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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

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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].

NTM and *Mycobacterium abscessus* among the rapidly growing NTM. Twenty-two PICO (Population, Intervention, 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].

BACKGROUND

The genus *Mycobacterium* consists of a diverse group of species and subspecies (http://www.bacterio.net/mycobacterium.html). With the exception of *Mycobacterium tuberculosis* complex, *Mycobacterium leprae* complex, and *Mycobacterium ulcerans* the rest of the species are referred to as NTM, and they can be found throughout our environment. The most common clinical presentation is that of pulmonary disease, often occurring in the setting of underlying structural airway disease such as bronchiectasis or chronic obstructive pulmonary disease [4]. The incidence and prevalence of NTM pulmonary disease are increasing in many areas of the world with rates particularly high in older individuals and those with underlying bronchiectasis [44–48]. The reasons for the increases in prevalence are not fully understood but are likely multifactorial including environmental, host, and microbial factors. Regardless of the reasons for the increase, it is clear that healthcare providers will be encountering these patients increasingly frequently in the coming years.

The availability of gene sequencing has improved taxonomy of mycobacteria, with an extraordinary increase in the number of validly published NTM species. Of the many known NTM species, only a small number appear to cause pulmonary disease

in humans. The most common slowly growing NTM to do so are members of *Mycobacterium avium* complex which now consists of 12 separate species [49]. The most common to cause pulmonary disease are *M. avium, M. intracellulare,* and *M. chimaera*. Other important NTM causing pulmonary disease are *M. kansasii* and *M. xenopi*. *M. abscessus* and its subspecies *abscessus, bolletii*, and *massiliense* are by far the most common causative agents of pulmonary disease due to rapidly growing mycobacteria.

Diagnosis of NTM pulmonary disease requires the synthesis of clinical, radiographic, and microbiology data. The ATS and IDSA developed a set of criteria to help guide clinicians in determining which patients are likely to have progressive disease [4]. Unfortunately, the predictive values of these criteria are not well studied, and thus they serve primarily as a guide to clinicians. The laboratory remains a critical component in the diagnosis of NTM pulmonary disease given the many species and variable pathogenicity. Identification of NTM to the species level and in the case of *M. abscessus*, to the subspecies level, can provide important clinical and epidemiologic information.

Treatment of NTM pulmonary disease varies depending on the species (in some cases subspecies), extent of disease, drug susceptibility results (with limitations), and underlying comorbidities. Regimens require the use of multiple antimicrobial agents that are often associated with clinically significant adverse reactions and must be administered for prolonged periods. Even so, treatment outcomes are often suboptimal, and reinfection with another strain or species is common. In many settings, expert consultation is helpful.

METHODS

Committee Composition

This guideline was developed by a multidisciplinary committee consisting of physicians and researchers with recognized NTM expertise (C.A., E.B., E.C., C.D., D.G., L.G., G.H., J.I., C.L., T.M., K.O., J.S., M.S., E.T., D.W., K.W., R.W.), methodologists (J.L.B. and J.M.I.), and a representative from an NTM nonprofit organization the goal of which is patient support, education, and research in NTM (P.L.). The patient representative was a full participant in each step of the development process but did not vote on specific recommendations. The committee was chaired by C.D. (ATS) and cochaired by C.L. (ERS), E.C. (ESCMID), and R.W. (IDSA), representing their respective societies. The committee worked with a medical librarian (S.K.) who had expertise in evidence synthesis and the guideline development process. All of the members who had potential financial and/or intellectual conflicts recused themselves or were excused by the chairs from discussions related to the recommendation formulation and grading, and voting on recommendations related to the potential conflict. The methodology team conducted systematic reviews and prepared evidence summaries following the GRADE approach [1, 2].

Formulating Clinical Questions

The committee developed potential questions to be addressed in the guideline using the 2007 guideline document [4] and their own clinical experience and expertise. Committee members were asked to rank questions in order of importance and priority with all questions deemed important and high priority included for the guideline. Twenty-two questions were chosen based on committee ranking pertinent to the treatment of NTM pulmonary disease. Some of these questions had been previously addressed in 2007 but required updating based on new evidence, whereas others were new questions that the committee felt were critical topics for NTM management. Outcomes of interest were selected a priori by the panel based on their experience and clinical expertise, using the approach suggested by the GRADE working group [1, 2, 50].

Literature Search and Review of Evidence

A medical librarian (S.K.) designed a search strategy using medical subject heading keywords and text words (see online supplement) limited to human studies and articles with English abstracts. Databases searched included MEDLINE, EMBASE, Cochrane Registry of Controlled Trials, Health Technology Assessment, and the Database of Abstracts of Reviews of Effects from 1946 through July 2015. An update was performed in May 2016 prior to the final meeting at the ATS International Conference and a final update was performed in June 2018 prior to manuscript submission.

Development of Clinical Recommendations

The committee developed recommendations that considered the certainty of the evidence from the GRADE evidence profiles, as well as other domains that inform decision-making. The GRADE evidence-to-decision framework was used to organize and document discussion for each recommendation [2, 50]. The committee considered each of the following in recommendation development: the quality of the evidence, the balance of desirable and undesirable consequences of compared management options, the values and preferences associated with the decision, the implications for resource use and health equity, the acceptability of the intervention to stakeholders, and the feasibility of implementation (see online supplement). The committee developed recommendations based on the GRADE evidence profiles for each question, with recommendations and their strength decided by committee consensus during face-to-face meetings.

Recommendations were either "strong" or "conditional," according to the GRADE approach (Table 1) [3]. Strength of the recommendations was based upon the confidence in the estimates of effect, the outcomes studied and associated importance

to patients, the desirable and undesirable consequences of treatment, the cost of treatment, the implications of treatment on health equity, the feasibility of treatment, and the acceptability of treatment to important stakeholders. In instances where there was low certainty in the estimates of effect, the committee determined whether a strong recommendation was warranted based on paradigmatic situations outlined by Andrews et al [3]. As suggested by GRADE, the phrase "we recommend" was used for strong recommendations and "we suggest" for conditional recommendations [3]. The Guideline, which was funded by ATS, ERS, ESCMID, and IDSA, will be reevaluated in 4 years to determine if an update is necessary.

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 collected over an interval of a week or more. 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].

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, patient's symptoms, 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.

LABORATORY DIAGNOSIS OF NONTUBERCULOUS MYCOBACTERIAL PULMONARY DISEASE

The clinical laboratory plays a critical role in the diagnosis of NTM pulmonary disease. A detailed review of the subject is beyond the scope of the Guideline but a brief review of clinically relevant laboratory issues is below.

Obtaining Respiratory Samples

Given the slow course of NTM pulmonary disease, a prolonged interval ensures that repeat positive cultures are unlikely to reflect a transient contamination of the tracheobronchial system after a single environmental exposure. To distinguish NTM pulmonary disease from occasional presence of NTM in the tracheobronchial tract, at least 3 respiratory samples are investigated, over an interval of at least a week. For cavitary NTM pulmonary disease, sputum samples often suffice for diagnosis [4]. Bronchoalveolar lavage fluid and bronchial washing cultures have been reported in several small studies to be more sensitive than spontaneously expectorated sputum culture to diagnose nodular/bronchiectatic NTM disease [51–54]. However, in the largest study, the yield of sputum culture and bronchial washing culture were equivalent [55]. Bronchoscopy is performed only in patients suspected of having NTM pulmonary disease from whom sputum specimens cannot be obtained spontaneously or through induction.

Sample Processing and Culture

Decontamination by 0.25% N-acetyl-L-cysteine and 1% NaOH (NALC-NaOH) is the preferred method. An increase of NaOH concentrations lowers contamination rates but decreases sensitivity of culture [56].

Culture of respiratory samples is performed on both liquid and solid media, to improve sensitivity. A meta-analysis [57] of 9 studies [58–65] showed an increase in the sensitivity of culture for NTM of 15% if a solid medium was incubated alongside a liquid culture system. In the few studies that applied multiple solid media and reported results per medium, the Löwenstein-Jensen medium was found to be most sensitive for the detection of NTM [59, 64]. However, the Clinical and Laboratory Standards Institute (CLSI) currently recommends use of 7H10 and 7H11 solid media [66]. CLSI has suggested incubations temperatures of 36 ± 1 °C for slow growers and 28 ± 2 °C for rapid growers [66]: higher temperatures (ie, 42°C) might accelerate growth of *M. xenopi* but lower incubation temperatures have not proven useful in diagnosing NTM pulmonary disease [67].

In patients with a high suspicion of NTM pulmonary disease but negative cultures, review of decontamination procedures and use of supplemented media and molecular detection may be helpful although supplemental media are rarely necessary to diagnose NTM pulmonary disease. For molecular detection, most use a mycobacterium genus specific assay used in conjunction with nucleic acid sequencing, to distinguish *M. tuberculosis* complex from NTM [68, 69].

Species Identification

Correct identification of NTM is important, as it can predict the clinical relevance of an isolate [8] as well as aid in the selection of a treatment regimen. Both molecular and mass spectrometry-based methods can be applied. Molecular identification is the preferred method and can be achieved using probes or gene sequencing. Probe-based assays are easier to perform and implement but lack discriminatory power, leading to misidentification and an oversimplified view of NTM phylogeny and epidemiology [70, 71]. Gene sequencing allows a higher level of discrimination, often up to subspecies level but is only feasible for laboratories with access to sequencing facilities. Several target genes have been described, eg, 16S rRNA, *hsp65, rpoB,* and the 16S–23S internal transcribed spacer (ITS) [72–75]. 16S rRNA gene sequencing alone offers limited discriminatory power, particularly for the *M. abscessus-M. chelonae* group [70]. The *hsp65* and *rpoB* genes and ITS are more discriminative [76]. Complementing 16S rRNA sequencing with additional targets where required yields the best discriminatory power, allowing identifications up to subspecies level (eg, for *M. abscessus*) [77, 78].

The discriminatory power of the matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) mass spectrometry method for NTM has increased with recent improvements in protein extraction protocols and databases but not all species and subspecies can be differentiated with this approach [79, 80]. These procedures work well for pure cultures [80, 81]; however, if applied to newly positive liquid cultures, only 50% of isolates can be immediately identified [82]. For the remainder, subculture on solid media until the occurrence of visual growth is needed to obtain good MALDI-TOF results [79].

All clinically relevant isolates of NTM should be identified by molecular methods, including follow-up isolates of patients undergoing NTM pulmonary disease treatment. Where possible, isolates from patients who are being treated for NTM pulmonary disease are frozen and saved in order to distinguish reinfection from relapse when recurrence occurs.

Drug Susceptibility Testing

In general, drug susceptibility testing is performed for drugs used in treatment regimens and for which there are clear correlations between in vitro activity and the in vivo outcomes of treatment. Such correlations have become increasingly clear for NTM, especially for macrolides and amikacin. CLSI provides guidelines for test procedures [14, 15].

For *M. avium* complex, there is a clear correlation between baseline macrolide susceptibility of the causative strain and the outcome of treatment with macrolide-ethambutol-rifampicin regimens [83, 84]. Acquired macrolide resistance in *M. avium* complex is due to point mutations in the 23S rRNA (*rrl*) gene [85, 86]. For amikacin, acquired resistance is due to resistance conferring mutations in the 16S rRNA (*rrs*) gene and are mostly isolated from patients with extensive exposure to amikacin and/or related aminoglycosides [55, 87]. The breakpoint for resistance is a MIC ≥ 64 µg/mL for parenteral amikacin and ≥128 ug/mL for amikacin liposome inhalation suspension (ALIS) [15], and finding such MICs would lead to cessation of intravenous or nebulized amikacin therapy [20]. Tentative breakpoints for linezolid and moxifloxacin are also provided by CLSI but for these, in vitro-in vivo correlations have not been established [15].

For *M. kansasii*, rifampicin and clarithromycin are the key drugs to test. Rifampicin resistance (MIC > 2 µg/mL) is rare but can occur in isolates from patients with significant rifamycin exposures and failure of treatment with a rifamycin containing regimen [15]. Resistance to clarithromycin is defined as an MIC ≥ 32 µg/mL [15]. When rifampicin resistance has been identified, susceptibilities to amikacin, ciprofloxacin, doxycycline, linezolid, minocycline, moxifloxacin, rifabutin, and trimethoprim-sulfamethoxazole are tested [88].

In *M. abscessus* pulmonary disease the association between in vitro drug susceptibility and in vivo outcome of treatment is evident for macrolides and amikacin [39, 89, 90]. Parenteral drugs with in vitro activity include amikacin, imipenem, cefoxitin, and tigecycline. Oral drugs with some activity are the macrolides, oxazolidinones (linezolid) and clofazimine. Clofazimine shows in vitro activity, acts synergistically with amikacin and macrolides [91, 92], and prevents the emergence of amikacin-resistant *M. abscessus* in vitro [92].

Strains of *M. abscessus* subsp. *abscessus* and *M. abscessus* subsp. *bolletii* have an erythromycin resistance methylase (*erm*) gene, named *erm*(41), that results in inducible resistance to macrolides [93]. This inducible resistance can be measured in vitro by prolonged (ie, up to 14 days) incubation of microdilution trays [40, 93] or can be investigated by molecular detection and characterization of the *erm*(41) gene. In *M. abscessus* subsp *massiliense*, the *erm*(41) gene is nonfunctional owing to a large deletion, thus rendering the strains macrolide susceptible. A nonfunctional gene also occurs in some *M. abscessus* subsp *abscessus* as a result of a C instead of a T at the nucleotide 28 position (Arg10 instead of Trp10) in the *erm*(41) gene [40, 94]. All of the 3 *M. abscessus* subspecies can develop constitutive macrolide resistance owing to 23S RNA (*rrl*) gene mutations [94]. Susceptibility testing panels for *M. abscessus* include at least amikacin, cefoxitin, imipenem, clarithromycin, linezolid, doxycycline, tigecycline, ciprofloxacin, and moxifloxacin.

CLSI recommends that drug susceptibility testing be performed by broth microdilution [88]. For patients whose NTM isolate is deemed to be clinically significant, drug susceptibility testing is performed for primary isolates as well as relapse/failure isolates.

RECOMMENDATIONS FOR SPECIFIC PICO QUESTIONS

Twenty-two PICO questions are addressed in this Guideline. For additional details please see the online supplement, which includes supporting supplemental evidence profiles for each question (Tables E3.1–22) and evidence to decision tables (Tables E4.1–22) for each recommendation. For specific pathogens (*M. avium* complex, *M. kansasii*, *M. xenopi*, and *M. abscessus*), the PICO questions 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)

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

Background: Treatment of NTM pulmonary disease with antimicrobial agents offers the possibility of cure of the disease. However, the potential benefits of antimicrobial treatment must be weighed against the potential adverse effects of treatment, low cure rates for some forms of infection, uncertain effect of treatment on quality and quantity of life, high costs of treatment, and the potential for reinfection.

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).

Summary of the Evidence: No randomized, controlled trials have been conducted to examine the impact of treatment on either survival or quality of life. Limited retrospective observational data have failed to demonstrate that treatment of NTM pulmonary disease prolongs survival over watchful waiting [95, 96]. The relative and absolute effect estimates and 95% confidence intervals (CIs) for each outcome (Table E3.1) and discussion of value preferences, feasibility, cost, acceptability, and health inequality (Table E4.1) can be found in the supplement.

Not all patients who have NTM isolated from a respiratory specimen or who meet ATS/IDSA diagnostic criteria will develop progressive NTM pulmonary disease. For example, among 488 patients with MAC pulmonary disease in Taiwan who met ATS/IDSA disease criteria and were followed for at least 1 year, 305 (62.5%) demonstrated progression of disease [97]. Progression was more likely to occur in patients who were acid-fast bacilli smear positive, had fibrocavitary disease or more extensive radiographic disease. Among those patients who met the 2007 ATS/IDSA criteria for MAC pulmonary disease and in whom treatment was not initiated, 51.6% underwent spontaneous sputum conversion during a median follow-up of 5.6 years [97]. Predictors of spontaneous sputum culture conversion included younger age, higher body mass index, and negative sputum acid-fast bacilli smears at initial diagnosis.

Observational cohorts have noted wide variability in the proportion of patients with NTM pulmonary disease who are offered treatment (20–81%) likely contributing to selection bias [95, 98–105]. NTM pulmonary disease has been associated with diminished quality of life that correlates with the severity of lung impairment [106, 107]. A single study using standardized methods for quality of life assessment demonstrated improvement of quality of life associated with treatment of *M. abscessus* infection [108].

Justification and Implementation Considerations: 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. Factors associated with relatively poor prognosis (eg, cavitary disease, low body mass index, low albumin, and/or elevated inflammatory markers) [97, 99, 102, 104, 109], isolation of an organism that is more virulent and/or more responsive to antimicrobial therapy (eg, *M. kansasii*), and underlying immune suppression were felt to move the balance toward antimicrobial treatment. Major symptoms such as severe fatigue with marked decrease in quality of life can also be major factors in starting therapy. Conversely, mild signs and symptoms of disease, higher potential for medication intolerance/toxicity and organisms less responsive to treatment (eg, *M. abscessus*) were felt to move the balance toward watchful waiting. Any treatment decision should include a discussion with the patient that outlines the potential adverse 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].

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

Background: Drug susceptibility testing for NTM is useful but only for antibiotics for which correlations between in vitro activity and microbiological response to treatment have been well documented [110, 111]. These include the macrolides (clarithromycin and azithromycin) [112] and amikacin [19, 20, 87] with MAC and *M. abscessus* [19, 113], and rifampicin with *M. kansasii* [114, 115].

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 committee members feel 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 should be performed to evaluate for potential inducible macrolide resistance.

Summary of the Evidence: Only one study was identified that reported treatment outcomes based on empiric treatment versus the results of drug susceptibility results [101]. The study was a retrospective observational study of 31 patients with various species causing NTM pulmonary disease who met the 1997 ATS case definition. Patients were treated with a variety of treatment regimens (13 different combinations were used). Adjusting treatment according to the results of drug susceptibility tests was not associated with any difference in median survival (75% with adjustment and 80% without). However, the study suffers from serious methodological flaws including lack of randomization, use of the 1997 ATS diagnostic criteria, and methods of determining and interpreting drug susceptibility that are no longer recommended. Discussion of value preferences, feasibility, cost, acceptability, and health inequality (Table E4.2) can be found in the supplement.

Although only 1 study was identified that attempted to evaluate the outcomes of treatment based on drug susceptibility results there are other studies that have correlated outcomes with in vitro activity. Trials of monotherapy with clarithromycin, rifampicin, ethambutol, or clofazimine for HIV-associated disseminated MAC demonstrated that only clarithromycin susceptibility results correlated with treatment outcomes [113, 116]. In MAC pulmonary disease, retrospective case series [83, 84, 112, 117, 118] have also shown that in vitro resistance to clarithromycin was associated with worse outcomes than susceptibility to clarithromycin, and a randomized trial found no association between in vitro susceptibility to either rifampicin or ethambutol and failure/relapse [119]. However, the latter study applied a drug susceptibility method not recommended for NTM and presented and analyzed only aggregate resistance data for all groups (MAC, *M. xenopi*, and *M. malmoense*) utilizing uniform discrete thresholds rather than considering MICs as a continuous variable to be explored for an association across species.

Amikacin is an important drug used for treatment of *M. abscessus* pulmonary disease. Resistance to amikacin is caused by a specific mutation (A1408G) in the 16S rRNA (*rrs*) gene that has been associated with a high MIC (>64 μg/mL) and previous exposure to amikacin [87, 120].

Recent phase II and III clinical trials evaluating the efficacy and safety of ALIS in patients with refractory pulmonary disease due to MAC (or *M. abscessus*) reported that when there was an A1408G mutation in the 16S rRNA gene and/or the MIC was >64 μg/mL in MAC isolates, no patients achieved culture conversion on ALIS; responses were seen with MIC values up to and including 64 μg/mL [19, 20]. Treatment failure occurred in 2 patients whose isolates had become resistant by mutation to amikacin [19]. In a randomized trial comparing intravenous streptomycin with placebo added to a standard 3-drug regimen, there was no association of treatment outcome with MIC to streptomycin; however, exact MIC values were not determined if above 4 μg/mL [121].

For *M. kansasii* pulmonary disease, resistance to rifampicin has been associated with treatment failure [114, 115], although no randomized trials have been conducted that associate baseline MICs to clinical outcome. For *M. xenopi* lung disease, few studies have correlated in vitro activity of specific antimycobacterial drugs with treatment outcomes [36, 101, 122, 123]. No association could be found between in vitro activity and treatment failure/relapse in a randomized trial comparing rifampicin plus ethambutol with or without isoniazid. The study had important limitations including a small sample size and the use of discrete thresholds (based on *M. tuberculosis*) rather than considering MIC values as a continuous variable [36].

Recent studies have reported poor treatment outcomes associated with macrolide resistance due to either mutational or inducible resistance related to the presence of a functional *erm*(41) gene in *M. abscessus* subsp. *abscessus* and *bolletii*. In a retrospective cohort treated with a standard regimen, the presence of in vitro resistance to clarithromycin was associated with worse outcomes [39]. In a follow-up study, patients with *M. abscessus* subsp. *massiliense* were more likely to convert cultures to negative compared with patients infected with *M. abscessus* subsp. *abscessus* (85% vs 25%, $P < .001$), presumably because of the presence of a nonfunctional *erm*(41) gene in the former (gene with major deletions) and inducible macrolide resistance due to a functional *erm*(41) gene in the latter [38, 40–42]. In addition, culture conversion rates were significantly higher in patients infected with an *M. abscessus* subsp. *abscessus* C28 sequevar isolate that does not exhibit inducible resistance to macrolides [12]. Alternatively, when *M. abscessus* subsp. *massiliense* develops mutational macrolide resistance with a mutation in the 23S rRNA gene, culture conversion is similar to that seen with subsp. *abscessus* and functional *erm*(41) gene [40, 124, 125].

Justification and Implementation Considerations: Although in vitro-in vivo correlations have been proven only for macrolides, amikacin and rifampicin (the latter only for *M. kansasii*), baseline susceptibility testing is recommended

by CLSI guidelines for NTM isolates from patients with definite disease [14, 15]. Based on studies reviewed above, there is evidence of poor outcomes in cases of macrolide-resistant MAC [16, 112] and *M. abscessus* [38, 39] and poor outcomes in rifampicin-resistant *M. kansasii* [114, 115]. Similarly, recent data from randomized clinical trials evaluating ALIS have demonstrated that high MICs of amikacin are associated with poor microbiological response as reported in a previous retrospective analysis of patients treated with parenteral amikacin [19, 20, 87]. Based on the studies and recommendations above, laboratories should provide drug susceptibility test results for the macrolides and amikacin for MAC and *M. abscessus* and rifampicin for *M. kansasii*. Precise subspeciation is helpful for *M. abscessus* as identification of subsp. *massiliense* is associated with a nonfunctional *erm*(41) gene and in vitro susceptibility (MIC below 4 μg/mL) [42], and thus the macrolides are active if constitutive resistance is not present. Alternatively, sequence analysis of the *erm*(41) gene can provide information (eg, truncated or C28 sequevar) that can exclude inducible macrolide resistance. Although other drugs are sometimes tested in order to guide *M. abscessus* therapy, there are insufficient data to make specific recommendations in this regard.

Because no studies could be identified that adequately addressed *M. xenopi* pulmonary disease and in the absence of drug susceptibility testing guidelines and breakpoints for *M. xenopi*, the panel was unable to provide recommendation for or against susceptibility-based treatment.

Treatment of MAC Pulmonary Disease (Questions III–IX)

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

Background: Macrolides (clarithromycin and azithromycin) have been the basis of therapy against MAC pulmonary disease because they were demonstrated in multiple trials to be effective in prophylaxis and multidrug treatment of disseminated MAC infection [126–130].

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).

Summary of the Evidence: In spite of the widespread use of macrolides for treating MAC disease, there have been only two randomized controlled trials comparing a macrolide-containing regimen with a nonmacrolide-containing regimen [131, 132]. A British Thoracic Society trial randomized 170 patients with primarily cavitary MAC pulmonary disease to receive standard doses of rifampicin and ethambutol with either clarithromycin or ciprofloxacin [131]. The results showed that the clarithromycin group had a lower failure/relapse rate than the ciprofloxacin group (13% vs 23%) and was tolerated better. However, all-cause mortality was higher in the clarithromycin group for unclear reasons (48% vs 30%). At 5 years only 30% of the clarithromycin group and 21% of the ciprofloxacin group were known to have completed therapy and been alive.

In a second small prospective trial from Japan [132], 27 patients with MAC pulmonary disease were treated for 1 year with rifampicin and ethambutol plus either gatifloxacin or low dose (600 mg) clarithromycin. The treatment outcomes were not significantly different between study arms: 11/13 (84.6%) in the gatifloxacin group and 9/14 (64%) patients in the clarithromycin group achieved sputum culture conversion to negative. The relative and absolute effect estimates and 95% CIs for each outcome (Table E3.3) and discussion of value preferences, feasibility, cost, acceptability, and health inequality (Table E4.3) can be found in the supplement.

The committee was concerned about several aspects of these 2 studies including, (a) small sample size, (b) underdosing of the macrolide, (c) populations not representative of nodular bronchiectatic MAC pulmonary disease patients encountered frequently in clinical practice, (d) the use of gatifloxacin which is not approved for use or no longer marketed in many countries worldwide, and (e) the high overall mortality seen in one study [131], which raised questions about the validity of the study.

There have been other noncomparator trials of macrolide-containing regimens that have reported varying culture conversion rates. A recent systematic review reported a sustained sputum culture conversion incidence rate ratio of 0.54 (95% CI .45–.63) for macrolide-containing regimens versus 0.38 (0.25–0.52) for macrolide-free regimens [133]. Sputum conversion increased in the macrolide-containing regimens compared with macrolide-free regimens as study quality improved. Another systematic review reported overall treatment success using macrolide-containing regimens was 52.3% (95% CI 44.7%–59.9%) and success increased to 61.4% if treated with an ATS/IDSA 3-drug regimen, and to 65.7% if further treated for at least 12 months [134]. The companion drugs and length of treatment are important factors in treatment success. Only regimens using rifamycin and ethambutol or clofazimine and ethambutol have been shown to prevent the emergence of macrolide resistance during treatment [22, 135].

Perhaps the strongest available evidence for the importance of the macrolide in the treatment regimen is demonstrated by its loss from the regimen. In the setting of macrolide-resistant disease, the sputum culture conversion rate falls from approximately 80% [22, 23] to only 5–36% [16–18, 136].

Justification and Implementation Considerations: Case series have demonstrated that macrolide-containing regimens are associated with higher culture conversion rates than

nonmacrolide-containing regimens [137]. Macrolide susceptibility has been a consistent predictor of treatment success for MAC pulmonary disease, whereas susceptibility to most other drugs has not been a predictor [112]. In a postmarketing study from Japan, among 271 patients with macrolide-susceptible MAC pulmonary disease who received a clarithromycin-based regimen, sputum culture conversion to negative occurred in 95% [136]. Although no well-designed randomized trials of macrolide therapy have been performed, the panel felt that macrolides are a critical component of MAC treatment based on poor patient outcomes if macrolides are not included in the treatment regimen. As such the panel members voted unanimously to make a strong recommendation despite the very low certainty of estimates of effect.

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

Background: The macrolides are considered to be key components in treatment regimens against MAC pulmonary disease. The 2007 Guideline expressed a preference for azithromycin over clarithromycin in initial treatment regimens [4].

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).

Summary of the Evidence: Both clarithromycin and azithromycin have demonstrated activity in MAC pulmonary disease, with early studies demonstrating some efficacy for monotherapy [117, 138], and subsequent studies demonstrating efficacy as part of multi-drug regimens administered both daily [83] and 3 times weekly [22, 139, 140]. Limited data are available from comparisons of treatment outcomes in patients treated with clarithromycin versus azithromycin [22, 141], and no significant difference was found in either microbiologic efficacy or tolerability, although there was a nonsignificant trend toward lower tolerability for clarithromycin in 1 study [141]. The relative and absolute effect estimates and 95% CIs for each outcome (Table E3.4) and discussion of value preferences, feasibility, cost, acceptability, and health inequality (Table E4.4) can be found in the supplement.

A recent systematic review reported no clinically significant differences between azithromycin and clarithromycin in sputum culture conversion at 6 months, end of therapy, or on sustained conversion after treatment nor was there a difference in the acquisition of macrolide resistance [133]. However, azithromycin has less potential for drug-drug interactions than clarithromycin [142]. The drug-drug interactions are particularly relevant when a rifamycin (rifampicin or rifabutin) is given concurrently; azithromycin serum concentrations are affected less by concurrent rifampicin or rifabutin administration than clarithromycin, but the interaction is bidirectional for clarithromycin and rifabutin, leading to increased concentration of rifabutin (but not rifampicin), which has been associated with uveitis [111, 143–145]. Other considerations that would favor azithromycin over clarithromycin include a lower pill burden, once daily dosing, and possibly lower costs.

Justification and Implementation Considerations: The preference for azithromycin is primarily based on the expert panel's perception of better tolerability of azithromycin and fewer drug-drug interactions mediated by the cytochrome P450 system [146] than with clarithromycin. Both azithromycin and clarithromycin have been reported to be associated with severe adverse effects, including sudden death presumably mediated by QTc prolongation [147, 148]. However, a systematic review that evaluated adverse events in people taking macrolides versus placebo for any indication reported no increase in cardiac disorders or mortality when compared with placebo [149]. Electrocardiographic monitoring may be considered for patients when concurrent medications that prolong the QTc interval are being used. In the same systematic review noted above [149], hearing loss was reported more frequently in patients taking macrolides than placebo; however, the differences were not statistically significant, and there were no studies of clarithromycin to address differences between macrolides. In older patients, hearing loss and gastrointestinal symptoms have been associated with higher doses (600 mg daily) and serum concentrations of azithromycin [150], whereas bitter taste, nausea, and elevated hepatic enzymes have been associated with higher doses (1000 mg twice daily) of clarithromycin [151]. Of note, all studies included some patients who did not tolerate azithromycin and were successfully switched to clarithromycin and *vice-versa*. Switching from one agent to the other is a strategy that may be considered in case of intolerance. The panel felt that azithromycin was preferred over clarithromycin because of likely better tolerance, less drug interactions, lower pill burden, single daily dosing, and equal efficacy. In places where azithromycin is not available, clarithromycin is an acceptable alternative although more drug interactions are possible.

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

Background: MAC isolates are usually susceptible in vitro to amikacin. Streptomycin was used in early noncomparative treatment trials during the initial months of treatment for both cavitary and nodular/bronchiectatic MAC pulmonary disease [83, 138]. Parenteral aminoglycoside therapy was recommended in some previous NTM guidelines during the initial

months of MAC therapy [152]. In the 2007 Guideline [4], parenteral aminoglycosides were recommended for initial therapy of fibrocavitary MAC pulmonary disease and severe or previously treated MAC pulmonary disease [4]. Amikacin or streptomycin administration have been viewed as an intensification of oral therapy although that assumption has not been rigorously tested.

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).

Summary of the Evidence: One randomized controlled trial was performed evaluating the impact of streptomycin addition to macrolide-based oral therapy for the initial three months of therapy [121]. One hundred forty-six patients with MAC pulmonary disease (both nodular/bronchiectatic and cavitary disease) were randomized to receive clarithromycin, ethambutol, and a rifamycin daily with (73) or without (73) streptomycin (15 mg/kg 3 times per week during the initial 3 months of therapy). The sputum culture conversion rate was significantly higher for patients who received streptomycin than for those who received oral therapy only (71.2% vs 50.7%). There were, however, no significant differences in microbiologic recurrence rates or clinical improvement (which included both clinical symptoms and radiological findings). There were also no significant differences in adverse reactions and abnormal laboratory findings between the 2 groups. Two additional retrospective studies have suggested that the inclusion of a parenteral aminoglycoside administered for ≥6 months in addition to adjunctive surgery improves outcome for patients with macrolide-resistant MAC pulmonary disease [16, 18]. There are no published data examining the relative efficacy of streptomycin versus amikacin for treating MAC pulmonary disease; streptomycin is no longer available in several countries. The relative and absolute effect estimates and 95% CIs for each outcome (Table E3.5) and discussion of value preferences, feasibility, cost, acceptability, and health inequality (Table E4.5) can be found in the supplement.

Justification and Implementation Considerations: In the absence of comparably effective oral medications there are few options other than parenteral aminoglycosides for "intensifying" standard oral MAC therapy. Although the evidence is limited, it appears that there is some improvement in microbiologic response with the addition of three months of streptomycin to macrolide-based oral MAC therapy [121] and when administered for a longer duration in the setting of macrolide resistant MAC pulmonary disease [16, 18]. Amikacin must be paired with adequate companion medications, such as a macrolide, ethambutol and possibly rifampicin and clofazimine, to prevent the emergence of acquired mutational resistance and predictable treatment failure [153]. Based on the results of one randomized trial [121] and the experiences of the panel members, the benefits were felt to outweigh risks in those patients with cavitary or advanced/severe bronchiectatic disease or those with macrolide-resistant MAC pulmonary disease. Administration of at least 2–3 months of an aminoglycoside was considered the best balance between risks and benefits.

Question 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?

Background: Amikacin is active against MAC and has been recommended for intravenous treatment of cavitary or severe bronchiectatic MAC pulmonary disease [4]. However, systemic use of parenteral amikacin has been associated with a high frequency of renal, auditory, and vestibular toxicity [154]. Delivery of amikacin by hand-held nebulization may be a potential way to improve efficacy and decrease drug-related toxicity.

Recommendations

1. In patients with newly diagnosed MAC pulmonary disease, we suggest neither inhaled amikacin (parenteral formulation) nor 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 instead of a standard oral regimen, only (strong recommendation, moderate certainty in estimates of effect).

Summary of the Evidence: Reports evaluating the use of inhaled amikacin as part of a multidrug regimen for NTM pulmonary disease, including patients with MAC pulmonary disease, have primarily targeted patients with treatment refractory disease. Five retrospective case series (N = 138 patients, 55 with MAC) with no comparator arm most commonly used inhaled doses of commercially available amikacin (parenteral forumation) ranging from 250 to 500 mg once daily up to 15 mg/kg once daily added to their oral antibiotic regimen [155–159]. Clinical responses were reported in 20–100% and sputum conversion was reported in 18–67% of treatment refractory MAC pulmonary disease. Reported side effects in these series ranged from 8 to 38% and included hoarseness, throat irritation, bitter taste, and thrush. Ototoxicity occurred in 0 to 19% of patients with nephrotoxicity reported in only 1 patient and vertigo in 2 patients [155–159]. The relative and absolute effect estimates and 95% CIs for each outcome (Table E3.6) and discussion of value preferences, feasibility, cost, acceptability, and health inequality (Table E4.6) can be found in the supplement.

A Phase II controlled trial randomized treatment refractory patients (eg, with culture positivity after at least 6 months of guideline-based treatment that included a macrolide) with predominantly MAC (n = 57) or *M. abscessus* (n = 32) pulmonary disease to investigational ALIS (n = 44) versus placebo (empty liposomes, n = 45) [19]. Although the primary endpoint of reduction in semiquantitative mycobacterial culture growth from baseline was not achieved, significantly more patients who received ALIS achieved culture conversion by day 84 and had greater improvement in distance achieved on 6-minute walk test. Adverse events were common (~90%) in both groups, but patients receiving ALIS had more dysphonia and oropharyngeal discomfort, cough, wheezing, chest discomfort, acute exacerbations of bronchiectasis, and fatigue [19].

A randomized controlled phase III trial recently reported that ALIS, when added to guideline-based regimen for treatment refractory MAC pulmonary disease, was associated with a higher proportion of patients with negative cultures at 6 months compared to those who continued to take the standard regimen only [20]: Culture conversion was achieved by 65 of 224 patients (29.0%) with ALIS + guideline-based therapy (GBT) compared with 10 of 112 (8.9%) with GBT alone (odds ratio, 4.22; 95% CI [2.08,8.57]; $P < .001$). Adverse reactions were very common in both treatment arms: treatment-emergent adverse events (TEAE) were reported in 98.2% and 91.1% of patients in the ALIS+GBT and GBT-alone arms, respectively. The most common TEAEs overall were respiratory events reported by 87.4% and 50.0% of patients in the ALIS+GBT and GBT-alone arms, respectively. TEAEs reported in ≥10% of patients in the ALIS+GBT arm included dysphonia, cough, hemoptysis, dyspnea, fatigue, diarrhea, nausea, and oropharyngeal pain. These events infrequently led to early discontinuation of ALIS (dyspnea, 3.1%; dysphonia, 2.2%; all others <1%) or withdrawal from the study. Audiological TEAEs were generally similar in both arms although tinnitus was reported in 17 patients (7.6%; 20 events) in the ALIS+GBT arm compared with one event (0.9%) in those receiving GBT alone. Vestibular TEAEs (dizziness, balance disorder, vertigo), although infrequent, were also more common in the ALIS+GBT arm than in the GBT alone arm. Serious TEAEs were reported in 45 patients (20.2%) and 20 patients (17.9%) in the ALIS+GBT and GBT-alone arms, respectively. During the study, more patients in the ALIS+GBT arm had MAC isolates with postbaseline amikacin MIC > 64 μg/mL than those receiving GBT alone (10.3% vs 2.7%). Of these 26.9% subsequently had MAC isolates with an MIC less than 64 mg/ml. Based on the phase II and III trial results, ALIS was approved by the US Food and Drug Administration for treatment of MAC pulmonary disease in patients who have failed therapy after at least 6 months of GBT.

Justification and Implementation Considerations: There are insufficient data to support the use of inhaled antibiotics as an initial treatment option. There may be a risk of developing acquired mutational amikacin resistance with either inadequate companion medications or poor and irregular antibiotic deposition in the lung with areas of low amikacin concentration. In patients who fail treatment with an initial MAC regimen, inhaled therapy should be used as part of a salvage regimen to aggressively treat MAC pulmonary disease in those whose isolates retain in vitro susceptibility to amikacin. The results of phase II and phase III randomized trials [19, 20] of ALIS show that addition of ALIS to patients with MAC pulmonary disease that failed to convert sputum cultures after 6 months of GBT leads to culture conversion in 29% of patients in comparison to 9% in patients who continue GBT only. Because 10% of patients in the ALIS-arm developed amikacin resistance, the addition of another companion drug to prevent resistance development needs to be considered in these patients, although the preventive effect of an additional medication has not been determined in this situation. Where ALIS is not yet available, addition of inhaled parenteral amikacin is a reasonable alternative.

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

Background: The poor response to treatment in AIDS patients with disseminated MAC in the premacrolide era and the rapid development of resistance with clarithromycin monotherapy reinforced the need for multiple drugs for treatment success. In contrast to the need for multidrug therapy, there is an opposing pressure to reduce the number of agents in MAC regimens to minimize drug-related adverse effects, the cost of the drug regimen, and the pill burden seen with 12–18 months of therapy.

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).

Summary of the Evidence: There are 2 randomized studies that compared a 2-drug regimen with a 3-drug regimen [21, 119], but only 1 of these studies included a macrolide-containing regimen [21]. In this single center open label study from Japan, patients with previously untreated nodular/bronchiectatic or fibrocavitary MAC pulmonary disease were randomly assigned to either a daily 3-drug (clarithromycin/ethambutol/rifampicin) or a daily 2-drug (clarithromycin/ethambutol) regimen for 12 months [21]. The drug doses (especially clarithromycin at 200 mg 3 times daily or twice daily based on body weight) were all lower than ATS/IDSA recommended dosing. The primary endpoint was sputum conversion (ie, 3 consecutive negative cultures). Fifty-nine patients were assigned to a 3-drug regimen and 60 to a 2-drug

regimen with lung cavitation present in approximately 50% of patients in both arms. In the intent to treat analysis, the sputum culture conversion rate was 40.6% with the 3-drug regimen and 55.0% with the 2-drug regimen. The incidence of adverse events leading to the discontinuation of treatment was 37.2% and 26.6% for the 3-drug and the 2-drug regimens, respectively. In the per protocol analysis (those who completed therapy) 24/32 (75%) converted on 3 drugs, and 33/40 (82.5%) converted on 2 drugs. No isolates in either group developed macrolide resistance, although the study was underpowered to detect a difference. This study has significant limitations making interpretation difficult. The study was unblinded with a small sample size, had significant drop out during the course of the study, and used low doses of clarithromycin administered in a nonstandard frequency of dosing [160]. When combined with rifampicin in the 3-drug regimen, this would have led to low and potentially ineffective clarithromycin levels. The relative and absolute effect estimates and 95% CIs for each outcome (Table E3.7) and discussion of value preferences, feasibility, cost, acceptability, and health inequality (Table E4.7) can be found in the supplement.

Justification and Implementation Considerations: A priority in MAC pulmonary disease therapy is preventing the development of macrolide resistance. Ethambutol is the best companion drug for preventing the emergence of macrolide resistance [16, 18, 161]. A 2-drug regimen including a macrolide and ethambutol is the regimen with the fewest possible drugs for treating MAC. The role of a rifamycin, or another third drug, is unclear. One possibility is that a third drug provides additional protection to that provided by ethambutol for preventing the emergence of macrolide resistance. In a randomized controlled trial of rifabutin added to clarithromycin and ethambutol for treatment of disseminated MAC infection, response rates, with or without rifabutin, were equivalent but development of macrolide resistance was lower ($P = .055$) in patients on the 3-drug regimen [161]. Until additional evidence is provided showing that acquired macrolide resistance is equally common among macrolide containing 3-drug and 2 drug regimens, the panel prefers a 3-drug regimen. A PCORI-funded randomized controlled trial to evaluate the safety and efficacy of a 2 versus 3 drug regimen is currently underway (https://www.pcori.org).

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

Background: The intermittent administration of antimycobacterial drugs has been a standard approach to drug susceptible tuberculosis therapy in North America for more than 2 decades [162] therefore, it seems reasonable that macrolide susceptible MAC pulmonary disease might also be effectively treated with intermittent antibiotic administration. In the prior Guideline [4], 3 times weekly therapy was recommended for patients with nodular/bronchiectatic MAC pulmonary disease but was not recommended for patients with cavitary disease, patients previously treated, or patients with moderate or severe disease [4, 163].

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 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)

Summary of the Evidence: No randomized trials have been performed that address this question; however, there are several cohort studies that have reported treatment outcomes with intermittent therapy. The first prospective noncomparative case series of patients receiving intermittent azithromycin-containing therapy for MAC pulmonary disease was reported in 1998 [164]. These preliminary results were followed by the results of 3 prospective noncomparative studies of azithromycin-containing regimens (including rifabutin or rifampicin, and ethambutol) for MAC pulmonary disease [140]. Patients received either intermittent azithromycin with daily companion medications, intermittent azithromycin with intermittent companion medications, or daily azithromycin with daily companion medicines. Conversion of sputum cultures to negative was observed in 17/29 (59%), 11/20 (55%), and 28/43 (65%) of patients, respectively. The microbiologic outcomes for the 3 regimens were not significantly different. In a subsequent study, 41 patients completed 6 months of therapy with clarithromycin 1000 mg, rifabutin 300–600 mg, and ethambutol 25 mg/kg administered 3 times per week [139]. Thirty-two (78%) of these patients converted sputum cultures to negative. Adverse events associated with this regimen were primarily due to rifabutin, and in 41% of patients the dosage was decreased or the drug discontinued. These initial 3 studies included both cavitary and nodular bronchiectatic MAC pulmonary disease patients [139, 140, 164].

A large retrospective case series that included 180 patients with nodular/bronchiectatic MAC pulmonary disease reported outcomes with either daily or intermittent macrolide-containing (either azithromycin or clarithromycin) regimens (with rifampicin and ethambutol) for a minimum of 12 months [22]. Conversion of sputum cultures to negative occurred in 147/172 (85%) of patients treated with the intermittent regimen compared to 7 of 8 (88%) patients who completed therapy with daily medication. A significantly greater number of patients treated with daily medications experienced medication intolerance and required a switch in regimen to intermittent therapy. None of the NTM

strains from patients in the study developed macrolide resistance. Another retrospective study compared daily (earlier temporal period, 99 patients) with intermittent (later temporal period, 118 patients) administration of clarithromycin, rifampicin, and ethambutol for nodular/bronchiectatic MAC pulmonary disease [23]. Significantly more patients on daily therapy required regimen modification because of medication intolerance than patients on intermittent therapy (46% vs 21%). Seventy-six percent of patients receiving daily therapy, and 67% of patients receiving intermittent therapy converted cultures to negative. Acquired macrolide resistance was not reported in the study.

In addition to the 2 recent studies showing that intermittent macrolide-containing regimens are better tolerated than daily regimens, there may be other benefits to intermittent regimens. A case series suggested that intermittent ethambutol administration was less often associated with ethambutol-related ocular toxicity than daily ethambutol administration [165]. A recent systematic review reported that the default rate was 12.0% (95% CI 8.9%–15.0%) in patients receiving 3 times weekly therapy compared to 16.0% (95% CI 12.3–19.7%) with daily administration [166]. A small study from South Korea on patients who were failing an intermittent regimen after 12 months of treatment reported that sputum culture conversion to negative was observed in approximately 30% of patients after switching to daily therapy [167].

Treatment outcomes with intermittent therapy are not as favorable in patients with cavitary pulmonary disease. A prospective open label multicenter trial reported a low culture conversion rate in patients with MAC pulmonary disease treated with 3 times weekly therapy [163]. Sputum culture conversion occurred in only 4% of patients with cavitary disease. Patients with noncavitary disease were approximately 4 times more likely than patients with cavitary disease to demonstrate sputum culture conversion and high-resolution computed tomography (CT), or symptom improvement. A recent case series from South Korea reported a high sputum culture conversion rate in patients with recurrent nodular/bronchiectatic disease who received an intermittent macrolide-based regimen [168]. In this case series, 86% of the recurrences were likely due to reinfection which would possibly explain the good outcomes. The relative and absolute effect estimates and 95% CIs for each outcome (Table E3.8) and discussion of value preferences, feasibility, cost, acceptability, and health inequality (Table E4.8) can be found in the supplement.

Justification and Implementation Considerations: These recommendations are based on several noncomparative case series with consistent microbiologic results showing that intermittent therapy is similar to daily therapy for nodular/bronchiectatic MAC pulmonary disease and also better tolerated than daily therapy. A critically important finding from the available studies is the lack of development of macrolide resistance with intermittent therapy [22, 23]. There is not similar evidence to justify or support intermittent therapy for cavitary MAC pulmonary disease and it is not recommended.

Question 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?

Background: Although MAC species are the most common organisms causing NTM pulmonary disease, the optimal treatment duration for MAC pulmonary disease has not been evaluated in a prospective randomized clinical trial. Although the duration of treatment of MAC pulmonary disease that is needed to achieve relapse-free cure is likely highly variable among individual patients, clinical guidance is needed for the recommendation of a general treatment duration.

Recommendation

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

Summary of the Evidence: There are no randomized studies or case series that address this question although there is one study that reported outcomes based on whether the patient received <12 months of treatment [22]. In a single center retrospective observational cohort study that evaluated and reported treatment outcomes of patients with nodular/bronchiectatic MAC pulmonary disease, 27 patients received treatment for <12 months and 180 patients for ≥12 months of a clarithromycin or azithromycin-based combination therapy, either daily or 3 times a week. Sputum culture conversion to negative was observed in 6 of the 27 patients (22%) who received treatment for <12 months, compared with 154 of 180 (86%) of patients who completed at least 12 months of therapy ($P < .001$). The relative and absolute effect estimates and 95% CIs for each outcome (Table E3.9) and discussion of value preferences, feasibility, cost, acceptability, and health inequality (Table E4.9) can be found in the supplement.

A recent systematic review reported that treatment success was higher in persons who received at least 12 months of macrolide-based therapy compared with <12 months [134]. Neither the aforementioned study nor the systematic review evaluated treatment outcomes by duration of treatment after culture conversion [134]. In a postmarketing study from Japan, bacteriologic relapse was noted in 5% of patients when treatment was continued for <15 months after sputum culture conversion and in zero patients who continued treatment for >15 months [136]. Given the lack of data on the optimal duration of therapy, the panel voted unanimously to continue to follow the recommendations from the 2007 Guideline.

Justification and Implementation Considerations: The optimal duration of therapy for MAC pulmonary disease is currently not known. Semiquantitative sputum culture scores from the third month of treatment onwards are predictive of sustained sputum conversion at 12 months of treatment, so regular (eg, monthly) sputum cultures are recommended during the treatment of MAC pulmonary disease [169]. There is currently not sufficient evidence to support bronchoscopy to obtain specimens for mycobacterial culture to determine the duration of therapy. Treatment outcome definitions have now been published to promote uniform outcome reporting in studies and gather more reliable data on optimal duration of therapy in MAC pulmonary disease [170]. In patients who fail to convert sputum cultures to negative after 6 months of treatment or who have extensive disease, expert consultation should be obtained.

Treatment of MAC Pulmonary Disease-summary

We recommend a 3-drug, macrolide-based regimen for patients with macrolide-susceptible MAC pulmonary disease (Tables 3 and 4). 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. The parenteral agent is typically administered for at least 2–3 months. We suggest a 3 times per week regimen in patients with nodular/bronchiectatic disease but a daily macrolide-based regimen in those with cavitary disease. We suggest that treatment be administered for at least 12 months after culture conversion. If sputum cultures have not converted to negative after 6 months of guideline-based treatment, we recommend the use of ALIS as part of the continuation treatment regimen. In the setting of disease caused by macrolide-resistant MAC, the expert panel suggests seeking expert consultation.

Treatment of *M. kansasii* Pulmonary Disease (Questions X–XIV)

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

Background: *M. kansasii* was one of the first NTM to be recognized to cause pulmonary disease [171]. Initially, a *M. tuberculosis*-like regimen including isoniazid was used, but treatment success was unsatisfactory [30, 172] until the introduction of rifampicin [29, 31]. Once rifampicin was included in the regimen, treatment outcomes improved dramatically, and thus a rifampicin-based regimen is recommended [4]. Because of the uncertain value of isoniazid [173] and excellent in vitro activity of the macrolides [174–177], some clinicians have begun to substitute a macrolide for isoniazid in rifampicin-containing regimens [178].

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).

Summary of the Evidence: No randomized clinical trials have directly compared an isoniazid-containing regimen with a macrolide-containing regimen, but there are case series that reported treatment outcomes of these regimens for treating *M. kansasii* pulmonary disease. A 3-drug regimen that includes isoniazid, rifampicin, and ethambutol was recommended in the 2007 Guideline [4]. Treatment outcomes with the 3-drug regimen when administered for 9–18 months have been excellent with cure rates of 80–100% and low relapse rates of 2.5–6.6% when administered for at least 12 months [27–29].

Untreated strains of *M. kansasii* are susceptible to macrolides, as minimal inhibitory concentrations of clarithromycin for *M. kansasii* range from 0.125 to 0.25 μg/mL [176]. Two small retrospective cohort studies evaluated treatment outcomes of regimens that substituted clarithromycin for isoniazid and reported similar cure rates of 80–100% [25, 26]. Among subjects who completed the treatment regimen, cure was 100%. Discussion of value preferences, feasibility, cost, acceptability, and health inequality (Table E4.10) can be found in the supplement.

Justification and Implementation Considerations: Isoniazid is widely used at present for treatment of *M. kansasii* pulmonary disease, and in the experience of the expert panel, there have been good outcomes when using a regimen consisting of rifampicin, ethambutol, and isoniazid irrespective of the result of 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 rifampin and ethambutol.

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

Background: Amikacin or streptomycin is sometimes used for treating NTM pulmonary disease. Studies that included 2–3 months of streptomycin added to a multidrug oral regimen demonstrated high rates of culture conversion and cure in patients with *M. kansasii* pulmonary disease [28, 29, 179]. However, their use in *M. kansasii* disease has not been recommended since the introduction of highly effective rifampicin-based regimens [4, 152, 173].

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).

Summary of the Evidence: There have been no randomized clinical trials addressing the use of amikacin or streptomycin for treating *M. kansasii* pulmonary disease, however three case

Table 3. Dosing Guidelines for Drugs Used in the Management of Nontuberculous Mycobacterial Pulmonary Disease

Drug	Daily Dosing	Thrice Weekly Dosing	Hepatic Impairment	Renal Impairment
Oral				
Azithromycin	250–500 mg per day	500 mg per day	N/A	N/A
Ciprofloxacin	500–750 mg twice per day	N/A	N/A	250–500 mg dosed at intervals according to CrCl
Clarithromycin	500 mg twice per day	500 mg twice per day	N/A	Reduce dose by 50% if CrCl < 30 mL/min
Clofazimine[a]	100–200 mg per day	N/A	Caution in severe hepatic impairment	N/A
Doxycycline	100 mg once to twice a day	N/A	N/A	N/A
Ethambutol	15 mg/kg per day	25 mg/kg per day	N/A	Increase dosing interval (eg, 15–25 mg/kg, 3 times per week)
Isoniazid	5 mg/kg up to 300 mg per day	N/A	Caution	N/A
Linezolid	600 mg once or twice per day[b]	N/A	N/A	N/A
Moxifloxacin	400 mg per day	N/A	N/A	N/A
Rifabutin	150–300 mg per day (150 mg per day with clarithromycin)	300 mg per day	Caution	Reduce dose by 50% if CrCl < 30 mL/min
Rifampicin (rifampin)	10 mg/kg (450 mg or 600 mg) per day	600 mg per day	Caution	N/A
Trimethoprim/sulfamethoxazole	800 mg/160 mg tab twice daily	N/A	Caution	Reduce dose by 50% if CrCl1 5–30 mL/min
Parenteral				
Amikacin (IV)	10–15 mg/kg per day[c], adjusted according to drug level monitoring[d]	15–25 mg/kg per day[c], adjusted according to drug level monitoring[d]	N/A	Reduce dose or increase dosing interval (eg, 15 mg/kg, 2–3 times per week)
Cefoxitin (IV)	2–4 g 2–3 times daily (maximum daily dose is 12 g/day)	N/A	N/A	Reduce dose or increase dosing interval
Imipenem (IV)	500–1000 mg, 2–3 times per day	N/A	N/A	Reduce dose or increase dosing interval
Streptomycin (IV or IM)	10–15 mg/kg per day, adjusted according to drug level monitoring	15–25 mg/kg per day, adjusted according to drug level monitoring	N/A	Reduce dose or increase dosing interval (eg, 15 mg/kg, 2–3 times per week)
Tigecycline (IV)	25–50 mg once or twice per day[b]	N/A	25 mg once or twice daily per day in severe hepatic impairment	N/A
Inhalation				
Amikacin liposome inhalation suspension	590 mg per day	N/A	N/A	N/A
Amikacin, parenteral formulation	250–500 mg per day	N/A	N/A	N/A

Abbreviations: CrCL, creatinine clearance; IM, intramuscular; IV, intravenous; N/A, not applicable.

[a]Clofazimine availability varies by country. In the United States, an investigational new drug application is required.

[b]Most experts recommend once daily dosing of linezolid and tigecycline due to the high rate of drug-related adverse reactions associated with twice daily dosing

[c]The use of the described regimens for 15 weeks was associated with permanent ototoxicity in approximately one third of patients, and the risk was associated with age and cumulative dose [154]. Given the high rates of ototoxicity, risks and benefits should be carefully considered in light of the goals of therapy. Clinicians should consider lower dose ranges and probably rely on intermittent dosing when more prolonged therapy is employed.

[d]Drug level monitoring: Trough < 5 mg/L; Peak with daily dosing 35–45 μg/mL; Peak with intermittent dosing 65–80 μg/mL [154].

series reported results with parenteral-containing regimens [28, 29, 179]. In one retrospective study including a mixture of NTM species, 16 patients with *M. kansasii* pulmonary disease were treated for 6 months to 2.5 years with regimens including streptomycin (n = 14) or capreomycin (n = 2) [179]. In the other 2 studies, 115 patients were treated with a rifampicin-based regimen that included isoniazid and ethambutol for 12 months, supplemented with streptomycin 3 days a week for the first 2 months [29]. The pooled culture conversion rate was 95.5% (42 of 44 patients in 2 studies) [29, 179], and recurrences were observed in 4.7% (6 of 127 patients in 3 studies) [28, 29, 179]. Significant adverse events were reported in one study (14.7%), leading to discontinuation of the parenteral agent in 9.5% [28]. Studies that have used oral regimens without inclusion of aminoglycosides have also demonstrated high culture conversion rates and cure with low relapse rates [25–27]. The relative and absolute effect estimates and 95% CIs for each outcome (Table E3.11) and discussion of value preferences, feasibility, cost, acceptability, and health inequality (Table E4.11) can be found in the supplement.

Justification and Implementation Considerations: In general, regimens of 3 oral agents, rifampicin and ethambutol, and either isoniazid or a macrolide, achieve high rates of sustained culture

Table 4. Recommended Treatment Regimens for *Mycobacterium avium* complex, *M. kansasii*, and *M. xenopi* Pulmonary Disease

Organism	No. of Drugs	Preferred Drug Regimen[a]	Dosing Frequency
M. avium complex			
Nodular-bronchiectatic	3	Azithromycin (clarithromycin) Rifampicin (rifabutin) Ethambutol	3 times weekly
Cavitary	≥3	Azithromycin (clarithromycin) Rifampicin (rifabutin) Ethambutol Amikacin IV (streptomycin)[b]	Daily (3 times weekly may be used with aminoglycosides)
Refractory[c]	≥4	Azithromycin (clarithromycin) Rifampicin (rifabutin) Ethambutol Amikacin liposome inhalation suspension or amikacin IV (streptomycin)[b]	Daily (3 times weekly may be used with aminoglycosides)
M. kansasii			
	3	Azithromycin (clarithromycin) Rifampicin (rifabutin) Ethambutol	Daily
	3	Azithromycin (clarithromycin) Rifampicin (rifabutin) Ethambutol	3 times weekly
	3	Isoniazid Rifampicin (rifabutin) Ethambutol	Daily
M. xenopi			
	≥3	Azithromycin (clarithromycin) and/or moxifloxacin Rifampicin (rifabutin) Ethambutol Amikacin[b]	Daily (3 times weekly may be used with aminoglycosides)

[a]See Table 3 for recommended dosages. Alternative drugs for patients who are intolerant of or whose isolate is resistant to first-line drugs include clofazimine, moxifloxacin, and linezolid. Some experts would consider bedaquiline or tedizolid.

[b]Consider for cavitary, extensive nodular/bronchiectatic disease or macrolide-resistant MAC. Amikacin or streptomycin may be given 3 times a week.

[c]Refractory disease is defined as remaining sputum culture positive after 6 months of guideline-based therapy. Amikacin liposome inhalation suspension (ALIS) has been shown to improve culture conversion when added to guideline-based therapy in treatment refractory patients with MAC pulmonary disease.

conversion and treatment success in the treatment of *M. kansasii* pulmonary disease. Therefore, given the good outcomes observed with oral regimens, the lack of data supporting the benefit of amikacin or streptomycin, and the potential risk of adverse effects associated with amikacin or streptomycin, the panel members 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.

Question 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?

Background: In vitro testing shows susceptibility of clinical *M. kansasii* isolates to fluoroquinolones [175, 177, 180, 181], and fluoroquinolones are currently recommended as part of a multidrug regimen to treat rifampicin-resistant *M. kansasii* pulmonary disease [4]. It is not known whether the in vitro activity translates into treatment success that would lead to a change in the current treatment recommendation.

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 1 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).

Summary of evidence: Although there is good in vitro activity of the fluoroquinolones against *M. kansasii*, no randomized clinical trial or case series have been published in which a fluoroquinolone was used for the treatment of *M. kansasii* pulmonary disease. Discussion of value preferences, feasibility, cost,

acceptability, and health inequality (Table E4.12) can be found in the supplement.

Justification and Implementation Considerations: 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. Although 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. For rifampicin-resistant disease, a regimen such as ethambutol, azithromycin, and a fluoroquinolone would likely to lead to successful treatment.

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

Background: A rifamycin-based multidrug regimen for treatment of *M. kansasii* pulmonary disease is associated with a high cure rate when administered daily for at least 12 months [25, 27, 182]. Three times weekly treatment has been used successfully in the treatment of noncavitary MAC pulmonary disease [22, 23] and may decrease side effects and increase tolerability without impacting treatment success in patients with *M. kansasii* pulmonary disease [26].

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 rather than 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 rather than 3 times weekly (conditional recommendation, very low certainty in estimates of effect).

Summary of Evidence: Treatment regimens using daily administration of rifampicin, isoniazid, and ethambutol are associated with high treatment success and low relapse rates [27–29]. There are no studies that have evaluated treatment outcomes of this regimen when given intermittently. In contrast, clarithromycin-based treatment regimens have been demonstrated to have similarly good success rates [25, 26], even when given 3 times per week (14/14 evaluable patients converted sputum cultures and remained relapse free after 46 ± 8.0 months); 9 of the 14 patients had cavitary disease [26]. The relative and absolute effect estimates and 95% CIs for each outcome (Table E3.13) and discussion of value preferences, feasibility, cost, acceptability, and health inequality (Table E4.13) can be found in the supplement.

Justification and Implementation Considerations: Cavitary NTM pulmonary disease has higher morbidity and mortality and warrants a more aggressive treatment approach than noncavitary disease [163, 183]. It is unclear to what extent this principle applies to patients with *M. kansasii* pulmonary disease given that 3 times weekly treatment can be effective in patients with nodular/bronchiectatic or cavitary disease [26]. However, because there are no randomized trials available and the small size of the single study that evaluated 3 times weekly therapy, the panel 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.

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

Background: Treatment for *M. kansasii* pulmonary disease with a rifampicin-based regimen for at least 12 months after negative sputum cultures was recommended by the 2007 ATS treatment guideline [4]. However, data from several studies suggest that a 12-month fixed duration may be enough to cure most patients [27–29].

Recommendation

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

Summary of the Evidence: There have been no randomized clinical trials comparing <12 months with ≥12 months of treatment after culture conversion, but a 12-month fixed duration regimen was evaluated in 3 studies [27–29], and a 9-month regimen in one [173]. A clinical trial randomized 28 patients into 2 groups of 14: one group received rifampicin, isoniazid and ethambutol daily for 6 months, followed by rifampicin and isoniazid to complete 12 months (14 patients), and the other group completed 18 months (14 patients) [27]. After 12–30 months of follow-up, one patient in the 12-month arm (7%) and none in the 18-month arm recurred after completing treatment. In a prospective study [29], 40 patients were treated with 1 g of streptomycin (twice weekly for the first 3 months) plus rifampicin, isoniazid, and

ethambutol for 12 months. One patient (2.5%) recurred 6 months after completing treatment. Using the same regimen in a series of 75 patients [28], 5 (6.6%) recurred after a median follow-up of 41.5 months. The pooled recurrence rate from these 3 studies was 5.4% (7 of 129 patients) [27–29]. The British Thoracic Society evaluated a 9-month regimen with rifampicin and ethambutol in 115 patients in a prospective study [173]. Although conversion of sputum to negative was achieved in 99.4% of patients, 10% experienced disease recurrence. The relative and absolute effect estimates and 95% CIs for each outcome (Table E3.14) and discussion of value preferences, feasibility, cost, acceptability, and health inequality (Table E4.14) can be found in the supplement.

Justification and Implementation Considerations: 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. Some of the reported relapses may actually be exogenous reinfections, as suggested by the long periods between treatment completion and recurrence [27, 173]. 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.

Treatment of *M. kansasii* Pulmonary Disease—Summary

We suggest a regimen of rifampicin, ethambutol, and either isoniazid or macrolide for patients with rifampicin-susceptible *M. kansasii* pulmonary disease (Tables 3 and 4). Neither parenteral amikacin nor streptomycin are recommended for routine use in these patients. We suggest that patients with nodular/bronchiectatic *M. kansasii* pulmonary disease receive either daily or 3 times weekly treatment when receiving a macrolide, rifampicin, and ethambutol. However, in patients with cavitary disease, the regimen should be administered daily. In addition, when patients are treated with a regimen that includes isoniazid, rifampicin, and ethambutol, we suggest treatment be given daily. 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. We suggest that all patients be treated for at least 12 months.

Treatment of *M. xenopi* Pulmonary Disease (Questions XV–XVIII)

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

Background: *M. xenopi* pulmonary disease is difficult to treat and associated with high all-cause mortality [35, 36, 131, 184, 185] that is higher than other NTM species, with a 5-year mortality of 51% and 43% in population-based studies from Denmark and Canada, respectively [34, 186]. The elevated mortality may be due to the underlying lung disease, frequent concomitant chronic pulmonary aspergillosis [187, 188], as well as frequent cavitation among patients with *M. xenopi* disease [189]. In vitro data suggest that MIC values of fluoroquinolones are low for *M. xenopi*: in vitro activity of moxifloxacin is equal to that of clarithromycin [190]. In murine models, adding either moxifloxacin or clarithromycin to a rifampicin-ethambutol combination leads to drug regimens of equal efficacy [191].

Recommendation

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

Summary of the Evidence: There are 2 systematic reviews that have reported treatment outcomes of *M. xenopi* pulmonary disease, and both noted a wide range of drugs and regimens used [184, 185]. Only 1 randomized clinical trial has been published that compared ciprofloxacin with clarithromycin when added to rifampicin and ethambutol in patients with *M. xenopi* pulmonary disease [131]. In this study, 34 patients were treated with either ciprofloxacin (n = 17) or clarithromycin (n = 17) in addition to rifampicin and ethambutol. No significant differences were found between the 2 regimens in term of death, cure, recurrence or adverse effects. However, the power of the study was too low to conclude which regimen was best (only 34 patients and 2 events). Moreover, in this study that also included patients with *M. avium* or *M. malmoense*, adverse events were not reported separately for *M. xenopi*. Preliminary data from a study in France in which randomized patients received either moxifloxacin or clarithromycin plus ethambutol and rifampicin reported no difference in the treatment success between the study arms [33]. The relative and absolute effect estimates and 95% CIs for each outcome (Table E3.15) and discussion of value preferences, feasibility, cost, acceptability, and health inequality (Table E4.15) can be found in the supplement.

Justification and Implementation Considerations: 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]. From this perspective, a multidrug regimen that utilizes a macrolide or fluoroquinolone would be likely more active.

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

Background: Despite the poor prognosis of *M. xenopi* pulmonary disease, there are few studies available on optimal treatment

[35]. Like in other NTM infections, a multidrug therapy is used to avoid selecting for drug resistance, but the optimal number and combination of drugs are not known.

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).

Summary of evidence: There are 2 systematic reviews that have reviewed treatment outcomes of *M. xenopi* pulmonary disease, and both noted a wide range of drugs and regimens used [184, 185]. The authors of these reviews were unable to recommend the optimal number of drugs to be used in the regimen, although in 1 review, fluoroquinolone-containing regimens were associated with a greater proportion of relapse-free success [185]. Two randomized controlled studies in patients with *M. xenopi* pulmonary disease were conducted by the British Thoracic Society [36, 119, 131]. The first study compared efficacy of a regimen containing rifampicin, ethambutol with or without isoniazid in 42 patients (20 vs 22) [36, 119]. No significant differences were found in terms of death, cure or recurrence between the 2 groups. Nevertheless, the power is probably insufficient, with few patients included and few events occurred. The main result of this study was the poor prognosis of these patients (5-year mortality of 57% with *M. xenopi* vs 31% in MAC disease and 25% in *M. malmoense* disease). In the second study, 34 patients with *M. xenopi* pulmonary disease were randomized to receive rifampicin, ethambutol, and either ciprofloxacin or clarithromycin. Treatment failure/relapse occurred in 24% of the clarithromycin group versus 6% in the ciprofloxacin group [131]. In a murine model of *M. xenopi* infection, a 4-drug regimen (rifampicin, ethambutol, amikacin, and clarithromycin or moxifloxacin) demonstrated better efficacy than a 3-drug regimen (rifampicin, ethambutol, and moxifloxacin or clarithromycin) [191]. The relative and absolute effect estimates and 95% CIs for each outcome (Table E3.16) and discussion of value preferences, feasibility, cost, acceptability, and health inequality (Table E4.16) can be found in the supplement.

Justification and Implementation Considerations: In animal and in vitro models, regimens of rifampicin, ethambutol, and either clarithromycin or moxifloxacin are efficacious and those that included amikacin (see Question 17) even more so. Given the very high mortality associated with *M. xenopi*, the committee felt the large risk of treatment failure with a 2-drug regimen warranted a strong recommendation for at least a 3-drug treatment regimen. However, the lack of confidence in the estimates of effect from the available studies tempered the recommendation. Additionally, the absence of universal access to moxifloxacin and the small amount of data for other fluoroquinolones has to be considered when choosing a regimen.

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

Background: Patients with *M. xenopi* pulmonary disease frequently present with cavitary disease [189], often respond poorly to treatment [35, 36, 184, 185], and suffer a higher all-cause mortality than other NTM species [34, 186]. Based on expert opinion, the 2007 Guideline suggested that adding streptomycin to a multidrug oral regimen is reasonable [4]. However, there is substantial uncertainty regarding best treatment regimens for *M. xenopi*.

Recommendation

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).

Summary of the Evidence: For the current Guideline, no high-quality studies addressing the question were identified. In a systematic review of *M. xenopi*pulmonary disease, data regarding parenteral therapy were found exclusively in retrospective series, and the data synthesis identified evidence against aminoglycosides [185]. Compared with patients who did not receive aminoglycosides, patients who received aminoglycosides had lower success rates both in the short term (56% versus 82%, $P = .019$) and long term (38% vs 68%, $P = .029$). However, the comparison was undoubtedly biased strongly by disease severity. Two studies in mice infected with *M. xenopi* have shown reduced colony forming units among mice treated with amikacin in addition to comparator regimens [191, 192]. One study used intravenously infected mice treated with clarithromycin, ofloxacin plus/minus amikacin [192], and the other study used an inhalational infection model and treatment with either clarithromycin/ethambutol/rifampicin or moxifloxacin/ethambutol/rifampicin plus/minus amikacin [191], and both studies identified microbiologic benefit of the addition of amikacin. Discussion of value preferences, feasibility, cost, acceptability, and health inequality (Table E4.17) can be found in the supplement.

Justification and Implementation Considerations: This recommendation is based on expert opinion and data from murine models of *M. xenopi* infection, wherein microbiologic benefit was observed in mice treated with amikacin [191, 192]. 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 panel considered the general acceptability and feasibility of parenteral therapy, and potential costs and toxicities, all based on clinical experience.

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

Background: The optimal duration of treatment for *M. xenopi* pulmonary disease is not known, neither is the effect of treatment duration on the frequency of disease recurrence. The 2007 Guideline suggested a treatment duration of 12 months beyond culture conversion, acknowledging that the optimal duration was unknown [4].

Recommendation

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).

Summary of the Evidence: No studies have specifically addressed this question. Two studies in the 1980s found that treatment durations had an effect on outcomes (typically with isoniazid-rifampicin-ethambutol regimens). Treatment duration over 18 months lead to relapse-free cure in 8/11 patients [122]; treatment regimens over 9 months of duration cured more patients (11/23) than shorter regimens (1/11) [37]. A 2009 systematic review concluded that the data available at the time of the review did not permit comment on the impact of treatment duration on treatment outcomes [185]. Subsequent case series could not address the specific question but found that treatment duration of <6 months was associated with higher mortality and with recurrence [35]. One clinical trial has examined 24-month long regimens for *M. xenopi* pulmonary disease; 12 of 34 (35%) patients treated showed a favorable response that could be sustained for 3 years after treatment; however, 18 patients (54%) deviated from the treatment protocol, for which no further details are available [131]. Three retrospective case series have reported on outcomes and mean or median treatment duration, but regimens varied and none of these studies specifically correlated treatment duration with outcomes. A study in France recorded 27% clinical and/or microbiological conversion with a median duration of treatment of 5 months in 122 patients [35]. In Croatia, 6 months of first-line antituberculosis treatment led to favorable outcomes in 10 of 20 patients (50%) [193]. In the Netherlands, 11 of 19 patients (58%) treated for a mean of 9 months achieved culture conversion sustained until end of treatment [123]. Mortality rates varying from 21% [123] to 41% [131] and even 69% [35] suggest that long-term treatment and follow-up are a significant challenge in this specific disease. The relative and absolute effect estimates and 95% CIs for each outcome (Table E3.18) and discussion of value preferences, feasibility, cost, acceptability, and health inequality (Table E4.18) can be found in the supplement.

Justification and Implementation Considerations: The data reviewed above suggest that treatment outcomes improve if the duration of treatment increases. The panel members felt that this outweighs the risk of adverse events associated with longer treatment and agrees with previous recommendations [4].

Treatment of *M. xenopi* Pulmonary Disease—Summary

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) (Tables 3 and 4). In patients with severe *M. xenopi* pulmonary disease, we suggest adding parenteral amikacin to the treatment regimen and obtaining expert consultation given the poor treatment outcomes. We suggest treatment be continued for ≥12 months after culture conversion.

Treatment of *M. abscessus* Pulmonary Disease (Questions XIX–XXI)

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

Background: Macrolides possess potent activity against *M. abscessus* as well as immunomodulatory effects. Macrolide resistance can develop through chromosomal mutations in the 23S rDNA (*rrl*) gene resulting in high level mutational resistance as well as through induction of the *erm*(41) gene that causes inducible resistance in the presence of a macrolide [125]. *M. abscessus* subsp. (*abscessus*, *bolletii*, and *massiliense*) are rapidly growing mycobacteria that differ in in vitro susceptibility to macrolides based on the functionality of the *erm*(41) gene [194]. The different mechanisms leading to macrolide resistance have made it difficult for clinicians to determine when to use a macrolide in the treatment of *M. abscessus* pulmonary disease.

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).

Summary of evidence: There were no studies identified that compared macrolide-containing regimens with nonmacrolide-containing regimens. A recent systematic review [195] reported that a single study reported the use of macrolide-free regimens in 120 patients of whom 8% experienced culture conversion [196]. This review included an additional 13 studies that used macrolide-containing regimens of which 10 were restrospective [38, 39, 89, 197–203] and 3 prospective cohort designs [12, 108, 204]. A second systematic review [184] included 10 studies including 2 [90, 205] that were not assessed in the other systematic review. Evidence from these studies has demonstrated the importance of macrolide susceptibility and treatment outcomes. Compared with the macrolide-free regimen, the macrolide-containing regimens had a pooled sustained sputum culture conversion of 34% with *M. abscessus* subsp *abscessus* and 54% with subsp. *massiliense* [195]. Overall, good treatment outcomes were noted in 84% of those with *M. abscessus* subsp. *massiliense* compared with 23% with subsp. *abscessus*.

Four studies compared treatment outcomes in patients with infections due to *M. abscessus* subsp. *abscessus* or *massiliense* [38, 198, 199, 203, 206, 207]. Among the over 200 patients included in the studies, culture conversion ranged between 25–42% and 50–96% among those with subsp. *abscessus* and *massiliense*, respectively. The very large differences in culture conversion between the 2 subspecies were likely related to the nonfunctional *erm*(41) gene (no inducible resistance) in subsp. *massiliense* and a functional gene in most isolates of subsp. *abscessus*. This strongly suggests that macrolides provide a very large benefit in the treatment of macrolide-suspectible *M. abscessus*. Additional data demonstrating the importance of the macrolide in treatment is a study that reported that only 1 (7%) patient with macrolide resistant *M. abscessus* subsp. *massiliense* had a favourable outcome with treatment [124]. The relative and absolute effect estimates and 95% CIs for each outcome (Table E3.19) and discussion of value preferences, feasibility, cost, acceptability, and health inequality (Table E4.19) can be found in the supplement.

Justification and Implementation Considerations: *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 [208]. The far better treatment outcomes in studies of *M. abscessus* subsp. *massiliense* versus subsp. *abscessus* (inactive vs active *erm*(41) gene), where treatment differences appear to depend on the activity of the macrolide, strongly suggest a major benefit from this drug class [38, 39, 203, 206, 207]. Despite the very low certainty in the estimates of effect, the committee felt a strong recommendation was appropriate given the high morbidity and mortality of *M. abscessus* infections and significant potential clinical impact of macrolides given their in vitro activity.

It is important to consider identification of the *M. abscessus* subsp. in addition to in vitro macrolide susceptibility testing, because of the difference in response to macrolide therapy based on the presence of a functional or nonfunctional *erm*(41) gene. The acquisition of treatment associated mutational macrolide resistance in patients with *M. abscessus,* with or without inducible macrolide resistance, suggests that mutations in 23S rRNA are responsible for high level macrolide resistance [125]. In this setting, macrolides are unlikely to be contributing to the antimicrobial effect of the treatment regimen.

Macrolides have been demonstrated to prevent exacerbations of bronchiectasis in patients with chronic *Pseudomonas* infection, despite the lack of antimicrobial activity against *Pseudomonas* [209, 210], which is a common copathogen in patients with bronchiectasis [211]. However, the risk of acquiring resistance to other coinfecting pathogens must be considered when macrolides are used for immunomodulatory purposes in patients whose isolate has documented inducible or mutational macrolide resistance [209, 210]. As with all patients receiving treatment, frequent sputum cultures should be obtained during the course of therapy to monitor for treatment response and survey for the appearance of other organisms such as *M. avium* complex. In this setting, the treatment regimen should be adjusted to cover the new isolates in order to avoid development of macrolide resistance in the new NTM.

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

Background: *M. abscessus* isolates display in vitro resistance to most oral antibiotics and are generally susceptible to a limited number of parenteral agents including tigecycline, imipenem, cefoxitin, and amikacin. Previous guidelines recommend using a multidrug regimen including ≥2 of these antibiotics to which the organism is susceptible in vitro. Recent work suggests a lack of consensus among treating physicians, with a variety of regimens employed against this organism ranging from 2 to 5 drugs in the initial phases of therapy [212].

Recommendation

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

Summary of the Evidence: There are 2 systematic reviews [184, 195] that have reported treatment outcomes in patients with *M. abscessus* pulmonary disease, but there are no studies that have directly compared the efficacy or safety of different multidrug regimens. Based on the systematic reviews, the

overall sputum culture conversion in patients with *M. abscessus* (not further subspeciated) treated with a multidrug, macrolide-containing regimen was 59%: culture conversion occurred in 34–41% in those with *M. abscessus* subsp. *abscessus* and 54–69.8% in those with *M. abscessus* subsp. *massiliense* [184, 195]. One observational retrospective study attempted to compare a macrolide plus amikacin regimen versus a 3-drug regimen consisting of a macrolide, amikacin, and either imipenem or cefoxitin [198]. However, they did not distinguish patients with *M. abscessus* isolates with and without functional *erm* genes. Accordingly, the interpretation of outcomes associated with these regimens was not possible. One additional observational retrospective study suggested that multidrug therapy is associated with improved quality of life in *M. abscessus* patients, but this study did not compare outcomes according to different drug regimens [108]. Importantly, the few cases series that have described treatment outcomes all used multidrug regimens with ≥3 drugs [184, 195]. The relative and absolute effect estimates and 95% CIs for each outcome (Table E3.20) and discussion of value preferences, feasibility, cost, acceptability, and health inequality (Table E4.20) can be found in the supplement.

Justification and Implementation Considerations: 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 expert panel suggests using a regimen consisting of ≥3 active drugs in macrolide susceptible disease and at least 4 drugs, when possible, in macrolide resistant disease. This is particularly true in the initial months of therapy when bacterial burdens are greater. Design of regimens beyond the initial intravenous phase is difficult given the lack of oral antimicrobials with activity against *M. abscessus*. Although macrolides might still be useful for immunomodulatory effects or antimicrobial effects against other coinfecting organisms, they are not counted as an active drug against *M. abscessus* when inducible or mutational resistance is noted. The committee members feel strongly that treatment regimens should be designed in collaboration with experts in the management of these complicated infections.

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

Background: The 2007 Guideline noted that no medication strategy could reliably achieve the goal of 12 months of negative sputum cultures while on therapy [4]. It was therefore suggested that periodic treatment courses, or aggressive treatment regimens including multiple parenteral agents for a few months, could be effective strategies. However, the optimum treatment duration of pulmonary disease caused by *M. abscessus* complex is currently unknown.

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 comparator, very low certainty in estimates of effect).

Summary of the Evidence: Only 1 study addressing this specific question was identified by the systematic review [213]. This observational, retrospective study included 30 patients with *M. abscessus* pulmonary disease who met the diagnostic criteria defined in the 2007 Guideline. Overall, 17 of the patients were treated for >1 month and had follow-up available for at least 1 year: 13 were treated for less than 12 months, and 4 were treated for ≥12 months. No significant difference was found in the cure rate between the 2 groups. No additional information was available with regard to lung involvement, nor to the subsp. of *M. abscessus*. The study methodology, notably no control for confounding, indirect comparisons with different regimens of various duration, and a wide confidence interval, indicate high risk of bias. Two recent systematic reviews did not address the optimum duration of therapy but noted that most patients with *M. abscessus* were treated for over 12 months with multidrug regimens including a minimum of 4 weeks of ≥1 parenteral antimicrobials [184, 195]. The relative and absolute effect estimates and 95% CIs for each outcome (Table E3.21) and discussion of value preferences, feasibility, cost, acceptability, and health inequality (Table E4.21) can be found in the supplement.

Given the better treatment outcomes with disease due to *M. abscessus* subsp. *massiliense*, a shorter or less intensive course of therapy may be possible. In a retrospective study of 128 patients with *M. abscessus*, patients with *M. abscessus* subsp. *massiliense* had better treatment outomes than patients with subsp. *abscessus* despite receiving shorter durations of parenteral and total treatment: patients with *M. abscessus* subsp. *massiliense* received a median of 4.7 months of parenteral therapy and 12.1 months of total treatment compared with 7.4 and 16.3 months in patients with *M. abscessus* subsp. *abscessus*, respectively [207]. In another study, 71 patients with *M. abscessus* subsp. *massiliense* were treated with either 2 or 4 weeks of intravenous amikacin and cefoxitin (or imipenem) along with an oral macrolide [204]. Those treated with a 2-week course of parenteral therapy followed by at least 12 months of an oral macrolide post conversion had a culture conversion rate of 91% compared with 100% in those who received a 4-week course and oral macrolide for 24 months. Two patients who received the shorter course of therapy developed acquired macrolide resistance. Although the expert panel does not recommend macrolide monotherapy for treatment of NTM pulmonary disease, the study demonstrated that similar treatment outcomes

could be obtained using shorter and less intensive treatment than used for *M. abscessus* subsp. *abscessus*.

Justification and Implementation Considerations: The 1 study identified had a very small sample size, only indirectly addressed this question, and was felt to be of too low quality to form the basis of a recommendation. The lack of studies evaluating treatment durations, the variation in drug and resource availability, as well as the diverse 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. Although the optimal duration of therapy is not known, most patients reported in the literature with *M. abscessus* were treated for >12 months, and the treatment was divided into an initial phase usually including parenteral drugs followed by a longer phase using oral and sometimes inhaled antibiotics [184, 195]. The panel members suggest that an expert in the management of patients with *M. abscessus* pulmonary disease be consulted prior to initiation of therapy in order to assist with determination of the duration of therapy.

Treatment of *M. abscessus* Pulmonary Disease—Summary

The optimal drugs, regimens, and duration of therapy are not known. Patients with *M. abscessus* pulmonary disease caused by strains *without* inducible (typically *M. massiliense*) or mutational macrolide resistance should be treated with a macrolide-containing multidrug regimen that includes at least 3 active drugs (guided by in vitro susceptibility) in the initial phase of treatment (the phase including intravenous agents) (Tables 3 and 5). In patients with *M. abscessus* pulmonary disease caused by strains *with* inducible (typically *M. abscessus* or *M. bolettii*) or mutational macrolide resistance, we suggest a regimen that includes at least 4 active drugs, when possible. 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. For the continuation phase of therapy (after the parenteral component), we suggest that at least 2–3 active drugs be given. Some experts would use intermittent courses of multidrug therapy instead of transitioning to a longer continuation phase, although almost all published studies treated patients for >12 months. In the absence of data to support a shorter or longer treatment course for *M. abscessus* pulmonary disease, the panel members suggest that expert consultation be obtained prior to initiation of therapy in order to assist with design of the regimen and determine whether a shorter or longer treatment regimen should be used.

Surgical Resection for Treatment of NTM Pulmonary Disease (Question XXII)

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

Background: NTM pulmonary disease is often difficult to cure with antimicrobial therapy alone. 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.

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).

Summary of the Evidence: We identified 15 observational studies [30, 39, 43, 89, 214–223] including approximately 700 patients who underwent various surgical resections including segmentectomies, lobectomies, and pneumonectomies. Most patients included in the studies had MAC pulmonary disease, with 1 study including only patients with *M. xenopi* pulmonary disease [221], 1 with *M. kansasii* only [30], and 2 including patients with *M. abscessus* pulmonary disease [39, 89]. Almost all of the patients who underwent surgery had received antimicrobial treatment before and after surgery. Three studies reported results for patients treated with combined antibiotic and surgical therapy, compared with antibiotic therapy alone [30, 39, 89].

Cure rate of the NTM disease, death, and recurrences were not significantly different between medical and surgical therapy in the 3 comparative studies that included a total of 296 patients with follow-up data (95 surgical plus medical and 201 medical only). Although there was more culture conversion observed in the patients who underwent surgery, the quality of evidence was very low, due to the small number of patients treated, inherent selection bias by treatment group, lack of adjustment for other clinical variables, and the fact that all patients were treated by medical therapy. The desirable anticipated effects were estimated to be moderate. Surgical complications (such as bronchopleural fistula, prolonged air leak, pneumonia) were observed in 7–35% of participants. There was no operative mortality and postoperative mortality was reported in 0–9% of patients. In 1 study that reported outcomes of patients who underwent video assisted thoracoscopic surgery (VATS), culture conversion occurred in 84% of the patients, postoperative complications occurred in 7% of patients, and there were no operative or postoperative deaths reported [216]. Undesirable effects were estimated as small, and the balance between desirable and undesirable probably favors the intervention. There was no evidence identified for costs, which were estimated as moderate

Table 5. Treatment Regimens for *Mycobacterium abscessus* by Macrolide Susceptibility (Mutational and Inducible Resistance)

Macrolide Susceptibility Pattern				
Mutational[a]	Inducible[b]	No. of Drugs[c]	Preferred Drugs	Frequency of Dosing
Susceptible	Susceptible	Initial phase ≥ 3	*Parenteral (choose 1–2)*	Daily (3 times weekly may be used for aminoglycosides)
			Amikacin	
			Imipenem (or Cefoxitin)	
			Tigecycline	
			Oral (choose 2)	
			Azithromycin (clarithromycin)[d]	
			Clofazimine	
			Linezolid	
		Continuation phase ≥ 2	*Oral/inhaled (choose 2–3)*	
			Azithromycin (clarithromycin)[d]	
			Clofazimine	
			Linezolid	
			Inhaled amikacin	
Susceptible	Resistant	Initial phase ≥ 4	*Parenteral (choose 2–3)*	Daily (3 times weekly may be used for aminoglycosides)
			Amikacin	
			Imipenem (or Cefoxitin)	
			Tigecycline	
			Oral (choose 2–3)	
			Azithromycin (clarithromycin)[e]	
			Clofazimine	
			Linezolid	
		Continuation phase ≥ 2	*Oral/inhaled (choose 2–3)*	
			Azithromycin (clarithromycin)[e]	
			Clofazimine	
			Linezolid	
			Inhaled amikacin	
Resistant	Susceptible or resistant	Initial phase ≥ 4	*Parenteral (choose 2–3)*	Daily (3 times weekly may be used for aminoglycosides)
			Amikacin	
			Imipenem (or Cefoxitin)	
			Tigecycline	
			Oral (choose 2–3)	
			Azithromycin (clarithromycin)[e]	
			Clofazimine	
			Linezolid	
		Continuation Phase ≥ 2	*Oral/inhaled (choose 2–3)*	
			Azithromycin (clarithromycin)[e]	
			Clofazimine	
			Linezolid	
			Inhaled amikacin	

[a]Mutational resistance: None present—Isolate determined to be phenotypically susceptible at 3–5 days of incubation in culture. Present—Isolate determined to be phenotypically resistant at 3–5 days of incubation or sequencing identifies *rrl* mutation know to confer resistance.

[b]Inducible resistance: Functional *erm*(41) gene—Isolate determined to be resistant after 14 days of incubation or sequencing identifies functional gene sequence. Nonfunctional *erm*(41) gene—Isolate determined to be susceptible after 14 days of incubation or sequencing identifies truncated sequence or C28 mutation (in subspecies *abscessus*).

[c]Initial phase refers to the time that the parenteral agents are being given. Continuation phase refers to the subsequent phase of therapy that typically includes oral antimicrobial agents sometimes paired with inhaled agents.

[d]Azithromycin (clarithromycin) is active in this setting and should be used whenever possible.

[e]Azithromycin (clarithromycin) activity is unlikely but can be added for its immunomodulatory effects but should not be counted as active against *M. abscessus* with a functional *erm*(41) gene. In this setting, frequent sputum cultures should be obtained to detect potentially new organisms like *M. avium* complex.

with regard to the duration of the disease. Therefore, surgery was estimated as acceptable to key stakeholders and feasible.

Justification and Implementation Considerations: The studies differed by location, the age and gender of patients, and the mycobacterial species involved (*M. avium* [214, 218, 220, 222], *M. kansasii* [30], *M. abscessus* [39, 89], *M. xenopi* [221] or a mix of species [89, 215–217, 219, 220, 223]). Moreover, the studies suffer from multiple potential biases including different reasons for performing surgery, patient selection, and subjective assessment of postsurgical outcomes. Even so, surgical resection was associated with improved treatment outcomes and for most of the patients (85–100%), conversion of sputum cultures to

Table 6. Common Adverse Drug Reactions and Monitoring Recommendations[a]

Drug	Adverse Reactions	Monitoring
Azithromycin	Gastrointestinal	Clinical monitoring
	Tinnitus/hearing loss	Audiogram
	Hepatotoxicity	Liver function tests
	Prolonged QTc	ECG (QTc)
Clarithromycin	Gastrointestinal	Clinical monitoring
	Tinnitus/hearing loss	Audiogram
	Hepatotoxicity	Liver function tests
	Prolonged QTc	ECG (QTc)
Clofazimine	Tanning of skin and dryness	Clinical monitoring
	Hepatotoxicity	Liver function tests
	Prolonged QTc	ECG (QTc)
Doxycycline	GI upset	Clinical monitoring
	Photosensitivity	Clinical monitoring
	Tinnitus/vertigo	Clinical monitoring
Ethambutol	Ocular toxicity	Visual acuity and color discrimination
	Neuropathy	Clinical monitoring
Isoniazid	Hepatitis	Liver function tests
	Peripheral neuropathy	Clinical monitoring
Linezolid	Peripheral neuropathy	Clinical monitoring
	Optic neuritis	Visual acuity and color discrimination
	Cytopenias	Complete blood count
Moxifloxacin	Prolonged QTc	ECG (QTc)
	Hepatotoxicity	Liver function tests
	Tendinopathy	Clinical monitoring
Trimethoprim/sulfamethoxazole	GI upset	Clinical monitoring
	Cytopenias	Complete blood count
	Hypersensitivity	Clinical monitoring
	Photosensitivity	Clinical monitoring
Rifabutin	Hepatotoxicity	Liver function test
	Cytopenias	Complete blood count
	Uveitis	Visual acuity
	Hypersensitivity	Clinical monitoring
	Orange discoloration of secretions	
Rifampicin (rifampin)	Hepatotoxicity	Liver function test
	Cytopenias	Complete blood count
	Hypersensitivity	Clinical monitoring
	Orange discoloration of secretions	
Amikacin, Streptomycin, Tobramycin	Vestibular toxicity	Clinical monitoring
	Ototoxicity	Audiograms
	Nephrotoxicity	BUN, creatinine
	Electrolyte disturbances	Calcium, magnesium, potassium
Amikacin liposome inhalation suspension	Dysphonia	Clinical monitoring
	Vestibular toxicity	Clinical monitoring
	Ototoxicity	Audiograms
	Nephrotoxicity	BUN, creatinine
	Cough	Clinical monitoring
	Dyspnea	Clinical monitoring
Cefoxitin	Cytopenias	Complete blood count
	Hypersensitivity	Clinical monitoring
Imipenem	Rashes	Clinical monitoring
	Cytopenias	Complete blood count
	Nephrotoxicity	BUN/Creatinine
Tigecycline	Nausea/vomiting	Clinical monitoring
	Hepatitis/pancreatitis	Liver function tests, amylase/lipase

Abbreviations: BUN, blood, urea, nitrogen; ECG, electrocardiogram; GI, gastrointestinal; QTc, corrected QT.

[a]The expert panel recommends that patients have a complete blood count, liver function tests, and metabolic panel every 1–3 months in patients on oral therapy and weekly when on intravenous therapy.
Monitoring frequency should be individualized based on treatment regimen, age, comorbidities, concurrent drugs, overlapping drug toxicities, and resources.

negative was observed after surgery. Therapy with antimicrobial agents continued during and after the surgery, and the activity of these agents varied with regard to the study and the species involved (eg, clarithromycin was given in recent studies but not in the older ones). Many experts feel it is desirable to achieve at least smear conversion prior to surgical resection, and the panel suggests that surgery be performed by a surgeon experienced in performing surgery on patients with mycobacterial disease [43].

Monitoring for Response to Therapy

Clinical, radiographic, and microbiologic data should be collected in order to assess whether or not a patient is responding to therapy. Chest radiographs or chest CT imaging may be beneficial for defining a radiographic response to therapy, although there can be wide variability in findings given the common occurrence of underlying lung disease. Because the duration of therapy is based on the time of culture conversion, frequent collection of sputum specimens is required in order to determine the recommended treatment duration. The expert panel would consider obtaining sputum specimens for culture every 1–2 months in order to document when sputum cultures become negative. Sputum should be induced with hypertonic saline if spontaneous sputum specimens cannot be collected. Bronchoscopy should only be considered in exceptional circumstances to determine whether culture conversion has occurred. In addition to microbiologic assessments, clinical and radiographic response to therapy should be used to determine if the patient is responding to therapy.

Monitoring for Adverse Reactions

The drugs used to treat NTM pulmonary disease are frequently associated with adverse reactions. A recent randomized clinical trial reported that >90% of subjects in each arm reported a treatment emergent adverse reaction [20]. Therefore, educating patients regarding potential reactions and monitoring for them is an important component of management. Rapid identification and management of an adverse reaction is likely to decrease the risk of treatment for the patient and possibly improve the chances of treatment completion. Table 6 lists common adverse reactions associated with the drugs used to treat NTM pulmonary disease and an approach to monitoring. Unfortunately, there are no studies that have identified the optimum frequency

or most cost-effective approach to monitoring for drug-related adverse reactions. Monitoring frequency should be individualized based on age, comorbidities, concurrent drugs, overlapping drug toxicities, and resources.

Therapeutic Drug Monitoring

Therapeutic drug monitoring (TDM) refers to the measurement of drug concentrations in serum specimens at some point after dosing to determine whether or not a specific target concentration has been obtained (Table 3). There are no randomized trials that have determined the clinical utility of performing TDM. However, studies have documented significant reductions in serum drug concentrations of clarithromycin with concurrent use of rifampicin and to a lesser extent with rifabutin [145, 224, 225]. Two studies described the association of serum concentrations of macrolides and treatment outcomes. The first study reported no association between the serum concentration of clarithromycin and treatment outcomes [224], whereas the second study noted a correlation between the peak serum concentration (Cmax) of azithromycin and favorable treatment outcomes when administered daily (250 mg) but not intermittently (500 mg) [226]. Experts would consider performing TDM in situations in which drug malabsorption, drug underdosing, or clinically important drug-drug interactions are suspected [227]. Examples of situations in which TDM may be useful include patients with delayed sputum culture conversion or treatment failure not explained by nonadherence or drug resistance, patients receiving amikacin or streptomycin therapy and thus at risk of ototoxicity and nephrotoxicity, and patients with medical conditions (eg, reduced renal function) that are suspected of leading to subtherapeutic or toxic drug concentrations.

Research Priorities

During the development of this Guideline, research gaps were identified for each of the PICO questions. Not surprisingly, there were many gaps and needs identified related to the treatment of NTM pulmonary disease. Many of the research priorities relate to the need for new drugs, treatment regimens, shorter regimens, and better tolerated regimens. Evaluation of new drugs will require standardized case definitions, outcome measures, and comparator regimens, as well as the ability to conduct multicenter trials [228]. A recent publication produced consensus definitions of microbiologic and functional endpoints [170]. In addition, a recent report of patient research priorities highlighted the importance of including quality of life outcomes in addition to microbiologic assessments in clinical trials [229]. The interested reader is referred to a separate publication that will follow highlighting these research gaps and priorities.

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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