Summary for Clinicians: 2020 Clinical Practice Guideline Summary for the Treatment of Nontuberculous Mycobacterial Pulmonary Disease

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The newly issued document provides a long-awaited update of the 2007 guideline. An extensive literature search was performed for systematic reviews of 22 PICO (Problem, Intervention, Comparator, and Outcome) questions to formulate 31 evidence-based recommendations using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach (Table 1). The focus was narrowed to pulmonary disease (PD) in adults (noncystic fibrosis, non–human immunodeficiency virus) caused by the four most common pathogens: *Mycobacterium avium* complex (MAC), *M. kansasii*, *M. xenopi*, and *M. abscessus* (1). For reasons incompletely understood, the rates of nontuberculosis mycobacterial PD (NTM-PD) are increasing in many parts of the world, underlining the need for a concise guideline for the busy clinician.

Laboratory Diagnosis

Diagnostic criteria have not changed since the release of the prior guidelines and require integration of clinical, radiographic, and microbiologic data (Table 2), with the laboratory playing a pivotal role. Given the environmental source of nontuberculosis mycobacteria (NTM), which can lead to transient colonization of airways, it is recommended that at least *three sputum samples over a period of 1 week or longer* be obtained, with two specimens positive for NTM indicating persistent NTM presence. A single specimen with a positive bronchoscopic result is sufficient to meet disease criteria in cases in which sputum cannot be obtained.

After decontamination, both liquid and solid media should be inoculated to improve sensitivity. Isolates should be identified by molecular methods to inform clinicians about clinical relevance (e.g., *M. kansasii* is usually a pathogen and *M. gordonae* rarely causes disease) and treatment modalities. Stored isolates can be used for comparison in recurrent disease.

Drug-susceptibility testing should be performed by broth microdilution. Because few drugs currently in use have clinically established minimal-inhibitory-concentration break points, results warrant careful interpretation. Currently recommended break points for first-line agents for NTM are shown in Table 3 (2).

Treatment of NTM-PD

- *In patients who meet the diagnostic criteria for NTM-PD, the panel suggests initiation of treatment rather than watchful waiting, especially in the context of positive acid-fast bacilli sputum smear results and/or cavitary lung disease (conditional recommendation, very low certainty in estimates of effect).*

The decision to start antibiotic therapy should be individualized on the basis of risk for progression and patient priorities. In a large cohort of patients with MAC-PD, 62% showed progression during 1 year, which was associated with positive acid-fast bacilli smear results, fibrocavitary disease, or advanced radiographic appearance. Conversely, spontaneous sputum conversion was linked to younger age, higher body mass index (BMI), and negative smear-result status (3).

Factors in favor of starting treatment are cavitary disease, low BMI, low albumin, and elevated inflammatory markers; the presence of more virulent species; underlying immune suppression; and major clinical symptoms. Watchful waiting may be appropriate for patients with mild symptoms, patients

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Table 1. Interpretation of strong and conditional (weak) recommendations*

	Strong Recommendations	Conditional Recommendations
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.

*Adapted from Reference 1.

with higher potential for medication intolerance, and organisms less responsive to treatment.

- *The panel suggests susceptibility-based treatment for macrolides and amikacin in patients with MAC-PD and for rifampicin in patients with* M. kansasii*–PD (conditional recommendation, very low certainty in estimates of effect).*
- *In patients with* M. xenopi*–PD, the committee members believe there is insufficient evidence to make a recommendation for or against susceptibility-based treatment.*
- *In patients with* M. abscessus*–PD the panel suggests 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) (erythromycin ribosomal methylase causing macrolide resistance of* M. abscessus*) gene should be performed.*

Clinical series have identified poor treatment outcomes for macrolide-resistant MAC and *M. abscessus* as well as rifampicin-resistant *M. kansasii*. Special attention should be given to *M. abscessus* isolates for presence of a functional *erm*(41) gene, which causes inducible macrolide resistance and requires gene sequencing or prolonged incubation to detect. Similarly, high minimal inhibitory concentrations for amikacin have been associated with a poor microbiologic response, which holds true for amikacin liposome inhalation suspension. Therefore, the Clinical and Laboratory Standards Institute (2) has provided different breakpoints for intravenous and inhaled amikacin (Table 3). No clinical correlations are available for *M. xenopi*.

Mycobacterium avium Complex

- *For macrolide-susceptible MAC-PD diagnosed in patients, the panel recommends using a three-drug regimen with inclusion of a macrolide (strong recommendation, very low certainty in estimates of effect) and ethambutol. Azithromycin is preferred (conditional recommendation, very low certainty in estimates of effect).*

Table 2. Clinical and microbiologic criteria for diagnosis of nontuberculous mycobacterial pulmonary disease*†

Clinical	Pulmonary or systemic symptoms	Both required
Radiologic	Nodular or cavitary opacities on chest radiograph, or a high-resolution computed tomographic scan that shows bronchiectasis with multiple small nodules	Both required
And	Appropriate exclusion of other diagnoses	
Microbiologic‡	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 result 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	

Definition of abbreviations: AFB = acid-fast bacilli; *M.* = *Mycobacterium*; NTM = nontuberculosis mycobacteria.
*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.
†Adapted from Reference 1.
‡When two 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.

Table 3. First-line antimicrobial agents with clinically established break points*

Antimicrobial Agents	MIC (μg/ml)		
	S	I	R
M. avium complex			
Clarithromycin†	≤8	16	≥32
Amikacin (IV)	≤16	32	≥64
Amikacin (liposomal, inhaled)	≤64	—	≥128
M. kansasii			
Clarithromycin†	≤8	16	≥32
Rifampin	≤1	—	≥2
M. abscessus‡			
Clarithromycin†§	≤2	4	≥8
Amikacin	≤16	32	≥64
Cefoxitin	≤16	32–64	≥128
Imipenem	≤4	8–16	≥32
Linezolid	≤8	16	≥32
Doxycycline	≤1	2–4	≥8
Tigecycline‖	—	—	—
Ciprofloxacin	≤1	2	≥4
Moxifloxacin	≤1	2	≥4

Definition of abbreviations: I = intermediate; IV = intravenous; *M.* = *Mycobacterium*; MIC = minimal inhibitory concentration; R = resistant; S = susceptible.
*Reprinted by permission from Reference 2.
†Clarithromycin is the class drug for macrolides.
‡Clinical outcome data for *M. abscessus* MIC values are available only for macrolides and IV amikacin.
§To detect inducible macrolide resistance, reading for clarithromycin should be at ≥14 days, unless resistance is recognized earlier. Alternatively, sequencing of the *erm*(41) (erythromycin ribosomal methylase causing macrolide resistance of *M. abscessus*) gene should be performed.
‖No clinical break points established; MIC values only should be reported.

The panel unanimously voted that treatment of MAC-PD should include a macrolide when culture demonstrates sensitivity. Data from small and clinically inconsistent randomized controlled trials were balanced with increasing and strong evidence that linked failure of sputum culture conversion to macrolide-sparing regimens. The panel also emphasizes that companion drugs aid in treatment largely by preventing macrolide resistance (4, 5). To this end, it is recommended to use three rather than two drugs, which is grounded on studies in disseminated MAC and observations that the addition of ethambutol or rifampicin lowers the development of macrolide resistance (6).

With limited head-to-head data on azithromycin *versus* clarithromycin available, azithromycin compares favorably, with fewer drug–drug interactions with rifabutin, lower prices in certain geographic areas, and a lower pill burden. Therefore, the committee suggests using azithromycin over clarithromycin, with the option to switch in case of intolerance.

- *In patients with cavitary, advanced/severe bronchiectatic, or macrolide-resistant PD, the panel suggests parenteral amikacin or streptomycin use for 2–3 months up front. (conditional recommendation, moderate certainty in estimates of effect)*

Currently, few options are available for severe or macrolide-resistant MAC-PD. Although trials using streptomycin or amikacin are few, they all demonstrate higher sputum conversion in cavitary or macrolide-resistant disease. Combined with clinical experience, the panel provided the above recommendation with the caveat that clinicians need to add appropriate companion drugs to avoid mutational resistance.

- *For MAC-PD newly diagnosed in patients, neither inhaled amikacin (parenteral formulation) nor an amikacin liposome inhalation suspension is suggested as part of the initial regimen (conditional recommendation, very low certainty in estimates of effect).*
- *In MAC-PD with failure to convert the sputum culture after 6 months of guideline-based therapy, the panel recommends initiating an amikacin liposome inhalation suspension (strong recommendation, moderate certainty in estimates of effect).*

A recent randomized controlled trial has demonstrated that the addition of an *amikacin liposome inhalation suspension* in patients failing to reach culture conversion after 6 months led to significantly higher conversion rates than in those who continued on guideline-based therapy alone (7). Yet there is insufficient data for the use of inhaled amikacin at initiation of therapy. Therefore, the committee recommends the use in refractory disease but not up front. This latter hesitancy is based on the risk of developing mutational amikacin resistance with inadequate companion medications.

- *In patients with macrolide-susceptible MAC-PD, a three-times-weekly macrolide-based regimen is suggested for noncavitary nodular/bronchiectatic disease, and daily therapy is for cavitary or severe/advanced nodular bronchiectatic disease. Treatment should continue for at least 12 months after culture conversion (conditional recommendations, very low certainty in estimates of effect).*

Sputum conversion rates were similar between intermittent- and daily-therapy groups for nodular/bronchiectatic MAC-PD, with better tolerance of intermittent therapy. No such evidence exists to support intermittent therapy for cavitary MAC-PD. The optimal duration of therapy is unknown; thus, the 2007 recommendations remained unchanged.

M. kansasii

- *In patients with rifampicin-susceptible* M. kansasii*–PD, the panel suggests a regimen of rifampicin, ethambutol, and either isoniazid or macrolide (conditional recommendation, very low certainty in estimates of effect). It also suggests that neither parenteral amikacin nor streptomycin be used routinely (strong recommendation, very low certainty in estimates of effect).*

The three-drug, isoniazid-based regimen achieves high cure rates of 80–100%, with low relapse rates when administered for 9–18 months (1, 8). On the basis of *M. kansasii*'s *in vitro* susceptibility to

macrolides and two small retrospective studies demonstrating comparable efficacy, the panel suggests that a three-drug regimen with either isoniazid or a macrolide is appropriate.

As a result of the excellent outcomes in patients treated with three-drug oral regimens, the paucity of literature demonstrating an added benefit of parenteral therapy, and the risk of adverse effects, the panel strongly recommends against the routine use of aminoglycosides for treatment of *M. kansasii* (1).

- *In patients with rifampicin-resistant* M. kansasii *or intolerance to one of the first-line antibiotics, the panel suggests that a fluoroquinolone (e.g., moxifloxacin) be used as part of a second-line regimen (conditional recommendation, very low certainty in estimates of effect).*

Although fluoroquinolones demonstrate strong *in vitro* activity against *M. kansasii*, no studies have evaluated their efficacy as an alternative to isoniazid- or macrolide-based regimens. Therefore, the panel recommends three-drug, rifamycin-based regimens including isoniazid or macrolides instead of a fluoroquinolone. Fluoroquinolones may be an alternative to rifampicin for rifampicin-resistant strains or may be used as a substitute for any of the first-line medications causing drug intolerance (1).

- *In patients with noncavitary nodular/bronchiectatic* M. kansasii*–PD treated with a macrolide-based regimen, the panel suggests either daily or three-times-weekly treatment. In patients with cavitary disease, and in all patients with an isoniazid-based regimen, daily treatment is suggested (conditional recommendations, very low certainty in estimates of effect).*

For noncavitary *M. kansasii*, the literature shows good outcomes with either daily or intermittent therapy with rifampicin, ethambutol, and macrolides (9, 10). No such evidence exists for cavitary disease. Because cavitary NTM-PD is associated with higher mortality and morbidity than noncavitary disease (11), the panel recommends a more aggressive approach with daily rifampicin, ethambutol, and macrolide treatment. Intermittent dosing of isoniazid-based regimens has not been studied for either cavitary or noncavitary disease; as a result, the panel recommends daily dosing for isoniazid-containing regimens.

- *The panel suggests that patients with rifampicin-susceptible* M. kansasii*–PD be treated for at least 12 months (conditional recommendation, very low certainty in estimates of effect).*

A fixed 12-month regimen is supported by low relapse rates of 6–10% (1), with no evidence that longer courses

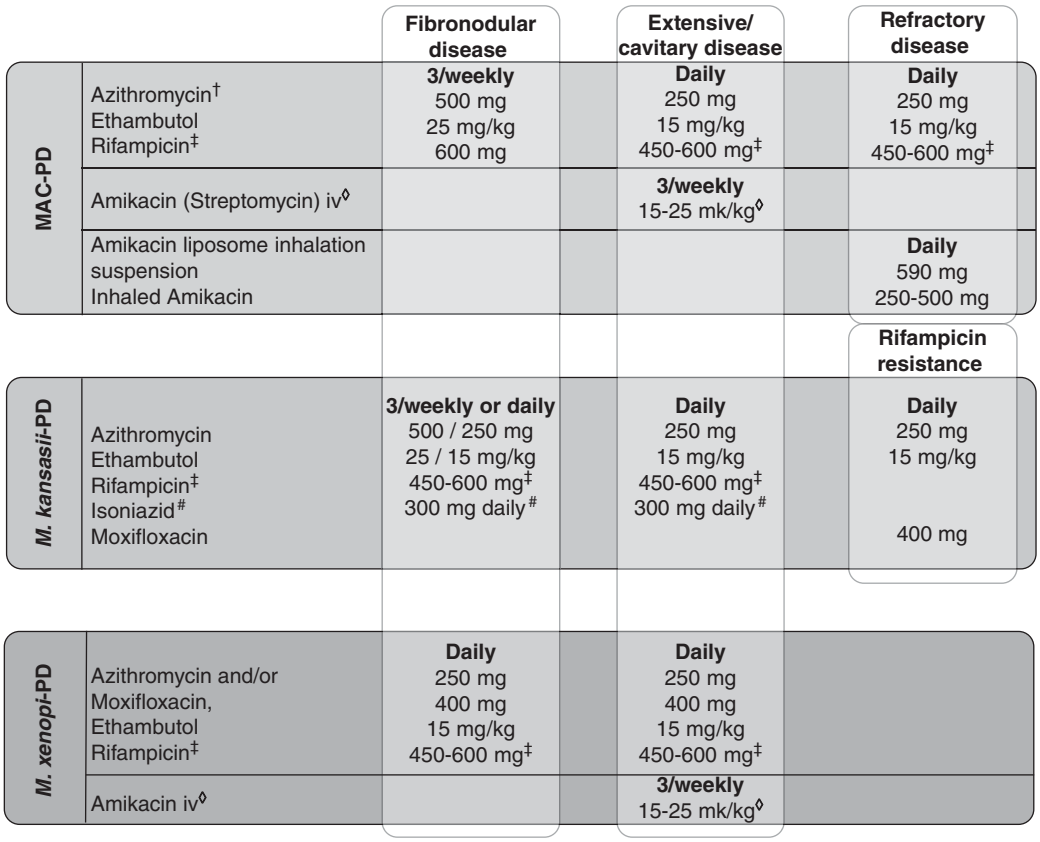

Figure 1. Recommended approach to treatment of slow-growing nontuberculosis mycobacterial PD. Adapted from Reference 1. †For MAC-PD, clarithromycin 500 mg twice daily may be substituted for azithromycin; alternative drugs include clofazimine, moxifloxacin, and linezolid. ‡Rifampicin dosing 10 mg/kg (450 or 600 mg) for daily regimen, 600 mg for 3/weekly regimen. ◊Drug level monitoring: Trough < 5 mg/L, peak 65–80 μg/ml with intermittent dosing. #*M. kansasii*: daily INH, Ethambutol, Rifampicin as alternative for macrolide-based regimen. INH = isoniazid; iv = intravenously; *M.* = *Mycobacterium*; MAC-PD = *M. avium* complex PD; PD = pulmonary disease.

could further reduce relapses. Therefore, the panel recommends at least 12 months of treatment.

M. xenopi

- *In patients with* M. xenopi*–PD, the panel suggests using a multidrug treatment regimen that includes moxifloxacin or macrolides (conditional recommendation, low certainty in estimates of effect). A daily regimen that includes at least three drugs (rifampicin, ethambutol, and a macrolide and/or a fluoroquinolone) is suggested (e.g., moxifloxacin; conditional recommendation, very low certainty in estimates of effect).*

Whether due to the organism itself, predisposing patient characteristics, or frequent concomitant chronic pulmonary aspergillosis, all-cause mortality associated with *M. xenopi*–PD is higher compared with all-cause mortality associated with all other NTM infections (12). *In vitro* data show activity of both fluoroquinolones and macrolides against *M. xenopi*, and clinical studies show no differences in efficacy in regimens including either moxifloxacin or clarithromycin (1). There are few data supporting the use of other fluoroquinolones.

There are insufficient clinical data to inform clinicians about the number of drugs to use. Animal and *in vitro* models demonstrate the efficacy of three-drug regimens. Given high associated mortality, the panel believes the high risk of treatment failure with a two-drug regimen justifies a treatment recommendation including at least three drugs.

- *In patients with cavitary or advanced/severe bronchiectatic* M. xenopi*–PD, the panel suggests adding parenteral amikacin to the treatment regimen and obtaining expert consultation (conditional recommendation, very low certainty in estimates of effect).*

No high-quality clinical studies have addressed the use of amikacin for *M. xenopi*–PD. The panel's recommendation was informed by the clinical severity and poor outcomes typical of *M. xenopi*–PD as well as by favorable microbiologic responses to amikacin in murine studies.

- *In patients with* M. xenopi*–PD, the panel suggests that treatment be continued for at least 12 months beyond culture conversion (conditional recommendation, very low certainty in estimates of effect).*

The panel noted the lack of studies specifically evaluating the optimal duration of therapy and unanimously voted for a conservative approach. Heterogeneous studies tend to suggest improved outcomes with longer durations.

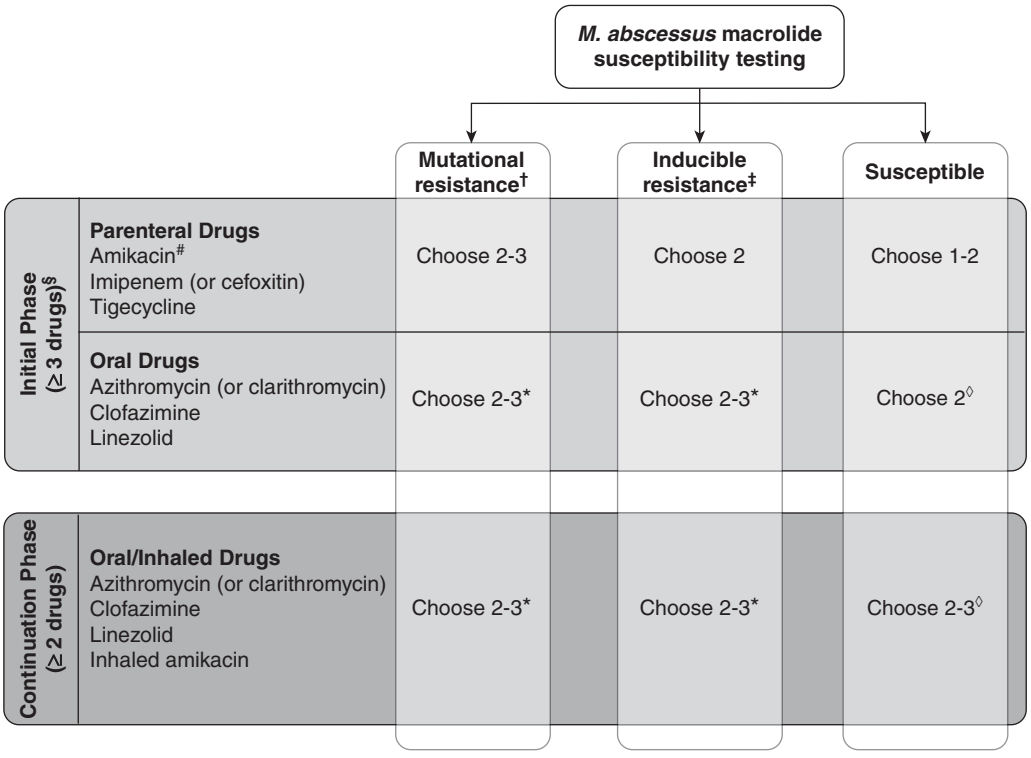

Figure 2. Recommended approach to treatment of *M. abscessus*, according to macrolide susceptibility. Adapted from Reference 1. †Mutational resistance = phenotypic resistance identified at 3-5 days of incubation or *rrl* mutation on sequencing. ‡Inducible resistance = phenotypic resistance identified after 14 days of incubation or functional *erm*(41) on sequencing. §When macrolide resistance is documented, ⩾ 4 drugs when possible. #Aminoglycosides may be administered thrice weekly but intermittent dosing is not recommended for other drugs. *Azithromycin and clarithromycin are not counted as active drugs in the setting of mutational or inducible resistance but may be used for their immunomodulatory effects. ◊Azithromycin or clarithromycin should be used whenever possible in the setting of macrolide susceptibility. *erm*(41) = erythromycin ribosomal methylase causing macrolide resistance of *M. abscessus*; *M.* = *Mycobacterium*; *rrl* = 23S ribosomal ribonucleic acid.

The recommended treatment approach for slow-growing NTM-PD is summarized in Figure 1.

M. abscessus

- *In patients with* M. abscessus*–PD caused by strains without inducible or mutational resistance, the panel recommends a macrolide-containing multidrug treatment regimen (strong recommendation, very low certainty in estimates of effect).*
- *In patients with* M. abscessus*–PD caused by strains with inducible or mutational macrolide resistance, the panel suggests a macrolide-containing regimen if the drug is being used for its immunomodulatory properties, although the macrolide is not counted as an active drug (conditional recommendation, very low certainty in estimates of effect).*

These recommendations highlight the prognostic significance of macrolide susceptibility in *M. abscessus*–PD and the importance of confirmatory laboratory testing as outlined above. Most isolates of subspecies (subsp.) *massiliense* possess a nonfunctional *erm*(41) gene and are associated with higher rates of culture conversion (50–96%) than subsp. *abscessus* (25–42%) (1). Furthermore, small retrospective studies have reported culture conversion in only 7% of cases of macrolide-resistant subsp. *massiliense* but in 93% of infections due to the C28 sequevar of subsp. *abscessus*, which lacks a functional *erm*(41) gene (13, 14).

Prescribers must be mindful that when macrolides are used for their immunomodulatory properties, they do not constitute an active component of the regimen. Moreover, the panel recommends surveillance cultures throughout therapy and adjustment of therapy as necessary to avoid emergent macrolide resistance in coinfecting NTM.

- *In patients with* M. abscessus*–PD, the panel suggests a multidrug regimen that includes at least three active drugs (guided by* in vitro *susceptibility; conditional recommendation, very low certainty in estimates of effect).*

Available evidence was judged to be of very low quality, as studies did not directly compare multidrug regimens and/or lacked determination of *erm*(41)-gene functionality, rendering outcomes uninterpretable. It was noted that multidrug regimens of three or more drugs were used in case series describing treatment outcomes and that considerable variation in treatment practices has been reported. The panel's recommendation is less prescriptive than the 2017 British Thoracic Society guideline (15), favoring construction of multidrug regimens in accordance with expert advice and *in vitro* drug-susceptibility testing (Figure 2).

- *In patients with* M. abscessus*–PD, the panel suggests that either a shorter or longer treatment regimen be used and that expert consultation be obtained (conditional recommendation for either the intervention of comparator, very low certainty in estimates of effect).*

The panel considered available comparative evidence to be insufficient to form the basis of a recommendation but noted that most patients in the literature received at least 12 months of therapy, including an initial phase of parenteral antimicrobials. It was believed that treatment duration should be informed by expert advice and factors such as radiologic extent and susceptibility data. In particular, macrolide-susceptible isolates may require shorter and less-intensive regimens than macrolide-resistant isolates (1).

Role of Surgery

- *In selected patients with NTM-PD, the panel suggests surgical resection as an adjuvant to medical therapy after expert consultation (conditional recommendation, very low certainty in estimates of effect).*

Indications for surgery are failure of medical therapy, drug-resistant infections, cavitary disease, and complications such as hemoptysis and severe bronchiectasis. Although relevant studies were heterogeneous with respect to key factors (e.g., mycobacterial species, age, sex, indication for surgery, and patient selection), culture conversion was documented for 85–100% of patients after surgery (1). Surgical complications occurred in 7–35% of cases. Operative mortality was 0%, and postoperative mortality was 0–9% (1). Medical therapy before and after surgery was standard, and many experts consider smear conversion be the goal of preoperative treatment. The panel suggests that surgeons be experienced in the surgical management of mycobacterial lung disease.

Monitoring for Adverse Reactions

Side effects of NTM treatment are common, and patient education and close monitoring are therefore essential. There are no data to provide recommendations on the frequency of or approach to monitoring, which should be individualized on the basis of age, comorbidities, and potential drug–drug interactions. Currently, experts consider obtaining serum drug concentrations (i.e., therapeutic drug monitoring) when a patient has comorbidities that could alter drug concentrations, such as renal dysfunction, delayed sputum culture conversion, treatment failure, or those receiving aminoglycosides. Concentrations may aid in the titration of the regimen in these specific populations; however, there are limited data on optimal amounts and treatment success. Therefore, universal use of therapeutic drug monitoring is not recommended presently.

Research Priorities

There remains an abundant need for research of diagnosis and treatment of NTM pulmonary infections. The guideline is written in such a way to stress the many gaps that remain throughout the document. We have emphasized many of these uncertainties within this article. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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