



FRANCIS J. CURRY
NATIONAL
TUBERCULOSIS
CENTER

Drug-Resistant Tuberculosis

A SURVIVAL GUIDE FOR CLINICIANS

2ND EDITION



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