Clinical Infectious Diseases

IDSA FEATURES

Treatment of Nontuberculous Mycobacterial Pulmonary Disease: An Official ATS/ERS/ESCMID/IDSA Clinical Practice Guideline

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Nontuberculous mycobacteria (NTM) represent over 190 species and subspecies, some of which can produce disease in humans of all ages and can affect both pulmonary and extrapulmonary sites. This guideline focuses on pulmonary disease in adults (without cystic fibrosis or human immunodeficiency virus infection) caused by the most common NTM pathogens such as *Mycobacterium avium* complex, *Mycobacterium kansasii,* and *Mycobacterium xenopi* among the slowly growing NTM and *Mycobacterium abscessus* among the rapidly growing NTM. A panel of experts was carefully selected by leading international respiratory medicine and infectious diseases societies (ATS, ERS, ESCMID, IDSA) and included specialists in pulmonary medicine, infectious diseases and clinical microbiology, laboratory medicine, and patient advocacy. Systematic reviews were conducted around each of 22 PICO (Population, Intervention, Comparator, Outcome) questions and the recommendations were formulated, written, and graded using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach. Thirty-one evidence-based recommendations about treatment of NTM pulmonary disease are provided. This guideline is intended for use by healthcare professionals who care for patients with NTM pulmonary disease, including specialists in infectious diseases and pulmonary diseases.

Keywords. nontuberculous; *Mycobacterium avium* complex; *Mycobacterium kansasii*; *Mycobacterium abscessus*; *Mycobacterium xenopi*.

EXECUTIVE SUMMARY

The American Thoracic Society (ATS), European Respiratory Society (ERS), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), and Infectious Diseases Society of America (IDSA) jointly sponsored the development of this Guideline to update the treatment recommendations for nontuberculous mycobacterial (NTM) pulmonary disease in adults. NTM represent over 190 species and subspecies (http://www.bacterio.net/mycobacterium.html), many of which can produce disease in humans of all ages and can affect both pulmonary and extrapulmonary sites. Attempting to cover such a broad array of species and disease in a guideline using current guideline development methods is impossible. Therefore, this guideline focuses on pulmonary disease in adults (without cystic fibrosis or human immunodeficiency virus [HIV] infection) caused by the most common NTM pathogens comprising *Mycobacterium avium* complex (MAC), *Mycobacterium kansasii,* and *Mycobacterium xenopi* among the slowly growing NTM and *Mycobacterium abscessus* among the rapidly growing NTM. Twenty-two PICO (Population, Intervention,

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Table 1. Interpretation of Strong and Conditional (Weak) Recommendations

	Recommendations	
	Strong	Conditional
Patients	• Most individuals in this situation would want the recommended course of action, and only a small proportion would not.	• The majority of individuals in this situation would want the suggested course of action, but many would not.
Clinicians	• Most individuals should receive the intervention. • Adherence to the 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.	• Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their values and preferences.
Policy makers	• The recommendation can be adopted as policy in most situations.	• Policy making will require substantial debate and involvement of various stakeholders.

Source: Grading of Recommendations Assessment, Development and Evaluation Working Group [1, 2].

Comparators, Outcomes) questions and associated recommendations are included in the Guideline. A panel of experts was carefully selected and screened for conflicts of interest and included specialists in pulmonary medicine, infectious diseases and clinical microbiology, laboratory medicine, and patient advocacy. The recommendations were developed based on the evidence that was appraised using GRADE (Grading of Recommendations Assessment, Development, and Evaluation) and are summarized below [1, 2]. Recommendations were either "strong" or "conditional" (Table 1), and as suggested by GRADE, the phrase "we recommend" was used for strong recommendations and "we suggest" for conditional recommendations [3].

This executive summary is a condensed version of the panel's recommendations for the 22 PICO questions. A detailed description of background, methods, evidence summary, and rationale that support each recommendation can be found online in the full text and accompanying supplementary material.

DIAGNOSTIC CRITERIA FOR NTM PULMONARY DISEASE

The 2007 guideline included clinical, radiographic, and microbiologic criteria for diagnosing NTM pulmonary disease [4]. The current guideline also recommends use of these criteria to classify patients as having NTM pulmonary disease (Table 2). The significance of NTM isolated from the sputum of individuals who meet the clinical and radiographic criteria in Table 2 must be interpreted in the context of the number of positive cultures and specific species isolated. Because NTM can be isolated from respiratory specimens due to environmental contamination and because some patients who have an NTM isolated from their respiratory tract do not show evidence of progressive disease, >1 positive sputum culture is recommended for diagnostic purposes, and the same NTM species (or subspecies in the case of *M. abscessus*) should be isolated in ≥2 sputum cultures. Clinically significant MAC pulmonary disease is unlikely in patients who have a single positive sputum culture during the initial evaluation [5–7] but can be as high as 98% in those with ≥2 positive cultures [5].

Table 2. Clinical and Microbiologic Criteria for Diagnosis of Nontuberculous Mycobacterial Pulmonary Disease[a]

Clinical	Pulmonary or Systemic Symptoms	
Radiologic	Nodular or cavitary opacities on chest radiograph, or a high-resolution computed tomography scan that shows bronchiectasis with multiple small nodules	Both Required
and	Appropriate exclusion of other diagnoses	
Microbiologic[b]	1. Positive culture results from at least two separate expectorated sputum samples. If the results are nondiagnostic, consider repeat sputum AFB smears and cultures **or** 2. Positive culture results from at least one bronchial wash or lavage **or** 3. Transbronchial or other lung biopsy with mycobacterial histologic features (granulomatous inflammation or AFB) and positive culture for NTM or biopsy showing mycobacterial histologic features (granulomatous inflammation or AFB) and one or more sputum or bronchial washings that are culture positive for NTM	

Source: Official ATS/IDSA statement [4].

Abbreviation: AFB, acid-fast bacilli; NTM, Nontuberculous mycobacteria.

[a]Expert consultation should be obtained when NTM are recovered that are either infrequently encountered or that usually represent environmental contamination. Patients who are suspected of having NTM pulmonary disease but do not meet the diagnostic criteria should be followed until the diagnosis is firmly established or excluded. Making the diagnosis of NTM pulmonary disease does not per se, necessitate the institution of therapy, which is a decision based on the potential risks and benefits of therapy for individual patients.

[b]When 2 positive cultures are obtained, the isolates should be the same NTM species (or subspecies in the case of *M. abscessus*) in order to meet disease criteria.

The pathogenicity of NTM varies significantly from organisms like *M. gordonae*, which rarely cause disease in humans, to *M. kansasii,* which should usually be considered pathogenic [8]. For species of low pathogenicity such as *M. gordonae*, several repeated positive cultures over months, along with strong clinical and radiological evidence of disease, would be required to determine if it was causing disease, whereas a single positive culture for *M. kansasii* in the proper context may be enough evidence to initiate treatment [9]. The pathogenicity of NTM species may differ between geographic areas [9, 10].

Importantly, just because a patient meets diagnostic criteria for NTM pulmonary disease does not necessarily mean antibiotic treatment is required. A careful assessment of the pathogenicity of the organism, risks and benefits of therapy, the patient's wish and ability to receive treatment as well as the goals of therapy should be discussed with patients prior to initiating treatment. In some instances, "watchful waiting" may be the preferred course of action.

RECOMMENDATIONS FOR SPECIFIC PICO QUESTIONS

Twenty-two PICO questions are addressed in this Guideline resulting in 31 recommendations. For each NTM covered, the recommendations are organized by the drugs to be included in the regimen, frequency of administration, and duration of therapy.

Treatment of NTM Pulmonary Disease (Questions I–II)

I: Should patients with NTM pulmonary disease be treated with antimicrobial therapy or followed for evidence of progression ("watchful waiting")?

Recommendation

1. In patients who meet the diagnostic criteria for NTM pulmonary disease (Table 2), we suggest initiation of treatment rather than watchful waiting, especially in the context of positive acid-fast bacilli sputum smears and/or cavitary lung disease (conditional recommendation, very low certainty in estimates of effect).

Remarks: The decision to initiate antimicrobial therapy for NTM pulmonary disease should be individualized based on a combination of clinical factors, the infecting species, and individual patient priorities. Any treatment decision should include a discussion with the patient that outlines the potential side effects of antimicrobial therapy, the uncertainties surrounding the benefits of antimicrobial therapy, and the potential for recurrence including reinfection (particularly in the setting of nodular/bronchiectatic disease) [11–13].

II: Should patients with NTM pulmonary disease be treated empirically or based on in vitro drug susceptibility test results?

Recommendations

1. In patients with MAC pulmonary disease, we suggest susceptibility-based treatment for macrolides and amikacin over empiric therapy (conditional recommendation, very low certainty in estimates of effect).
2. In patients with *M. kansasii* pulmonary disease, we suggest susceptibility-based treatment for rifampicin over empiric therapy (conditional recommendation, very low certainty in estimates of effect).
3. In patients with *M. xenopi* pulmonary disease, the panel members felt there is insufficient evidence to make a recommendation for or against susceptibility-based treatment.
4. In patients with *M. abscessus* pulmonary disease we suggest susceptibility-based treatment for macrolides and amikacin over empiric therapy (conditional recommendation, very low certainty in estimates of effect). For macrolides, a 14-day incubation and/or sequencing of the *erm*(41) gene is required in order to evaluate for potential inducible macrolide resistance.

Remark: Although in vitro-in vivo correlations have not yet been proven for all major antimycobacterial drugs, baseline susceptibility testing to specific drugs is recommended according to the Clinical and Laboratory Standards Institute (CLSI) guidelines [14, 15] for NTM isolates from patients with definite disease. Testing of other drugs may be useful, but there is insufficient data to make specific recommendations.

Mycobacterium avium Complex (Questions III–IX)

III: Should patients with macrolide-susceptible MAC pulmonary disease be treated with a 3-drug regimen with a macrolide or without a macrolide?

Recommendation

1. In patients with macrolide-susceptible MAC pulmonary disease, we recommend a 3-drug regimen that includes a macrolide over a 3-drug regimen without a macrolide (strong recommendation, very low certainty in estimates of effect).

Remarks: Although no well-designed randomized trials of macrolide therapy have been performed, macrolide susceptibility has been a consistent predictor of treatment success for pulmonary MAC [16–18]. Loss of the macrolide from the treatment regimen is associated with a markedly reduced rate of conversion of sputum cultures to negative and higher mortality [16–18]. Therefore, the panel members felt strongly that a macrolide should be included in the regimen.

IV: In patients with newly diagnosed macrolide-susceptible MAC pulmonary disease, should an azithromycin-based regimen or a clarithromycin-based regimen be used?

Recommendation

1. In patients with macrolide-susceptible MAC pulmonary disease we suggest azithromycin-based treatment regimens rather than clarithromycin-based regimens (conditional recommendation, very low certainty in estimates of effect).

Remarks: The panel felt that azithromycin was preferred over clarithromycin because of better tolerance, less drug-interactions, lower pill burden, single daily dosing, and equal efficacy. However, when azithromycin is not available or not tolerated, clarithromycin is an acceptable alternative.

V: Should patients with MAC pulmonary disease be treated with a parenteral amikacin or streptomycin-containing regimen or without a parenteral amikacin or streptomycin-containing regimen?

Recommendation

1. For patients with cavitary or advanced/severe bronchiectatic or macrolide-resistant MAC pulmonary disease, we suggest that parenteral amikacin or streptomycin be included in the initial treatment regimen (conditional recommendation, moderate certainty in estimates of effect).

Remarks: In the absence of comparably effective oral medications there are few options other than parenteral aminoglycosides for "intensifying" standard oral MAC therapy. The committee thought that the benefits outweighed risks in those patients with cavitary or advanced/severe bronchiectatic or macrolide-resistant MAC pulmonary disease and that administration of at least 2–3 months of an aminoglycoside was the best balance between risks and benefits.

VI: In patients with macrolide-susceptible MAC pulmonary disease, should a regimen with inhaled amikacin or a regimen without inhaled amikacin be used for treatment?

Recommendations

1. In patients with newly diagnosed MAC pulmonary disease, we suggest neither inhaled amikacin (parenteral formulation) nor amikacin liposome inhalation suspension (ALIS) be used as part of the initial treatment regimen (conditional recommendation, very low certainty in estimates of effect).
2. In patients with MAC pulmonary disease who have failed therapy after at least 6 months of guideline-based therapy, we recommend addition of ALIS to the treatment regimen rather than a standard oral regimen, only (strong recommendation, moderate certainty in estimates of effect).

Remarks: Randomized controlled trials have demonstrated the efficacy and safety of ALIS when added to guideline-based therapy for treatment refractory MAC pulmonary disease [19, 20]. ALIS is currently approved by the United States Federal Drug Administration for treatment of refractory MAC pulmonary disease. As noted in question 5, we suggest that parenteral amikacin or streptomycin be included in the initial treatment regimen in patients with cavitary or advanced/severe bronchiectatic or macrolide-resistant MAC pulmonary disease.

VII: In patients with macrolide-susceptible MAC pulmonary disease, should a 3-drug or a 2-drug macrolide-containing regimen be used for treatment?

Recommendation

1. In patients with macrolide-susceptible MAC pulmonary disease, we suggest a treatment regimen with at least 3 drugs (including a macrolide and ethambutol) over a regimen with 2 drugs (a macrolide and ethambutol alone) (conditional recommendation, very low certainty in estimates of effect).

Remarks: A priority in MAC pulmonary disease therapy is preventing the development of macrolide resistance. The panel members were concerned that the currently available data [21] were insufficient to determine the risk of acquired macrolide resistance with a 2-drug regimen and therefore suggest a 3 drug macrolide-containing regimen.

VIII: In patients with macrolide susceptible MAC pulmonary disease, should a daily or a 3-times weekly macrolide-based regimen be used for treatment?

Recommendations

1. In patients with noncavitary nodular/bronchiectatic macrolide-susceptible MAC pulmonary disease, we suggest a 3 times per week macrolide-based regimen rather than a daily macrolide-based regimen (conditional recommendation, very low certainty in estimates of effect).
2. In patients with cavitary or severe/advanced nondular bronchiectatic macrolide-susceptible MAC pulmonary disease we suggest a daily macrolide-based regimen rather than 3 times per week macrolide-based regimen (conditional recommendation, very low certainty in estimates of effect).

Remarks: Intermittent therapy has similar sputum conversion rates as daily therapy for nodular/bronchiectatic MAC pulmonary disease and is also better tolerated than daily therapy [22, 23]. A critically important finding from the available studies is the lack of development of macrolide resistance with intermittent therapy. There is not similar evidence to justify or support intermittent therapy for cavitary MAC pulmonary disease and it is not recommended.

IX: In patients with macrolide-susceptible MAC pulmonary disease, should patients be treated with <12 months of treatment after culture negativity or ≥12 months of treatment after culture negativity?

Recommendation

1. We suggest that patients with macrolide-susceptible MAC pulmonary disease receive treatment for at least 12 months after culture conversion (conditional recommendation, very low certainty in estimates of effect).

Remarks: The optimal duration of therapy for pulmonary MAC disease is not currently known. The panel felt that in the absence of evidence identifying an optimal treatment duration that the recommendation from the 2007 Guideline should be followed [4].

Mycobacterium kansasii (Questions X–XIV)

X: In patients with rifampcin-susceptible *M. kansasii* pulmonary disease, should an isoniazid-containing regimen or a macrolide-containing regimen be used for treatment?

Recommendation

1. In patients with rifampicin-susceptible *M. kansasii* pulmonary disease, we suggest a regimen of rifampicin, ethambutol, and either isoniazid or macrolide (conditional recommendation, very low certainty in estimates of effect).

Remarks: Isoniazid is widely used at present for treatment of *M. kansasii* pulmonary disease, and in the experience of the panel members, there have been good outcomes when using a regimen consisting of rifampicin, ethambutol, and isoniazid irrespective of the result of minimal inhibitory concentrations (MICs) for isoniazid and ethambutol [24]. Based on the in vitro activity of macrolides against *M. kansasii*, and 2 studies that demonstrated good treatment outcomes when clarithromycin was substituted for isoniazid [25, 26], the panel suggests that either isoniazid or a macrolide can be used in combination with rifampicin and ethambutol.

XI: In patients with rifampicin-susceptible *M. kansasii* pulmonary disease, should parenteral amikacin or streptomycin be included in the treatment regimen?

Recommendation

1. We suggest that neither parenteral amikacin nor streptomycin be used routinely for treating patients with *M. kansasii* pulmonary disease (strong recommendation, very low certainty in estimates of effect).

Remarks: Regimens of 3 oral agents, rifampicin and ethambutol, and either isoniazid or a macrolide, achieve high rates of sustained culture conversion and treatment success in the treatment of *M. kansasii* pulmonary disease. Therefore, given the good outcomes observed with oral regimens and the high risk of adverse effects associated with parenteral amikacin or streptomycin, the committee felt strongly that the use of these parenteral agents is not warranted, unless it is impossible to use a rifampicin-based regimen or severe disease is present.

XII: In patients with rifampicin-susceptible *M. kansasii* pulmonary disease, should a treatment regimen that includes a fluoroquinolone or a regimen without a fluoroquinolone be used?

Recommendations

1. In patients with rifampicin-susceptible *M. kansasii* pulmonary disease, we suggest using a regimen of rifampicin, ethambutol, and either isoniazid or macrolide instead of a fluoroquinolone (conditional recommendation, very low certainty in estimates of effect).
2. In patients with rifampicin-resistant *M. kansasii* or intolerance to one of the first-line antibiotics we suggest a fluoroquinolone (eg, moxifloxacin) be used as part of a second-line regimen (conditional recommendation, very low certainty in estimates of effect).

Remarks: Treatment success of *M. kansasii* pulmonary disease with a rifamycin-based drug regimen is usually excellent but the optimal choice of companion drugs is not clear. While ethambutol is usually the preferred companion drug, the choice of an additional companion drug may be isoniazid, a macrolide or a fluoroquinolone. As there is more experience and better evidence for treatment regimens that include isoniazid or a macrolide as a companion drug, these drugs are preferred [25–28]. For rifampicin-resistant disease, a regimen such as ethambutol, azithromycin, and a fluoroquinolone would be likely to lead to successful treatment.

XIII: In patients with rifampicin-susceptible *M. kansasii* pulmonary disease, should a 3 times per week or daily treatment regimen be used?

Recommendations

1. In patients with noncavitary nodular/bronchiectatic *M. kansasii* pulmonary disease treated with a rifampicin, ethambutol, and macrolide regimen, we suggest either daily or 3 times weekly treatment (conditional recommendation, very low certainty in estimates of effect)
2. In patients with cavitary *M. kansasii* pulmonary disease treated with a rifampicin, ethambutol, and macrolide-based regimen, we suggest daily treatment instead of 3 times weekly treatment (conditional recommendation, very low certainty in estimates of effect).
3. In all patients with *M. kansasii* pulmonary disease treated with an isoniazid, ethambutol, and rifampicin regimen, we suggest treatment be given daily instead of 3 times weekly (conditional recommendation, very low certainty in estimates of effect).

Remarks: Because there are no randomized trials available and the small size of the single study that evaluated 3 times weekly therapy [26], the committee did not feel that they could recommend intermittent therapy in the setting of cavitary disease until more evidence was available. Similarly, there are no data to support the use of isoniazid on a 3 times weekly basis in patients with *M. kansasii* pulmonary disease.

XIV: In patients with rifampicin susceptible *M. kansasii* pulmonary disease, should treatment be continued for <12 months or ≥12 months?

Recommendation

1. We suggest that patients with rifampin susceptible *M. kansasii* pulmonary disease be treated for at least 12 months (conditional recommendation, very low certainty in estimates of effect).

Remarks: Current rifampicin-based treatment regimens are associated with a high rate of success if used for at least 12 months [27, 29]. Randomized controlled trials comparing shorter treatment regimens are currently lacking. Although some experts would favor 12 months of treatment after culture conversion, there is no evidence that relapses could be prevented with treatment courses longer than 12 months. Therefore, the panel members felt that *M. kansasii* could be treated for a fixed duration of 12 months instead of 12 months beyond culture conversion. Because sputum conversion at 4 months of rifampicin-based regimens is usually observed [29–31], expert consultation should be obtained if cultures fail to convert to negative by that time.

Mycobacterium xenopi (Questions XV–XVIII)

XV: In patients with *M. xenopi* pulmonary disease, should a treatment regimen that includes a fluoroquinolone or a regimen without a fluoroquinolone be used?

Recommendation

1. In patients with *M. xenopi* pulmonary disease, we suggest using a multidrug treatment regimen that includes moxifloxacin or macrolide (conditional recommendation, low certainty in estimates of effect).

Remarks: There is in vitro evidence that macrolides and fluoroquinolones are active against *M. xenopi*, whereas rifampicin and ethambutol are inactive in vitro alone and in combinations [32]. Preliminary data from a study in France that randomized patients to receive either moxifloxacin or clarithromycin plus ethambutol and rifampicin reported no difference in the treatment success between the study arms [33].

XVI: In patients with *M. xenopi* pulmonary disease, should a 2-, 3-, or 4-drug regimen be used for treatment?

Recommendation

1. In patients with *M. xenopi* pulmonary disease, we suggest a daily regimen that includes at least 3 drugs: rifampicin, ethambutol, and either a macrolide and/or a fluoroquinolone (eg, moxifloxacin) (conditional recommendation, very low certainty in estimates of effect).

Remarks: Given the high mortality associated with *M. xenopi* disease, the panel members felt the large risk of treatment failure with a 2-drug regimen warranted at least a 3-drug treatment regimen. However, the absence of universal access to moxifloxacin and the small amount of data for other fluoroquinolones has to be considered when choosing a regimen.

XVII: In patients with *M. xenopi* pulmonary disease, should parenteral amikacin or streptomycin be included in the treatment regimen?

1. In patients with cavitary or advanced/severe bronchiectatic *M. xenopi* pulmonary disease, we suggest adding parenteral amikacin to the treatment regimen and obtaining expert consultation (conditional recommendation, very low certainty in estimates of effect).

Remarks: Barring compelling evidence to the contrary, *M. xenopi* patients should be treated aggressively given the high mortality of the disease [34–36]. In addition to the high mortality, the committee considered the general acceptability and feasibility of parenteral therapy, and potential costs and toxicities, all based on clinical experience.

XVIII: In patients with *M. xenopi* pulmonary disease, should treatment be continued for <12 months or ≥12 months after culture conversion?

1. In patients with *M. xenopi* pulmonary disease, we suggest that treatment be continued for at least 12 months beyond culture conversion (conditional recommendation, very low certainty in estimates of effect).

Remarks: Data suggest that treatment outcomes improve if the duration of treatment increases [35, 37]. The panel felt that this outweighs the risk of adverse events associated with longer treatment and agrees with previous recommendations [4].

Mycobacterium abscessus (Questions XIX–XXI)

XIX: In patients with *M. abscessus* pulmonary disease, should a macrolide-based regimen or a regimen without a macrolide be used for treatment?

Recommendations

1. In patients with *M. abscessus* pulmonary disease caused by strains *without* inducible or mutational resistance, we recommend a

macrolide-containing multidrug treatment regimen (strong recommendation, very low certainty in estimates of effect).

2. In patients with *M. abscessus* pulmonary disease caused by strains *with* inducible or mutational macrolide resistance, we suggest a macrolide-containing regimen if the drug is being used for its immunomodulatory properties although the macrolide is not counted as an active drug in the multidrug regimen (conditional recommendation, very low certainty in estimates of effect).

Remarks: *M. abscessus* infections can be life-threatening, and the use of macrolides is potentially of great benefit. Macrolides are very active in vitro against *M. abscessus* strains without a functional *erm*(41) gene, and evidence supports use of macrolides in patients with disease caused by macrolide-susceptible *M. abscessus* [38, 39]. It is important to perform in vitro macrolide susceptibility testing including detection of a functional or nonfunctional *erm*(41) gene [40–42].

XX: In patients with *M. abscessus* complex pulmonary disease, how many antibiotics should be included within multidrug regimens?

Recommendation

1. In patients with *M. abscessus* pulmonary disease, we suggest a multidrug regimen that includes at least 3 active drugs (guided by in vitro susceptibility) in the initial phase of treatment (conditional recommendation, very low certainty in estimates of effect).

Remarks: Given the usual disease severity of *M. abscessus* pulmonary disease, the variable and limited in vitro drug susceptibility of these organisms, the potential for the emergence of drug resistance, and the potential for more rapid progression of *M. abscessus* pulmonary disease, the panel members suggest using a regimen consisting of three or more active drugs. The panel members felt strongly that treatment regimens should be designed in collaboration with experts in the management of these complicated infections.

XXI: In patients with *M. abscessus* pulmonary disease, should shorter or longer duration therapy be used for treatment?

Recommendation

1. In patients with *M. abscessus* pulmonary disease, we suggest that either a shorter or longer treatment regimen be used and expert consultation obtained (conditional recommendation for either the intervention or the comparison, very low certainty in estimates of effect).

Remarks: The lack of studies, the variation in drug availability, resources, and practice settings made it difficult to come to a consensus on the optimum duration of therapy. In addition, the panel members felt that some subgroups of patients should be considered separately in determining the length of therapy such as: patients with nodular/bronchiectatic versus cavitary disease, patients affected by lung disease caused by different *M. abscessus* subspecies and importantly, depending on susceptibility to macrolides and amikacin. The panel members suggest that an expert in the management of patients with *M. abscessus* pulmonary disease be consulted.

Surgical Resection (Question XXII)

XXII: Should surgery plus medical therapy or medical therapy alone be used to treat NTM pulmonary disease?

Recommendation

1. In selected patients with NTM pulmonary disease, we suggest surgical resection as an adjuvant to medical therapy after expert consultation (conditional recommendation, very low certainty in estimates of effect).

Remarks: Selected patients with failure of medical management, cavitary disease, drug resistant isolates, or complications such as hemoptysis or severe bronchiectasis may undergo surgical resection of the diseased lung. The decision to proceed with surgical resection must be weighed against the risks and benefits of surgery. The panel suggests that surgery be performed by a surgeon experienced in mycobacterial surgery [43].

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Dedication. This Guideline is dedicated to the memory of Won-Jung Koh, MD, whose passion, leadership, and work led to evidence that helped to support recommendations in this Guideline. His tireless effort to improve the diagnosis and treatement of NTM disease will never be forgotten.

Potential conflicts of interest. C. L. D. served on advisory committees for Cipla, Horizon, Insmed, Johnson & Johnson, Matinas Biopharma, Otsuka America Pharmaceutical, Paratek, and Spero; received research support from Beyond Air, Insmed, and Spero; served as a consultant for Meiji. C. L. served as a speaker for Berlin Chemie, Chiesi, Gilead, Janssen, Lucane, and Novartis; served on an advisory committee for Oxford Immunotec. R. J. W. served as the director of a university clinical laboratory that does NTM identification, molecular strain comparison, and susceptibility testing; received research support from Insmed as mycobacterial reference laboratory for a trial of the inhaled liposomal amikacin. C. A. received research support from Insmed. E. C. B. served as a consultant for AID Diagnostika, Becton Dickinson, and COPAN; provided expert testimony for Shuttleworth & Ingersoll law firm. D. E. G. served on an advisory committee, as a consultant, as a speaker and received research

support from Insmed; served as a consultant for Johnson & Johnson, Merck, and Spero. G. A. H. served on an advisory committee for Hill-Rom and Insmed. P. L. served as the president of NTM Info & Research, Inc, during which time the organization received support from Insmed, Grifols, BeyondAir, Aradigm, Spero Therapeutics, Johnson & Johnson, Hill-Rom, International Biophysics, Electromed, RespirTech, Maxor Specialty Pharmacy, PantherX, and Kroger Specialty Pharmacy. T. K. M. served as a consultant and received research support from Insmed; served as a speaker for AstraZeneca and Novartis; served as a consultant for Horizon, Spero, and RedHill Biopharma. K. N. O. received research support from AIT Therapeutics, Insmed, and Matinas Biopharma. M. S. received personal fees from DiaSorin SPA and Vircell SL. J. V. I. served on an advisory committee and as a consultant for Insmed; served on advisory committees for Janssen Pharmaceuticals and Spero. D. W. served as a speaker for Cepheid GmbH; received research support and travel expenses from Insmed. K. L. W. served on an advisory committee for Insmed, Johnson and Johnson, Paratek, Redhill Biopharma, and Spero; served as a consultant for Bayer Healthcare, Bristol-Myers Squibb, Horizon, Lilly, Pfizer, and RedHill Biopharma; received research support from Bristol-Myers Squibb, Cellestis, and Insmed; served on data safety and monitoring boards for Abbvie, Biomarin, Gilead, Roche, and UCB. J. M. I., E. C., J. B., L. G., S. L. K., J. E. S., and E. T. reported no relationships with relevant commercial interests. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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