AMERICAN THORACIC SOCIETY DOCUMENTS

Treatment of Drug-Resistant Tuberculosis

An Official ATS/CDC/ERS/IDSA Clinical Practice Guideline: Executive Summary

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This official clinical practice guideline was approved by the American Thoracic Society, the European Respiratory Society, and the Infectious Diseases Society of America September 2019, and was cleared by the U.S. Centers for Disease Control and Prevention September 2019

Background: The American Thoracic Society, U.S. Centers for Disease Control and Prevention, European Respiratory Society, and Infectious Diseases Society of America jointly sponsored this new practice guideline on the treatment of drug-resistant tuberculosis (DR-TB). The document includes recommendations on treatment of multidrug-resistant TB (MDR-TB), as well as isoniazid-resistant but rifampin-susceptible TB.

Methods: Published systematic reviews, meta-analyses, and a new individual patient data meta-analysis from 12,030 patients, in 50 studies, across 25 countries with confirmed pulmonary rifampin-resistant TB were used for this guideline. Meta-analytic approaches included propensity score (PS) matching to reduce confounding. Each recommendation was discussed by an expert committee, screened for conflicts of interest, according to the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology.

Results: Twenty-one Population, Intervention, Comparator, and Outcomes questions were addressed, generating 25 GRADE-based recommendations. Certainty in the evidence was judged to be very low because the data came from observational studies with significant loss to follow-up and imbalance in background regimens between comparator groups. Good practices in the management of MDR-TB are described. On the basis of the evidence review, a clinical strategy tool for building a treatment regimen for MDR-TB is also provided.

Conclusions: New recommendations are made for the choice and number of drugs in a regimen, the duration of intensive and continuation phases, and the role of injectable drugs for MDR-TB. On the basis of these recommendations, an effective all-oral regimen for MDR-TB can be assembled. Recommendations are also provided on the role of surgery in treatment of MDR-TB, for treatment of contacts exposed to MDR-TB, and treatment of isoniazid-resistant TB.

Keywords: MDR-TB; tuberculosis; duration of treatment; drug treatment; treatment monitoring

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Supported by the American Thoracic Society, the United States Centers for Disease Control and Prevention, the European Respiratory Society, and the Infectious Diseases Society of America.

This Executive Summary is part of the full official ATS clinical practice guideline, which readers may access online at http://www.atsjournals.org/doi/abs/10.1164/rccm.201909-1874ST. Only the Executive Summary is appearing in the print edition of the *Journal*. The article of record, and the one that should be cited, is: Treatment of Drug-Resistant Tuberculosis. An Official ATS/CDC/ERS/IDSA Clinical Practice Guideline. *Am J Respir Crit Care Med* 2019;200:e93–e142.

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This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org.

Am J Respir Crit Care Med Vol 200, Iss 10, pp 1208–1218, Nov 15, 2019

DOI: 10.1164/rccm.201909-1874ST
Internet address: www.atsjournals.org

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Introduction

The American Thoracic Society, U.S. Centers for Disease Control and Prevention (CDC), European Respiratory Society, and Infectious Diseases Society of America jointly sponsored this new practice guideline on the treatment of drug-resistant tuberculosis (DR-TB), including the treatment of multidrug-resistant TB (MDR-TB) and treatment of isoniazid-resistant but rifampin-susceptible TB. This is an executive summary of the full-length guidelines available online.

In these guidelines, MDR-TB is defined specifically as resistance to at least isoniazid and rifampin, the two most important first-line drugs. Extensively drug-resistant tuberculosis (XDR-TB) is a subset of MDR-TB with additional resistance to a fluoroquinolone and a second-line injectable agent. Because XDR-TB evolves from MDR-TB in two steps, the term "pre–XDR-TB" was introduced to identify MDR-TB with additional resistance to either one but not both these classes of drugs. In these guidelines, we also provide recommendations for the treatment of isoniazid-resistant TB.

This practice guideline is supported by scientific evidence, including results of a propensity score (PS)-matched individual patient data meta-analysis (IPDMA) of more than 12,000 patient records from 50 published cohorts in 25 countries (*see* Appendix A: Methodology in the online supplement) (1). We used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach to appraise the quality of evidence and to formulate, write, and grade most recommendations (2, 3). A carefully selected panel of experts, screened for conflicts of interest, including specialists in pulmonary medicine, infectious diseases, pediatrics, primary care, public health, epidemiology, economics, pharmacokinetics, microbiology, systematic review methodology, and patient advocacy, was assembled to assess the evidence supporting each recommendation. The treatment of drug-resistant TB can be complicated and thus is necessarily preceded and accompanied by important components of care relating to the access to TB experts, microbiological and molecular diagnosis, education, monitoring and follow-up, and global patient-centered strategies. The writing committee considered that these topics are crucial but do not require formal and extensive evidence appraisal in the context of the present guidelines. Following GRADE guidance, it was thus decided that these practices would be addressed in good practice statements. In this executive summary, six ungraded good practice statements and 25 GRADE-based recommendations addressing 21 Population, Intervention, Comparator, and Outcomes (PICO) questions (Table 1) are provided. Questions were selected according to their importance to clinical practice, as determined by the guideline panel, expert advisors, and patient advocates. The implications of the strength of recommendation, conditional or strong, for patients, clinicians, and policy makers are described in Appendix A and shown in Table 2. Detailed and referenced information on treatment of MDR-TB, including summaries of the evidence, benefits, harms, and additional considerations, is available online in the full-length version of the guideline. A summary of key differences between this ATS/CDC/ERS/IDSA practice guideline and the WHO 2019 Consolidated Guidelines on Drug-Resistant Tuberculosis Treatment (4) is also provided in the full-text version of the guidelines available online.

Treatment of TB, regardless of drug susceptibility testing (DST), focuses on both curing the individual patient and minimizing transmission of *Mycobacterium tuberculosis* to others. Treating DR-TB is complex compared with drug-susceptible TB disease, including needing additional molecular and phenotypic diagnostic tests to determine drug susceptibility, prolonged treatment durations, and the use of second-line drugs, which have harmful toxicities that must be balanced against their benefits.

Good Practices for Treating DR-TB

TB care rests on timely diagnosis and initiation of appropriate therapy with ongoing support and management to ensure patients are cured. The provider or program is responsible for ensuring successful completion of treatment, not only the patient (5). A patient-centered approach requires involving the patient in decision-making. We recommend seeking consultation with an expert in TB when there is suspicion or confirmation of DR-TB (ungraded good practice statement). In the United States, DR-TB experts can be found through CDC-supported TB Centers of Excellence for Training, Education, and Medical Consultation (http://www.cdc.gov/tb/education/rtmc/default.htm), through local health department TB Control Programs (https://www.cdc.gov/tb/links/tboffices.htm), and through international MDR-TB expert groups such as the British Thoracic Society MDR-TB Clinical Advisory Service (http://mdrtb.brit-thoracic.org.uk/) and the Global TB Network (6).

Diagnosing TB and Identification of Drug Resistance

The potential for drug resistance is considered in every patient. Providers should be familiar with phenotypic and molecular laboratory services available in their locale. In the United States, the CDC's Division of Tuberculosis Elimination Laboratory Branch provides testing services for both clinical specimens and isolates of *M. tuberculosis* (https://www.cdc.gov/tb/topic/laboratory/default.htm). The CDC's Molecular Detection of Drug Resistance

Table 1. Questions Regarding the Treatment of Drug-Resistant Tuberculosis Selected by the Guideline Writing Committee

Number of effective drugs in a regimen for MDR-TB
1. Should patients with MDR-TB be prescribed five effective drugs vs. more or fewer agents during the intensive and continuation phases of treatment?

Duration of intensive and continuation phases of treatment for MDR-TB
2. Should patients with MDR-TB undergoing intensive-phase treatment be treated for ⩾6 mo after culture conversion or <6 mo after culture conversion?
3. Should patients with MDR-TB undergoing continuation-phase treatment be treated for ⩾18 mo after culture conversion or <18 mo after culture conversion?

Drug and drug classes for the treatment of MDR-TB
4. In patients with MDR-TB, are outcomes safely improved when regimens include amoxicillin/clavulanate compared with regimens that do not include amoxicillin/clavulanate?
5. In patients with MDR-TB, are outcomes safely improved when regimens include bedaquiline compared with regimens that do not include bedaquiline?
6. In patients with MDR-TB, are outcomes safely improved when regimens include carbapenems with clavulanic acid compared with regimens that do not include them?
7. In patients with MDR-TB, are outcomes safely improved when regimens include clofazimine compared with regimens that do not include clofazimine?
8. In patients with MDR-TB, are outcomes safely improved when regimens include cycloserine compared with regimens that do not include cycloserine?
9. In patients with MDR-TB, are outcomes safely improved when regimens include delamanid compared with regimens that do not include delamanid?
10. In patients with MDR-TB, are outcomes safely improved when regimens include ethambutol compared with regimens that do not include ethambutol?
11. In patients with MDR-TB, are outcomes safely improved when regimens include ethionamide/prothionamide compared with regimens that do not include ethionamide/prothionamide?
12. In patients with MDR-TB, are outcomes safely improved when regimens include fluoroquinolones compared with regimens that do not include fluoroquinolones?
13. In patients with MDR-TB, are outcomes safely improved when regimens include an injectable compared with regimens that do not include an injectable?
14. In patients with MDR-TB, are outcomes safely improved when regimens include linezolid compared with regimens that do not include linezolid?
15. In patients with MDR-TB, are outcomes safely improved when regimens include macrolides compared with regimens that do not include macrolides?
16. In patients with MDR-TB, are outcomes safely improved when regimens include *p*-aminosalicylic acid compared with regimens that do not include *p*-aminosalicylic acid?
17. In patients with MDR-TB, are outcomes safely improved when regimens include pyrazinamide compared with regimens that do not include pyrazinamide?

Use of a standardized, shorter-course regimen of <12 mo for the treatment of MDR-TB
18. In patients with MDR-TB, does treatment with a standardized MDR-TB regimen for ⩽12 mo lead to better outcomes than treatment with an MDR-TB regimen for 18–24 mo?

Treatment of isoniazid-resistant, rifampin-susceptible TB:
19a. Should patients with isoniazid-resistant TB be treated with a regimen composed of a fluoroquinolone, rifampin, ethambutol, and pyrazinamide for 6 mo compared with rifampin, ethambutol, and pyrazinamide (without a fluoroquinolone) for 6 mo?
19b. Should patients with isoniazid-resistant TB be treated with a regimen composed of fluoroquinolone, rifampin, and ethambutol for 6 mo and pyrazinamide for the first 2 mo compared with a regimen composed of a fluoroquinolone, rifampin, ethambutol, and pyrazinamide for 6 mo?

Surgery as adjunctive therapy for MDR-TB:
20. Among patients with MDR/XDR TB receiving antimicrobial therapy, does lung resection surgery (i.e., lobectomy or pneumonectomy) lead to better outcomes than no surgery?

Management of contacts exposed to an infectious patient with MDR-TB:
21. Should contacts exposed to an infectious patient with MDR-TB be offered LTBI treatment vs. followed with observation alone?

Definition of abbreviations: LTBI = latent TB infection; MDR = multidrug resistant; TB = tuberculosis; XDR = extensively drug resistant.

service uses DNA sequencing to rapidly detect mutations most frequently associated with resistance to both first (e.g., rifampin, isoniazid, ethambutol, and pyrazinamide) and second-line drugs (https://www.cdc.gov/tb/topic/laboratory/MDDRsubmissionform.pdf). Recently published ATS/CDC/IDSA Official Practice Guidelines for the diagnosis of TB provide additional details on the optimal use of diagnostic tools and algorithms (7).

Treatment, Monitoring, and Case Management of DR-TB

Consistent with stewardship of antibiotics, drugs known to be ineffective, on the basis of *in vitro* growth-based or molecular testing, or suspected to be ineffective because of resistance in the index case or a high population prevalence of resistance, should not be used (8). Drugs should be selected based on efficacy and tolerability. Treatment response is monitored clinically, radiographically, and bacteriologically, and patients should be educated about adverse effects, with all adverse effects investigated and ameliorated (9–12). Case management should be used as a collaborative care model that entails engaging with patients; comprehensively assessing, monitoring, and attending to their needs; care planning; medication management; facilitating access to services; and functioning as patient advocate/agent (5, 13–21).

Summary of Good Practices

For patients being evaluated and treated for any form of DR-TB, the following six ungraded good practices are emphasized, as the writing committee had high confidence in their net benefit:

1. Consultation should be requested with a TB expert when there is suspicion of or confirmation of DR-TB. In the United States, TB experts can be found through the CDC-supported TB Centers of Excellence for Training, Education, and Medical Consultation (http://www.cdc.gov/tb/education/rtmc/default.htm), through local health department TB control programs (https://www.cdc.gov/tb/links/tboffices.htm), and through international MDR-TB expert groups such as the Global TB Network (6).
2. Molecular DSTs should be obtained for rapid detection of mutations associated with resistance. When rifampin resistance is detected, additional DST should be performed immediately for first-line drugs, fluoroquinolones, and aminoglycosides. Resistance to fluoroquinolones should be excluded whenever isoniazid resistance is found.
3. Regimens should include only drugs to which the patient's *M. tuberculosis* isolate has documented or high likelihood of susceptibility (hereafter

Table 2. Implications of Strong and Conditional Recommendations

	Strong Recommendation ("We recommend . . .")	Conditional Recommendation ("We suggest . . .")
For patients	The overwhelming majority of individuals in this situation would want the recommended course of action, and only a small minority would not.	The majority of individuals in this situation would want the suggested course of action, but a sizeable minority would not.
For clinicians	The overwhelming majority of individuals should receive the recommended course of action. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Different choices will be appropriate for different patients, and you must help each patient arrive at a management decision consistent with her or his values and preferences. Decision aids may be useful to help individuals make decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working toward a decision.
For policy makers	The recommendation can be adapted as policy in most situations, including for the use as performance indicators.	Policy making will require substantial debates and involvement of many stakeholders. Policies are also more likely to vary between regions. Performance indicators would have to focus on the fact that adequate deliberation about the management options has taken place.

defined as effective). Drugs known to be ineffective based on *in vitro* growth-based or molecular resistance should NOT be used. This recommendation applies to all drugs and treatment regimens discussed in this practice guideline, unless reliable methods of testing susceptibility for a drug have yet to be developed.

4. Treatment response should be monitored clinically, radiographically, and bacteriologically, with cultures obtained at least monthly for pulmonary TB. When cultures remain positive after 3 months of treatment, susceptibility tests for drugs should be repeated. Weight and other measures of clinical response should be recorded monthly.
5. Patients should be educated and asked about adverse effects at each visit. Adverse effects should be investigated and ameliorated.
6. Patient-centered case management helps patients understand their diagnoses, understand and participate in their treatment, and discuss potential barriers to treatment. Patient-centered strategies and interventions should be used to minimize barriers to treatment.

Summary of Clinical Practice Guideline Recommendations

The guideline writing committee considered the following drugs and drug classes: amoxicillin/clavulanate, bedaquiline, carbapenem with clavulanic acid, clofazimine, cycloserine, delamanid, ethambutol, ethionamide, fluoroquinolones, injectable agents, linezolid, macrolides, *p*-aminosalicylic acid, and pyrazinamide (*see* Figure 1, with additional details on drugs and other outcomes of interest provided in the full-length version of these guidelines and in Appendix B: Evidence Profiles in the online supplement). Of note, pretomanid in combination with bedaquiline and linezolid was recently approved by the U.S. Food and Drug Administration (FDA) for the treatment of a specific limited population of adults with pulmonary XDR-TB or treatment-intolerant or nonresponsive MDR-TB; however, the preparation and completion of these guidelines predated this approval (22). For each drug or drug class, the following PICO question was addressed: In patients with MDR-TB, are outcomes safely improved when regimens include the specific drug or drug class compared with regimens without them?

For the selection of an effective MDR-TB treatment regimen and duration of MDR-TB treatment:

1. We suggest using at least five drugs in the intensive phase of treatment and four drugs in the continuation phase of treatment (conditional recommendation, very low certainty in the evidence).
2. We suggest an intensive-phase duration of treatment of between 5 and 7 months after culture conversion (conditional recommendation, very low certainty in the evidence).
3. We suggest a total treatment duration of between 15 and 21 months after culture conversion (conditional recommendations, very low certainty in the evidence).
4. In patients with pre–XDR-TB and XDR-TB, which are both subsets of MDR-TB, we suggest a total treatment duration of between 15 and 24 months after culture conversion (conditional recommendations, very low certainty in the evidence).

For the selection of oral drugs for MDR-TB treatment (in order of strength of recommendation):

5. We recommend including a later-generation fluoroquinolone (levofloxacin or moxifloxacin) (strong recommendation, low certainty in the evidence).
6. We recommend including bedaquiline (strong recommendation, very low certainty in the evidence).
7. We suggest including linezolid (conditional recommendation, very low certainty in the evidence).
8. We suggest including clofazimine (conditional recommendation, very low certainty of evidence).
9. We suggest including cycloserine (conditional recommendation, very low certainty in the evidence).
10. We suggest including ethambutol only when other more effective drugs

Drug / Drug Class	Recommendation		Certainty in the evidence	Relative (95% CI) Death	Relative (95% CI) Success
	FOR	AGAINST			
Bedaquiline	Strong		Very Low	aOR 0.4 (0.3 to 0.5)	aOR 2.0 (1.4 to 2.9)
Fluoroquinolone: Moxifloxacin	Strong		Very Low	aOR 0.5 (0.4 to 0.6)	aOR 3.8 (2.8 to 5.2)
Fluoroquinolone: Levofloxacin	Strong		Very Low	aOR 0.6 (0.5 to 0.7)	aOR 4.2 (3.3 to 5.4)
Linezolid	Conditional		Very Low	aOR 0.3 (0.2 to 0.3)	aOR 3.4 (2.6 to 4.5)
Clofazimine	Conditional		Very Low	aOR 0.8 (0.6 to 1.0)	aOR 1.5 (1.1 to 2.1)
Cycloserine	Conditional		Very Low	aOR 0.6 (0.5 to 0.6)	aOR 1.5 (1.4 to 1.7)
Injectables: Amikacin	Conditional		Very Low	aOR 1.0 (0.8 to 1.2)	aOR 2.0 (1.5 to 2.6)
Injectables: Streptomycin	Conditional		Very Low	aOR 0.8 (0.6 to 1.1)	aOR 1.5 (1.1 to 2.1)
Ethambutol	Conditional		Very Low	aOR 1.0 (0.9 to 1.2)	aOR 0.9 (0.7 to 1.1)
Pyrazinamide	Conditional		Very Low	aOR 0.7 (0.6 to 0.8)	aOR 0.7 (0.5 to 0.9)
Injectables: Carbapenems w/ clavulanic acid	Conditional		Very Low	aOR 1.0 (0.5 to 1.7)	aOR 4.0 (1.7 to 9.1)
Delamanid	Concur with WHO conditional recommendation				
Ethionamide Prothionamide		Conditional	Very Low	aOR 0.9 (0.8 to 1.0)	aOR 0.8 (0.7 to 0.9)
Injectables: Kanamycin		Conditional	Very Low	aOR 1.1 (0.9 to 1.2)	aOR 0.5 (0.4 to 0.6)
P-Aminosalicylic Acid		Conditional	Very Low	aOR 1.2 (1.1 to 1.4)	aOR 0.8 (0.7 to 1.0)
Injectables: Capreomycin		Conditional	Very Low	aOR 1.4 (1.1 to 1.7)	aOR 0.8 (0.6 to 1.1)
Macrolides: Azithromycin Clarithromycin		Strong	Very Low	aOR 1.6 (1.2 to 2.0)	aOR 0.6 (0.5 to 0.8)
Amoxicillin-clavulanate		Strong	Very Low	aOR 1.7 (1.3 to 2.1)	aOR 0.6 (0.5 to 0.8)

Figure 1. Summary of recommendations on drugs for use in a treatment regimen for patients with multidrug-resistant tuberculosis, including strength of recommendation, certainty in the evidence, and relative effects on death and treatment success. Additional details and other outcomes of interest are provided in the full-length guideline and in Appendix B: Evidence Profiles in the online supplement. Success is defined as end of treatment cure or treatment completion. aOR = adjusted odds ratio; CI = confidence interval; WHO = World Health Organization.

cannot be assembled to achieve a total of five drugs in the regimen (conditional recommendation, very low certainty in the evidence).

11. We suggest including pyrazinamide in a regimen for treatment of patients with MDR-TB or with isoniazid-resistant TB, when the *M. tuberculosis* isolate has not been found resistant to pyrazinamide (conditional recommendation, very low certainty in the evidence).
12. The guideline panel was unable to make a clinical recommendation for or against delamanid because of the absence of data in the IPDMA conducted for this practice guideline (1). We make a research recommendation for the conduct of randomized clinical trials and cohort studies evaluating the efficacy, safety, and tolerability of delamanid in combination with other oral agents. Until additional data are available, the guideline panel concurs with the conditional recommendation of the 2019 WHO Consolidated Guidelines on Drug-Resistant Tuberculosis Treatment that delamanid may be included in the treatment of patients with MDR/rifampin-resistant TB aged ⩾3 years on longer regimens (4).

For selected oral drugs previously included in regimens for the treatment of MDR-TB:

13. We recommend NOT including amoxicillin–clavulanate, with the exception of when the patient is receiving a carbapenem wherein the inclusion of clavulanate is necessary (strong recommendation, very low certainty in the evidence).
14. We recommend NOT including the macrolides azithromycin and clarithromycin (strong recommendation, very low certainty in the evidence).
15. We suggest NOT including ethionamide/prothionamide if more effective drugs are available to construct a regimen with at least five effective drugs (conditional recommendation, very low certainty in the evidence).
16. We suggest NOT including *p*-aminosalicylic acid in a regimen if more effective drugs are available to construct a regimen with at least five effective drugs (conditional

recommendation, very low certainty in the evidence).

For the selection of drugs administered through injection when needed to compose an effective treatment regimen for MDR-TB:

17. We suggest including amikacin or streptomycin when susceptibility to these drugs is confirmed (conditional recommendation, very low certainty in the evidence).
18. We suggest including a carbapenem (always to be used with amoxicillin-clavulanic acid) (conditional recommendation, very low certainty in the evidence).
19. We suggest NOT including kanamycin or capreomycin (conditional recommendation, very low certainty in the evidence).

Of note, our recommendations for the use of bedaquiline, moxifloxacin, and levofloxacin in the treatment of MDR-TB are strong despite very low certainty in the evidence because the writing committee viewed the large reductions in mortality, improved treatment success rates, and relatively few adverse effects of these drugs as corresponding to the notably favorable balances of benefits and harms. Despite linezolid-containing regimens showing similar large reduction in mortality and improved treatment success, the increased adverse effects noted for linezolid correspond to a balance of benefits and harms that is less favorable compared with bedaquiline and later-generation fluoroquinolones. Furthermore, our recommendations against the use of amoxicillin–clavulanate (except to provide clavulanate when using a carbapenem) and macrolides are strong despite the evidence being judged to be of very low certainty because we viewed the increased mortality and decreased likelihood of treatment success associated with the use of these drugs as having a notably unfavorable balance of benefits to potential harms.

Building a Treatment Regimen for Multidrug-Resistant Tuberculosis

The guideline committee proposes a strategy for building a treatment regimen for MDR-TB depicted in Table 3 on the basis of the evidence, balancing benefits and harms for each drug, the experience of MDR-TB experts on the committee, as well as perspectives of patients. This strategy encourages an oral regimen with five effective drugs (to which the isolate is susceptible, or has low likelihood of resistance). In our PS-matched IPDMA, significant favorable synergies were identified with improved treatment success and reduced mortality when bedaquiline was used in combination with linezolid or clofazimine (1). As noted, amikacin and streptomycin show modest effectiveness when the patient's isolate is susceptible to these drugs; however, because of their toxicities, aminoglycosides should be reserved for when a more-effective or less-toxic regimen cannot otherwise be assembled. The final choice of drugs and drug classes depends on many factors, including patient preferences, harms and benefits, the capacity to monitor for adverse effects, drug–drug interactions, comorbidities, and drug availability. Final regimen development, therefore, is individualized and may differ from the approach in Table 3. Doses are provided in Table 4, modified and updated from the 2016 ATS/CDC/IDSA Treatment of Drug-Susceptible TB Practice Guidelines (5).

Shorter-Course, Standardized, 9- to 12-Month Regimen for MDR-TB

The WHO-recommended standardized shorter-course 9- to 11-month regimen for MDR-TB was estimated by the guidelines committee to have minimal desirable effects (on treatment success, mortality, culture conversions) and small to moderate undesirable effects (adverse events, the use of drugs for which there is documented or high likelihood of resistance [e.g., isoniazid, ethionamide, pyrazinamide], limited applicability, and the use of kanamycin as part of the regimen).

For the use of the WHO-recommended standardized shorter-course 9- to 12-month regimen for MDR-TB:

20. The shorter-course regimen is standardized with the use of kanamycin (which the committee recommends against using) and includes drugs for which there is documented or high likelihood of resistance (e.g., isoniazid, ethionamide, pyrazinamide). Although the STREAM (Standard Treatment Regimen of Anti-Tuberculosis Drugs for Patients with MDR-TB) Stage 1 randomized trial found the shorter-course regimen to be noninferior to longer injectable-containing regimens with respect to the primary efficacy outcome (23), the guideline committee cannot make a recommendation either for or against this standardized shorter-course regimen, compared with longer individualized all-oral regimens that can be composed in accordance with the recommendations in this practice guideline. We make a research recommendation for the conduct of randomized clinical trials evaluating the efficacy, safety, and tolerability of modified shorter-course regimens that include newer oral agents, exclude injectables, and include drugs for which susceptibility is confirmed or deemed to be highly likely.

Role of Surgery for MDR-TB

Data from a published IPDMA of surgery in MDR-TB including 26 studies comprising 6,431 patients with MDR-TB were used to generate recommendations (24). Patients with partial lung resection had a higher probability of treatment success, defined as no treatment failure and no relapse (risk difference, 16 more per 100), and a lower risk of death (risk difference, 6 fewer per 100). The best estimates of the effects of pneumonectomy showed increased risk of death (risk difference, 10 more per 100) and lower probability of treatment success (risk difference, 4 fewer per 100).

For the role of surgery in the treatment of MDR-TB:

21. We suggest elective *partial* lung resection (e.g., lobectomy or wedge resection), rather than medical therapy alone, for adults with MDR-TB receiving antimicrobial-based therapy (conditional recommendation, very low certainty in the evidence). The writing committee believes this option would be beneficial for patients for whom clinical judgement, supported by bacteriological and radiographic data, suggests a strong risk of treatment failure or relapse with medical therapy alone.
22. We suggest medical therapy alone, rather than including elective *total* lung

Table 3. Clinical Strategy to Build an Individualized Treatment Regimen for MDR-TB

- Build a regimen **using five or more drugs to which the isolate is susceptible (or has low likelihood of resistance)**, preferably with drugs that have not been used to treat the patient previously.
- Choice of drugs is contingent on capacity to appropriately monitor for significant adverse effects, patient comorbidities, and preferences/values (choices therefore subject to program and patient safety limitations).
- In children with TB disease who are contacts of infectious MDR-TB source cases, the source case's isolate DST result should be used if an isolate is not obtained from the child.
- **TB expert medical consultation is recommended (ungraded good practice statement).**

Step 1: Choose one later-generation fluoroquinolone	Levofloxacin Moxifloxacin
Step 2: Choose both of these prioritized drugs	Bedaquiline Linezolid
Step 3: Choose both of these prioritized drugs	Clofazimine Cycloserine/terizidone
Step 4: If a regimen cannot be assembled with five effective oral drugs, *and the isolate is susceptible*, use one of these injectable agents*	Amikacin Streptomycin
Step 5: If needed or if oral agents preferred over injectable agents in Step 4, use the following drugs†	Delamanid‡ Pyrazinamide Ethambutol
Step 6: If limited options and cannot assemble a regimen of five effective drugs, consider use of the following drugs	Ethionamide or prothionamide§ Imipenem–cilastatin/clavulanate or meropenem/clavulanate‖ *p*-Aminosalicylic acid¶ High-dose isoniazid**
The following drugs are no longer recommended for inclusion in MDR-TB regimens:	Capreomycin and kanamycin Amoxicillin/clavulanate (when used without a carbapenem) Azithromycin and clarithromycin

Definition of abbreviations: DST = drug susceptibility testing; INH = isoniazid; IPDMA = individual patient data meta-analyses; MDR = multidrug-resistant; PS = propensity score; TB = tuberculosis.

*Amikacin and streptomycin should be used only when the patient's isolate is susceptible to these drugs. Because of their toxicity, these drugs should be reserved for when more-effective or less-toxic therapies cannot be assembled to achieve a total of five effective drugs.

†Patient preferences in terms of the harms and benefits associated with injectables (the use of which is no longer obligatory), the capacity to appropriately monitor for significant adverse effects, consideration of drug–drug interactions, and patient comorbidities should be considered in selecting Step 5 agents over injectables. Ethambutol and pyrazinamide had mixed/marginal performance on outcomes assessed in our PS-matched IPDMA; however, some experts may prefer these drugs over injectable agents to build a regimen of at least five effective oral drugs. Use pyrazinamide and ethambutol only when the isolate is documented as susceptible.

‡Data on dosing and safety of delamanid are available in children ⩾3 years of age.

§Mutations in the inhA region of the *Mycobacterium tuberculosis* genome can confer resistance to ethionamide/prothionamide as well as to INH. In this situation, ethionamide/prothionamide may not be a good choice unless the isolate is shown to be susceptible with *in vitro* testing.

‖Divided daily intravenous dosing limits feasibility. Optimal duration of use not defined.

¶Fair/poor tolerability and low performance. Adverse effects reported to be less common in children.

**Data not reviewed in our PS-matched IPDMA, but high-dose isoniazid can be considered despite low-level isoniazid resistance but not with high-level INH resistance.

resection (pneumonectomy), for adults with MDR-TB receiving antimicrobial therapy (conditional recommendation, very low certainty evidence).

Treatment of Isoniazid-Resistant TB

A recent systematic review and meta-analysis compared the treatment outcomes of isoniazid-resistant TB to outcomes of drug-susceptible TB and found that treatment of isoniazid-resistant TB with first-line drugs resulted in suboptimal outcomes, with higher treatment failure (11% vs. 1%) and relapse (10% vs. 5%) (25). In an IPDMA of 33 datasets with 6,424 patients, of whom 3,923 patients in 23 studies received regimens related to isoniazid-resistant TB, adding a fluoroquinolone to this regimen was associated with significantly greater treatment success (adjusted odds ratio [aOR], 2.8; 95% CI, 1.1–7.3), but with no significant effect on mortality (aOR, 0.7; 95% CI, 0.4–1.1) or acquired rifampicin resistance (aOR, 0.1; 95% CI, 0.0–1.2) (1). When evaluating the impact of shortening the duration of pyrazinamide (ranging from 1 to 3 mo) in a regimen that contains a fluoroquinolone, the treatment success was very high, with 117 of 118 patients achieving treatment success. On the other hand, comparisons of shorter pyrazinamide regimens with regimens including both a fluoroquinolone and pyrazinamide for ⩾6 months did not show significantly different results (aOR, 5.2; 95% CI, 0.6–46.7).

Table 4. Doses of Drugs for Treatment of Adults and Children with Multidrug-Resistant Tuberculosis

Step	Drug	Route of Administration	Adults	Children	Reduced Renal Function*
1	Levofloxacin	p.o./i.v.	750–1,000 mg daily†	15–20 mg/kg/d once daily†	3 times/wk
	Moxifloxacin	p.o./i.v.	400 to (600–800 mg) daily‡	10–15 mg/kg/d once daily	No change needed
2	Bedaquiline	p.o.	400 mg daily × 14 d then 200 mg 3 times/wk	⩾12 yr and ⩾30 kg: adult dose Studies ongoing in lower age groups and weights. Based on expert opinion, for children >6 yr and weight 15–30 kg, half the adult dose can be used (200 mg/d × 2 wk then 100 mg M/W/F for 22–24 wk	No change needed
	Linezolid	p.o./i.v.	600 mg daily	⩾12 yr: 10 mg/kg once daily (300 or 600 mg) <12 yr: based on modeled pharmacokinetic data for lower weight bands (4, 11, 28): 5–9 kg: 15 mg/kg once daily 10–23 kg: 12 mg/kg once daily >23 kg: 10 mg/kg once daily	No change needed
3	Clofazimine	p.o.	100 mg daily	2–5 mg/kg/d	No change needed
	Cycloserine/terizidone	p.o.	250–750 mg daily§ to achieve serum 20–35 mg/L in plasma‖	15–20 mg/kg/d	Start with 250 mg daily and verify with TDM in setting of renal disease
4	Amikacin	i.v./i.m.	15 mg/kg daily. Some clinicians prefer 25 mg/kg 3 times/wk	15–20 mg/kg/d	Patients with decreased renal function may require the 15 mg/kg dose to be given only 2–3 times/wk to allow for drug clearance
	Streptomycin	i.v./i.m.	15 mg/kg daily. Some clinicians prefer 25 mg/kg 3 times/wk	15–20 mg/kg daily or 25–30 mg/kg twice weekly¶	Patients with decreased renal function may require the 15 mg/kg dose to be given only 2–3 times/wk to allow for drug clearance
5	Delamanid	p.o.	100 mg twice daily	⩾35 kg: adult dose ⩾6 yr and 20–34 kg: 50 mg twice daily >3–5 yr and 10–20 kg: 25 mg twice daily Lower age/weight: studies ongoing	Mild to moderate renal insufficiency: no change. Severe insufficiency: limited data, use with caution
	Ethambutol	p.o./i.v.	Low dose (companion drug): 15 mg/kg daily High dose (bacteriostatic drug): 25 mg/kg daily	20–25 mg/kg/d	3 times/wk
	Pyrazinamide	p.o.	25–40 mg/kg daily	30–40 mg/kg/d	3 times/wk

(Continued)

Table 4. (*Continued*)

Step	Drug	Route of Administration	Adults	Children	Reduced Renal Function*
6	Ethionamide	p.o.	15–20 mg/kg total (usually 250–500 mg once or twice daily)**	15–20 mg/kg total (divided 1–2 times/d)	No change needed
	Prothionamide	p.o.	15–20 mg/kg total (usually 250–500 mg once or twice daily)**	15–20 mg/kg total (divided 1–2 times/d)	No change needed
	Imipenem–cilastatin	i.v.	1,000 mg 3–4 times/d	(imipenem component) 15–25 mg/kg/dose 4 times/d	May reduce frequency
	Meropenem	i.v.	1,000 mg 3 times/d††	20–40 mg/kg/dose 3 times/d	May reduce frequency
	Clavulanate (component of amoxicillin–clavulanate) for coadministration with carbapenems (imipenem–cilastatin and meropenem)	p.o./i.v.	250 mg 3 times/d	25 mg/kg/dose of amoxicillin component 3 times/d	May reduce frequency to match carbapenem
	p-Aminosalicylic acid	p.o./i.v.	4 g 2–3 times/d‡‡	200–300 mg/kg/d in two divided doses§§	No change needed
	High-dose isoniazid||||	p.o./i.v.	15 mg/kg daily	15–20 mg/kg/d	No change needed

Definition of abbreviations: M/W/F = Monday/Wednesday/Friday; TDM = therapeutic drug monitoring.
Updated and modified from References 5, 10, 29, and 30.
*Dosages may not apply to patients with severely decreased kidney function, including in the setting of dialysis, for which consultation with a nephrologist is advised.
†Levofloxacin doses of up to 1,250 mg have been used safely when needed to achieve therapeutic concentrations. A recent population pharmacokinetic study in South African children found that higher levofloxacin doses from 18 mg/kg/d for younger children, up to 40 mg/kg/d for older children, may be required to achieve adult-equivalent exposures (31).
‡Higher moxifloxacin doses have been used safely when the isolate is resistant to ofloxacin and the minimum inhibitory concentration for levofloxacin or moxifloxacin suggests higher doses may overcome resistance. Higher doses also are used in cases of malabsorption.
§Cycloserine doses can be divided if needed (typically twice daily). Doses >750 mg are difficult for many patients to tolerate.
||Cycloserine dose may be lowered if serum concentrations exceed 35 μg/ml, even if patient is not experiencing toxicity, to prevent central nervous system toxicity.
¶Modified from adult intermittent dose of 25 mg/kg, and accounting for larger total body water content and faster clearance of injectable drugs in most children. Dosing can be guided by serum concentrations.
**Ethionamide can be given at bedtime or with a meal to reduce nausea. Experienced clinicians suggest starting with 250 mg once daily and gradually increasing the dose over 1 week. Serum concentrations may be useful in determining the appropriate dose. Few patients tolerate 500 mg twice daily.
††Studies are ongoing evaluating meropenem at higher doses (ClinicalTrials.gov identifiers: NCT03174184 and NCT02349841).
‡‡Some experts prescribe *p*-aminosalicylic acid at 6 g, and up to12 g, administered once daily (10, 32).
§§For children, some experts prescribe *p*-aminosalicylic acid at 200 mg/kg administered once daily (32).
||||Isoniazid is tested at two concentrations. Some experts use these results (or resistance conferred through mutations in *inhA*) to select a higher dose when it tests resistant at the lower concentration and susceptible at the higher concentration. The higher dose may achieve *in vivo* concentrations sufficiently high to overcome low-level resistance (10, 32).

For the treatment of isoniazid-resistant TB:

23. We suggest adding a later-generation fluoroquinolone to a 6-month regimen of daily rifampin, ethambutol, and pyrazinamide for patients with isoniazid-resistant TB (conditional recommendation, very low certainty in the evidence).
24. In patients treated with a daily regimen of a later-generation fluoroquinolone, rifampin, ethambutol, and pyrazinamide, we suggest that the duration of pyrazinamide can be shortened to 2 months in selected situations (i.e., noncavitary and lower burden disease or toxicity from pyrazinamide) (conditional recommendation, very low certainty in the evidence).

Treatment of Contacts Exposed to MDR-TB

Using data from five comparison studies included in the systematic review of 21 published observational studies, MDR-TB developed in 2 of 190 (1.1%) patients treated for MDR latent TB infection (LTBI), compared with 18 of 126 (14.3%) in those who received no MDR LTBI treatment (26). The estimated MDR-TB incidence reduction was 90% (9–99%), using a negative binomial model controlling for person time and overdispersion (27). From 11 studies having data by regimen on treatment discontinuation due to adverse effects, 51% of patients taking pyrazinamide-containing regimens discontinued treatment (27). About one-third of patients taking fluoroquinolone-containing regimens without

pyrazinamide had adverse effects, but only 2% discontinued treatment.

For the management of contacts to patients with MDR-TB:

25. We suggest offering treatment for LTBI for contacts to patients with MDR-TB versus observation alone (conditional recommendation, very low certainty in the evidence). We suggest 6 to 12 months of treatment with a later-generation fluoroquinolone alone or with a second drug, on the basis of drug susceptibility of the source-case *M. tuberculosis* isolate. On the basis of evidence of increased toxicity, adverse events, and discontinuations, pyrazinamide should not be routinely used as the second drug.

Summary

In this practice guideline for the treatment of MDR-TB, new recommendations are made for the choice and number of drugs in a regimen, the duration of intensive and continuation phases, and the role of injectable drugs. On the basis of these recommendations, an effective all-oral regimen for MDR-TB can be assembled. Recommendations are also provided on the role of surgery in treatment of MDR-TB, for treatment of contacts exposed to MDR-TB, and for treatment of isoniazid-resistant TB. Good practices for treating drug-resistant TB, detailed information on drugs, treatment in special situations (children, pregnant women, and HIV-infected patients), approaches to monitoring treatment including the role of therapeutic drug monitoring, key research priorities, as well as a summary of key differences between this ATS/CDC/ERS/IDSA practice guideline and the WHO 2019 Consolidated Guidelines on Drug-Resistant Tuberculosis Treatment (4) are provided in the full-text version of the guidelines available online. ■

This official clinical practice guideline was prepared by an *ad hoc* subcommittee of the ATS, CDC, ERS, and IDSA.

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Author Disclosures: G.H.B. served as a speaker for Johnson & Johnson. C.L.D. served on an advisory committee for Insmed, Otsuka Pharmaceutical, Horizon, Johnson & Johnson, Paraek, and Spero; served on a data and safety monitoring board for Otsuka Pharmaceutical and Sanofi; and received research support from Insmed. C.R.H. served on a data and safety monitoring board for Janssen. F.A.K. received support from the World Health Organization for meta-analysis of this paper. C.D.M. served as a consultant for Otsuka Pharmaceuticals; and received research support from Janssen and Unitaid. H.S.S. received research support from the U.S. NIH, IMPAACT, and Otsuka Pharmaceuticals. J.R.S. served on a data and safety monitoring board for Otsuka Pharmaceuticals. P.N., G.B.M., T.C., S.R.M., B.S., J.L.B., A.C., J.P.C., L.C., T.L.D., R.D., F.F., F.K., Z.L., A.L., M.L., J.M.M., S.M.M., L.M., D.M., D.M.N., F.P., C.A.P., A.R., N.S.S., G.S., J.W.W., and J.M.W reported no relevant commercial relationships.

Acknowledgment: This practice guideline was prepared by an *ad hoc* subcommittee from the American Thoracic Society, Centers for Disease Control and Prevention, European Respiratory Society, and Infectious Diseases Society of America. The authors thank Lindsay McKenna, as part of the writing committee, and the Treatment Action Group, New York, NY, for providing patient advocacy and community engagement input. They also thank Dennis Falzon (World Health Organization) for contributions as an observer. They also thank Kevin Wilson, Kimberly Lawrence, and Judy Corn (American Thoracic Society); Marc Miravitlles and Valérie Vaccaro (European Respiratory Society); Phil LoBue, Angela Starks, Tracy Ayers, Sapna Bamrah Morris (CDC), and Jennifer Padberg (Infectious Diseases Society of America).

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