB care should refer the patient to an experienced provider **and** all providers should notify the public health department within 1 working day if they are treating a patient that they suspect has TB.
- Cultures should be collected from all practical sites.
- When INH resistance is considered, initiate **at least** RIF, PZA, and EMB.

CASE EXAMPLE 4

Sam is a 29-year-old injection drug user serving time in U.S. federal prison.

5/10/99 Sam converts his TST during an incarceration at a county jail. His chest radiograph is normal and he has no symptoms of active TB. He is diagnosed as having LTBI and completes 9 months of INH by directly observed therapy (DOT) at another facility.

6/30/01 Sam complains of an increasing cough that is not improved by antibiotics. The possibility of TB is entertained, but Sam relays to the providers that he has already received 9 months of INH.

While INH treatment for LTBI reduces the risk of progression to active TB for susceptible isolates by 85% to 90%, it has no impact on high-level INH resistance. Additionally, some patients who report prior completion of LTBI in fact have not been completely adherent; other patients have been reinfected by another strain. Patients with signs and symptoms of TB should be evaluated by chest radiography and sputum collection if indicated.

10/1/01 Sam's cough is treated for several months as reactive airways disease and on his third visit to the clinic he begins to cough up blood. The prison nurse calls for records regarding Sam's prior TB treatment and 1 month later, receives information that: 1) Sam did receive a full course of INH; and 2) after Sam's release from the first jail, an MDR-TB case and a number of conversions attributable to that case were identified. Investigations show that Sam and the MDR-TB case had been housed in areas of "shared air" and that the source case was symptomatic in the months before Sam converted his skin test.

11/3/01 Sputum is collected, the local health department is notified of the case, and Sam is treated with an expanded regimen based on the 1999 source case susceptibilities (PZA, amikacin, levofloxacin, ethionamide, and cycloserine).

*If the epidemiologic link between Sam and the MDR case had not been strong, an empiric regimen using **first-line** drugs and at least 3 drugs to which the suspected source case was susceptible could have been employed. This allows a strong regimen in case this is a pan-susceptible isolate or an MDR isolate.*

11/20/01 Sam is transferred to the county hospital for isolation and is later diagnosed with TB resistant to INH, RIF, EMB, and SM.

Comparison of drug susceptibility patterns can assist in linking cases epidemiologically. Alternatively, genotyping methods can be used if both isolates are still available.

11/30/01 The case manager meets with the county hospital staff to ensure that they are informed about the care required for drug-resistant TB (DOT of all medication, required monitoring, respiratory isolation requirements, etc.) and to establish a process for coordination of TB care.

CASE EXAMPLE 4 continued

1/3/02 The local health officer is notified that although Sam is still smear-positive, he is being transferred back to the prison to serve out his sentence because his condition is stable, he is tolerating the expanded regimen, and the prison has a room where he can continue respiratory isolation. The health department case manager contacts the prison nurse and provides information about the drug-resistant TB treatment and care required for Sam.

2/20/02 As a measure of quality assurance, the case manager asks to review Sam's health and treatment records. Through much perseverance, the case manager discovers that Sam has stopped receiving his cycloserine dose because the prison had run out of the drug, and it was improperly recorded as taken. The case manager assists with obtaining the cycloserine, provides ongoing education and instruction on required toxicity monitoring, and promptly addresses lapses in Sam's care during the several months he is in the prison.

Lessons Learned

- TST converters should be treated for LTBI once TB disease has been ruled out. In addition, inmates with positive TSTs and risk factors for progression to active TB (such as injection drug use) should be treated for LTBI. If the source case has drug-resistant TB, the LTBI regimen should be tailored to the source case susceptibility results.
- Patients who have completed LTBI treatment can still develop TB for various reasons: drug resistance, poor adherence, exogenous reinfection, or bad luck.
- Not all patients with MDR-TB are foreign-born or have previously received treatment for active TB.
- Contact investigations should prioritize activities to those with the highest level of exposure and higher risk of progression to active TB. Contacts should be sought who interfaced with the source case beginning 3 to 6 months before symptoms began.
- When a hospital notifies the health department about an active TB case, the case manager assigned to the case should meet with hospital staff to ensure that the hospital staff is informed about appropriate TB care.
- TB training is essential for correctional staff, and correctional facilities should have a TB protocol in place to be able to house inmates with active TB.

CASE EXAMPLE 5

Anna is a 57-year-old diabetic Filipino woman.

7/10/98

Anna entered the U.S. with B-notification, Class B2 status (pulmonary TB suspect) and was not considered clinically active. Sputa were not collected overseas.

7/17/98

Anna is screened at the TB clinic.

Past history: Treated for TB in the Philippines from 1993 to 1996 with "pills and some injections," followed by irregular use of Rifater (combination of INH, RIF, and PZA) until the time of the exam.

Symptoms: Chronic cough with white sputum, fatigue, anorexia, and fever for months.

Anna's immigration chest radiograph (February 17, 1998) reveals extensive pathology with a right upper lobe cavitary infiltrate with volume loss and fibro-nodular infiltrates of the right lower lobe and left mid-lung field. Her repeat chest radiograph in clinic shows no significant change.

7/17/98 – 7/20/98

Two out of three sputum samples collected are AFB smear-positive and all 3 specimens eventually grow *M. tuberculosis.*

7/21/98

Anna is treated with INH, RIF, PZA, and EMB by DOT.

Serious consideration should have been given to initiation of an expanded regimen. The irregular nature of Anna's prior treatment and immigration from an area of high levels of resistance put her at great risk. Additionally, her cavitary disease and high bacillary load put her at risk for amplification of resistance if the wrong regimen is chosen. Delay in correct treatment also prolongs risk of transmission to contacts.

8/30/98

Anna's *M. tuberculosis* is found to be resistant to INH, RIF, and EMB by broth methods and the laboratory sets up confirmatory tests using the agar proportion method.

9/20/98

Anna's case manager inquires as to the susceptibility results and is only now told of the "preliminary" susceptibility results. Anna has not appreciably improved clinically or microbiologically.

Laboratories should notify the provider and public health department of "preliminary" results unless they have strong reasons to consider them inaccurate. In this case, Anna's risk of resistance is so high, the laboratory could have been asked to perform direct susceptibility tests, which could have hastened the results, and first- and second-line susceptibilities could have been ordered as soon as growth of M. tuberculosis *was detected.*

Anna's provider and case manager should have been suspicious when the susceptibility results were not sent several weeks after the initial growth of M. tuberculosis *was reported.*

Drug susceptibilities confirm resistance to INH, RIF, and EMB (the laboratory does not perform PZA susceptibility tests). Anna's isolate is sent to a reference lab for second-line susceptibility testing, and a new sputum is sent immediately for first- and second-line susceptibility testing to determine whether amplification of resistance had occurred.

CASE EXAMPLE 5 continued

9/27/98	Cycloserine, SM, and levofloxacin are added; INH, RIF, and EMB are discontinued.
12/2/98	Sputum culture becomes negative 2 months after institution of an appropriate regimen. Anna has resolution of cough, fever, fatigue, and anorexia. Her weight has increased by 10 pounds.

Lessons Learned

- Overseas immigration screening is not always reliable. Do not allow overseas tests and evaluations to drive an immigrant's evaluation upon arrival in the U.S. A chest radiograph consistent with active disease, including cavitary lesions, requires sputum collection before immigration. Immigrants with positive sputum smears are barred from U.S. entry until they become smear-negative. Notify CDC's Division of Quarantine whenever a newly arriving "classified" immigrant is smear-positive on initial evaluation. Any immigrant with a chest radiograph consistent with active TB, whether symptomatic or not, should have TB ruled out using appropriate laboratory and clinical evaluations.
- Drug resistance should be suspected in someone with prior TB treatment, especially with irregular drug administration and limited treatment documentation.
- Once suspicious of drug resistance, utilize the resources of the lab by asking for direct susceptibilities from smear-positive sputum and ordering first- and second-line drug susceptibility testing **as soon as growth is detected.** If available, seek rapid susceptibility information with molecular techniques from smear-positive sputum, growth in broth, or colonies on agar.
- Strongly consider an expanded empiric regimen in a patient with such an irregular history of previous TB treatment and risk of resistance amplification. An initial regimen with at least 3 drugs to which the isolate is susceptible will hasten clinical improvement, lessen risk of amplification of resistance, and prevent transmission to contacts.

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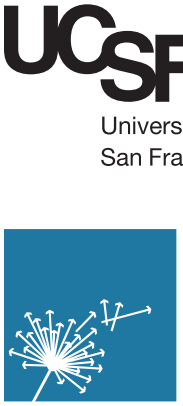

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