



CURRY  
INTERNATIONAL  
TUBERCULOSIS  
CENTER

# Drug-Resistant Tuberculosis

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A SURVIVAL GUIDE FOR CLINICIANS

3RD EDITION



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STATE OF CALIFORNIA

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CALIFORNIA HEALTH &  
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*Drug-Resistant Tuberculosis: A Survival Guide for Clinicians, Third Edition* was created through a collaboration of the Curry International Tuberculosis Center (CITC) and the State of California Department of Public Health, Tuberculosis Control Branch (CDPH).

CITC is a project of the University of California, San Francisco, funded by the Centers for Disease Control and Prevention (CDC). The development of the third edition of this *Guide* was funded through CDC Cooperative Agreement 1U52/PS004088-01. The views expressed in written materials or publications do not necessarily reflect the official policies of the Department of Health and Human Services, nor does the mention of trade names, commercial practices, or organizations imply endorsement by the U.S. Government.

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Second printing. Correction made to Chapter 6, **Pediatrics**, Page 163, Pediatric Drug Dosing, Table 4, Pyrazinamide.

Online update:

June 7, 2016

October 25, 2016

Suggested citation:

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Curry International Tuberculosis Center and California Department of Public Health, 2016: *Drug-Resistant Tuberculosis: A Survival Guide for Clinicians, Third Edition* [inclusive page numbers].

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This publication is available on the Curry International Tuberculosis Center website: <http://www.currytbcenter.ucsf.edu/products/drug-resistant-tuberculosis-survival-guide-clinicians-3rd-edition>

Design: Edi Berton Design

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## Acknowledgements

Special appreciation is extended to the members of the **MDR-TB Service of the Tuberculosis Control Branch at the California Department of Public Health (CDPH)**. Their systematic approach to providing expert consultation on cases of drug-resistant TB in California provided the initial inspiration to produce this *Guide*, and their shared expertise is reflected in its pages. The editorial board also thanks **James Watt, MD, MPH**, Chief of the Division of Communicable Disease Control, CDPH, for his leadership and support.

Many individuals were involved in the writing, editing, research, and review of two previous editions of *Drug-Resistant Tuberculosis: A Survival Guide for Clinicians*. The editors and editorial board of this third edition gratefully acknowledge the ongoing legacy of their contributions.

We would also like to acknowledge: **Jennifer J. Furin, MD, PhD**, Case Western Reserve University and the Sentinel Project (Chapter 6); and **Ellen Murray, RN, BSN**, Southeastern National Tuberculosis Center (Chapter 8), for sharing their specific expertise.

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**Supplemental materials are available online:**

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

# Introduction to this *Survival Guide*

## The need for expertise

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

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

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

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

- Updated epidemiology of TB and MDR-TB is featured in **Chapter 1, *Epidemiology and Background***.
- Find updated information about diagnosing TB disease and drug-resistance, including the use of rapid molecular testing, in **Chapter 2, *Diagnosis***.
- **Chapter 3, *Laboratory***, is a new chapter presenting information about the laboratory tests used to confirm TB disease and drug resistance, including detailed discussions on understanding critical concentrations and minimum inhibitory concentration (MIC), advanced molecular detection methods, and the genes and mutations associated with drug resistance .
- **Chapter 4, *Treatment***, includes information based on current evidence and expert consensus for the treatment of drug-resistant TB, including information on the use of new drugs and therapeutic drug monitoring.
- Updated information about 23 medications used to treat tuberculosis is found in **Chapter 5, *Medication Facts Sheets***, including 5 new fact sheets not included in the second edition of the *Guide*: bedaquiline, clarithromycin, delamanid, meropenem, and rifapentine. Also new in Chapter 5 is a diagram illustrating “New anti-TB drugs in the pipeline.”
- Expanded information about diagnosing and treating drug-resistant TB disease and LTBI in children is now devoted to its own chapter—**Chapter 6, *Pediatrics***.
- New sections on “TB and Diabetes” and “Solid Organ Transplant” have been added to **Chapter 7, *Co-Morbidities and Special Situations***.
- Two previous chapters were reconfigured into an expanded single **Chapter 8, *Monitoring and Case Management***.
- **Chapter 9, *Adverse Reactions***, and **Chapter 10, *Contacts***, contain the latest information and best practice recommendations.
- Streamlined **Appendices** offer updated lists of resources and contact information.

## Description of the *Guide* and target audience

The *Guide* contains information and user-friendly tools and templates for use by any U.S.-based clinician who participates in the management of patients with drug-resistant TB. From physicians to pharmacists, infection control practitioners to public health nurses, the *Guide* arms all healthcare providers in the fight against drug-resistant TB and should serve as an useful adjunct to expert consultative services. The 10 chapters cover major topics pertaining to epidemiology, diagnosis, laboratory issues, treatment, TB medications, pediatric TB, co-morbidities and special situations, monitoring and case management, adverse reactions, and management of contacts. While readers are encouraged to review all sections of the *Guide*, each section is designed to be self-contained. For example, when a reader needs details about specific anti-tuberculosis drugs, he/she can refer to **Chapter 5, Medication Fact Sheets**, to find the properties and details of individual drugs. When a patient is experiencing a potential side effect, the clinician can turn to **Chapter 9, Adverse Reactions**, for a review of appropriate management of toxicity, or to **Chapter 5** for the individual fact sheets about the medications the patient is receiving.

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

### A lack of data

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

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

### Areas of practice variation

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

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

- **Total duration of therapy:** Some experts recommend 18-24 months of therapy total, and some treat 18-24 months from the time of culture conversion. International guidelines (WHO) recommend at least 20 months total duration. Recommendations based on expert consensus in this version of the *Survival Guide* recommend a total duration of at least 18 months beyond culture conversion. Pediatric series have used shorter durations of therapy.
- **Number of drugs in the regimen:** Newer series suggest that better outcomes are associated with more drugs. Expert opinion varies: some experts begin with 4 to 6 drugs to which the isolate is susceptible with the goal of using 3 to 4 oral drugs to complete the therapy. Others would initially use as many drugs as are available. This strategy allows room to eliminate drugs from the regimen as toxicity develops and as more susceptibility results become available.
- **Duration of daily aminoglycoside/capreomycin therapy:** Assuming good clinical and microbiologic response, some experts feel comfortable using daily injectable therapy for as little as 1-2 months before changing to 3-times-weekly therapy. Others use 6 months of daily therapy (barring toxicity or renal impairment) before changing to intermittent therapy.
- **Dose of aminoglycoside/capreomycin:** The standard daily/intermittent dose for the aminoglycosides is 15 mg/kg/dose. Some authors use up to 25 mg/kg/dose for intermittent therapy and tolerate peak levels up to 65 to 80 mcg/ml. Experts who treat with longer courses of injectable drugs are comfortable with peak levels as low as 20 to 35 mcg/ml. Note: Doses achieving lower levels than these will not achieve the desired effect in the regimen and may lead to amplification of resistance.
- **Use of therapeutic drug monitoring (TDM):** Several indications for use of TDM are universally agreed upon: 1) aminoglycoside/capreomycin levels in the setting of renal impairment, change in renal function or concerns about ototoxicity; 2) routine cycloserine levels to keep the level below 35 mcg/ml (associated with marked increase risk of central nervous system [CNS] toxicity); and 3) ethambutol level monitoring in the setting of renal impairment (increased risk of ophthalmic toxicity). TDM is also used by some providers who are concerned about possible malabsorption of drugs (especially in failing treatment regimens, patients with HIV, patients with history of stomach surgery, patients with extremely low body mass index, and those with diarrheal processes). Some experts use TDM routinely and serially, especially for monitoring the levels of injectable drugs.
- **Treatment of MDR-LTBI and use of window prophylaxis for MDR-TB contacts:** Some providers use fluoroquinolone monotherapy for MDR-LTBI, and some use 2-drug therapy. Some experts and jurisdictions use window prophylaxis for contacts to MDR-TB, typically with 2 drugs to which the isolate is susceptible.

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

# Acronyms and Abbreviations

<b>AFB</b>	acid-fast bacilli
<b>AIDS</b>	acquired immunodeficiency syndrome
<b>AK</b>	amikacin
<b>ALT</b>	alanine aminotransferase
<b>ANA</b>	antinuclear antibodies
<b>AMX/CLV</b>	Amoxicillin/clavulanate
<b>ART</b>	antiretroviral therapy
<b>AST</b>	aspartate aminotransferase
<b>ATS</b>	American Thoracic Society
<b>BAL</b>	bronchoalveolar lavage
<b>BCG</b>	bacille Calmette-Guérin
<b>BDQ</b>	bedaquiline fumarate
<b>BID</b>	twice a day
<b>BMI</b>	body mass index
<b>BUN</b>	blood urea nitrogen
<b>CAPD</b>	continuous ambulatory peritoneal dialysis
<b>CBC</b>	complete blood count
<b>CDC</b>	Centers for Disease Control and Prevention
<b>CDPH</b>	California Department of Public Health
<b>CFZ</b>	clofazimine
<b>CITC</b>	Curry International Tuberculosis Center
<b>CLR</b>	clarithromycin
<b>CM</b>	capreomycin
<b>CNS</b>	central nervous system
<b>CS</b>	cycloserine
<b>CSF</b>	cerebrospinal fluid

<b>CXR</b>	chest x-ray
<b>DLM</b>	delamanid
<b>DM</b>	diabetes mellitus
<b>DOT</b>	directly observed therapy
<b>DST</b>	drug-susceptibility testing
<b>EMB</b>	ethambutol
<b>ETA</b>	ethionamide
<b>FDA</b>	Food and Drug Administration
<b>FQN</b>	fluoroquinolone
<b>GI</b>	gastrointestinal
<b>HEPA</b>	high efficiency particulate air
<b>HIV</b>	human immunodeficiency virus
<b>IDSA</b>	Infectious Diseases Society of America
<b>IGRA</b>	interferon gamma release assay
<b>IM</b>	intramuscular
<b>IMP/CLN</b>	imipenem/cilastatin
<b>INH</b>	isoniazid
<b>IRIS</b>	immune reconstitution inflammatory syndrome
<b>IUATLD</b>	International Union Against Tuberculosis and Lung Disease
<b>IV</b>	intravenous
<b>KM</b>	kanamycin
<b>LFT</b>	liver function test
<b>LFX</b>	levofloxacin
<b>LPA</b>	line probe assay
<b>LTBI</b>	latent tuberculosis infection
<b>LZD</b>	linezolid

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

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