Drug-Resistant Tuberculosis

A SURVIVAL GUIDE FOR CLINICIANS, 2011

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 Curry International Tuberculosis Center (CITC) 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 CITC 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.

- 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.
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<td>interferon gamma release assay</td>
</tr>
<tr>
<td>IM</td>
<td>intramuscular</td>
</tr>
<tr>
<td>INH</td>
<td>isoniazid</td>
</tr>
<tr>
<td>IUATLD</td>
<td>International Union Against Tuberculosis and Lung Disease</td>
</tr>
<tr>
<td>IV</td>
<td>intravenous</td>
</tr>
<tr>
<td>KM</td>
<td>kanamycin</td>
</tr>
<tr>
<td>LFT</td>
<td>liver function test</td>
</tr>
<tr>
<td>LFX</td>
<td>levofloxacin</td>
</tr>
<tr>
<td>LTBI</td>
<td>latent tuberculosis infection</td>
</tr>
<tr>
<td>MAC</td>
<td>Mycobacterium avium complex</td>
</tr>
<tr>
<td>MAO</td>
<td>monoamine oxidase</td>
</tr>
<tr>
<td>M. bovis</td>
<td>Mycobacterium bovis</td>
</tr>
<tr>
<td>M. tuberculosis</td>
<td>Mycobacterium tuberculosis</td>
</tr>
<tr>
<td>MDR-TB</td>
<td>multidrug-resistant tuberculosis (resistant to at least isoniazid and rifampin)</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------------------------------------------</td>
</tr>
<tr>
<td>Mg</td>
<td>magnesium</td>
</tr>
<tr>
<td>MIC</td>
<td>minimum inhibitory concentration</td>
</tr>
<tr>
<td>MIRU</td>
<td>mycobacterial interspersed repetitive units</td>
</tr>
<tr>
<td>NAAT</td>
<td>nucleic acid amplification test</td>
</tr>
<tr>
<td>NIOSH</td>
<td>National Institute for Occupational Safety and Health</td>
</tr>
<tr>
<td>NJMRC</td>
<td>National Jewish Medical and Research Center</td>
</tr>
<tr>
<td>NPO</td>
<td>nothing by mouth</td>
</tr>
<tr>
<td>NSAID</td>
<td>nonsteroidal anti-inflammatory drug</td>
</tr>
<tr>
<td>NTM</td>
<td>nontuberculous mycobacteria</td>
</tr>
<tr>
<td>OB</td>
<td>obstetrics</td>
</tr>
<tr>
<td>od</td>
<td>right eye</td>
</tr>
<tr>
<td>os</td>
<td>left eye</td>
</tr>
<tr>
<td>PAP</td>
<td>patient assistance program</td>
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<tr>
<td>PAS</td>
<td>para-aminosalicylate</td>
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<tr>
<td>PCR</td>
<td>polymerase chain reaction</td>
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<tr>
<td>Plt</td>
<td>platelet</td>
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<tr>
<td>PO</td>
<td>by mouth</td>
</tr>
<tr>
<td>PPD</td>
<td>purified protein derivative</td>
</tr>
<tr>
<td>PR</td>
<td>per rectum</td>
</tr>
<tr>
<td>PRN</td>
<td>as needed</td>
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<tr>
<td>PRUCOL</td>
<td>Permanent Residence Under Color of Law</td>
</tr>
<tr>
<td>PZA</td>
<td>pyrazinamide</td>
</tr>
<tr>
<td>qam</td>
<td>every morning</td>
</tr>
<tr>
<td>qd</td>
<td>once a day</td>
</tr>
<tr>
<td>qhs</td>
<td>every evening</td>
</tr>
<tr>
<td>qid</td>
<td>four times a day</td>
</tr>
<tr>
<td>QFT-G</td>
<td>QuantiFERON®-TB Gold</td>
</tr>
<tr>
<td>QFT-GIT</td>
<td>QuantiFERON®-TB Gold In Tube</td>
</tr>
<tr>
<td>QT</td>
<td>the interval from the beginning of the QRS complex to the end of the T wave on an electrocardiogram</td>
</tr>
<tr>
<td>RFB</td>
<td>rifabutin</td>
</tr>
<tr>
<td>RIF</td>
<td>rifampin</td>
</tr>
<tr>
<td>SGPT</td>
<td>serum glutamic-pyruvic transaminase</td>
</tr>
<tr>
<td>SIRE</td>
<td>streptomycin, isoniazid, rifampin, ethambutol</td>
</tr>
<tr>
<td>SJS</td>
<td>Stevens Johnson Syndrome</td>
</tr>
<tr>
<td>SM</td>
<td>streptomycin</td>
</tr>
<tr>
<td>SSRI</td>
<td>selective serotonin reuptake inhibitor</td>
</tr>
<tr>
<td>TB</td>
<td>tuberculosis</td>
</tr>
<tr>
<td>TEN</td>
<td>toxic epidermal necrolysis</td>
</tr>
<tr>
<td>TID</td>
<td>three times a day</td>
</tr>
<tr>
<td>TSH</td>
<td>thyroid stimulating hormone</td>
</tr>
<tr>
<td>TST</td>
<td>tuberculin skin test</td>
</tr>
<tr>
<td>WBC</td>
<td>white blood cell</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>XDR-TB</td>
<td>extensively drug-resistant tuberculosis</td>
</tr>
</tbody>
</table>