An Official ATS/IDSA Statement: Diagnosis, Treatment, and Prevention of Nontuberculous Mycobacterial Diseases

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SUMMARY

Diagnostic Criteria of Nontuberculous Mycobacterial Lung Disease

The minimum evaluation of a patient suspected of nontuberculous mycobacterial (NTM) lung disease should include the following: (*1*) chest radiograph or, in the absence of cavitation, chest high-resolution computed tomography (HRCT) scan; (*2*) three or more sputum specimens for acid-fast bacilli (AFB) analysis; and (*3*) exclusion of other disorders, such as tuberculosis (TB). Clinical, radiographic, and microbiologic criteria are equally important and all must be met to make a diagnosis of NTM lung disease. The following criteria apply to symptomatic patients with radiographic opacities, nodular or cavitary, or an HRCT scan that shows multifocal bronchiectasis with multiple small nodules. These criteria fit best with *Mycobacterium avium* complex (MAC), *M. kansasii*, and *M. abscessus*. There is not enough known about most other NTM to be certain that these diagnostic criteria are universally applicable for all NTM respiratory pathogens.

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Clinical.

1. Pulmonary symptoms, nodular or cavitary opacities on chest radiograph, or an HRCT scan that shows multifocal bronchiectasis with multiple small nodules.

and

2. Appropriate exclusion of other diagnoses.

Microbiologic.

1. Positive culture results from at least two separate expectorated sputum samples. (If the results from the initial sputum samples 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 histopathologic features (granulomatous inflammation or AFB) and positive culture for NTM or biopsy showing mycobacterial histopathologic features (granulomatous inflammation or AFB) and one or more sputum or bronchial washings that are culture positive for NTM.
4. Expert consultation should be obtained when NTM are recovered that are either infrequently encountered or that usually represent environmental contamination.
5. Patients who are suspected of having NTM lung disease but who do not meet the diagnostic criteria should be followed until the diagnosis is firmly established or excluded.
6. Making the diagnosis of NTM lung disease does not, *per se*, necessitate the institution of therapy, which is a decision based on potential risks and benefits of therapy for individual patients.

Key Laboratory Features of NTM

1. The preferred staining procedure is the fluorochrome method. Specimens should be cultured on both liquid and solid media. Species that require special growth conditions and/or lower incubation temperatures include *M. haemophilum*, *M. genavense*, and *M. conspicuum*. These species can cause cutaneous and lymph node disease.
2. In general, NTM should be identified to the species level. Methods of rapid species identification include commercial DNA probes (MAC, *M. kansasii*, and *M. gordonae*) and high-performance liquid chromatography (HPLC). For some NTM isolates, especially rapidly growing mycobacterial (RGM) isolates (*M. fortuitum*, *M abscessus*, and *M. chelonae*), other identification techniques may be necessary including extended antibiotic *in vitro* susceptibility testing, DNA sequencing or polymerase chain reaction (PCR) restriction endonuclease assay (PRA).
3. Routine susceptibility testing of MAC isolates is recommended for clarithromycin only.
4. Routine susceptibility testing of *M. kansasii* isolates is recommended for rifampin only.
5. Routine susceptibility testing, for both taxonomic identification and treatment of RGM (*M. fortuitum*, *M abscessus*, and *M. chelonae*) should be with amikacin, imipenem (*M. fortuitum* only), doxycycline, the fluorinated quinolones, a sulfonamide or trimethoprim-sulfamethoxazole, cefoxitin, clarithromycin, linezolid, and tobramycin (*M. chelonae* only).

Health Care– and Hygiene-associated Disease Prevention

Prevention of health care–related NTM infections requires that surgical wounds, injection sites, and intravenous catheters not be exposed to tap water or tap water–derived fluids. Endoscopes cleaned in tap water and clinical specimens contaminated with tap water or ice are also not acceptable.

Prophylaxis and Treatment of NTM Disease

1. Treatment of MAC pulmonary disease. For most patients with nodular/bronchiectatic disease, a three-times-weekly regimen of clarithromycin (1,000 mg) or azithromycin (500 mg), rifampin (600 mg), and ethambutol (25 mg/kg) is recommended. For patients with fibrocavitary MAC lung disease or severe nodular/bronchiectatic disease, a daily regimen of clarithromycin (500–1,000 mg) or azithromycin (250 mg), rifampin (600 mg) or rifabutin (150–300 mg), and ethambutol (15 mg/kg) with consideration of three-times-weekly amikacin or streptomycin early in therapy is recommended. Patients should be treated until culture negative on therapy for 1 year.
2. Treatment of disseminated MAC disease. Therapy should include clarithromycin (1,000 mg/d) or azithromycin (250 mg/d) and ethambutol (15 mg/kg/d) with or without rifabutin (150–350 mg/d). Therapy can be discontinued with resolution of symptoms and reconstitution of cell-mediated immune function.
3. Prophylaxis of disseminated MAC disease. Prophylaxis should be given to adults with acquired immunodeficiency syndrome (AIDS) with $CD4^+$ T-lymphocyte counts less than 50 cells/μl. Azithromycin 1,200 mg/week or clarithromycin 1,000 mg/day have proven efficacy. Rifabutin 300 mg/day is also effective but less well tolerated.
4. Treatment of *M. kansasii* pulmonary disease. A regimen of daily isoniazid (300 mg/d), rifampin (600 mg/d), and ethambutol (15 mg/kg/d). Patients should be treated until culture negative on therapy for 1 year.
5. Treatment of *M. abscessus* pulmonary disease. There are no drug regimens of proven or predictable efficacy for treatment of *M. abscessus* lung disease. Multidrug regimens that include clarithromycin 1,000 mg/day may cause symptomatic improvement and disease regression. Surgical resection of localized disease combined with multidrug clarithromycin-based therapy offers the best chance for cure of this disease.
6. Treatment of nonpulmonary disease caused by RGM (*M. abscessus*, *M. chelonae*, *M. fortuitum*). The treatment regimen for these organisms is based on *in vitro* susceptibilities. For *M. abscessus* disease, a macrolide-based regimen is frequently used. Surgical debridement may also be an important element of successful therapy.
7. Treatment of NTM cervical lymphadenitis. NTM cervical lymphadenitis is due to MAC in the majority of cases and treated primarily by surgical excision, with a greater than 90% cure rate. A macrolide-based regimen should be considered for patients with extensive MAC lymphadenitis or poor response to surgical therapy.

INTRODUCTION

This is the third statement in the last 15 years dedicated entirely to disease caused by NTM (1, 2). The current unprecedented high level of interest in NTM disease is the result of two major recent trends: the association of NTM infection with AIDS and recognition that NTM lung disease is encountered with

increasing frequency in the non-AIDS population. Furthermore, NTM infections are emerging in previously unrecognized settings, with new clinical manifestations. Another major factor contributing to increased awareness of the importance of NTM as human pathogens is improvement in methodology in the mycobacteriology laboratory, resulting in enhanced isolation and more rapid and accurate identification of NTM from clinical specimens. Consistent with the advances in the mycobacteriology laboratory, this statement has an emphasis on individual NTM species and the clinical disease–specific syndromes they produce. A major goal is facilitating the analysis of NTM isolates by the health care provider, including determination of the clinical and prognostic significance of NTM isolates and therapeutic options.

There are controversies in essentially all aspects of this very broad field and, whenever possible, these controversies are highlighted. Hence, an attempt is made to provide enough information so that the clinician understands the recommendations in their appropriate context, especially those made with inadequate or imperfect supporting information. Also, when there is not compelling evidence for one recommendation, alternative recommendations or options are presented.

This statement also includes new topics not addressed in previous statements, including advances in the understanding of the pathogenesis of NTM disease, descriptions of new NTM pathogens, clinical areas of emerging NTM disease such as cystic fibrosis, new NTM disease manifestations such as hypersensitivity-like lung disease, and public health implications of NTM disease such as prevention and surveillance. This statement will also take advantage of web-based resources through the American Thoracic Society (ATS) website for illustration and amplification of selected topics, discussion of additional topics not included in this document, as well as the capacity for updating information in this rapidly changing field.

Large gaps still exist in our knowledge. Limitations in systematic data have made it necessary for many of the recommendations in this document to be based on expert opinion rather than on empirically derived data. Unquestionably, more and better studies of NTM diseases must be done. The committee organized to create this document is composed of scientists and physicians residing in the United States. This document, therefore, represents a United States' perspective of NTM diseases that may not be appropriate for NTM diseases in other parts of the world.

METHODS

Review of the available literature and subsequent grading of recommendations were accomplished by the members of the writing committee. The search for evidence included hand-searching journals, reviewing previous guidelines, and searching electronic databases including MEDLINE and PubMed. Only articles written in English were considered. Final decisions for formulating recommendations were made by voting among committee members. The recommendations are rated on the basis of a system developed by the U.S. Public Health Service and the Infectious Diseases Society of America (IDSA) (3). The rating system includes a letter indicating the strength of the recommendation, and a roman numeral indicating the quality of the evidence supporting the recommendation (3) (Table 1). Thus, clinicians can use the rating to differentiate among recommendations based on data from clinical trials and those based on the opinions of the experts comprising the writing committee, who are familiar with the relevant clinical practice and scientific rationale for such practice when clinical trial data are not available. Ratings following each numbered recommendation pertain to all points within the numbered recommendation. Each member of the writing committee has declared any conflict of interest. These guidelines were developed with funding provided by the ATS.

TAXONOMY

When the last ATS statement about NTM was prepared in 1997, there were approximately 50 NTM species that had been identified. Currently, more than 125 NTM species have been cataloged (4, 5). A list of NTM species identified since 1990 is provided in the online supplement. A comprehensive list of all validated NTM species can be found online at www.bacterio.cict.fr/m/mycobacterium.html. There has been a dramatic recent increase not only in the total number of mycobacterial species but also in the number of clinically significant species. Clinicians might reasonably ask, "Why are there so many new NTM species?" The increase relates to improved microbiologic techniques for isolating NTM from clinical specimens and, more importantly, to advances in molecular techniques with the development and acceptance of 16S rRNA gene sequencing as a standard for defining new species.

Early taxonomic studies compared up to 100 growth and biochemical tests of large numbers of strains in multiple collaborative laboratories. Work focused around the International Working Group on Mycobacterial Taxonomy. New species were defined on the ability to phenotypically separate the new taxon from established species. This work was time and labor intensive and not adequate for separating many NTM species. Subsequently, species were identified by comparisons of genomic DNA; new species had similarity (homology) of less than 70% on DNA–DNA pairing experiments with established species. This type of comparison was highly technical, highly labor intensive, and required comparison of possible new species to all established related species. By its very nature, this technique limited identification of new species.

The dramatic change in mycobacterial taxonomy came with the ready availability and reliability of DNA sequencing. Investigators recognized that the mycobacterial 16S rRNA gene was highly conserved, and that differences in the sequence of 1% or greater generally defined a new species (4, 5). Also critical to the dramatic change was the appearance of publicly available databases that stored the 16S rRNA gene sequences of established mycobacterial species. Recognition of a novel NTM species is now relatively simple: perform 16S rRNA gene sequence analysis of a suspected new species and compare the results with those in the databases. Numerous new species are appearing from laboratories all over the world rather than from a small number of mycobacterial taxonomists. It is likely that the number of new species will continue to expand rapidly as 16S rRNA gene sequencing analysis is performed on increasing numbers of isolates of clinical disease that cannot be identified with commercial nucleic acid probes. It is possible that the number of NTM species will increase to more than 150 before the publication of the next NTM disease statement.

This expansion in new NTM species is, therefore, largely a consequence of newer identification techniques that are capable of separating closely related NTM species, as opposed to the sudden appearance of new NTM species. For instance, *M. triplex*, *M. lentiflavum*, *M. celatum*, and *M. conspicuum* (among others) might previously have been identified as MAC based on traditional biochemical and/or phenotypic analyses. The clinical significance of these species separations may be subtle or negligible, but the clinician inevitably will continue to be confronted by new NTM species designations.

EPIDEMIOLOGY

NTM are widely distributed in the environment with high isolation rates worldwide (6, 7). Organisms can be found in soil and

TABLE 1. THE STRENGTH OF RECOMMENDATIONS BASED ON QUALITY OF EVIDENCE (ADAPTED FROM THE INFECTIOUS DISEASE SOCIETY OF AMERICA/UNITED STATES PUBLIC HEALTH SERVICE RATING SYSTEM)

Categories Reflecting the Strength of Each Recommendation for or against Its Use		Grades Reflecting the Quality of Evidence on Which Recommendations Are Based	
Category	Definition	Grade	Definition
A	Good evidence to support a recommendation for use	I	Evidence from at least one properly randomized, controlled trial
B	Moderate evidence to support a recommendation for use	II	Evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than one center), from multiple time-series studies or from dramatic results in uncontrolled experiments
C	Poor evidence to support a recommendation for or against use	III	Evidence from opinion of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees
D	Moderate evidence to support a recommendation against use		
E	Good evidence to support a recommendation against use		

water, including both natural and treated water sources (*M. kansasii*, *M. xenopi*, and *M. simiae* are recovered almost exclusively from municipal water sources and rarely, if ever, from other environmental sources). When identical methods are used, isolation rates of NTM from the environment are remarkably similar in diverse geographic areas (6, 7). There is no evidence of animal-to-human or human-to-human transmission of NTM (7–11). Even in patients with cystic fibrosis (CF), an apparently highly susceptible population and a population in which other opportunistic organisms are clearly passed between patients, there has been no documentation of human-to-human transmission of NTM (12). Human disease is suspected to be acquired from environmental exposures, although the specific source of infection usually cannot be identified (13).

NTM may cause both asymptomatic infection and symptomatic disease in humans. Rates of asymptomatic infection have been inferred from both antibody and skin test studies. In areas where infection with *M. tuberculosis* is uncommon, antibody to a common mycobacterial antigen, lipoarabinomannin (LAM), can be assumed to be due predominantly to NTM infection. Antibody to LAM is detectable among children in the United States, rising rapidly between the ages of 1 and 12 years, then appearing to plateau (14). Skin test studies in adults indicate that a substantial proportion have had prior and presumably asymptomatic infection with NTM (15, 16). Skin test studies with an *M. intracellulare* purified protein derivative (PPD-B) conducted among U.S. Navy recruits in the 1960s showed that reactions of greater than 4 mm induration were more common in the southeastern than northern United States, suggesting higher background rates of NTM infection in these areas (16). Reactions to skin tests derived from NTM are not sufficiently species specific to indicate which nontuberculous mycobacterium might have been responsible for these asymptomatic infections, and it is possible that cross-reactivity with *M. tuberculosis* infection contributed to some of these reactions. However, because MAC organisms are the most common cause of NTM disease in the United States, it is likely that MAC was also the most common cause of infection. In these patients, asymptomatic infection with NTM has not been shown to lead to latent infection, so that in contrast to TB, there is currently no evidence that NTM are associated with reactivation disease.

NTM diseases have been seen in most industrialized countries; incidence rates vary from 1.0 to 1.8 cases per 100,000 persons (17). These overall incidence rates are estimates based on numbers of NTM isolates reported. MAC is the most common NTM species causing disease in most series, but many species have been implicated (Table 2). Rates appear to be similar in most developed countries, but surveillance information is limited. Because NTM diseases are not communicable, they are not reportable in the United States. Although several reports have suggested that the incidence of NTM diseases has increased over the past several decades, this observation has not been conclusively established due to the lack of comprehensive surveillance efforts. The most common clinical manifestation of NTM disease is lung disease, but lymphatic, skin/soft tissue, and disseminated disease are also important (18, 19). In the United States between 1981 and 1983, 94% of the NTM isolates reported to the Centers for Disease Control and Prevention (CDC) laboratory were pulmonary, whereas 3% were lymph node and 3% were skin/soft tissue isolates (19). In the late 1980s and early 1990s, NTM isolates associated with disseminated disease in patients with AIDS were reported almost as frequently as pulmonary isolates (20, 21). More recently, the CDC published the results of NTM isolates reported by state public health laboratories to the Public Health Laboratory System (PHLIS) database for the period 1993 through 1996 (22). During this period, of the NTM isolated, 75% were pulmonary, whereas 5% were from blood, 2% from skin/soft tissue, and 0.4% from lymph node isolates. The most frequently reported potentially pathogenic species and corresponding report rates over the 4-year period (per 1,000,000 population) were as follows: MAC, 29 to 36 isolates; *M. fortuitum*, 4.6 to 6 isolates; and *M. kansasii*, 2 to 3.1 isolates. Regionally, all three NTM species were reported most often from the southeastern United States. There are, however, significant limitations interpreting and extrapolating these data. Reporting of NTM species suspected to be involved in disease to PHLIS was voluntary, and not all states participated. Therefore, the data do not represent the absolute occurrence and distribution of NTM species in the United States. In addition, the numbers of isolates are presented as "report rates," "*to reflect a lack of verification of clinical significance of the report*" (emphasis in report). Because the reports were not verified, interpreting the association of these isolates with clinical data is problematic.

Overall, there is not substantially more or better information about NTM disease prevalence than that published in the 1997 ATS statement on NTM, except that, in most state public health laboratories, NTM isolates, especially MAC isolates, are more common than *M. tuberculosis* isolates (21, 22).

More epidemiologic information is provided in the discussions of specific disease syndromes and for individual NTM species, and in Table 2.

PATHOGENESIS

Over the past two decades, three important observations have been made regarding the pathogenesis of NTM infections:

TABLE 2. CLINICAL DISEASE CAUSED BY NONTUBERCULOUS MYCOBACTERIA (ALPHABETICAL ORDER BY SPECIES)

Common	Page	Comment	Uncommon	Page	Comment
		Pulmonary Disease			
M. abscessus	396	Worldwide; may be found concomitant with MAC	*M. asiaticum**		Rarely isolated
M. avium complex	386	Worldwide; most common NTM pathogen in U.S.	*M. celatum**		Cross-reactivity with TB-DNA probe
M. kansasii	395	U.S., Europe, South Africa, coal-mining regions	*M. chelonae*	398	
M. malmoense	399	U.K., northern Europe; uncommon in U.S.	*M. fortuitum*	398	Associated with aspiration
			M. haemophilum	399	Rarely isolated
M. xenopi	402	Europe, Canada; uncommon in U.S.; associated with pseudoinfection	*M. scrofulaceum*	400	South Africa; uncommon in U.S.
			*M. shimoidei**		Rarely isolated
			M. simiae	401	Southwest U.S., associated with pseudo-outbreaks
			M. smegmatis	401	Rarely isolated
			M. szulgai	401	Rarely isolated, not an environmental contaminant
		Lymphadenitis			
M. avium complex	386	Worldwide; most common NTM pathogen in U.S.	*M. abscessus*		Rarely isolated
M. malmoense	399	U.K., northern Europe (especially Scandinavia)	*M. chelonae*	398	
M. scrofulaceum	400	Worldwide; previously common, now rarely isolated in U.S.	*M. fortuitum*	398	
			M. genavense	399	Fastidious species (*See* Laboratory Procedures)
			M. haemophilum	399	Fastidious species (*See* Laboratory Procedures)
			M. kansasii		Rarely isolated
			M. szulgai	401	Rarely isolated
		Disseminated Disease			
M. avium complex	386	Worldwide; AIDS; most common NTM pathogen in U.S.	*M. abscessus*	396	Non-AIDS immunosuppressed
			*M. celatum**		AIDS
M. chelonae	398	U.S.; non-AIDS immunosuppressed skin lesions	*M. conspicuum**		AIDS, non-AIDS immunosuppressed
			M. fortuitum	398	Non-AIDS immunosuppressed
M. haemophilum	399	AIDS; U.S., Australia; non-AIDS immunosuppressed	*M. genavense*	399	AIDS
M. kansasii	395	AIDS; U.S., South Africa	*M. immunogenum*	399	Rare, associated with pseudo-outbreaks
			M. malmoense	399	U.K., northern Europe; non-AIDS immunosuppressed
			M. marinum	400	Worldwide; AIDS
			M mucogenicum	400	Central venous catheter infections
			M. scrofulaceum	400	Rarely isolated
			M. simiae	401	Southwest U.S., associated with pseudoinfection
			M. szulgai	401	Rarely isolated
			M. xenopi	402	Europe, Canada, associated with pseudoinfection
		Skin, Soft Tissue, and Bone Disease			
M. abscessus	396	Penetrating injury	*M. avium* complex	386	Worldwide
M. chelonae	398	U.S., associated with keratitis and disseminated disease	*M. haemophilum*	399	Extremities, cooler body sites
			M. immunogenum	399	Rarely isolated, associated with pseudo-outbreaks
M. fortuitum	398	Penetrating injury, footbaths	*M. kansasii*		Rarely isolated
M. marinum	400	Worldwide, fresh- and saltwater	*M. malmoense*	399	U.K., northern Europe
M. ulcerans	402	Australia, tropics, Africa, Southeast Asia, not U.S.	*M. nonchromogenicum*	400	Tenosynovitis
			M. smegmatis	401	Rarely isolated
			M. szulgai	401	Rarely isolated
			M. terrae complex	402	Tenosynovitis
		Specimen Contaminant			
M. gordonae	399	Most common NTM contaminant			
M. haemophilum	399				
M. mucogenicum	400				
M. nonchromogenicum	400				
M. terrae complex	402				

Definition of abbreviations: MAC = *Mycobacterium avium* complex; NTM = nontuberculous mycobacteria.
* *See* the online supplement.

1. In patients infected with HIV, disseminated NTM infections typically occurred only after the $CD4^+$ T-lymphocyte number had fallen below 50/μl, suggesting that specific T-cell products or activities are required for mycobacterial resistance (23, 24).
2. In the HIV-uninfected patient group, genetic syndromes of disseminated NTM infection have been associated with specific mutations in interferon (IFN)-γ and interleukin (IL)-12 synthesis and response pathways (25, 26) (IFN-γ receptor 1 [IFNγR1], IFN-γ receptor 2 [IFNγR2], IL-12 receptor β1 subunit [IL12Rβ1], the IL-12 subunit p40 [IL12p40], the signal transducer and activator of transcription 1 [STAT1], and the nuclear factor-κβ essential modulator [NEMO]).
3. There is also an association between bronchiectasis, nodular pulmonary NTM infections and a particular body habitus, predominantly in postmenopausal women (e.g., pectus excavatum, scoliosis, mitral valve prolapse) (27).

Host Defense and Immune Defects

Mycobacteria are initially phagocytosed by macrophages, which respond with production of IL-12, which in turn up-regulates

IFN-γ (28). IFN-γ activates neutrophils and macrophages to kill intracellular pathogens, including mycobacteria. There is a positive feedback loop between IFN-γ and IL-12, which is critical for the control of mycobacteria, as well as certain other intracellular infections. Disseminated NTM disease is a definite manifestation of immunologic defect, either acquired, such as HIV and iatrogenic factors, or genetic, caused by defects in the above IFN-γ/IL-12 pathway genes. However, these genetic factors only predispose to disseminated disease.

Pulmonary Disease

Lung disease due to NTM occurs commonly in structural lung disease, such as chronic obstructive pulmonary disease (COPD), bronchiectasis, CF, pneumoconiosis, prior TB, pulmonary alveolar proteinosis, and esophageal motility disorders (12, 19, 29–32). Abnormal CF genotypes and α_1-antitrypsin (AAT) phenotypes may predispose some patients to NTM infection (33–35). NTM lung disease also occurs in women without clearly recognized predisposing factors (32, 36–38). Bronchiectasis and NTM infection, usually MAC, often coexist, making causality difficult to determine. These patients may carry multiple MAC strains over time, suggesting either polyclonal infection or recurrent infection with distinct strains (38). It is unclear whether this problem is due to local abnormalities (e.g., bronchiectasis) or to immune defects. In one study from Japan, 170 patients with MAC lung infection were studied: of 622 siblings of those patients, 3 had MAC lung disease. The implication is that the sibling risk for MAC infection is much higher than previously estimated population prevalence (11).

Body Morphotype

Women with nodular NTM pulmonary infections associated with bronchiectasis have similar clinical characteristics and body type, sometimes including scoliosis, pectus excavatum, mitral valve prolapse, and joint hypermobility (27). These phenotypic characteristics may represent markers for specific genotypes that affect both body morphotype and NTM infection susceptibility. Alternatively, the morphotype itself may influence mycobacterial infection susceptibility, through such features as poor tracheobronchial secretion drainage or ineffective mucociliary clearance.

Tumor Necrosis Factor Inhibition

IFN-γ and IL-12 control mycobacteria in large part through the up-regulation of tumor necrosis factor (TNF)-α, made predominantly by monocytes/macrophages. The critical role of TNF-α in controlling intracellular infections is made clear through the use of TNF-α blocking agents. The potent TNF-α blocking antibodies infliximab and adalimumab and the soluble receptor etanercept are effective antiinflammatory agents and lead to relatively high rates of development of active TB in those who are latently infected (39, 40). The onset of TB after administration of infliximab ranges from weeks to months. In addition to TB, the TNF-α blocking agents predispose to invasive fungal infections, such as aspergillus, histoplasmosis, and coccidioidomycosis (41). Infections with mycobacteria and fungi are seen with all three agents, but significantly more with infliximab than etanercept. Adalimumab should be regarded as having similar risks. The risk posed by TNF-α blocking agents for predisposing to NTM infections or promoting progression of active NTM infection is unknown. Until more information is available, expert opinion is that patients with active NTM disease should receive TNF-α blocking agents only if they are also receiving adequate therapy for the NTM disease.

LABORATORY PROCEDURES

Since the publication of the last ATS statement on NTM, the Clinical and Laboratory Standards Institute (CLSI), formerly known as the National Committee for Clinical Laboratory Standards (NCCLS), has published an approved standard for NTM susceptibility testing by mycobacteriology laboratories (42, 43). The institute provides a global forum for the development of standards and guidelines. All proposed standards from the institute are subjected to an accredited consensus process before being published as "accepted standards." The institute suggests that to maintain efficiency, effectiveness, and consistency in the interpretation of test results, it is important that other health care–associated organizations ascribe to the same standards and practices as approved by the CLSI. Unless noted in the text, recommendations in this document are consistent with CLSI published standards.

Collection, Digestion, Decontamination, and Staining of Specimens

Specimens for mycobacterial identification and susceptibility testing may be collected from almost any area of the body. Collection of all specimens should avoid potential sources of contamination, especially tap water, because environmental mycobacteria are often present. Specimens should be submitted without fixatives. Observing routine safety precautions by collecting samples in sterile, leak-proof, disposable, labeled, laboratory-approved containers is important. Transport media and preservatives are not usually recommended, although refrigeration of samples at 4°C is preferred if transportation to the laboratory is delayed more than 1 hour. For diagnostic purposes, it may be necessary to collect multiple respiratory specimens on separate days from outpatients. Specimens for mycobacterial analysis can be shipped or mailed. Overnight shipping with refrigerants such as cold packs is optimal, although mycobacteria can still be recovered several days after collection even without these measures. The longer the delay between collection and processing, however, the greater is the risk of bacterial overgrowth. Treatment with commonly used antibiotics such as macrolides and quinolones might adversely affect the yield of NTM recovery. Therefore, if possible, antibiotic use should be limited during diagnostic evaluation of NTM diseases.

Respiratory Specimens

To establish the diagnosis of NTM lung disease, the collection of three early-morning specimens on different days is preferred. For patients unable to produce sputum, sputum can also be induced. Induced sputum is an effective method for diagnosing TB; however, similar data establishing the effectiveness of sputum induction for diagnosing NTM lung disease are not available (44). In addition, the optimal methodology for sputum induction in this setting has not been determined. If sputum cannot be obtained, bronchoscopy with or without lung biopsy may be necessary. Because of clinical similarities between NTM lung disease and TB, appropriate precautions to prevent the nosocomial transmission of TB should be followed when performing these procedures. It is also important to perform appropriate cleaning procedures for bronchoscopes that include the avoidance of tap water, which may contain environmental mycobacteria.

Body Fluids, Abscesses, and Tissues

Aseptic collection of as much body fluid or abscess fluid as possible by needle aspiration or surgical procedures is recommended. Swabs are not recommended for sample collection because they often are not aggressively applied, resulting in limited culture material, and are also subject to dessication, thus

decreasing chances for recovery of NTM. If a swab is used, the swab should be saturated with the sampled fluid to assure an adequate quantity of material for culture. When submitting tissue, the specimen should not be wrapped in gauze or diluted in liquid material. If only a minute amount if tissue is available, however, it may be immersed in a small amount of sterile saline to avoid excessive drying.

Blood

Several commercial mycobacterial blood culture systems for NTM are available (*see* online supplement). Coagulated blood or blood collected in ethylenediaminetetraacetic acid (EDTA) is unacceptable. For rapidly growing mycobacteria (RGM), these special mycobacterial systems are not required as most RGM species grow well in routine blood culture systems.

Specimen Processing

To minimize contamination or overgrowth of cultures with bacteria and fungi, digestion and decontamination procedures should be performed on specimens collected from nonsterile body sites. Samples from contaminated sites contain other organisms that may grow more rapidly than NTM and interfere with the recovery of mycobacteria. Because NTM, especially RGM, are much more susceptible to decontamination than *M. tuberculosis*, these procedures should not be so severe as to eliminate the mycobacteria potentially present. Tissue samples or fluids from normally sterile sites do not require decontamination. Tissues should be ground aseptically in sterile physiological saline or bovine albumin and then directly inoculated onto the media.

The most widely used digestion–decontamination method uses N-acetyl-L-cysteine–sodium hydroxide (NALC-NaOH). This method is often used in conjunction with a 5% oxalic acid procedure ("double processing") for specimens from patients with CF or bronchiectasis whose sputa are known to be contaminated with aerobic gram-negative rods, especially *Pseudomonas aeruginosa* (42, 45). Instructions for commonly used digestion–decontamination methods are described elsewhere (46–48). Because NTM may be sensitive to oxalic acid decontamination, with reduced yield on culture, another option is to use a two-step decontamination approach reserving oxalic acid only for those specimens overgrown by bacteria other than NTM (47–49).

Smear Microscopy

The recommended method for staining clinical specimens for AFB, including both *M. tuberculosis* and NTM, is the fluorochrome technique, although the Ziehl-Neelsen method or Kinyoun stain are acceptable but less sensitive alternatives. The Gram stain is not adequate for detection of mycobacteria. In many cases, the NTM, especially the RGM, may be more sensitive to the AFB decolorization procedure and may not stain at all with fluorochrome stains. Therefore, if RGM are suspected, it may be prudent to use a weaker decolorizing process. It is also noteworthy that negative smears do not necessarily mean that NTM, especially RGM, are not present in a clinical sample.

Semiquantitative analysis of smears can be useful for diagnostic purposes. Fluorochrome smears are graded from 1+ (1–9 organisms per 10 high-power fields) to 4+ (> 90 organisms per high-power field) (47). The burden of organisms in clinical material is usually reflected by the number of organisms seen on microscopic examination of stained smears. Environmental contamination, which usually involves small numbers of organisms, rarely results in a positive smear examination. Previous studies have indicated that specimens with a high number of mycobacteria isolated by culture are associated with positive smears and, conversely, specimens with a low number of mycobacteria isolated by culture are less likely to have positive smears (50).

Culture Techniques

All cultures for mycobacteria should include both solid and broth (liquid) media for the detection and enhancement of growth (43). However, broth media cultures alone may not be satisfactory because of bacterial overgrowth. Cultures in broth media have a higher yield of mycobacteria and produce more rapid results than those on solid media. The advantages of solid media over broth media are that they allow the observation of colony morphology, growth rates, recognition of mixed (more than one mycobacterial species) infections, and quantitation of the infecting organism, and serve as a backup when liquid media cultures are contaminated.

Broth media. One of the most widely used broth systems is the nonradiometric mycobacteria growth indicator tube (MGIT) (Becton Dickinson, Sparks, MD), which contains a modified Middlebrook 7H9 broth in conjunction with a fluorescence quenching–based oxygen sensor to detect mycobacterial growth. As the mycobacteria grow and deplete the oxygen present, the indicator fluoresces when subjected to ultraviolet light. For detailed discussion of broth (liquid) media culture techniques, *see* the online supplement.

Solid media. Recommended solid media include either egg-based media, such as Löwenstein-Jensen agar or agar-based media such as Middlebrook 7H10 and 7H11 media. The agar-based media may also be used for susceptibility testing. Biphasic media, such as the Septi-Chek System (Becton Dickinson), provide enhanced recovery of most NTM in one system, but these are not rapid detection systems.

Semiquantitative (0–4+) reporting of NTM colony counts on solid media is recommended by the CLSI. A single positive respiratory sample with a low colony count (e.g., broth culture positive only) is less likely to be clinically significant than a sample with a high colony count (e.g., growth on both solid and broth media). This approach also helps in the assessment of response to therapy. After successful therapy of MAC lung disease and at least 10 months of negative cultures during therapy, a single positive culture that is AFB smear negative and of low culture positivity (< 10 colonies on solid media and/or positive in the broth media only) generally represents either contamination (false-positive culture) or transient new infections and not relapse of the original infecting strain (38, 51).

M. haemophilum, *M. genavense*, *M. avium* subsp. *paratuberculosis* (formerly *M. paratuberculosis*), and *M. ulcerans* are examples of fastidious NTM that require special supplementation for recovery on culture. *M. haemophilum* grows only on media supplemented with iron-containing compounds such as ferric ammonium citrate, hemin, or hemoglobin. Because *M. haemophilum* has a predilection for skin and the body's extremeties, all specimens from skin lesions, joints, or bones should be cultured in a manner suitable for recovery of this species. *M. genavense* and *M. avium* subsp. *paratuberculosis* require mycobactin J, and *M. ulcerans* may be optimally recovered with egg yolk supplementation.

Incubation of NTM Cultures

The optimal temperature for most cultures for NTM is between 28° and 37°C. Most clinically significant slowly growing mycobacteria grow well on primary isolation at 35° to 37°C with the exception of the following: the newly described *M. conspicuum,* which requires temperatures from 22° to 30°C for several weeks and only grows at 37°C in liquid media, *M. haemophilum*, which prefers temperatures from 28° to 30°C, *M. ulcerans*, which grows slowly at 25° to 33°C, and some strains of *M. chelonae*, which

require temperatures between 28° and 33°C (5). Cultures for RGM and *M. marinum* should be incubated at 28° to 30°C. All skin, joint fluid, and bone specimens should be cultured at 28° to 30°C and at 35° to 37°C. Optimal recovery of all species may require duplicate sets of media at two incubation temperatures.

Most NTM grow within 2 to 3 weeks on subculture. To detect *M. ulcerans* or *M. genavense,* cultures should be incubated for at least 8 to 12 weeks. Rapidly growing mycobacteria usually grow within 7 days of subculture. Earlier detection of NTM can be expected with liquid-based systems. When stated on the laboratory report, the time in days to the detection of mycobacterial growth can be helpful to clinicians as an indication of isolation of a rapidly growing species.

***Recommendations*:**

1. As much material as possible for NTM culture should be provided with clear instructions to the laboratory to culture for mycobacteria (C, III).
2. All cultures for NTM should include both a rapid detection broth (liquid) media technique and solid media cultures (C, III).
3. Quantitation of the number of colonies on plated culture media should be performed to aid clinical diagnosis (C, III).
4. Supplemented culture media and special culture conditions (lower incubation temperatures) should be used for material cultured from skin lesions, joints, and bone (A, II).
5. The time (in days) to detection of mycobacterial growth should be stated on the laboratory report (C, III).

NTM Identification

Because of differences in antimicrobial susceptibility that determine treatment options, species-level identification of the NTM is becoming increasingly clinically important (43). Several factors increase the likelihood of clinical significance of NTM isolates, including the recovery from multiple specimens or sites, recovery of the organism in large quantities (AFB smear–positive specimens), or recovery of an NTM isolate from a normally sterile site such as blood. For initial clinical mycobacterial isolates, however, it is sometimes difficult to determine the clinical significance of the isolate without species identification. Therefore, identification of most mycobacterial isolates to the species level and not merely as groups, such as "*M. chelonae/abscessus* group" is strongly recommended. If, after consultation between the clinician and the laboratorian and in the event that a specific laboratory does not have the necessary technology for species identification of an NTM isolate, the isolate could be sent to a reference laboratory for further analysis.

It is equally important to recognize that not all clinically obtained NTM isolates, especially from sputum, will need extensive identification efforts. For instance, a pigmented rapidly growing mycobacterium recovered in low numbers from only one of multiple sputum specimens from a patient undergoing therapy for MAC lung disease would not need an extensive effort for identification of that isolate as it would not likely be clinically significant. Awareness of the context from which an NTM isolate is obtained can be critically important in determining the need for speciation of that isolate. Again, communication between the clinician and laboratorian is critical for making this type of determination.

Phenotypic testing. Preliminarily, NTM can be categorized by growth rate and pigmentation, which will help guide in the selection of proper testing procedures, including appropriate media selection and incubation temperatures. Recent studies have shown, however, that identification using only conventional biochemical analysis is both time consuming and increases turnaround time, leading to significant delays in diagnosis (52).

Detailed descriptions of methods, procedures, and quality control measures have been published (47, 48). Isolates of NTM, which form colonies on subculture in 7 days or fewer, are referred to as "rapidly growing mycobacteria" or RGM. Conversely, those isolates of NTM that require more than 7 days to form mature colonies on subculture are termed "slowly growing mycobacteria." Although many of the conventional and traditional laboratory tests for mycobacterial evaluation are not routinely used, the rate of growth is still useful for preliminary broad classification of a nontuberculous mycobacterium.

Traditionally, NTM have also been divided into three groups based on the production of pigment. These growth characteristics are rarely detailed in modern mycobacterial laboratories, but the presence of pigmentation and smooth colony morphology quickly exclude the isolate as belonging to the *M. tuberculosis* complex that forms nonpigmented and rough colonies.

Biochemical testing of NTM uses a battery of tests, again based on the growth rate of the NTM. The use of conventional testing alone does not allow identification of many of the newly described NTM and thus newer methods, including HPLC and molecular methods, must be used.

Chemotaxonomic testing: HPLC. HPLC is a practical, rapid, and reliable method for identifying many slowly growing species of NTM. HPLC can also be used in the direct analysis of primary cultures of mycobacteria grown in BACTEC 7H12B medium (Becton Dickinson) and the identification of MAC directly from samples with AFB smear–positive results (53). However, HPLC has limitations. Recognition of some newer species and species within the *M. simiae* complex is difficult. It has also been reported that some species within the *M. fortuitum* group and the *M. smegmatis* group are difficult to separate, and distinction between *M. abscessus* and *M. chelonae* may not be possible (54). HPLC analysis will be less useful in the future, as identification of NTM species will be accomplished by molecular methods.

Genotypic methods for identification of NTM. COMMERCIALLY AVAILABLE MOLECULAR PROBES. Acridium ester–labeled DNA probes specific for MAC (or separately for *M. avium* and *M. intracellulare*), *M. kansasii*, and *M. gordonae* have been approved by the U.S. Food and Drug Administration (FDA) and are currently used in many clinical laboratories (AccuProbe; Gen-Probe, Inc., San Diego, CA) for the rapid identification of NTM. This technique is based on the release of target 16S rRNA from the organism. Testing can be performed using isolates from solid or liquid culture media and identification of these species can be achieved within 2 hours. Studies have shown 100% specificity with a sensitivity between 85 and 100%. Only a few NTM species have available probes, representing a major limitation. In addition, there is the potential for cross-reaction of the probe for *M. tuberculosis* with *M. celatum* (55).

PRA. The current PRA method widely adopted for the identification of NTM is based on the coupling of the PCR of a 441-bp sequence of the gene encoding the 65-kD heat shock protein (*hsp65*) followed by restriction enzyme digestion. The size of the restriction fragments is generally species specific (56–59). In one study, 100% of 129 nonpigmented RGM were identified using PRA (60). However, some taxa may require additional endonucleases for species identification (60).

The PRA method is relatively rapid, does not require viable organisms, and identifies many NTM species that are not identifiable by phenotypic or chemotaxonomic techniques alone. However, this system is not commercially available; therefore, the

clinician may need to work closely with a public health or reference laboratory to determine the best method for species identification for a particular NTM isolate.

DNA SEQUENCE ANALYSIS. The 16S rRNA is an approximately 1,500 nucleotide sequence encoded by the 16S ribosomal DNA (rDNA), which is a highly conserved gene with regions common to all organisms (conserved regions) and also areas where nucleotide variations occur (variable regions). For purposes of mycobacterial identification, sequence analysis focuses on two hypervariable sequences known as regions A and B. The sequence of region A is usually adequate to identify most NTM species, although sequencing of region B may be necessary, especially in the identification of undescribed species or those species which cannot be differentiated by sequence of the region A alone (5). Examples include *M. kansasii*/*M. gastri*, as well as *M. ulcerans* and *M. marinum*, and *M. shimoidei* and *M. triviale*. Isolates of *M. chelonae* and *M. abscessus* cannot be differentiated within the regions A and B, although they do vary at other 16S rRNA gene sites (although only by a total of 4 bp) (60, 61).

Problems with this method are that species of recent divergence may contain highly similar 16S rRNA gene sequences. For example, the difference between *M. szulgai* and *M. malmoense* is two nucleotides, although it is well established that these are two distinct species. In addition, no interstrain nucleotide sequence difference value that unequivocally defines different species has been established for mycobacteria (48).

The automation of sequence analysis by the introduction of commercial systems like the MicroSeq 500 16S rDNA Bacterial Sequencing Kit (PE Applied Biosystems, Foster City, CA), in which a 500-bp sequence of the NTM is analyzed and compared with a commercially prepared database, has made sequencing more efficient for use in the clinical laboratory. One of the major limitations of this system, however, is that the MicroSeq database has only one entry per species (generally the type strain) (61). This is particularly problematic when the unknown isolate does not have an exact match in the databases. Currently, isolates may be reported as "most closely related to" a species depending on the sequence difference between the unknown isolate and the database entry (62, 63).

***Recommendations*:**

1. Clinically significant NTM isolates should be routinely identified to the species level. An important exception is MAC because the differentiation between *M. avium* and *M. intracellulare* is not yet clinically significant. Although not routinely recommended, this differentiation may be important epidemiologically and, in the future, therapeutically (C, III).
2. The RGM (especially *M. chelonae*, *M. abscessus*, and *M. fortuitum*) should be identified to species level using a recognized acceptable methodology, such as PRA or biochemical testing, not HPLC alone (A, II).
3. Susceptibility of RGM for eight agents, including amikacin, cefoxitin, clarithromycin, ciprofloxacin, doxycycline, linezolid, sulfamethoxazole, and tobramycin, can also be used to facilitate identification of *M. abscessus*, *M. chelonae*, and *M. fortuitum* (C, III).
4. Communication between the clinician and laboratorian is essential for determining the importance and extent of the identification analysis for a clinical NTM isolate (C, III).

Antimicrobial Susceptibility Testing for NTM

***Context*:**

There is ongoing debate about the role of *in vitro* susceptibility testing for managing patients with NTM disease. The controversy primarily stems from the observation that, unlike *M. tuberculosis*, MAC response to anti-TB drugs such as rifampin and ethambutol may not be reliably predicted on the basis of current *in vitro* susceptibility test methods. NTM such as *M. kansasii*, *M. marinum*, or *M. fortuitum* are susceptible *in vitro* to multiple antimicrobial drugs and the clinical response to therapeutic agents appears to closely parallel the *in vitro* susceptibility pattern, although this observation has not been evaluated by randomized controlled trials. In contrast, MAC has limited *in vitro* susceptibility, and clinical response has been shown to correlate only with the macrolides. Last, organisms such as *M. abscessus* and *M. simiae* have limited *in vitro* susceptibility, with limited evidence for a correlation between *in vitro* susceptibility to any agent and clinical response in the treatment of pulmonary disease caused by these agents. Interestingly, for skin and soft tissue infections caused by *M. abscessus*, there does appear to be a correlation between *in vitro* susceptibility and clinical response, although this observation has not been prospectively evaluated. Susceptibility breakpoints have been defined in the laboratory to distinguish populations of mycobacteria that are labeled susceptible and resistant. For many NTM, however, these laboratory cutoffs have not been confirmed to be clinically meaningful, so that there are few data to validate susceptibility testing for many NTM species as a guide for choosing antibiotics. Until the relationship between *in vitro* susceptibility of many NTM and their clinical response to antimicrobial drugs is better understood and clarified, the clinician should use *in vitro* susceptibility data with an appreciation of its limitations and with the awareness that, unlike TB, some NTM disease may not be eradicated in a given patient with therapy based on *in vitro* susceptibility results. The use of *in vitro* susceptibility testing for NTM is outlined below and consistent with CLSI recommendations.

Slowly growing mycobacteria. For the slowly growing NTM, no single susceptibility method is recommended for all species. For isolates of MAC, the CLSI has recommended a broth-based method with both microdilution or macrodilution methods being acceptable (43). Until further multicenter studies have been performed with the other slowly growing mycobacteria, broth and solid methods of susceptibility testing may be performed with the caveat that each laboratory must validate each method for each species tested, and quality control and proficiency testing requirements should be enforced.

MAC. Initial isolates from patients with previously untreated MAC lung disease should be tested to clarithromycin to establish baseline values. The isolate may also be saved for future testing, especially to determine if future isolates represent relapse or new infections by comparative DNA fingerprinting of baseline and subsequent isolates (51). Other isolates to be tested include the following:

1. Isolates from patients who previously received macrolide therapy to determine whether or not the isolates are still macrolide susceptible.
2. Isolates from patients with MAC pulmonary disease on macrolide-containing regimens who relapse or fail after 6 months of macrolide-containing therapy.
3. Isolates from patients with AIDS who develop bacteremia on macrolide prophylaxis.

4. Positive blood cultures after 3 months of treatment with macrolide-containing regimens for patients with disseminated MAC.

Untreated MAC isolates usually have minimum inhibitory concentrations (MICs) of 4 μg/ml or less to clarithromycin and are considered susceptible. In contrast, relapse strains after treatment inevitably have a clarithromycin MIC of 32 μg/ml or greater and no longer respond to treatment with macrolides. Isolates of MAC have only a single copy of the ribosome, and hence, macrolide monotherapy carries a significant risk of the development of mutational resistance. Not unexpectedly, all high-level clarithromycin-resistant isolates have mutations in the adenine at position 2058 or 2059 of the 23S rRNA gene, which is the presumed macrolide binding site on the ribosomal unit (64, 65). Expert consultation should be sought for management of patients with macrolide-resistant MAC isolates.

Strains that appear intermediate in susceptibility to clarithromycin rarely occur and should be confirmed by another testing event. Patients with these intermediate MICs should be followed closely for possible emergence of macrolide resistance. Macrolides should be included in treatment regimens for these patients unless the isolate is found on subsequent testing to be macrolide resistant.

Because no correlation between *in vitro* susceptibility results for MAC and clinical response for agents other than macrolides has been established, the 2003 CLSI document states that clarithromycin is the only drug for which susceptibility testing for MAC isolates is recommended (43).

The role of extended *in vitro* susceptibility testing for macrolide-resistant MAC isolates is unproven. However, some experts suggest that it may be reasonable to test other antimicrobials such as the 8-methoxy fluoroquinolone moxifloxacin and linezolid for patients who fail initial macrolide-based therapy (43). Although there is a paucity of published data, some experts feel that moxifloxacin has *in vitro* activity against MAC at clinically achievable serum levels. It was recently reported that out of 189 isolates of MAC, only 13% of the isolates studied had MICs of 8 μg/ml or less for linezolid; however, there have been reports of successful multidrug therapy with linezolid in the treatment of MAC (66, 67). Testing of anti-TB medications does not provide useful clinical information.

M. kansasii. The 2003 CLSI document states that only susceptibility to rifampin should be routinely performed for isolates of *M. kansasii* (43). MICs of all agents in untreated (wild) strains fall in a narrow range and treatment failure is usually associated with resistance to rifampin. Resistance to isoniazid and ethambutol acquired on therapy may also occur, but resistance to these agents is usually associated with resistance to rifampin (68). Isolates that are susceptible to rifampin are also susceptible to rifabutin, which may be substituted for rifampin in HIV-infected patients being treated with highly active antiretroviral therapy (HAART), including some protease inhibitors and nonnucleoside reverse transcriptase inhibitors (*see* Disseminated MAC Disease). If the isolate proves to be rifampin resistant, susceptibility to secondary agents, including amikacin, ciprofloxacin, clarithromycin, ethambutol, rifabutin, streptomycin, sulfonamides, and isoniazid, should be tested. Susceptibility to the new 8-methoxy fluoroquinolone, moxifloxacin, should be performed separately because ciprofloxacin is the class representative for ciprofloxacin, ofloxacin, and levofloxacin only. In addition, the standard critical concentrations of 0.2 and 1 μg/ml for isoniazid used for testing strains of *M. tuberculosis* should not be tested as MICs for untreated strains between 0.5 and 5 μg/ml. Thus, the 0.2-μg/ml standard concentration appears resistant and the 1.0-μg/ml standard concentration may yield variable results, even with multiple cultures of the same strain (43).

M. marinum. Routine susceptibility testing of this species is not recommended (43). There is no documentation of significant risk of mutational resistance to the antimycobacterial agents and there is no appreciable variability in susceptibility patterns to clinically useful agents (69). Disease involving *M. marinum* is typically localized and the number of organisms present is low; 95% of tissue biopsy cultures are AFB smear negative (2). Isolates of *M. marinum* are susceptible to clarithromycin, as well as the sulfonamides, the tetracyclines, rifampin, and ethambutol. Ciprofloxacin is not recommended because some strains are resistant and monotherapy carries the risk of mutational resistance (70). However, some experts report anecdotally that the newer 8-methoxy fluoroquinolone, moxifloxacin, is more active *in vitro* and could be considered for multidrug therapy. Susceptibility testing should be considered for patients who remain culture positive after more than 3 months of therapy.

Miscellaneous slowly growing NTM (*M. simiae* complex, *M. terrae/nonchromogenicum* complex, *M. malmoense, M. xenopi*). Because too few isolates of each species have been studied, no specific susceptibility method can be recommended at this time for the less commonly isolated NTM including several newly described species (5, 43). Until further data are available, testing should be performed as for rifampin-resistant *M. kansasii* (i.e., rifampin and secondary agents should be tested) (43).

RGM. The CLSI has recommended the broth microdilution MIC determination for susceptibility testing of RGM. Agar tests, including the E-test (epsilometer test), cannot be recommended due to inconsistency of results (71). The broth microdilution technique is described in the 2003 NCCLS M24A-approved document (40). MICs for imipenem are problematic with isolates of *M. chelonae*, *M. abscessus*, and *M. immunogenum* because of the lack of reproducibility (43, 72). For the majority of *M. abscessus* and *M. chelonae* isolates, imipenem is the preferred carbapenem over meropenem and ertapenem (73). Imipenem may still be useful clinically in treatment regimens for these organisms. In contrast, MICs for imipenem with isolates of the *M. fortuitum* group, *M. smegmatis* group, and *M. mucogenicum* are reproducible.

True aminoglycoside resistance with *M. abscessus* is unusual but does occur, especially in patients on long-term treatment with aminoglycosides, such as patients with CF or chronic otitis media. *In vitro* susceptibility studies suggest that tobramycin is the most active aminoglycoside for *M. chelonae*; therefore, it is recommended to report tobramycin MICs only for this species (43).

In vitro testing of clarithromycin may present interpretation problems with RGM. Thus, the CLSI has recommended that isolates of the *M. fortuitum* group with indeterminate or unclear susceptibility endpoints with clarithromycin should be reported as resistant until further data are available with these isolates (43). Recent studies have shown that all isolates of *M. fortuitum* contain an inducible erythromycin methylase gene *erm* (39), which confers macrolide resistance (74). The presence of this gene with variable expression is likely responsible for this phenomenon. Similar erm genes have been reported in other RGM species that are macrolide resistant (e.g., *M. smegmatis*) but not in *M. abscessus* despite its general poor response to macrolide therapy (75).

Fastidious species of NTM. As for the previous group of less commonly recovered NTM, no current standardized method can be recommended at this time due to lack of experience and available data concerning methods and results.

M. haemophilum. Isolates are generally susceptible to the first-line anti-TB agents (except ethambutol), clarithromycin, and the sulfonamides (76).

M. genavense, *M. avium* subsp. paratuberculosis, *M. ulcerans.* Susceptibility testing of these species is difficult since they do not grow in standard susceptibility media without

supplementation and extended incubation; therefore, standardized guidelines for *in vitro* susceptibility procedures are not available for testing these species (77–82).

***Recommendations*:**

1. Clarithromycin susceptibility testing is recommended for new, previously untreated MAC isolates. Clarithromycin is recommended as the "class agent" for testing of the newer macrolides because clarithromycin and azithromycin share cross-resistance and susceptibility. No other drugs are recommended for susceptibility testing of new, previously untreated MAC isolates. There is no recognized value for testing of first-line antituberculous agents with MAC using current methodology (A, II)
2. Clarithromycin susceptibility testing should be performed for MAC isolates from patients who fail macrolide treatment or prophylaxis regimens (A, II).
3. Previously untreated *M. kansasii* strains should be tested *in vitro* only to rifampin. Isolates of *M. kansasii* that show susceptibility to rifampin will also be susceptible to rifabutin (A, II).
4. *M. kansasii* isolates resistant to rifampin, should be tested against a panel of secondary agents, including rifabutin, ethambutol, isoniazid, clarithromycin, fluoroquinolones, amikacin, and sulfonamides (A, II).
5. *M. marinum* isolates do not require susceptibility testing unless the patient fails treatment after several months (A, II).
6. There are no current recommendations for one specific method of *in vitro* susceptibility testing for fastidious NTM species and some less commonly isolated NTM species (C, III).
7. Validation and quality control should be in place for susceptibility testing of antimicrobial agents with all species of NTM (C, III).

Molecular Typing Methods of NTM

Molecular typing methods have become valuable epidemiologic tools in the investigation of outbreaks, pseudo-outbreaks, and epidemics involving NTM. If a laboratory that performs molecular typing methods of NTM isolates cannot be readily identified, the clinician or investigator should contact the state's Department of Health or the CDC for advice about laboratories that can assist with this analysis.

Pulsed-field gel electrophoresis. Pulsed-field gel electrophoresis (PFGE) is one of the most widely used and valuable methods of molecular typing of NTM. This technique involves embedding the isolates in agarose gels, lysing the DNA, and digesting chromosomal DNA with specific restriction endonucleases (79–81). This is a time-consuming procedure because the organisms must be actively grown such that a sufficient biomass is available to yield accurate results. Furthermore, more than one-half of the DNA from strains of *M. abscessus* will spontaneously lyse or be digested during the procedure, although this can be corrected with the addition of thiourea to stabilize the running buffer (79–81).

Despite its limitations, however, PFGE is currently the most common typing method for strain differentiation of RGM and other NTM. Unrelated strains of most species of RGM are highly heterogeneous and restriction fragment length polymorphism (RFLP) patterns for the same strain are identical or indistinguishable (83–86).

Other typing methods. Other methods have been used for strain comparison, including random amplified polymorphic DNA PCR, multilocus enzyme electrophoresis using multiple housekeeping cellular enzymes, and hybridization with multicopy insertional elements in *M. avium* but not *M. intracellulare*.

CLINICAL PRESENTATIONS AND DIAGNOSTIC CRITERIA

Pulmonary Disease

Epidemiology. Chronic pulmonary disease is the most common clinical manifestation of NTM (19, 87, 88). MAC, *M. kansasii*, and *M. abscessus*, in that order, were the most frequent NTM pulmonary pathogens in the United States between 1981 and 1983 (19). In that study, there was a predominance of males with NTM pulmonary disease in general and in disease caused by all species except *M. chelonae* (probably *M. abscessus*) and *M. simiae* (19). The mean age of patients with NTM pulmonary disease was 57 years (19). In the CDC report from the mid-1990s, MAC, *M. kansasii*, and *M. fortuitum* were the most frequent pulmonary pathogens in the United States between 1993 and 1996 (22). Males predominated in disease caused by all species except *M. abscessus* and the majority of isolates were from patients 50 years of age or older. In light of more recent information that reflects a postmenopausal female patient predominance for MAC lung disease, it is likely that these epidemiologic estimates are not currently valid (36, 37).

Symptoms and signs. The symptoms of NTM pulmonary disease are variable and nonspecific. However, virtually all patients have chronic or recurring cough. Other symptoms variably include sputum production, fatigue, malaise, dyspnea, fever, hemoptysis, chest pain, and weight loss. Constitutional symptoms are progressively more prevalent with advancing NTM lung disease. Evaluation is often complicated by symptoms caused by coexisting lung diseases, such as bronchiectasis, chronic obstructive airway disease associated with smoking, CF, and pneumoconiosis.

Physical findings are nonspecific and reflect underlying pulmonary pathology, such as bronchiectasis and chronic obstructive lung disease. On chest auscultation, findings may include rhonchi, crackles, wheezes, and squeaks. Patients with nodular/bronchiectatic MAC disease tend to be postmenopausal women, many of whom also have a characteristic morphotype with a thin body habitus and may also have scoliosis, pectus excavatum, and mitral valve prolapse (27).

Radiographic studies. Radiographic features of NTM lung disease depend on whether the lung disease is primarily fibrocavitary (similar to TB) or characterized by nodules and bronchiectasis (nodular/bronchiectatic disease) (*see* the online supplement). Compared with the radiographic findings in TB, patients with NTM disease and predominantly fibrocavitary radiographic changes tend to have the following characteristics: (*1*) thin-walled cavities with less surrounding parenchymal opacity, (*2*) less bronchogenic but more contiguous spread of disease, and (*3*) to produce more marked involvement of pleura over the involved areas of the lungs (2, 88, 89). None of these differences, however, is sufficiently specific to exclude the diagnosis of TB on the basis of the radiographic appearance. NTM may produce dense airspace disease or a solitary pulmonary nodule without cavitation. Basal pleural disease is not often found, and pleural effusion is rare.

For patients with predominantly noncavitary disease, the abnormalities on chest radiograph are primarily found in the mid- and lower lung field. Studies with HRCT of the chest have shown that up to 90% of patients with mid- and lower lung field noncavitary disease with MAC have associated multifocal

bronchiectasis, with many patients having clusters of small (< 5 mm) nodules in associated areas of the lung (90–94). These findings correspond histopathologically to bronchiectasis, bronchiolar and peribronchiolar inflammation, and granuloma formation (94). Cavitation also frequently accompanies these abnormalities. Other NTM species, including *M. abscessus*, *M. chelonae*, *M. simiae*, and *M. kansasii* (and probably other species), can also be associated with this radiographic appearance (32, 95).

A plain chest radiograph may be adequate for evaluating patients with fibrocavitary disease. However, HRCT of the chest is now routinely indicated to demonstrate the characteristic abnormalities of nodular/bronchiectatic NTM lung disease.

Mycobacterial cultures. Presumptive diagnosis based on clinical and radiographic features is not adequate for initiation of therapy. Isolation of NTM in culture is essential for the diagnosis of NTM lung disease. It should be stressed that NTM are found widely in nature; therefore, contamination of respiratory specimens occurs. A single positive sputum culture, especially with a small number of organisms, is generally regarded as indeterminant for diagnosis of NTM lung disease. NTM species that are generally not pathogenic and usually isolated due to contamination when recovered from respiratory specimens include *M. gordonae*, *M. terrae* complex, *M. mucogenicum*, and *M. scrofulaceum* (Table 2). Other species known to be present in tap water that may reflect contamination when recovered from a single sample include *M. simiae* and *M. lentiflavum.*

Patients should have at least three sputum specimens collected on separate days and analyzed for AFB to optimize positive predictive value of sputum analysis. In a study evaluating the association of MAC isolated from sputum and new cavitary or infiltrative lesions on chest radiograph (96), 114 patients had a single isolation of MAC (from three specimens) and only 2 of these patients, both with specimens that were AFB smear positive, subsequently developed new chest radiographic abnormalities. In addition, 26 of 29 (90%) patients who had MAC isolated from two specimens and 39 of 40 (98%) patients with MAC isolated from three specimens had progressive radiographic abnormalities. All 116 patients who had four or more MAC isolates had progressive radiographic abnormalities. Furthermore, 181 of 185 (98%) patients who had two or more MAC isolates, generally on the initial three sputum specimens collected, also had progressive radiographic abnormalities.

Clinical studies have established the validity of bronchial washings as a culture source for *M. tuberculosis* (44). Limited data suggest that bronchial lavage may also be useful for diagnosing NTM (MAC) lung disease (97). There is expert consensus that bronchial washings are more sensitive than routine expectorated sputum testing and less likely to be affected by environmental contamination if the bronchoscopic specimens are protected from tap water (*see* HEALTH CARE– AND HYGIENE-ASSOCIATED DISEASE AND DISEASE PREVENTION). The routine use of bronchoscopy for diagnosis and follow-up of patients with NTM lung disease is not established.

The recovery of NTM from sputum can sometimes obfuscate or delay the diagnosis of other important lung diseases (98, 99). In patients with nondiagnostic microbiologic and radiographic studies (i.e., patients who do not clearly meet diagnostic criteria), or if there is concern about the presence of another disease producing radiographic abnormalities, a lung biopsy (bronchoscopic or surgical) may be required for diagnosis. If a tissue sample from a transbronchial, percutaneous, or open-lung biopsy yields an NTM organism and shows histopathologic changes typical of mycobacterial disease (i.e., granulomatous inflammation with or without the presence of AFB), this by itself is sufficient to establish the diagnosis of NTM lung disease. If the lung biopsy is negative on culture (which may occur when transbronchial biopsies are performed because of the small size of the tissue sample) but demonstrates mycobacterial histopathology features (without a history of other granulomatous or mycobacterial disease), NTM lung disease is considered to be present when one or more sputum specimens or bronchial washes are culture positive for NTM.

Other tests. There has been a great deal of interest in the availability of species-specific skin test antigens. Unfortunately, many antigenic epitopes are shared by different mycobacterial species and extensive cross-reactions are observed with different mycobacterial skin test antigens. Dual skin testing with PPD tuberculin and *M. avium* sensitin can help discriminate between culture-positive lung disease due to MAC and that due to *M. tuberculosis* (100). However, *M. avium* sensitin is not being developed for commercial use as an intradermal skin test.

***Recommendations*:**

1. The minimum evaluation of a patient suspected of NTM lung disease should include (*1*) chest radiograph or, in the absence of cavitation, chest HRCT scan; (*2*) three or more sputum specimens for AFB analysis; and (*3*) exclusion of other disorders such as TB and lung malignancy. In most patients, a diagnosis can be made without bronchoscopy or lung biopsy (A, II).
2. Disease caused by *M. tuberculosis* is often in the differential diagnosis for patients with NTM lung disease. Empiric therapy for TB, especially with positive AFB smears and results of nucleic acid amplification testing, may be necessary pending confirmation of the diagnosis of NTM lung disease (C, III).

Diagnostic criteria. Overly rigorous criteria might delay or prevent the diagnosis, with the subsequent risk for progressive disease. Conversely, criteria that are too lenient could result in unnecessary exposure of patients to potentially toxic and expensive therapy. Because NTM lung disease is generally slowly progressive (relative to TB), there is usually sufficient time to collect adequate clinical material, specifically multiple respiratory specimens, necessary for making a diagnosis. For patients in whom the diagnosis is unclear, expert consultation should be sought.

Given the large number of identified NTM species, the wide spectrum of NTM virulence, and the variable host susceptibility for NTM, it is unlikely that a single set of diagnostic criteria would be useful or accurate for all NTM species in all clinical circumstances. A limitation of all diagnostic criteria developed so far is that, by necessity, they were developed based on experience with common and well-described respiratory pathogens such as MAC, *M. kansasii,* and *M. abscessus.* It is assumed, but not proven, that the concepts outlined in these guidelines are pertinent for other less common NTM respiratory pathogens. Suggested criteria for diagnosing NTM lung disease are listed in Table 3.

The previous ATS guidelines included recommendations based on quantitation of smears and cultures in the diagnostic criteria. Many laboratories, however, do not report quantitative smear and culture results, especially those using only liquid (broth) culture media. Therefore, the diagnosis of NTM lung disease must sometimes be made on the basis of smear and culture positivity or negativity without quantitation. As noted in LABORATORY PROCEDURES, both liquid and solid media cultures are recommended, as is quantitation of mycobacterial growth on solid media cultures.

It has been previously suggested that the respiratory tract can be infected with NTM without disease, particularly in

TABLE 3. CLINICAL AND MICROBIOLOGIC CRITERIA FOR DIAGNOSING NONTUBERCULOUS MYCOBACTERIAL LUNG DISEASE*

Clinical (both required)

1. Pulmonary symptoms, nodular or cavitary opacities on chest radiograph, or a high-resolution computed tomography scan that shows multifocal bronchiectasis with multiple small nodules (A, I)*

and

2. Appropriate exclusion of other diagnoses (A, I)

Microbiologic

1. Positive culture results from at least two separate expectorated sputum samples (A, II). If the results from (1) are nondiagnostic, consider repeat sputum AFB smears and cultures (C, III).

or

2. Positive culture result from at least one bronchial wash or lavage (C, III)

or

3. Transbronchial or other lung biopsy with mycobacterial histopathologic features (granulomatous inflammation or AFB) and positive culture for NTM or biopsy showing mycobacterial histopathologic features (granulomatous inflammation or AFB) and one or more sputum or bronchial washings that are culture positive for NTM (A, II)
4. Expert consultation should be obtained when NTM are recovered that are either infrequently encountered or that usually represent environmental contamination (C, III)
5. Patients who are suspected of having NTM lung disease but do not meet the diagnostic criteria should be followed until the diagnosis is firmly established or excluded (C, III)
6. Making the diagnosis of NTM lung disease does not, *per se*, necessitate the institution of therapy, which is a decision based on potential risks and benefits of therapy for individual patients (C, III)

* For evidence quality, *see* Table 1.

patients with chronic respiratory disease (18, 19, 84). This condition has been referred to as "colonization," and was described most often with MAC. The concept of airway colonization by NTM has never been tested rigorously. There is not enough known about the pathophysiology of NTM lung disease to be sure that colonization is not, in fact, indolent or slowly progressive infection. No pathologic studies have been done to demonstrate the absence of tissue invasion, and more recent studies with HRCT have shown that these patients often have a combination of multifocal bronchiectasis and nodular parenchymal disease now believed to be due to mycobacterial disease (90–94). Colonization without infection (i.e., no tissue invasion) is an unproven condition for NTM. Given the generally slow progression of NTM lung disease, it is incumbent on the clinician to collect enough respiratory specimens for AFB analysis and to follow patients for an adequate period of time for confirmation or refutation of the diagnosis of NTM lung disease. If the diagnosis remains in question, the patient should remain under observation and expert consultation sought.

Because NTM can be isolated due to environmental contamination, including contamination of clinical specimens, in general more than one culture-positive specimen for NTM is necessary for diagnostic purposes. The exception, outlined in the diagnostic guidelines above, is the patient with classic symptoms and radiographic findings for nodular/bronchiectatic NTM lung disease who is unable to produce sputum for AFB analysis. For this specific type of patient, the isolation of NTM, especially MAC, from one bronchoscopic specimen is considered adequate for the diagnosis of NTM lung disease. For most NTM other than MAC, expert consultation would be required to determine the significance of NTM isolated from a single bronchoscopic specimen. The significance of a single sputum specimen culture positive for a nontuberculous mycobacterium is more uncertain. In a study of 118 men in a gold-mining workforce in South Africa from whom NTM were isolated, only 27% met the ATS case definitions for pulmonary NTM disease (2, 101). This patient population had a high incidence of TB and HIV infection; therefore, most patients (70%) were started on empiric anti-TB therapy before species identification of the mycobacterial isolate. *M. kansasii*, which is susceptible to anti-TB drugs, was the most common NTM species isolated. For many patients, therefore, follow-up (confirmatory) respiratory AFB specimens had negative results. The authors concluded that (1997) ATS case definitions were difficult to apply in their high-risk study population. For selected patients, therefore, treatment decisions can be guided by the pathogenic potential of NTM isolates, especially a virulent NTM species such as *M. kansasii*, even if multiple specimens are not positive or available. Expert consultation may be helpful for making this decision. In most circumstances and for most NTM respiratory isolates, however, one positive culture is not adequate for making a diagnosis of NTM lung disease.

Conversely, there may also be circumstances where patients meet diagnostic criteria for NTM lung disease but do not, in fact, have progressive disease or sufficiently severe disease to warrant therapy. Such a circumstance could arise with the repeated isolation of low-virulence NTM, such as *M. fortuitum*, or NTM usually associated with specimen contamination (*see* Table 2). These patients require careful clinical evaluation and collection of multiple specimens for AFB analysis over time and, sometimes, more invasive diagnostic procedures. A strength of the diagnostic guidelines is the emphasis on longitudinal patient follow-up, an opportunity provided by the generally indolent nature of NTM disease. Most diagnostic uncertainty can be overcome with this approach, including determining the significance of the recovery of relatively less virulent NTM species (e.g., *M. fortuitum*), and NTM species that are usually contaminants (*M. gordonae* and *M. terrae* complex). This determination may also require expert consultation.

The interpretation of NTM in the sputum of HIV-infected patients presents a particular problem. In general, for patients with abnormal chest radiographs, the diagnostic criteria recommended for immunocompetent hosts are still applicable, with an emphasis on the exclusion of other possible pulmonary pathogens. In the absence of radiographic evidence of pulmonary disease, respiratory isolates of NTM in HIV-seropositive persons may be due to disseminated NTM disease or can be a harbinger of disseminated disease or represent transient infection (102). In addition, some NTM species that are generally considered nonpathogenic have been associated with pulmonary disease in the HIV-infected host. Given these considerations, the diagnosis of lung disease caused by NTM is usually not difficult if a combination of clinical, radiographic, and bacteriologic criteria is used.

Last, there are clinical problems not directly addressed by these diagnostic guidelines. For instance, the significance of an

NTM isolated from a patient during therapy for pulmonary TB is uncertain. The significance of two NTM species isolated simultaneously from a patient is also unknown. The combination of MAC and *M. abscessus* is especially well recognized. Unfortunately, there is not sufficient information to answer these issues broadly so that patients in these circumstances must be approached on an individual basis. Both these events are likely to occur with increased frequency because of improved recovery of NTM by mycobacteriology laboratories. Patients who present with these clinical scenarios must be evaluated carefully, on an individual basis, and may require expert consultation.

Cystic Fibrosis

Epidemiology. Before 1990, NTM were uncommonly associated with CF (103). Since that time, multiple centers across the United States and in Europe have reported a prevalence of NTM in respiratory specimens ranging from 4 to 20% in the CF population screened. In a recent large cross-sectional assessment of NTM prevalence in the United States, three respiratory specimens were systematically collected over the course of a year from approximately 1,000 subjects aged 10 years and older from 21 geographically dispersed CF centers (12). NTM were recovered from at least one of these specimens in 13% of the subjects. Most of these had a single positive culture (70%), but 16% had two and 13% had three positive cultures. Smear results were positive in 26% of culture-positive specimens. The most common species recovered were MAC (76%) and *M. abscessus* (18%), with a few subjects (4%) having both species. The prevalence of NTM seems to be highly correlated with age, approaching 40% in patients older than 40 years (12), although pediatric patients have a higher proportion of *M. abscessus* and are more likely to meet the ATS microbiologic criteria for disease (104, 105).

Pathophysiology. The reasons for the high prevalence of NTM in patients with CF are not clear. The underlying structural airway disease and altered mucociliary clearance may be predisposing factors. A similar prevalence of NTM has been described in primary ciliary dyskinesia, also characterized by bronchiectasis and altered mucociliary clearance (106). An increased prevalence of mutations in the CF gene (CF transmembrane conductance regulator [CFTR]) has been noted in elderly persons with NTM and nodular bronchiectatic lung disease, suggesting a possible role of CFTR in predisposing to NTM infection (33–35). The transmissibility of other pathogens between patients with CF, such as *Burkholderia cepacia*, and the frequent aggregation of patients on hospital wards for prolonged periods of time raise questions about person-to-person transfer or nosocomial acquisition from institutional water supplies. Two single-center and a large multicenter study using molecular epidemiologic techniques have failed to show any evidence of person-to-person transfer (12, 104, 107). Similarities in frequency of clinic visits, days hospitalized, and aerosol inhalational device use among patients with CF with and without positive cultures suggest no greater exposure to medical water reservoirs among NTM-positive patients with CF (12, 104). Although not likely common sources of acquisition, institutional water reservoirs remain potential sources of concern as was noted in a recent study of an *M. simiae* outbreak, which included a patient with CF with multiple smear-positive isolates (108).

Diagnosis. In general, the diagnostic criteria for NTM lung disease listed earlier in this statement are applicable for patients with CF as well. However, diagnosing disease caused by these organisms can be quite difficult due to overlapping symptoms and radiographic changes attributable to the underlying CF. It can be difficult to exclude other causes given the frequent presence of other organisms such as *P. aeruginosa* and *Staphylococcus aureus*, which are associated with similar clinical disease. Although there is overlap, the findings on HRCT scans associated with nodular bronchiectatic disease may be distinguishable from background findings of CF (29, 92, 109, 110) (*see* online supplement).

Treatment. Although the majority of patients with CF from whom NTM are recovered will likely not meet microbiologic criteria for disease at the time of an initial positive culture, close surveillance of these patients is warranted. There have been numerous reports of clinical deterioration and death temporally associated with persistent recovery of these organisms, particularly heavy growth of *M. abscessus* from lower respiratory specimens (111–120). It is important that nonmycobacterial pathogens be maximally treated before initiating specific antimycobacterial treatment, given the overlapping spectrum of antimycobacterial drugs for common CF pathogens, to facilitate assessment of the clinical response to antimycobacterial treatment. Assessment of the effect of NTM treatment on clinical parameters like FEV_1 may be further confounded by the possible immunomodulatory effect of the macrolides in CF (121). A potential consequence of the broad adoption of the low-dose and long-term azithromycin therapy in patients with CF is the evolution of macrolide-resistant NTM. A careful evaluation for possible pulmonary NTM infection, including multiple sputum cultures for NTM, should precede any initiation of macrolide monotherapy, and cultures for NTM should be obtained periodically thereafter. Obtaining an HRCT scan of the chest and serial measures of lung function, weight, and other clinical measures before initiating specific antimycobacterial treatment may be helpful in the subsequent assessment of treatment response. Erratic absorption of oral drugs in patients with CF with pancreatic insufficiency and possible drug–drug interactions may affect the levels of these drugs in respiratory secretions (122).

Surgical management of NTM disease in the setting of CF may be associated with an increased risk of mortality. Surgical resection, lobectomy or pneumonectomy, should be reserved for those who have an FEV_1 greater than 30% predicted and have severe, symptomatic, localized disease that fails to respond to aggressive medical therapy (123–125). A recent study of NTM recovered from patients with CF pre- and post-transplantation found a strong correlation between presence of NTM pretransplant and recovery post-transplant. However, NTM disease post-transplant was relatively uncommon, and mortality in patients with NTM disease post-transplant was not different from those without NTM disease (105). Poor control of the mycobacterial infection with medical management and, particularly, isolation of *M. abscessus* pretransplant may be risk factors for development of post-transplant NTM disease (105, 126, 127). If the disease is manageable with medical therapy pretransplant, the risk and impact of NTM recovery post-transplant may be less of a concern (105, 116, 128–130).

***Recommendations*:**

1. Adult and adolescent patients with CF should have periodic, at least yearly, screening cultures for NTM. During periods of clinical decline while unresponsive to treatment for non–NTM pathogens, all patients with CF, including children, should be evaluated for NTM (A, II).
2. Patients being considered for macrolide monotherapy as immunotherapy for CF should have sputum cultured for NTM before starting therapy and periodically thereafter, and those with repeated isolation of NTM should not receive macrolide monotherapy (C, III).
3. The diagnostic criteria and treatment regimens for NTM pulmonary infection in patients with CF are the same as for

patients without CF, although they may be more difficult to apply because of underlying disease and concomitant infections (C, III).

Hypersensitivity-like Disease

An NTM pulmonary disease syndrome with a presentation similar to hypersensitivity lung disease has recently been recognized. This syndrome has previously been termed "hot tub lung." Although debated, there appear to be components of both lung inflammation and infection leading to unique features that differ distinctly from other NTM lung diseases (131–138). It is unclear as to whether the MAC antigens are solely responsible for host response or whether there are other hot-tub cofactors (organic or inorganic) or host predispositions that may be contributing to the disease process. In this discussion, the term "hot tub" refers to any indoor, chronically undrained spa, usually including an aeration system. Although described primarily with standing-water sources, this syndrome has been reported in at least one case associated with a household shower (137). Because of the potential for acquiring this disorder from multiple sources, it will be referred to generally as hypersensitivity-like disease.

Epidemiology. MAC exposure associated with hot-tub lung represents a commonly recognized form of hypersensitivity-like NTM pulmonary disease. NTM other than MAC also have the potential to result in hypersensitivity-like lung disease associated with hot tubs. MAC, like other mycobacterial organisms, has a predisposition for growth in indoor hot tubs (139–141). Mycobacteria are relatively resistant to disinfectants and may be able to grow in a wide range of temperatures (especially high temperatures). In addition, mycobacteria are also quite resistant to agents used for disinfection, including quaternary ammonium compounds, phenolics, iodophors, and glutaraldehyde. Disinfection of swimming pools, therapy pools, and spas or hot tubs with chlorine would be expected to kill nonmycobacterial flora and therefore could permit the growth of mycobacteria in the absence of competitors for nutrients. Also contributing to the increased NTM growth is a lack of adherence to the manufacturer's recommended specifications regarding cleaning and maintenance. Patients often enter the hot tub before bathing, adding contamination. Interestingly, patients will often spend additional time in the hot tub once respiratory symptoms begin, desiring additional therapeutic relief, only to result in a more intense pulmonary response.

A syndrome similar to hypersensitivity-like pneumonitis associated with NTM may also be associated with occupational exposures to metalworking fluids (142, 143). Mycobacteria grow in the organic compounds in these Avids, including the paraffins, pine oils, and polycyclic aromatic hydrocarbons (144). Mycobacteria are also resistant to the heavy metals in metalworking fluids (145). Exposure to these aerosols leads to hypersensitivity-like pneumonitis similar to that seen with hot-tub exposure but associated almost exclusively with *M. immunogenum*, a rapidly growing mycobacterium (142, 143). Despite disinfection with multiple agents, *M. immunogenum* has been recovered from metalworking fluid and is associated with recurrence of hypersensitivity-like pneumonitis (142, 146–148). This observation suggests that *M. immunogenum* is resistant to most of the biocides used for routine disinfection of the metalworking fluids. Notably, however, *M. immunogenum* has not been recovered from the lungs of affected workers. It is not clearly established that *M. immunogenum* is the causative agent for hypersensitivity-like disease in this setting or that this syndrome is identical to hypersensitivity-like disease associated with hot tubs.

Diagnosis. The distinctive MAC hypersensitivity-like lung presentation has been compared with other groups of MAC-associated pulmonary disease. Patients are usually younger than individuals with MAC- or other NTM-associated pulmonary disease (131). Symptom onset is subacute. Dyspnea, cough, and fever are the most common symptoms. Occasionally, hypoxemic respiratory failure requires hospitalization or intensive care unit admission. Patients are usually nonsmokers, similar to patients with other forms of hypersensitivity pneumonitis. Although still unreported, chronic forms of NTM hypersensitivity-like lung disease may be possible.

Microbiologic data are critical for the diagnosis of MAC hypersensitivity-like lung disease, but not in isolation nor without clinical, radiographic, or pathologic findings consistent with MAC hypersensitivity-like disease. Cultures when obtained from sputum, bronchial wash, bronchoalveolar lavage, tissue biopsy, and hot-tub water demonstrate MAC isolates. Identical matching of these MAC isolates from hot-tub water and cultures from patient specimens have been demonstrated when analyzed by PFGE of genomic DNA or multilocus enzyme electrophoresis. The histopathology is that of nonnecrotizing granulomas although necrotizing granulomas, organizing pneumonia, or interstitial pneumonia may also be described in some patients (149). The distribution of these discrete granulomas is generally centrilobular and bronchiocentric, differentiating MAC hypersensitivity-like lung from sarcoidosis or other hypersensitivity pneumonitis. The histopathology alone is not sufficiently distinctive to allow the diagnosis of hypersensitivity-like disease without visualization of the organism or culture of a nontuberculous mycobacterium. Even if nonspecific, identifying characteristic histopathology on biopsy may be sufficient to raise suspicion for diagnosis.

Chest radiographs and chest CT scans are abnormal in all cases (*see* online supplement). Findings include diffuse infiltrates with prominent nodularity throughout all lung fields. In addition, ground glass opacities are often present on HRCT chest scans as well as a mosaic pattern. Pulmonary function testing demonstrates mixed abnormalities. Blood tests are not sufficiently specific to be of diagnostic value.

Establishing a diagnosis of MAC hypersensitivity-like disease is quite similar to establishing a diagnosis of other NTM pulmonary disease. Key elements to a diagnosis are a compatible clinical history (including a hot-tub exposure), microbiology, radiographic studies, and histopathology, when available. Even without pathology, a diagnosis of MAC-associated hypersensitivity-like lung disease can be established by the following: subacute onset of respiratory symptoms; hot-tub exposure; characteristic radiographic findings; and MAC isolates in sputum, bronchoalveolar lavage, tissue, and hot-tub water.

Treatment. The treatment of MAC hypersensitivity-like disease speaks to the controversy of whether this is an inflammatory process, infectious process, or a combination of inflammation and infection. There are no substantive data on which to base specific treatment recommendations; therefore, recommendations are based on expert opinion. In addition to the requirement of removing the patient from the inciting exposure of the MAC antigen source (contaminated hot tub), the use of antimycobacterial therapy, corticosteroids, or a combination of both or neither is debated. Corticosteroids may hasten recovery and improve gas exchange. In contrast to other forms of MAC pulmonary disease, antimycobacterial therapy may be effectively given for a shorter period of time (i.e., 3 to 6 mo), provided that symptoms resolve, sputum clears, and chest radiographs improve. Not all MAC hypersensitivity-like disease needs treatment with antimycobacterial therapy. Prognosis can generally expected to be good, even without antimycobacterial therapy (448).

For prevention of hypersensitivity-like disease, following manufacturers' recommendations of regular maintenance procedures for hot tubs is recommended. Bathing before hot-tub use

is also universally recommended. For those patients with documented MAC hypersensitivity-like disease, avoidance of MAC antigen is believed to be paramount. Although the use of corticosteroids and antimicrobials remains controversial, there is expert consensus that patients should completely avoid reexposure to indoor hot tubs. At a minimum, an indoor hot tub in a patient's home should be placed outdoors. Some experts advocate complete removal of the hot tub from the patient's premises.

Similarly, for metal grinders, avoidance of mycobacterial (*M. immunogenum*) antigen is the basis of therapy. Corticosteroid administration may also be associated with clinical improvement. *M. immunogenum* is resistant *in vitro* to all but a few antimicrobial agents and the role of antibiotic therapy is not established.

***Context*:**

1. Currently, there are no known methods for eliminating NTM from a standing indoor water source or industrial metalworking fluids.
2. The optimal therapy for hypersensitivity-like pneumonitis–related MAC and hypersensitivity pneumonitis–related *M. immunogenum* lung disease is unknown.

***Recommendations*:**

1. For indoor pools and hot tubs, manufacturers universally recommend following regular maintenance procedures (including draining and thorough cleaning of the tub and filtering system) and bathing before hot-tub use (C, III).
2. For any patient with documented hypersensitivity pneumonitis (hot-tub lung)–related disease, complete avoidance of mycobacterial antigen is paramount. For hot-tub lung, avoidance of MAC antigen, including avoidance of indoor hot-tub use, and for metal grinders, avoidance of *M. immunogenum* antigen, including avoidance of metalworking fluid, is recommended (A, II).
3. Patients with severe disease or respiratory failure should receive prednisone at 1 to 2 mg/kg/day tapered over 4 to 8 weeks (C, III).
4. For immunocompromised patients, patients with persistent disease after removal from MAC antigen exposure (with or without corticosteroids), or patients with bronchiectasis, begin antimicrobial drugs with activity against MAC as recommended elsewhere in this document, with consideration given to shorter (3–6 mo) duration of therapy (C, III).

Transplant Recipients

Infection with NTM has occurred with varying frequency in hematopoetic stem cell transplant recipients; however, a recent series suggests that the rate may be increasing. In a series of 571 patients, approximately 3% had NTM infection with pulmonary infection as the most common site (150). Pulmonary infection with NTM is uncommon in transplant recipients of solid organs other than lung. Among lung transplant recipients, NTM may be more common than *M. tuberculosis* as a cause of pulmonary infection. The organisms that are most likely encountered are MAC and *M. kansasii* (151–153). Pulmonary infection tends to occur late in the post-transplantation course and has been frequently associated with preexistent chronic rejection (130).

Disseminated Disease

Epidemiology. Disseminated disease due to NTM is among the most common and severe infections in persons with advanced HIV infection. Although a number of different species of NTM have been reported, the overwhelming majority (> 90%) of these infections are caused by MAC, with more than 90% of these infections due to *M. avium* (20, 154–159). Although MAC and *M. kansasii* isolates are reported most frequently from the southeastern United States, disseminated NTM occur with similar rates in all geographic regions and in all HIV risk groups, likely reflecting the degree of vulnerability to NTM infection in this population (22, 159). The mechanism of acquisition of the organism in persons with HIV is not known, although it is assumed to be through ingestion of the organism from an environmental source. Patients who have colonization of their respiratory and gastrointestinal tracts are at higher risk of developing disseminated disease (102). Of the infections caused by other organisms, *M. kansasii* has been reported most frequently; however, other NTM, including *M. scrofulaceum*, *M. gordonae*, *M. haemophilum*, *M. genavense*, *M. celatum*, *M. conspicuum*, *M. xenopi*, *M. fortuitum*, *M. marinum*, *M. malmoense*, and *M. simiae*, have also been described as a cause of pulmonary or disseminated NTM disease in AIDS (20, 160–169).

Disseminated disease due to NTM in persons with HIV infections occurs only in patients who are severely immunocompromised, as evidenced by very low $CD4^+$ T-cell counts (20, 154–157). Natural history studies of persons with AIDS in the pre–antiretroviral therapy era, showed that almost 40% of patients with less than 10 $CD4^+$ T cells/μl developed disseminated NTM within 1 year (156). In series of patients with confirmed disseminated NTM, the average $CD4^+$ T-cell count at presentation has usually been less than 25 cells/μl (156, 157). All persons with less than 50 $CD4^+$ T cells/μl are at risk of disseminated NTM, with the risk increasing with progressively lower numbers of cells. Disseminated disease due to MAC has also been shown to be polyclonal in some patients (170). It is currently unknown why some NTM pathogens rarely cause disseminated disease in this setting. For instance, *M. abscessus* causes lung disease in similar clinical settings to MAC, but is not associated with disseminated infection in patients with AIDS. Similarly, *M. intracellulare* is responsible for most MAC lung disease in the United States, but *M. avium* is responsible for most disseminated MAC in patients with AIDS.

Disseminated NTM disease is very rare with any form of immunosuppression other than advanced HIV disease. However, dissemination of NTM in adult patients without AIDS has been reported in immunosuppressed patients with renal or cardiac transplantation, chronic corticosteroid use, and leukemia. The RGM species *M. chelonae* and *M. abscessus* are most commonly involved, but other species, including MAC, *M. kansasii*, and *M. haemophilum*, have been reported to cause disease in this setting (87, 160, 171–178). As noted in Pathogenesis, rare genetic disorders may also be associated with disseminated NTM infection.

Clinical presentation. In patients with advanced HIV infection, the clinical manifestations of disseminated NTM are protean, and may be confused with a number of other infections. Classic complaints in persons with disseminated MAC are fever (> 80%), night sweats (> 35%), and weight loss (> 25%) (156). In addition, many patients with MAC develop abdominal pain or diarrhea. Physical findings in patients with MAC are nonspecific, and may include abdominal tenderness or hepatosplenomegaly, although palpable lymphadenopathy is not common. Laboratory abnormalities may include severe anemia, with a hematocrit of less than 25%, an elevated alkaline phosphatase, and an eleveated lactate dehydrogenase (20, 157, 179). The physical and laboratory abnormalities associated with MAC tend to occur within 1 to 2 months before the onset of bacteremia with the organism (180).

For patients without AIDS and disseminated NTM infection, the disease caused by MAC usually presents as a fever of unknown origin, whereas disease caused by *M. kansasii*, *M. chelonae*, *M. abscessus*, and *M. haemophilum* generally presents as

multiple subcutaneous nodules or abscesses that may spontaneously drain (88, 160, 171, 174–177).

Autopsy studies have demonstrated that patients with AIDS and disseminated MAC have involvement of most internal organs, even if localizing signs and symptoms are not apparent (171). Clinical involvement of the lungs is not common in patients with AIDS. In one series of 200 patients with documented disseminated MAC, only 5 patients (2.5%) were found to have concomitant pulmonary disease due to MAC (181). MAC has occasionally been reported as a cause of pulmonary infection in HIV-infected patients without evidence of dissemination (182). Although MAC is not a frequent cause of pulmonary parenchymal disease, it is commonly isolated from the respiratory tract in HIV-infected patients. In a natural history study of patients with fewer than 50 $CD4^+$ T cells/μl, approximately 10% had MAC isolated from a respiratory sample at some time during follow-up (102). In this study, of those with MAC in the sputum, none had active pulmonary disease, although a high percentage of these persons eventually developed disseminated infection with MAC. Therefore, the finding of MAC in a respiratory sample should alert the clinician to investigate for disseminated disease and to consider preventive therapy. Prospective screening of respiratory samples is, however, not recommended.

In addition to the natural clinical presentation of MAC in persons with AIDS, as described above, persons who have initiated antiretroviral therapy may develop an "immune reconstitution syndrome" or "paradoxical reaction" due to MAC (183–186). These labels describe the reaction of patients who have recently started highly active therapy for HIV infection and then develop local inflammatory symptoms related to their underlying MAC infection. Suppurative lymphadenopathy, with swollen and painful cervical, axillary, or inguinal nodes, is the most common manifestation of this syndrome. Other manifestations may include pulmonary infiltrates, soft tissue abscesses, or skin lesions. Patients frequently have fever but do not have the other components of the syndrome seen in patients with MAC bacteremia.

The method of diagnosis of disseminated MAC is usually noninvasive, with over 90% of persons diagnosed with disseminated MAC having positive blood cultures. For asymptomatic persons with low $CD4^+$ T-cell counts, routine cultures are not recommended. For symptomatic patients with two negative blood cultures, biopsy and culture of bone marrow or liver are sometimes indicated. For persons with lymphadenopathy, excision of a readily accessible node for histopathology and culture is frequently indicated, because most of these persons do not have bacteremia. Patients with intrathoracic, intraabdominal, or retroperitoneal adenopathy may require fine needle aspiration of the involved lymph nodes for diagnosis.

Lymphatic Disease

Epidemiology. The most common form of NTM disease in children is cervical adenitis (187). Infection of the submandibular, submaxillary, cervical, or preauricular lymph nodes in children between 1 and 5 years old is the most common presentation of NTM lymphadenitis (187–191). In the absence of HIV infection, NTM lymphadenitis rarely affects adults. Cases of cervical adenitis are most common at the same time that antibody to LAM is increasing rapidly in the population. These findings may reflect that children at this age are likely to have frequent contact with NTM sources such as soil and water. Adults with positive skin tests to NTM antigens have probably acquired asymptomatic infection during these childhood years. Rates of MAC cervical adenitis began to increase sharply in the United States in the late 1970s (189). No risk factors predisposing to cervical lymphadenitis in children have been identified, but children with bacille Calmette-Guérin immunization have a reduced risk of MAC cervical adenitis (192, 193).

Currently, approximately 80% of culture-proven cases of NTM lymphadenitis are due to MAC (189). In the United States and Australia, the remaining cases are caused by *M. scrofulaceum,* whereas in Scandinavia, the United Kingdom, and other areas of northern Europe, *M. malmoense* and *M. haemophilum* have emerged as major pathogens after MAC (194–197). The predominance of MAC is a change from 30 years ago, when most geographic areas reported *M. scrofulaceum* as the most common etiologic agent (187, 189). It has been speculated that tap water was the source of *M. scrofulaceum*, and the widespread use of chlorination resulted in disappearance of this species that is relatively chlorine sensitive, compared with other NTM species.

Clinical presentation. The disease occurs insidiously, and is rarely associated with systemic symptoms. The involved lymph nodes are generally unilateral (95%) and not tender. The nodes may enlarge rapidly, and even rupture, with formation of sinus tracts that result in prolonged local drainage. Other nodal groups outside of the head and neck may be involved occasionally, including mediastinal nodes (189). Contrast-enhanced axial CT of NTM lymphadenitis typically shows asymmetric adenopathy with ring-enhancing masses that may involve the fat and skin but with minimal inflammatory stranding of the subcutaneous fat (191).

The most important alternative diagnosis is tuberculous lymphadenitis. In the United States, only about 10% of the culture-proven mycobacterial cervical lymphadenitis in children has been reported to be due to *M. tuberculosis* (189). In contrast, in adults, more than 90% of the culture-proven mycobacterial lymphadenitis is due to *M. tuberculosis* (2). Distinguishing tuberculous from NTM lymphadenitis is critical, because the former not only requires drug therapy but public health tracking as well. With NTM lymphadenitis, there is typically no history of exposure to TB, screening tuberculin PPD skin tests of family members are usually negative, and the chest radiograph is normal. Although the results are not diagnostic, all patients, children and adults, with suspected mycobacterial lymphadenitis should have a tuberculin skin test. Children with NTM lymphadenitis tested with intermediate strength (5 tuberculin unit) PPD tuberculin have a range of reactions from negative to positive; up to one-third in one series showed reactions of 10 mm or more of induration (198). No commercial NTM skin test material is currently available for clinical use in the United States.

Diagnosis. The utility of fine needle aspiration for obtaining diagnostic material is variable (199–201). However, granulomata or other compatible cytopathology, such as a mixture of degenerating granulocytes, lymphocytes, and epithelioid histiocytes, is seen in most cases.

The presumptive diagnosis of NTM lymphadenitis is based on the histopathologic appearance of the lymph node showing caseating granulomata with or without AFB and, in the majority of cases, a negative tuberculin skin test. Failure of the lymph node culture to yield *M. tuberculosis* provides stronger presumptive evidence for the diagnosis of NTM lymphadenitis.

A definite diagnosis of NTM lymphadenitis is made by recovery of the causative organism from lymph node cultures. Fine needle aspiration biopsy or incision and drainage of the involved lymph nodes, without complete surgical excision of the involved nodes, may be followed by formation of fistulae with chronic drainage (188). Excisional biopsy is also sometimes used. One cautionary note must be stressed: excisional biopsy of preauricular lymph nodes entails a significant risk of injury to the facial nerve. Even with excised nodes showing compatible histopathology, only 50 to 82% will yield positive cultures (188, 189). Some

of these cases with smear-positive, culture-negative results may be due to fastidious species such as *M. haemophilum* or *M. genavense* (162, 202). Therefore, culture of suspected NTM lymphadenitis should include procedures to isolate these fastidious species (*see* LABORATORY PROCEDURES).

Treatment. Treatment recommendations for NTM lymphadenitis are outlined in discussions of individual NTM species. The guiding principle for most localized NTM lymphadenitis that occurs in immunocompetent patients, due to any NTM species, is complete surgical excision of the involved lymph nodes.

Skin, Soft Tissue, and Bone Disease

Epidemiology. The NTM species that most commonly cause localized infections of the skin and subcutaneous tissue are *M. fortuitum*, *M. abscessus*, *M. chelonae*, *M. marinum*, and *M. ulcerans* (88, 173, 203). However, virtually all species of NTM have been described as a cause of cutaneous disease (87, 88, 203).

Clinical presentation. Examples of NTM skin lesions can be viewed in the online supplement. Localized drainage or abscess formation at the site of puncture wounds (such as occurs after stepping on a nail) or open traumatic injuries or fractures are most often due to the RGM species *M. fortuitum*, *M. abscessus*, or *M. chelonae* (173). Nosocomial skin and soft tissue infections caused by these three species are also seen (83, 173, 204–213). These include infections of long-term intravenous or peritoneal catheters, postinjection abscesses, infections after liposuction, or surgical wound infections of the skin after augmentation mammaplasty, infections after cardiac bypass surgery or corneal infections after laser *in situ* keratomileusis (LASIK) (173, 204, 209, 211, 214–217). Diagnosis is made by culture of the specific pathogen from drainage material or tissue biopsy. Tissue biopsy is the most sensitive means of obtaining a specimen for culture.

Chronic granulomatous infection caused by NTM may develop in tendon sheaths, bursae, joints, and bones after direct inoculation of the organisms through accidental traumas, surgical incisions, puncture wounds, or injections including intraarticular or bursal steroids. *M. marinum* and MAC are particularly prone to causing tenosynovitis of the hand, although *M. fortuitum*, *M. abscessus*, *M. chelonae*, and *M. kansasii* have also been implicated (87, 203, 218, 219). *M. terrae* complex (especially *M. nonchromogenicum*) has also been isolated from synovial tissue of the hand or wrist, and it tends to be associated with an indolent, chronic type of disease. NTM osteomyelitis after blunt trauma has been noted in one series of patients (220). Occasionally, axial bones and extremities have been infected without apparent trauma, presumably due to hematogenous infection. After open heart surgery, osteomyelitis of the sternum caused by *M. abscessus* or *M. fortuitum* has been described, with both epidemic and sporadic disease (204, 205, 209, 216).

Health Care– and Hygiene-associated Disease and Disease Prevention

Previous NTM statements did not specifically address NTM disease prevention. Because NTM are ubiquitous in the environment and many questions about NTM disease acquisition and pathophysiology remain unanswered, it has been difficult to devise practical and effective strategies for avoidance of disease caused by NTM. Knowledge in these areas is gradually emerging, however, and enough has been learned to begin a realistic discussion of NTM disease prevention. An expansive or all-encompassing discussion of disease prevention still awaits better understanding and identification of the reservoir(s) responsible for most NTM diseases (especially lung disease), factors associated with disease transmission, and host susceptibility risks. The two major areas where NTM disease prevention is currently most relevant are, not coincidentally, two areas in which the source of the organism is clear: health care–associated transmission of skin and soft tissue disease and hypersensitivity lung disease from indoor standing-water sources.

In the past two decades, multiple single cases of NTM disease as well as health care–associated outbreaks (multiple or recurrent NTM infections associated with a single facility or procedure) and pseudo-outbreaks (presumed outbreaks due to false-positive NTM cultures) have been described. Investigations of health care–associated outbreaks or pseudo-outbreaks caused by NTM, including the use of chromosomal DNA fingerprinting with PFGE, have demonstrated that tap water, ice prepared from tap water, processed tap water used for dialysis, and distilled water used for preparing solutions such as gentian violet are the usual sources of the organisms involved (83, 209–211, 213, 206, 212, 221, 222). NTM have been found in municipal water supplies or treated water supplies from 95 of 115 (83%) dialysis centers throughout the United States (223). In a study of potable water supplies in Los Angeles, California, MAC isolates were recovered from 42 of 108 (32%) tested locations, which included homes, hospitals, commercial buildings, and reservoirs (224). *M. kansasii*, *M. xenopi*, and *M. simiae* are recovered almost exclusively from municipal water sources and rarely, if ever, from other environmental sources (225). Several mycobacterial species, including *M. xenopi*, *M. smegmatis*, *M. simiae*, and MAC, are thermophilic and survive and grow well at 45°C. These species are capable of growing in hospital water kept at temperatures as high as 55°C. Other NTM species, including *M. kansasii*, *M. gordonae*, *M. fortuitum*, *M. chelonae*, *M. abscessus*, and *M. mucogenicum*, do not tolerate temperatures of 45°C or above and are generally found only in cold-water systems.

Biofilms, which are the filmy layer at the solid (pipe) and liquid (water) interface, are recognized as a frequent site for mycobacterial growth (226). The mycobacterial fatty acid– and wax-rich impermeable cell wall results in a hydrophobic cell surface that permits adherence to solid substrates (e.g., pipes and leaves) in aquatic environments, which results in the persistence of the mycobacteria and their resistance to being washed away in high flow rates. In one study of 50 biofilm samples within a variety of piped water systems from Germany, 90% of the sampled biofilms contained mycobacteria (226). This film appears to be present in almost all collection and piping systems and likely provides the nutritional support for the organisms.

Most of the health care–associated mycobacterial outbreaks and pseudo-outbreaks have involved RGM, especially *M. fortuitum* and *M. abscessus*. These mycobacterial species as well as others are incredibly hardy, and resist the activity of organomercurials, chlorine, 2% concentrations of formaldehyde and alkaline glutaraldehyde, and other commonly used disinfectants (225).

Health care–associated NTM outbreaks include those associated with cardiac surgery (primarily median sternotomy wounds), injections, especially with alternative care medicine (due to contaminated biologicals or multidose vials), plastic surgery, liposuction, LASIK, dialysis-related outbreaks, long-term central intravenous catheters, middle ear typanostomy tube replacement, and a variety of miscellaneous surgical procedures (83, 206, 213, 215–217, 222, 227–239). The common factor in health care–associated outbreaks is presumed to be exposure of a susceptible individual to NTM-infected liquid, usually tap water.

Recently, mycobacterial outbreaks of *M. fortuitum* and *M. mageritense* (the latter a newly described RGM) furunculosis associated with footbaths at nail salons have been reported in California and Georgia (240–243). In all of the cases, NTM were cultured from the patients and from the inlet suction screens of the whirlpool footbaths (foot spas) that contained hair and other debris. The whirlpool isolates were subsequently molecularly

identified as the same strains as those recovered from patients. In addition, for each patient, prior shaving of the legs was a major risk factor.

Sporadic infections in the health care setting have been described in the same setting as mycobacterial outbreaks, and pseudo-outbreaks. The most common health care–associated sporadic infection is catheter sepsis involving long-term central venous catheters. Surgical wound infections are most commonly seen after breast surgery (augmentation or reduction but rarely for mastectomy for breast cancer). However, they have also been reported after insertions of prosthetic devices such as (but not limited to) prosthetic heart valves, artificial knees and hips, lens implants, and metal rods inserted into the vertebrae or long bones to stabilize fractures (244, 245).

Health care–associated pseudo-outbreaks have most commonly been associated with bronchoscopy including the use of contaminated topical anesthesia, contaminated and/or malfunctioning individual bronchoscopes, contaminated terminal rinse water (tap water), and contaminated automated endoscope washers that used a terminal tap water rinse cycle (246–249). Bronchoscopy is considered a nonsterile procedure, but, from the perspective of health care–associated NTM infections, tap water is not acceptable, especially for a terminal rinse. The bronchoscope-related pseudo-outbreaks have most commonly involved RGM (especially *M. abscessus* and *M. immunogenum*) but have involved slow-growing NTM species as well (143).

Multiple nonbronchoscopic pseudo-outbreaks have also been reported and generally involve RGM and contaminated tap water solutions (liquid or ice). Sixty-five *M. simiae* isolates from 62 patients at a community teaching hospital in Houston, Texas, were recently described (250). The organism was grown in various water samples obtained in the hospital and a professional building. None of the patients from whom *M. simiae* was recovered were believed to have clinical disease and none received antimicrobial therapy. Thirty-one environmental and human outbreak–related *M. simiae* isolates had indistinguishable or closely related patterns on PFGE and were considered clonal. The reservoir for this pseudo-outbreak was identified as a contaminated hospital water supply. A similar outbreak has been described in San Antonio, Texas (108). Again, tap water was established as the organism source.

Health care–associated mycobacterial pseudo-outbreaks are problematic for a number of reasons. These include inappropriate therapy for suspected TB, the risks of drug-related adverse events, unnecessary expense incurred by the hospital and patients, the psychological stress for patients of being told they have a serious disease when in fact they do not, and the potential for medical legal complications. False-positive cultures also delay the ordering of tests to identify an alternative diagnosis.

***Recommendations*:**

1. Prevention of health care–associated NTM outbreaks and pseudo-outbreaks:
   a. Intravenous catheters: Patients with indwelling central catheters, especially bone marrow transplant recipients, should avoid contact or contamination of their catheter with tap water (B, II).
   b. Fiberoptic endoscopes: The use of tap water should be avoided in automated endoscopic washing machines as well as in manual cleaning. The instruments should have a terminal alcohol rinse. The reader should consult the "Association for Professionals in Infection Control (APIC) Guidelines for Infection Prevention and Control in Flexible Endoscopy" at www.apic.org for a detailed discussion of cleaning and disinfection of endoscopic equipment (A, II).
   c. Local injections: Avoid benzalkonium chloride (e.g., Zephiran) as a skin disinfectant as it allows growth of mycobacteria such as *M. abscessus.* Avoid use of multidose vials (A, II).
   d. Recognize and avoid the risk of alternative medicine practices that provide injections of unknown or unapproved substances (C, III).
   e. Surgery: (*1*) Do not use tap water and/or ice prepared from tap water in the operating room, especially during cardiac surgery or augmentation mammoplasty (A, II). (*2*) Do not wash or contaminate open wounds with tap water (A, II). (*3*) Outpatient facilities performing plastic surgery procedures such as liposuction or augmentation mammoplasty must carefully follow recommended sterilization guidelines (C, III).
   f. Sputum collection: Do not allow a patient to drink or rinse the mouth with tap water before collecting an expectorated specimen (C, III).
2. Recognition of outbreaks: Be familiar with the settings for health care–associated outbreaks and pseudo-outbreaks and the organisms (usually RGM) most frequently involved, and intervene as soon as possible to interrupt this transmission (C, III).

Recommendations for preventing NTM lung disease remain elusive. Identifying the environmental sources responsible for the acquisition of many NTM is very difficult. For instance, genomic typing of clinical MAC isolates reveals great heterogeneity in recovered MAC strains, perhaps due to prolonged and widespread environmental habitation by these organisms. There appear to be almost as many MAC strains as MAC isolates. This strain diversity will make identification of specific sources of MAC infection difficult. However, the fact that populations susceptible to NTM infection, such as patients with CF and postmenopausal female patients who are reinfected by NTM, raises the question, Can environmental shielding protect patients against NTM lung infection? For instance, indoor showerheads are a known source of NTM, especially MAC (137). Should patients with known or previous mycobacterial lung disease or known bronchiectasis avoid showers (or other sources of aerosolized water)? A consensus among experts has not been reached on these important questions.

Also problematic are public or hospital water systems known to be contaminated with mycobacterial species such as *M. xenopi*, *M. avium*, *M. kansasii*, and *M. simiae*. Although known for association with pseudo-outbreaks, in a susceptible host (e.g., a patient with bronchiectasis) these species can cause human disease (108). This issue is yet to be assessed or addressed by public health personnel.

NTM SPECIES: CLINICAL ASPECTS AND TREATMENT GUIDELINES

NTM species that are encountered clinically are discussed below. Because MAC and *M. kansasii* are the most frequently encountered clinically significant NTM (in the United States), they are discussed first. The remaining NTM are listed in alphabetical order by species name.

The first clue to the identity of a nontuberculous mycobacterium, after a negative result for *M. tuberculosis* from a nucleic acid amplification test, is frequently the rate of growth of the NTM isolate, especially if there is rapid growth. Because the RGM are frequently isolated under similar clinical circumstances,

members of this group of organisms are noted with the abbreviation RGM.

There are some important considerations for reviewing the following information.

***Context and General Recommendations*:**

1. NTM are uncommonly encountered clinical pathogens; some species, in fact, are much more likely to be isolated as a result of specimen contamination than as a result of disease. However, even these species can, under some circumstances, cause clinical disease. The clinician, therefore, must always know the context in which an NTM isolate was obtained to assess accurately the clinical significance of that isolate. When questions about the clinical significance of an NTM isolate arise, expert consultation is strongly encouraged (C, III).
2. Treatment recommendations for infrequently encountered NTM are made on the basis of only a few reported cases. With that limitation in mind, unless otherwise stated, the duration of therapy for most pulmonary NTM pathogens is based on treatment recommendations for more frequently encountered species such as MAC and *M. kansasii* (e.g., 12 mo of negative sputum cultures while on therapy). For disseminated disease, treatment duration for most NTM pathogens is the same as for disseminated MAC infection (C, III).
3. The treatment of NTM disease is generally not directly analogous to the treatment of TB. *In vitro* susceptibilities for many NTM do not correlate well with clinical response to antimycobacterial drugs. Recommendations for routine *in vitro* susceptibility testing of NTM isolates are limited (*see* Laboratory Procedures). The clinician should use *in vitro* susceptibility data with an appreciation for its limitations. *See* an expanded discussion of *in vitro* susceptibilities in Laboratory Procedures (B, II).
4. Empiric therapy for suspected NTM lung disease is not recommended (C, III).
5. There are no widely accepted criteria for choosing patients with NTM lung disease for resectional surgery. In general, the more difficult an NTM pathogen is to treat medically, the more likely surgery should be considered from a risk/benefit perspective. Expert consultation is strongly encouraged (C, III).

Mycobacterium avium Complex (MAC)

The organism. *M. avium* complex or MAC (also referred to as MAI) includes at least two mycobacterial species, *M. avium* and *M. intracellulare*. These two species cannot be differentiated on the basis of traditional physical and biochemical tests. There are specific DNA probes for identification of and differentiation between *M. avium* and *M. intracelluare*. *M. avium* is the more important pathogen in disseminated disease, whereas *M. intracellulare* is the more common respiratory pathogen. Currently, there is no prognostic or treatment advantage for the routine separation of MAC isolates into *M. avium* or *M. intracellulare*. However, such a separation may be important for research purposes and may have prognostic and therapeutic implications in the future.

Epidemiology. MAC organisms are common in many environmental sites, including water and soil, and in animals (17, 88). MAC has been found to colonize natural water sources, indoor water systems, pools, and hot tubs (133, 139, 251–253). MAC pulmonary disease appears to be more common in the southeastern United States than in other regions of the country, but, as noted previously, data are quite limited (22). It is generally believed that environmental sources, especially natural waters, are the reservoir for most human infections caused by MAC. Aerosols of fresh- and saltwater may contain MAC, and these have also been proposed as vehicles leading to transmission of MAC respiratory disease (140, 252). Specific sites from which patients acquire MAC are rarely identified, but exposure to recirculating hot-water systems has been identified as one route of acquisition of MAC in persons with AIDS (251, 253). Less than 15% of cases, however, can be traced to this source, suggesting that other environmental reservoirs are also important. Persons infected with MAC do not appear to be a reservoir for acquisition of the organisms by others nor is there evidence of animal-to-human transmission.

MAC lung disease. Clinical presentations. The natural history of MAC lung disease depends on which of two types of clinical disease are present. Chest radiographs and HRCT scans showing typical abnormalities of the two forms of MAC lung disease are provided in the online supplement. The traditionally recognized presentation of MAC lung disease has been as apical fibrocavitary lung disease, sometimes with large cavities, in males in their late 40s and early 50s who have a history of cigarette smoking and, frequently, excessive alcohol use (254, 255). If left untreated, this form of disease is generally progressive within a relatively short time frame, 1 to 2 years, and can result in extensive cavitary lung destruction and respiratory failure (254, 255).

MAC lung disease also presents with nodular and interstitial nodular infiltrates frequently involving the right middle lobe or lingula, predominantly in postmenopausal, nonsmoking, white females (36, 37, 90, 91, 256). MAC lung disease in this population is sometimes labeled the "Lady Windomere syndrome" (256). This form of disease, termed "nodular bronchiectasis" or "nodular bronchiectatic disease," tends to have a much slower progression than cavitary disease, such that long-term follow-up (months to years) may be necessary to demonstrate clinical or radiographic changes. Even with this more indolent form of disease, however, death may be related to disease progression (36). This form of MAC lung disease is radiographically characterized by HRCT findings that include multiple, small peripheral pulmonary nodules centered on the bronchovascular tree and cylindrical bronchiectasis. The HRCT pattern of these predominantly peripheral, small nodular densities has been termed "tree-in-bud," and reflects inflammatory changes including bronchiolitis.

In support for MAC as a pathogen in this setting, HIV-seronegative patients with clusters of small nodules in the periphery of the lung associated with ectatic changes of the draining bronchi frequently have positive respiratory cultures for MAC and granulomatous inflammation recovered by transbronchial biopsy, suggesting tissue invasion by MAC rather than airway colonization (109). In addition, culture-positive patients who received therapy directed at MAC responded with sputum conversion or radiographic improvement.

Patients with nodular/bronchiectatic MAC lung disease often have additional microbiologic findings associated with bronchiectasis, including respiratory cultures positive for *P. aeruginosa* and occasionally for other NTM such as *M. abscessus*. Nonmycobacterial exacerbations of the bronchiectasis often complicate the assessment and management of the MAC disease, and strategies aimed at bronchiectasis *per se*, such as airway clearance, may improve patients' symptoms.

It is unknown if bronchiectasis is the result of the mycobacterial infection or due to some other process and a predisposition for subsequent mycobacterial infection. The observations noted above are compatible with mycobacterial infection and granulomatous inflammation as the process causing bronchiectasis in some patients, but they do not provide proof (109). One recent

study examined excised lung tissue from patients with cavitary MAC lung disease, and also suggested that granulomatous inflammation was the etiology for the bronchiectasis (257). In some diseases such as CF or prior pulmonary TB, however, the bronchiectasis clearly antedates the MAC disease. The routine evaluation of underlying causes of bronchiectasis, such as CF and AAT deficiency, in patients with nodular/bronchiectatic MAC disease is currently primarily a research tool, with the exception of high-risk individuals. There is no consensus about the routine use of tests for these conditions in all patients with nodular bronchiectatic MAC.

Drug treatment of MAC (*M. avium, M. intracellulare*) lung disease. Medical treatment of MAC pulmonary disease in HIV-negative patients with anti-TB medications has yielded inconsistent results. The major limitations for effective therapy were the absence of antimicrobial agents with low toxicity and good *in vivo* activity against the organism. Most first-line anti-TB drugs have 10 to 100 times less *in vitro* activity against MAC isolates than against *M. tuberculosis*. In the few studies in which initial sputum conversion rates were high (> 50%), long-term follow-up to establish continued sputum conversion was usually not documented (258–261). Two studies evaluating long-term treatment response to anti-TB medications suggested an approximately 50% long-term favorable response (258, 262). Relapses after medical therapy with anti-TB treatment regimens were common, and the best outcomes were frequently in those patients who underwent resectional surgery (263, 264).

The role of *in vitro* susceptibility testing, especially for anti-TB drugs, has not been established. A recently published prospective and comparative study evaluating anti-TB medications for treatment of MAC lung disease was begun in the late 1980s in Great Britain (255). Patients received rifampin and ethambutol or rifampin, ethambutol, and isoniazid. There was no correlation between treatment response and *in vitro* susceptibility of the patient's MAC isolate to the anti-TB drugs. One study suggested that initial response to therapy in patients with MAC lung disease correlated with the number of drugs in the treatment regimen to which MAC showed *in vitro* susceptibility (265). A significant correlation between treatment response and number of drugs with *in vitro* susceptibility was not present, however, in long-term follow-up of these patients. Two more recent studies from Japan have also failed to show a correlation between *in vitro* susceptibility for rifampin, ethambutol, and streptomycin, and clinical response for MAC disease (449, 450). Important and unresolved questions about MAC and *in vitro* susceptibility testing remain, including what drug concentrations should be tested and whether evaluation of drug combinations would be more predictive than single drugs for clinical outcome.

The major therapeutic advance in the treatment of pulmonary MAC disease was the introduction of the newer macrolides, clarithromycin and azithromycin, which have substantial *in vitro* and clinical activity against MAC. Structurally, azithromycin is an azalide; however, because of the close similarity of azalides to macrolides, the term "macrolide" will be used to refer to both. Although clarithromycin MICs for MAC are in the range of peak achievable serum levels (1–4 μg/ml), perhaps the greatest potential advantage of these newer drugs is their increased concentration in phagocytes and tissues, including lung (266–268).

In the first published study of macrolide-containing regimens for MAC lung disease, clarithromycin was given in doses of 500 to 2,000 mg per day in a multicenter open trial to HIV-negative patients with MAC lung disease (269). Although limited by variable and inconsistent drug combinations, this study demonstrated a relationship between *in vitro* macrolide susceptibility and clinical response to clarithromycin monotherapy and clarithromycin-containing regimens for MAC lung disease.

In a separate prospective, noncomparative trial, patients with MAC lung disease received clarithromycin 500 mg twice daily initially as monotherapy, with companion medications (streptomycin, ethambutol, and rifabutin or rifampin) added either after 4 months of macrolide monotherapy or with conversion of sputum to AFB culture negative, whichever occurred first (270). While receiving clarithromycin monotherapy, 18 of 19 patients (95%) showed an improvement in sputum cultures, chest radiographs, or both. The development of clarithromycin-resistant MAC isolates (MICs > 32 μg /ml) was associated with microbiologic relapse. In a noncomparative trial with similar design, patients with MAC lung disease received azithromycin 600 mg/day initially as monotherapy (271). After the addition of companion drugs similar to those from the clarithromycin monotherapy trial, sputum conversion rates at 6 months were comparable between azithromycin- and clarithromycin-containing regimens (67 vs. 74%).

These studies in patients with MAC lung disease, combined with macrolide monotherapy trials for HIV-seropositive patients with disseminated MAC disease, form the basis for the assertion that macrolides are the only agents used for treatment of MAC disease for which there is a correlation between *in vitro* susceptibility and *in vivo* (clinical) response (266, 269–272). All untreated strains of MAC are macrolide susceptible (clarithromycin MICs of 0.25 of 4.0 μg/ml), whereas microbiologic relapses associated with symptom recurrence reveal isolates with MICs of 32 μg/ml or greater, with most isolates having MICs of 1,024 μg/ml or greater (273). These relapse isolates have a point mutation in the macrolide-binding region (peptidyltransferase) of the 23S rRNA gene not seen in susceptible untreated strains (52, 53). This mutation results in cross-resistance between clarithromycin and azithromycin, and presumably all other macrolides. Patients with either pulmonary or disseminated disease who have MAC isolates that are macrolide resistant do not respond favorably to standard macrolide-containing regimens (274).

In an analysis of 50 patients treated with clarithromycin-containing regimens at one center, 36 of 39 patients (92%) who completed at least 6 months of therapy had conversion of sputum to AFB culture negative with 12 months of negative sputum cultures on therapy (266). In another study, 32 patients with MAC lung disease received a daily azithromycin-containing regimen with companion drugs similar to those given in the clarithromycin study (266, 275). Seventeen of 29 patients (59%) with at least 6 months of therapy had sputum conversion with 12 months of negative sputum AFB cultures. A study from Japan evaluated the effect of a four-drug clarithromycin-based regimen in HIV-seronegative patients with MAC lung disease (276). Excluding patients infected with clarithromycin-resistant strains, the sputum conversion of patients infected with susceptible strains was 84%. Another similar study, however, failed to show a similar benefit of clarithromycin-containing regimens (277).

The results of multidrug macrolide-containing treatment trials in patients with AIDS with disseminated MAC disease confirm the superiority of macrolide-containing regimens for treating MAC in that setting as well (278, 279).

Three-times-weekly drug therapy. Intermittent therapy for MAC lung disease offers the potential advantages of lower medication costs and fewer medication side effects. Two trials of intermittent azithromycin administration for MAC lung disease have been reported (275, 280, 281). In the first trial, azithromycin was given three times weekly, whereas companion medications were given daily. In a second trial, azithromycin and all companion medications were given on a three-times-weekly basis. For patients who completed at least 6 months of therapy, 55% of patients with the first regimen and 65% of patients receiving the second (all intermittent) regimen met the treatment success

criterion of 12 months of sputum culture negativity while on therapy. The results at 6 months have been reported for one additional study with three-times-weekly clarithromycin and companion drugs (281). Of the 41 patients who completed at least 6 months of therapy, 32 (78%) had conversion of sputum to AFB culture negative. In the control arm of a recent multicenter trial of three-times-weekly macrolide-based regimens with or without inhaled interferon gamma (IFN-γ) for patients with severe and/or previously treated MAC lung disease, the success rate for sputum conversion was extremely low. Factors contributing to the poor response to therapy included cavitary disease, previous treatment for MAC lung disease, and a history of chronic obstructive lung disease or bronchiectasis (282).

Controversies and unresolved questions in the treatment of MAC lung disease. Together, the above studies form the basis for the recommendation that macrolides are the most important element in multidrug treatment regimens for MAC lung disease. Although these studies were prospective and had consistent treatment regimens, they also had significant limitations because they were mostly single-center, noncomparative studies that included small numbers of patients. Although clinical and microbiologic response rates were relatively high, many important and unresolved questions about MAC lung disease treatment have not been directly addressed by these noncomparative trials. Some of the important unresolved controversies in the management of MAC lung disease are outlined in Table 4. More detailed discussion of these controversies is provided in the online supplement.

These controversies highlight some important differences in the therapeutic approach to patients with MAC lung disease and disseminated MAC disease. First, although there is dose-dependent toxicity and intolerance of clarithromycin and azithromycin in elderly patients with MAC, there has not been demonstration of increased mortality with clarithromycin doses greater than 100 mg/day as has been demonstrated in patients with AIDS (283–285). Second, rifampin is the rifamycin of choice for most patients with MAC lung disease, whereas rifabutin is generally used in treatment regimens for disseminated MAC disease. Rifabutin is effective in multidrug MAC treatment regimens, it is generally well tolerated in the younger HIV population, and has less severe drug–drug interactions than rifampin, which is critically important with complicated antiretroviral regimens (286–289). Rifabutin also affects clarithromycin metabolism (and levels) less than rifampin; however, clarithromycin enhances rifabutin toxicity (16, 278). The critical elements, however, for choosing rifampin over rifabutin for patients with MAC lung disease are that rifabutin is much less well tolerated in older patients with MAC lung disease, even at very attenuated doses (e.g., 150 mg/d), than in younger patients (266, 270, 271, 275, 276, 290–292). In the collective experience of MAC lung disease experts, older patients with MAC lung disease do not tolerate or adhere to rifabutin-containing regimens. In addition, even though rifampin lowers clarithromycin levels more than rifabutin, there is no clear outcome advantage of rifabutin over rifampin in MAC lung disease (266, 275, 276). Based on these two considerations, rifampin is the recommended rifamycin for most patients with MAC lung disease.

Recommended drug treatment for MAC lung disease. Drug therapy for MAC disease involves multiple drugs; therefore, the risk of adverse drug reactions and/or toxicities is relatively high. In addition, the optimal therapeutic regimen has yet to be established. For these reasons, the treatment of MAC disease may be best accomplished by physicians experienced in the treatment of mycobacterial diseases. This recommendation is especially important for patients with intolerance to first-line agents, with an infection with a macrolide-resistant MAC isolate, or those who have failed prior drug therapy.

It is also clearly necessary to include companion drugs with the macrolide (albeit drugs with less activity against MAC) to prevent the emergence of macrolide-resistant MAC isolates. The macrolides should *never* be used as monotherapy for treatment of MAC lung disease.

The choice of therapeutic regimen for a specific patient depends to some degree on the goals of therapy for that patient. For instance, the most aggressive therapy (e.g., including an injectable agent) might be appropriate for patients with extensive (especially cavitary) disease, for whom microbiologic and clinical improvement is important and feasible. Less aggressive therapy might be appropriate for patients with indolent disease, especially those patients with drug intolerances and potential drug interactions. Some experts believe that because of frequent and severe adverse drug events that microbiologic cure may not be possible, especially for older, frail individuals with comorbid conditions who have difficulty tolerating multidrug MAC treatment regimens. For these patients, MAC infection can be viewed as a chronic, usually indolent, incurable disease, and less aggressive, or even suppressive, treatment strategies may be appropriate. The choice of therapeutic regimen, therefore, may be different for different patient populations. These guidelines offer a choice of several treatment options that can be selected based on the clinical presentation and needs of an individual patient.

Treatment regimen options for MAC lung disease are outlined in Table 5. The cornerstones of MAC therapy are the macrolides, clarithromycin and azithromycin, and ethambutol. These agents are then combined with companion drugs, usually a rifamycin and, possibly, an injectable aminoglycoside. Multiple combinations of these drugs are possible, frequently dictated by

TABLE 4. CONTROVERSIES AND UNRESOLVED QUESTIONS IN THE MANAGEMENT OF *MYCOBACTERIUM AVIUM* COMPLEX LUNG DISEASE

1. There have been no head-to-head comparative trials between clarithromycin- and azithromycin-containing regimens for MAC lung disease. There is, therefore no demonstrated superiority of one macrolide in the management of MAC lung disease.
2. Although frequently used in prior studies, there is no unambiguous advantage of routinely including an injectable agent (amikacin or streptomycin) early in MAC treatment regimens (266, 270, 271, 275, 276, 449).
3. There is no demonstrated superiority of one rifamycin (rifabutin or rifampin) in the treatment of MAC lung disease, but because of frequent adverse events with rifabutin, most experts recommend rifampin (266, 270, 271, 275, 276, 286–292).
4. There have not been studies evaluating two- versus three-drug regimens for the treatment of MAC lung disease, but in general, two-drug regimens are not recommended because of concern about the development of macrolide resistance (293).
5. The roles for other medications such as fluoroquinolones and clofazimine in the treatment of MAC lung disease are not established (281, 294, 295).
6. Previous unsuccessful or failed therapy for MAC lung disease, with or without a macrolide, decreases the chances for subsequent treatment success, even with macrolide-susceptible MAC isolates (266, 275, 276).
7. Some beneficial effect of macrolide-containing treatment regimens for patients with bronchiectasis could be due to immune-modulating effects of the macrolide (296).

For more detailed discussion of these controversies, *see* the online supplement.

the tolerance of the patient to specific drugs and drug combinations. Some commonly recommended regimens are described in detail below.

For most patients with nodular/bronchiectatic disease, or those with fibrocavitary disease who cannot tolerate daily therapy, or those who do not require an aggressive treatment strategy (i.e., patients for whom disease suppression is an appropriate goal), intermittent, three-times-weekly, therapy is recommended. Recommended intermittent drug dosages include (*1*) clarithromycin 1,000 mg or azithromycin 500–600 mg, (*2*) ethambutol 25 mg/kg, and (*3*) rifampin 600 mg given three times weekly.

The recommended regimen for patients with fibrocavitary disease or severe nodular/bronchiectatic disease includes (*1*) clarithromycin 1,000 mg/day (or 500 mg twice daily) or azithromycin 250 mg/day, (*2*) ethambutol 15 mg/kg/day, and (*3*) rifampin 10 mg/kg day (maximum, 600 mg/d). For many patients, the doses of clarithromycin may need to be split (e.g., 500 mg twice daily) because of gastrointestinal intolerance. Also, for patients with small body mass (< 50 kg) or older than 70 years, reducing the clarithromycin dose to 500 mg/day or 250 mg twice a day may be necessary because of gastrointestinal intolerance. Some patients who do not tolerate daily medications, even with dosage adjustment, should be tried on an intermittent treatment regimen. Parenteral drugs are an option based on disease severity and treatment response.

A more aggressive and less well tolerated treatment regimen for patients with severe and extensive (multilobar), especially fibrocavitary, disease consists of clarithromycin 1,000 mg/day (or 500 mg twice a day) or azithromycin 250 mg/day, rifabutin 150–300 mg/day or rifampin 10 mg/kg/day (maximum 600 mg/day), ethambutol (15 mg/kg/d), and consideration of inclusion of either amikacin or streptomycin for the first 2 or 3 months of therapy (*see below*). Selected patients in this disease category might be considered for surgery as well. Patients receiving clarithromycin and rifabutin should be carefully monitored for rifabutin-related toxicity, especially hematologic (leukopenia) and ocular (uveitis) toxicity.

Realistically, the dosing of medications for patients with nodular/bronchiectatic MAC disease may require some creativity and improvisation to maintain patients on multiple medications. These mostly older female patients frequently require gradual introduction of medications (i.e., one medication added to the medication regimen at 1–2 weekly intervals), to evaluate tolerance to each medication and medication dose. Starting the nodular/bronchiectatic patient on all drugs at once on full doses of each medicine frequently results in adverse drug reactions requiring cessation of all medications and alterations in drug therapy. Some experts recommend starting with the macrolide at attenuated doses, then gradually increasing the desired therapeutic dose over 1 to 2 weeks. Ethambutol and then the rifamycin are subsequently added at 1- to 2-week intervals. Once-daily dosing for MAC medications is desirable, as is recommended for anti-TB medications, but some patients will require splitting the medication dose to tolerate adequate medication doses. Patients who require even more complicated medication manipulation should have expert guidance of therapy.

Intermittent amikacin or streptomycin for the first 2 to 3 months of therapy should be considered for extensive, especially fibrocavitary, disease or patients who have failed prior drug therapy. A recent prospective comparative trial of MAC treatment regimens with or without streptomycin demonstrated better sputum conversion rates in patients receiving streptomycin (449). The collective clinical experience also supports the use of the parenteral aminoglycoside therapy in extensive or drug-refractory MAC infection. Although streptomycin has been used more in this clinical setting than amikacin, there are no data demonstrating superiority of one agent over the other. The doses of streptomycin or amikacin in MAC therapy will depend on the patient's age, weight, and renal function. Recent data suggest that patients tolerate amikacin or streptomycin at 25 mg/kg three times weekly during the initial 3 months of therapy (297). This dosage would, however, be impractical for intramuscular administration and may be difficult to tolerate for longer periods. For older patients with nodular/bronchiectatic disease or patients who require long-term parenteral therapy (e.g., 6 mo or longer), some experts recommend that a dose of 8 to 10 mg/kg two to three times weekly may be necessary, with a maximum dose of 500 mg for patients older than 50 years (2). For extensive disease, at least 2 months of intermittent (twice or three times weekly) streptomycin or amikacin is recommended, although longer parenteral aminoglycoside therapy may be desirable in patients with very extensive disease or for those who do not tolerate other agents.

Because ototoxicity and vestibular toxicity due to aminoglycosides are usually irreversible, patients who receive streptomycin or amikacin should be instructed in the signs and symptoms of toxicity (unsteady gait, tinnitus, diminished hearing) at the start of therapy and again on subsequent visits, with discontinuation or decrease in dosage or frequency if signs suggestive of toxicity occur. Baseline audiometry testing, together with repeat interval testing while receiving parenteral aminoglycoside therapy, should be performed. Some experts prefer amikacin to streptomycin due to a perceived difference in the severity of vestibular toxicity between the two drugs.

As listed in MAC treatment controversies, there have been no studies evaluating the efficacy of two-drug versus three-drug

TABLE 5. THERAPY FOR *MYCOBACTERIUM AVIUM* COMPLEX LUNG DISEASE: RECOMMENDATIONS ACCORDING TO DISEASE STATUS AND/OR SEVERITY

	Initial Therapy for Nodular/Bronchiectatic Disease*	Evidence Quality†	Initial Therapy for Cavitary Disease	Evidence Quality†	Advanced (Severe) or Previously Treated Disease	Evidence Quality†
Macrolide	Clarithromycin 1,000 mg TIW or azithromycin 500–600 mg TIW	B, II	Clarithromycin 500‡–1,000 mg/d or azithromycin 250–300 mg/d	A, II	Clarithromycin 500‡–1,000 mg/d or azithromycin 250–300 mg/d	B, II
Ethambutol	25 mg/kg TIW		15 mg/kg/d		15 mg/kg/d	
Rifamycin	Rifampin 600 mg TIW		Rifampin 450‡–600 mg/d		Rifabutin 150‡–300 mg/d or rifampin 450‡–600 mg/d	
IV aminoglycoside	None		Streptomycin or amikacin§ or none		Streptomycin or amikacin§	

Definition of abbreviations: IV = intravenous; TIW = three times weekly.

* Not recommended for severe or previously treated disease.

† Rating for entire multidrug regimen, not necessarily for individual agents. For evidence quality, *see* Table 1.

‡ Lower dose for weight < 50 kg.

§ *See* text for dosing recommendation.

regimens for MAC lung disease. There are also concerns that a two-drug regimen for patients with cavitary MAC disease might promote the emergence of macrolide-resistant MAC isolates. Overall, clarithromycin or azithromycin with ethambutol on a daily basis would be acceptable for some patients (i.e., mild disease, medication intolerance, disease suppression) with nodular/bronchiectatic MAC disease. No other two-drug regimen is recommended (*see* the online supplement).

The efficacy and methods for treating pediatric patients (e.g., those with underlying CF) with the above regimens have not been studied, nor have drug doses or serum drug levels for agents such as clarithromycin and rifabutin.

Monitoring of disease during therapy and treatment endpoint. The goals of therapy include symptomatic, radiographic, and microbiologic improvement. The primary microbiologic treatment endpoint for MAC lung disease is the conversion of sputum cultures to negative. A successful patient response to therapy should be documented by sputum cultures negative for MAC. Therefore, AFB smears and cultures of sputum should be obtained monthly during therapy for pulmonary MAC disease to assess response. Patients should show clinical improvement within 3 to 6 months and should convert their sputum to negative within 12 months on macrolide-containing regimens (266). Failure to respond in these time periods should prompt investigation for possible noncompliance (perhaps due to drug intolerance) or macrolide resistance or the presence of anatomic limitations to successful therapy (e.g., focal cystic or cavitary disease). For patients whose disease has failed to respond to a macrolide-containing regimen and who have progressive, symptomatic disease, an alternative drug regimen or surgery will be necessary. Symptomatic improvement is also important, but can be complicated by the progression or exacerbation of underlying diseases such as bronchiectasis and COPD. Similarly, although radiographic improvement is expected and desirable, radiographic assessment can be difficult both because of concomitant lung disease and limited potential for improvement of MAC-related abnormalities. The radiographic evolution of nodular/bronchiectatic MAC disease in either treated or untreated patients is not well defined.

Previous studies suggest that culture-negative status for 12 months while receiving a clarithromycin- or azithromycin-containing regimen is adequate for most patients (266–269). Recent genotyping studies support 12 months of culture-negative sputum as a reasonable treatment endpoint because new positive sputum cultures for MAC after initial sputum conversion and culture negativity for 10 to 12 months are usually due to reinfection (new MAC genotype) rather than disease relapse (51).

***Context*:**

The following recommendations are for patients with macrolide-susceptible MAC isolates.

***Recommendations*:**

1. The recommended initial regimen for most patients with nodular/bronchiectatic MAC lung disease is a three-times-weekly regimen including clarithromycin 1,000 mg or azithromycin 500 mg, ethambutol 25 mg/kg, and rifampin 600 mg administered three times per week (A, II).
2. The recommended initial regimen for fibrocavitary or severe nodular/bronchiectatic MAC lung disease includes clarithromycin 500–1,000 mg/day or azithromycin 250 mg/day, ethambutol 15 mg/kg/day, and rifampin 10 mg/kg/day (maximum, 600 mg). An initial 2 months of ethambutol at 25 mg/kg/day is no longer recommended (A, II). Alternative treatment recommendations, including the use of parenteral agents, are illustrated in Table 5 (B, II).
3. Intermittent drug therapy is not recommended for patients who have cavitary disease, patients who have been previously treated, or patients who have moderate or severe disease (C, III).
4. The primary microbiologic goal of therapy is 12 months of negative sputum cultures while on therapy; therefore, sputum must be collected from patients for AFB examination throughout treatment (A, II).
5. Macrolides should not be used as monotherapy for MAC because of the risk for developing macrolide-resistant MAC isolates (A, II).
6. A macrolide with a single companion drug, ethambutol, may be adequate for nodular/bronchiectatic MAC disease but should not be used in patients with fibrocavitary disease because of the risk of emergence of macrolide resistance (A, II).
7. Patients respond best to MAC treatment regimens the first time they are administered; therefore, it is very important that patients receive recommended multidrug therapy the first time they are treated for MAC lung disease (A, II).
8. Expert consultation should be sought for patients who have difficulty tolerating MAC treatment regimens or who do not respond to therapy (C, III).

Treatment of macrolide-resistant MAC lung disease. The management of macrolide-resistant MAC involves complex clinical decision making, drug choices, and protracted duration of therapy, analogous to the drug management of multidrug-resistant TB. Given the complexities of management, the risk of complications, and the need for obtaining an optimal outcome in a problematic clinical situation, therapy of macrolide-resistant MAC should be undertaken only in consultation with an expert experienced in MAC therapy. Extensive use of additional agents before referral may compromise the patient's optimal chance for therapeutic response.

Patients with macrolide resistance can have either upper lobe cavitary disease or nodular/bronchiectatic disease. The two major risk factors for macrolide-resistant MAC disease are macrolide montherapy or treatment with macrolide and inadequate companion medications (274). In a recent study of patients with macrolide-resistant MAC lung disease, the treatment strategy associated with the most success included both the use of a parenteral aminoglycoside (streptomycin or amikacin) and surgical resection ("debulking") of disease (for patients with either cavitary or nodular/bronchiectatic disease) (274). The optimal drug regimen for treating macrolide-resistant strains is a major issue to be addressed in future studies as resistant strains become more prevalent. The four-drug regimen of isoniazid (300 mg/d), rifampin (600 mg/d), and ethambutol (25 mg/kg/d for the first 2 mo, then 15 mg/kg/d) with streptomycin for the initial 3 to 6 months of therapy was reported to be effective for selected patients with MAC lung disease in the pre–macrolide era (259). In the opinion of some experts, rifabutin should be substituted for rifampin in this situation because of the generally poor response to medications and better *in vitro* activity of rifabutin against MAC. In addition, amikacin could be substituted for streptomycin, and isoniazid should be considered optional for these patients. A number of other drugs have been used in multidrug regimens in the past, but they are limited by little or no evidence of clinical efficacy and toxicity (e.g., clofazamine, cycloserine, ethionamide, and capreomycin). The newer 8-methoxy fluoroquinolone moxifloxacin has better *in vitro* activity against MAC than older quinolones, but most MAC isolates are resistant *in vitro* and no data are available about its *in vivo* activity in

MAC lung disease. Including a macrolide in treatment regimens for macrolide-resistant MAC isolates is not recommended. The long-term success rate in the macrolide era for salvage regimens, without surgery, for treating macrolide-resistant disease is very poor.

The role of immune therapy in patients who fail drug therapy has not been established. The preliminary review of data from a recent unpublished, large, multicenter trial of inhaled IFN-γ adjunctive therapy for pulmonary MAC infection appears to show no added benefit of this therapy when included in a macrolide-based three-drug treatment regimen. IFN-γ is used for treatment of NTM infection in selected patients with IFN-γ deficiency. Similarly, the role of inhaled antibiotics, such as tobramycin and amikacin, has not been established.

Treatment failure. Patients are considered treatment failures if they have not had response (microbiologic, clinical or radiographic) after 6 months of appropriate therapy or achieved conversion of sputum to AFB culture negative after 12 months of appropriate therapy. Multiple factors can interfere with the successful treatment of MAC lung disease, including medication nonadherence, medication side effects or intolerance, prior therapy of MAC lung disease, lack of response to a medication regimen, or the emergence of a macrolide-resistant MAC isolate.

MAC reinfection. For patients who initially have sputum conversion (three consecutive AFB-negative cultures) while on medication but who then subsequently develop positive cultures for MAC after discontinuing therapy, it has been shown that many of these patients are reinfected by new MAC strains (genotypes) rather than manifesting disease due to relapse with their initial MAC strain (genotype) (38, 51). The timing of the positive culture is strongly associated with either relapse or reinfection. Patients whose sputum cultures become negative on therapy and discontinue antimycobacterial therapy after fewer than 10 months of negative cultures and then have multiple positive cultures are likely to have relapse of disease with the original MAC strain (genotype). Patients who complete 10 to 12 months of negative cultures on therapy, however, but then have either single or multiple positive MAC cultures are more likely to have reinfection with a new MAC strain. The reinfection isolates are uniformly susceptible to macrolides, even when they occur during therapy, and are almost exclusively seen in patients with underlying bronchiectasis (51). The clinical significance of reinfection MAC isolates is variable. Multiple isolates are usually associated with recurrence of clinical symptoms and usually indicate renewed clinical disease and require reinstitution of MAC therapy, whereas single reinfection MAC isolates that occur after completion of therapy may not be a harbinger of renewed or progressive MAC disease that requires therapy. This reinfection phenomenon also demonstrates that, for some patients, MAC is a chronic recurring condition and the reinfections are a reflection of an underlying condition, probably bronchiectasis, which may or may not have been initially caused by MAC infection. The role of MAC genotyping in the routine care of patients on drug therapy is not yet determined; however, it can be helpful for determining the significance of positive cultures from patients with MAC lung disease either during or after therapy.

Drug toxicity and toxicity monitoring. The multidrug MAC treatment regimens are frequently associated with medication-related adverse events, including toxicities, side effects, and allergic reactions, especially in elderly patients with nodular/bronchiectatic disease whose weight is often in the 45- to 55-kg range (Table 6). Clarithromycin toxicity is dose and serum-level related (283, 284). Adult patients generally cannot tolerate clarithromycin at more than 1,000 mg/day, although some elderly patients with low creatinine clearances or low body weight require even lower doses (i.e., 250–500 mg/d) because of toxicity (283, 284). The most common toxicities seen with clarithomycin are gastrointestinal (metallic taste, nausea, and vomiting).

Azithromycin toxicity is dose and serum-level related. Most adult patients with MAC lung disease do not tolerate azithromycin doses of greater than 300 mg/day because of frequent adverse events, including gastrointestinal symptoms (primarily diarrhea) and reversible hearing impairment (285). Hence, the maximum recommended doses are 250 mg/day or 500 mg three times weekly.

Rifabutin toxicity is dose related, common, and frequently requires dosage adjustment. Clarithromycin has been shown to more than double rifabutin serum levels, likely by inhibiting hepatic metabolism of rifabutin. Rifabutin toxicity, including gastrointestinal symptoms, uveitis, and polyarthralgia syndrome, is common in patients receiving 450 to 600 mg/day of rifabutin who are also receiving clarithromycin for pulmonary MAC disease (291, 292). The most common toxicity with rifabutin is fever, chills, and a flulike illness. Resolution of these symptoms will occur with a decrease in rifabutin dosage. A reduction in total white blood cell count below 5,000 cells/μl is also common with doses of rifabutin at 300 to 600 mg/day, although a reduction in white blood cell counts to below 2,000 cells/μl or an absolute granulocyte count of below 1,000 cells/μl is unusual (291). Although 300 mg/day of rifabutin may be an appropriate dose in some circumstances, a reduction to 150 mg/day, especially in older patients with nodular/bronchiectatic disease, may be necessary when rifabutin is combined with clarithromycin.

Rifampin-related toxicity includes gastrointestinal symptoms, hepatotoxicity, hypersensitivity reactions, and, rarely, severe immunologic reactions (acute renal failure, thrombocytopenia). Most experts feel that toxicity with rifampin is much less frequently encountered than with rifabutin. A major consideration for use of rifampin in the older population with MAC lung disease is the possibility of drug interactions due to induction of hepatic microsomal enzymes. These patients are frequently receiving multiple other medications whose efficacy may be compromised by rifampin coadministration.

Ethambutol ocular toxicity occurs more frequently in the treatment of patients with MAC lung disease than in patients taking ethambutol for therapy for TB, probably due to the longer duration of exposure to ethambutol in MAC disease compared with TB where ethambutol is generally administered for not more than 2 months. The risk appears to be greater when ethambutol is given on a daily basis versus intermittent (three times weekly) administration (298). In one study of 229 patients receiving ethambutol as part of MAC lung disease therapy, 6% of patients on daily therapy compared with 0% on three-times-weekly therapy developed ethambutol ocular toxicity (298).

Monitoring of patients for toxicity, given the number of drugs and the older age of these patients, is essential. Monitoring should include visual acuity (ethambutol and rifabutin), red-green color discrimination (ethambutol), liver enzymes (clarithromycin, azithromycin, rifabutin, rifampin, isoniazid, ethionamide), auditory and vestibular function (streptomycin, amikacin, clarithromycin, azithromycin), renal function (streptomycin and amikacin), and leukocyte and platelet counts (rifabutin) (284, 285, 292, 299). Patients who receive both clarithromycin and rifabutin must be monitored for the development of toxicity related to the interaction of these drugs (292, 299). Clarithromycin enhances rifabutin toxicity (especially uveitis), whereas the rifamycins, rifampin more than rifabutin, lower clarithromycin serum drug levels (300). Details are provided in the section on monitoring for drug toxicity.

Surgical treatment of MAC lung disease. Patients whose disease is predominantly localized to one lung and who can tolerate resectional surgery might also be considered for surgery under

TABLE 6. COMMON SIDE EFFECTS AND TOXICITIES OF DRUGS USED FOR THERAPY OR PROPHYLAXIS OF NONTUBERCULOUS MYCOBACTERIAL DISEASE

Drug	Major Side Effects/Toxicity	Monitoring Procedures
Isoniazid	Hypersensitivity (fever, rash)	Clinical symptoms
	Hepatitis	Clinical symptoms; periodic ALT or AST determinations, especially in first 3 mo of therapy
	Increased serum levels of phenytoin (Dilantin)	Monitor serum levels
	Peripheral neuropathy related to pyridoxine deficiency	Clinical symptoms
Ethambutol	Optic neuritis (loss of red/green color discrimination, loss of visual acuity)	Discontinue drug immediately with subjective visual loss; periodic and symptomatic testing for red/green color discrimination and visual acuity (monthly if receiving 25 mg/kg/d); ophthalmology evaluation for symptomatic patients
Rifampin, rifabutin	Orange discoloration of secretions and urine; staining of soft contact lenses	None
	Gastrointestinal disturbance (nausea, vomiting)	Clinical symptoms
	Hypersensitivity (fever, rash)	Clinical symptoms
	Hepatitis	Clinical symptoms; AST or ALT determination based on symptoms
	Increased hepatic metabolism of numerous agents, including birth control pills, ketoconazole, quindine, prednisone, oral hypoglycemics (sulfonylureas), digitalis, methadone, warfarin, clarithromycin, and protease inhibitors	Monitor clinical status and appropriate serum levels when possible.
	"Flu-like" syndrome, thrombocytopenia, renal failure	Clinical symptoms; platelet count, serum creatinine as indicated
Rifabutin only	Polymyalgia, polyarthralgia, leukopenia, granulocytopenia, anterior uveitis (rifabutin with clarithromycin)	Clinical symptoms; periodic WBC counts
Streptomycin, amikacin, tobramycin	Vestibular/auditory toxicity (dizziness, vertigo, ataxia, tinnitus, hearing loss)	Clinical symptoms including changes in hearing, ability to walk, dizziness; periodic hearing tests in high-risk patients or those with auditory/vestibular symptoms; periodic amikacin serum levels
Azithromycin, clarithromycin	Gastrointestinal disturbance (nausea, vomiting, diarrhea)	Clinical symptoms
	Decreased hearing	Clinical symptoms
	Hepatitis	Periodic alkaline phosphatase, AST and ALT for first 3 mo
Clarithromycin only	Inhibited hepatic metabolism of several agents, including rifabutin, some protease inhibitors	Monitor clinical status and appropriate serum levels when possible
Ciprofloxacin, Ofloxacin	Gastrointestinal disturbance (nausea, vomiting, diarrhea)	Clinical symptoms
	Central nervous system (headache, insomnia)	Clinical symptoms
Moxifloxacin	Gastrointestinal disturbance (nausea, vomiting, diarrhea)	Clinical symptoms
	Central nervous system (insomnia, agitation, anxiety)	Clinical symptoms
	Musculoskeletal (tendonitis)	Clinical symptoms
Cefoxitin	Hypersensitivity (fever, rash, eosinophilia)	Clinical symptoms
	Hematologic (anemia, leukopenia)	Periodic blood counts
Tetracyclines (doxycycline, minocycline)	Gastrointestinal disturbance (nausea, vomiting, diarrhea)	Clinical symptoms
	Cutaneous (photosensitivity, rash, hyperpigmentation)	Clinical symptoms
	Central nervous system (dizziness, vertigo [minocycline])	Clinical symptoms
Sulfonamides, trimethoprim/ sulfamethoxazole	Gastrointestinal disturbance (nausea, vomiting, diarrhea)	Clinical symptoms
	Hematologic (leukopenia, anemia, thrombocytopenia)	Periodic blood counts
	Hypersensitivity (fever, rash, Stevens-Johnson syndrome)	Clinical symptoms
Imipenem	Gastrointestinal disturbance (nausea, vomiting, diarrhea)	Clinical symptoms
	Hypersensitivity (anaphylaxis, rash)	Clinical symptoms
	Central nervous system (seizures, confusion state)	Clinical symptoms
	Hepatitis	Periodic hepatic enzymes
	Hematologic (leukopenia, anemia, thrombocytopenia, pancytopenia)	Periodic blood counts
Linezolid	Gastrointestinal disturbance (nausea, vomiting, diarrhea)	Clinical symptoms
	Hematologic (leukopenia, anemia, thrombocytopenia, pancytopenia)	Periodic blood counts
	Peripheral neuropathy	Clinical symptoms

Definition of abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; WBC = white blood cell.

some circumstances. These include the following: poor response to drug therapy, the development of macrolide-resistant MAC disease, or the presence of significant disease-related complications such as hemoptysis. For some patients successfully treated by surgical resection, the prognosis has been better than for patients treated medically (263, 264). Whenever possible, this surgery should be performed at centers with thoracic surgeons who have considerable experience with this type of surgery because lung resectional surgery for mycobacterial disease is potentially associated with significant morbidity and mortality (301, 302).

Several single-center, retrospective studies including small numbers of patients suggest that surgery can be associated with favorable treatment outcome (301–306). Some experts interpret these studies as suggesting a benefit of surgery for highly selected patient groups whose MAC disease has responded poorly to drug therapy (e.g., the patients with macrolide-resistant MAC disease). There are, however, significant limitations to the wide application of these findings. First, there are no widely accepted or uniform criteria for the selection of patients with MAC lung infection for surgical therapy. Presumably, patients would need to meet preoperative criteria similar to those for patients undergoing lung resection for cancer. Second, these studies are reported from centers with experience in the surgical management of mycobacterial diseases. Even in experienced hands, this type

of surgery is associated with a relatively high morbidity. Third, these data likely represent very highly selected patient populations, and the results from these reports may not reflect the likely more variable clinical and microbiologic results expected in patients with complex, advanced disease. A special circumstance that merits discussion is the surgical removal of a solitary pulmonary nodule caused by MAC. Although there are few data directly assessing this problem, expert consensus is that, in the absence of other MAC-related disease radiographically, surgical resection of the solitary nodule is curative with no antibiotic therapy necessary. It is unknown if this approach is applicable to other NTM.

***Context*:**

1. There are no established criteria for patient selection.
2. There are potentially severe perioperative complications.
3. There are few centers with extensive experience with mycobacterial surgery.

***Recommendations*:**

1. Surgical resection of limited (focal) disease in a patient with adequate cardiopulmonary reserve to withstand partial or complete lung resection can be successful in combination with multidrug treatment regimens for treating MAC lung disease (B, II).
2. Surgical resection of a solitary pulmonary nodule due to MAC is considered curative (C, III).
3. Mycobacterial lung disease surgery should be performed in centers with expertise in both medical and surgical management of mycobacterial diseases (C, III).

Considerations in delaying or withholding treatment. The distinction between colonization and invasive disease is not relevant; rather, the distinction is between those patients with nodular/bronchiectatic MAC disease who require immediate therapy directed at MAC and those in whom such a decision can be delayed. If a decision is made to observe such a patient (e.g., one with minimal symptoms and radiographic findings such that the treatment seems worse than the disease, or one with other major medial problems), it is incumbent on the treating physician to continue collecting respiratory specimens for AFB analysis as well as follow-up radiographic studies, usually HRCT scans, over a relatively long period of time (perhaps the patient's lifetime), as the MAC disease will likely progress at some time and the patient's symptoms and chest radiographs will likely worsen. We recommend careful evaluation of each respiratory MAC isolate in the context of the patient's overall status. In contrast, patients with upper lobe fibrocavitary disease have more rapidly progressive and destructive disease. Withholding therapy for these patients has no benefit.

Adjunctive treatment of MAC infection. Consideration should also be given to the use of adjunctive therapies, in addition to antibiotics, for patients with MAC lung infection. These therapies are principally directed at the management of the bronchiectasis associated with nodular/bronchiectatic MAC infection. In the past, some patients with nodular bronchiectatic MAC disease were treated with a variety of nonspecific measures, including bronchodilators, postural drainage, smoking cessation, and broad-spectrum antibiotics, rather than specific antimycobacterial therapy for their pulmonary disease (254). Clearly, these measures may be appropriate and can be associated with symptomatic and objective improvement in bronchiectasis unrelated to any effect on MAC (254). Newer methods for increased mucus clearance in patients with bronchiectasis include autogenic drainage, oscillating positive expiratory pressure devices, and high-frequency chest compression devices. These modalities offer additional mucus clearance advantages to patients, and should be considered in individuals with significant mucus production and clearance problems. Smoking cessation is important for improved airway function. Other potentially important considerations include nutrition and weight gain, and exercise and cardiovascular fitness.

MAC lymphadenitis. EPIDEMIOLOGY. An estimated 300 cases of culture-confirmed MAC lymphadenitis occur in the United States each year (19). This number, however, is likely to be an underestimate, because, in many cases of lymphadenitis, specimens are not cultured or cultures fail to grow an organism. The frequency of this form of MAC disease appears to be increasing in the United States (189). MAC cervical adenitis is almost exclusively a disease of children, with most cases occurring in those under the age of 3 years. The disease shows a modest female predominance, and nearly all reported cases are in whites (307). MAC lymphadenitis is also seen in HIV-infected persons, particularly as a manifestation of the immune reconstitution syndrome; cervical, mediastinal, or intraabdominal nodes may be involved (183–186).

TREATMENT. Excisional surgery without chemotherapy is the recommended treatment for children with NTM cervical lymphadenitis, including those with disease caused by MAC and *M. scrofulaceum* (188, 308–310). The success rate with this procedure is approximately 95% (308). Successful treatment with excisional surgery frequently follows diagnosis with fine needle aspiration or incisional biopsy. Incisional biopsy alone or the use of anti-TB drugs alone (without a macrolide) has frequently been followed by persistent clinical disease, including sinus tract formation and chronic drainage, and should be avoided (188–191, 195). For children with recurrent disease, a second surgical procedure is usually performed. An alternative for recurrent disease or for children in whom surgical risk is high (e.g., risk of facial nerve involvement with preauricular nodes) may be the use of a clarithromycin multidrug regimen such as that used for pulmonary disease (188, 307–311). Experience with such an approach is limited but the proven activity of clarithromycin against MAC in other clinical settings and preliminary reports support this combined approach.

A difficult clinical problem arises when a child who has granulomatous disease, with or without AFB on examination of the excised lymph nodes, also has a PPD tuberculin skin test that is strongly positive (e.g., > 15 mm). A course of anti-TB therapy while awaiting the results of the lymph node culture is recommended, especially when there are any risk factors for TB (e.g., positive family history and foreign-born child). If the cultures fail to yield any mycobacteria, anti-TB therapy should be discontinued unless there are significant risk factors for TB.

Skin, tissue, and skeletal disease. For adult patients with extrapulmonary, localized MAC disease involving skin, soft tissue, tendons and joints, and, occasionally, bone, a combination of excisional surgery (or surgical debridement) and chemotherapy is usually performed. The recommended drug regimen for these infections is the same as for MAC pulmonary disease. Whether a three-drug regimen alone in this setting would be adequate is not known. The optimal duration of treatment is also unknown, but 6 to 12 months of chemotherapy is usually recommended.

Disseminated MAC disease. EPIDEMIOLOGY. Disseminated MAC occurs largely in patients with AIDS. This manifestation of MAC disease was extremely rare before 1980 but rose to an estimated 37,000 cases in the United States in 1994 (17). The incidence of disseminated MAC disease has declined markedly since that time (312). Children with AIDS have rates of disseminated MAC similar to adults.

Untreated disseminated MAC is a life-threatening illness. In the pre–antiretroviral era, of 191 patients with AIDS diagnosed with disseminated MAC, only 13% survived 1 year without treatment (289). Deaths in this group of patients were attributable to both MAC and other complications of HIV.

Treatment. Successful treatment of disseminated MAC in persons with AIDS is based on treatment of both the mycobacterial infection and the HIV infection—the latter to improve the underlying immunosuppression. This is frequently a difficult task, requiring the patient to adhere to a large number of medications and contending with the possibility of numerous adverse drug effects. The clinician is required to be aware of the pharmacokinetic interactions of the antimycobacterial and antiretroviral drugs. Good clinical care, therefore, usually necessitates expertise or consultation with experts in this field.

The cornerstone of therapy for disseminated MAC is a macrolide, because a variety of treatment regimens without a macrolide have been proven to be ineffective. Although monotherapy with clarithromycin has been shown to be effective in reducing the level of MAC bacteremia, resistance and failure developed in almost half of the patients treated with clarithromycin alone (272). Monotherapy for disseminated MAC is therefore contraindicated. Both clarithromycin and azithromycin have been shown to be effective in combination regimens for the treatment of disseminated MAC (282, 293); however, clarithromycin has been shown to clear bacteremia more rapidly than azithromycin (282), and has been more fully evaluated in treatment regimens. Ethambutol is considered as the second drug to be used, with a macrolide, in all treatment regimens for disseminated MAC.

Many clinicians add a rifamycin as the third drug in the treatment of disseminated MAC, although it is not certain that there is added benefit. If a rifamycin is used, most experts would use rifabutin, as it is both more active *in vitro* against MAC than rifampin, and it is easier to use with most antiretroviral agents. In a non–macrolide-containing regimen, rifabutin was shown to be effective in reducing MAC bacteremia, but the results have been less clear when rifabutin has been added to a regimen of clarithromycin and ethambutol (288). In one study, rifabutin at a dose of 300 mg/day provided no additional clinical benefit to the two-drug regimen but did result in reducing relapse due to macrolide-resistant strains (293). In another study, rifabutin at a dose of 450 mg/day did appear to offer modest clinical benefit when used as a third drug (313).

Initial therapy for the treatment of disseminated MAC is shown in Table 7. All patients should be treated with clarithromycin, 1,000 mg/day or 500 mg twice daily, or as an alternative, azithromycin at a dose of 500 mg daily. Ethambutol should be given at a dose of 15 mg/kg daily. Rifabutin, if added, should be used at a dose of 300 mg daily, with adjustments for interactions with antiretroviral drugs as discussed below. For patients with macrolide-resistant strains, treatment regimens are far less successful. Drugs that should be considered for inclusion are aminoglycosides, such as amikacin, and a quinolone, such as moxifloxicin. Clofazimine has been associated with excess mortality in the treatment of disseminated MAC disease and should not be used (281, 295). There have been no studies of intermittent therapy for disseminated MAC as have been done in patients with MAC lung disease.

Treatment of disseminated MAC in patients with AIDS is complicated by adverse drug effects and by drug–drug interactions. Combinations of clarithromycin and rifabutin may result in high serum levels of rifabutin and have been associated with arthralgias, uveitis, neutropenia, and liver function abnormalities (314, 315). If these adverse effects occur, rifabutin will need to be used at a lower dose or stopped altogether. Clarithromycin should not be used in doses above 500 mg twice daily, as higher doses have been associated with excess mortality in this population (316). Rifabutin has been shown to reduce serum clarithromycin levels, which is also a concern when combining the two drugs (290). Furthermore, rifabutin is an inducer of cytochrome P-450 isoenzymes and therefore interferes with the metabolism of many of the protease inhibitors and nonnucleoside reverse transcriptase inhibitor drugs used in the treatment of HIV infection. Rifabutin cannot be used with certain of these drugs and must be used at a modified dose with others. Current guidelines for the use of rifabutin with HIV therapies can be found at www.cdc.gov/nchstp/tb/TB_HIV_DRUGS/TOC.htm.

Treatment of MAC in patients with AIDS should be considered lifelong, unless immune restoration is achieved by antiretroviral therapy. Routine monitoring is not indicated unless the patient has signs or symptoms of active MAC infection. MAC treatment may be stopped, with a low risk of reoccurrence, for patients who are asymptomatic, and have achieved a $CD4^+$ T-cell count of over 100 cells/μl for at least 12 months (312). Patients are at low risk for recurrence of MAC when they have completed at least 12 months of treatment for MAC, remain asymptomatic with respect to MAC signs and symptoms, and have a sustained increase (e.g., > 6 mo) in their $CD4^+$ T-lymphocyte counts to greater than 100 cells/μl after HAART. Secondary prophylaxis should be reintroduced if the $CD4^+$ T-lymphocyte count decreases to less than 100 cells/μl.

Treatment of disseminated disease due to NTM other than MAC has not been as well studied in HIV-infected persons. Most of the reports of treatment of *M. kansasii* were in the era before HAART. Short-term responses to antimycobacterial therapy were quite favorable, especially in persons with disease localized to the lungs (317–319). Treatment regimens for persons with *M. kansasii* and other non-MAC species should follow the guidelines for treatment of non–HIV-infected persons, with the consideration for a longer duration of treatment. In particular, persons with blood culture isolates should be treated with antimycobacterial drugs for at least 6 to 12 months after immune restoration.

Prevention. On the basis of the high rate of occurrence and the severe morbidity and mortality, preventive therapy for disseminated MAC is strongly recommended for all HIV-infected patients with fewer than 50 $CD4^+$ T cells/μl (312). On the basis of both efficacy and ease of use, azithromycin—given as 1,200 mg

TABLE 7. REGIMENS FOR TREATMENT AND PREVENTION OF DISSEMINATED *MYCOBACTERIUM AVIUM* IN HIV-INFECTED PATIENTS

Preferred (A, I)*	Alternative (B, I)*
Treatment	
Clarithromycin 500 mg orally twice daily + Ethambutol 15 mg/kg orally daily ± Rifabutin† 300 mg orally daily	Azithromycin 500 mg daily Ethambutol 15 mg/kg daily Rifabutin† 300–450 mg orally daily
Prevention‡	
Azithromycin 1,200 mg orally weekly	Clarithromycin 500 mg orally twice daily or Rifabutin† 300 mg orally daily

* For evidence quality, *see* Table 1.

† Rifabutin dose may need to be modified based on drug–drug interactions (*see* text).

‡ Preventive therapy indicated for persons with < 50 $CD4^+$ cells/μl; may stop if > 100 cells/μl.

once weekly—is the preferred agent (Table 6) (320). Clarithromycin is also effective; however, because it must be given twice daily and the risk of breakthrough with macrolide-resistant strains is higher with daily clarithromycin than with weekly azithromycin, it is considered only an alternative agent (321). Rifabutin is somewhat less effective and should only be used when a macrolide cannot be tolerated (289).

Before prophylaxis is initiated, disseminated MAC disease should be ruled out by clinical assessment, which might include obtaining a blood culture for MAC if warranted.

Because treatment with rifabutin could result in rifampin resistance among persons who have active TB, active TB should also be excluded before rifabutin is used for prophylaxis.

Discontinuing primary prophylaxis. Primary MAC prophylaxis should be discontinued among adult and adolescent patients who have responded to HAART with an increase in $CD4^+$ T-lymphocyte counts to more than 100 cells/μl for more than 3 months (312, 322). Primary prophylaxis should be reintroduced if the $CD4^+$ T-lymphocyte count decreases to less than 50 to 100 cells/μl.

Although detecting MAC organisms in the respiratory or gastrointestinal tract might predict disseminated MAC infection, no data are available regarding efficacy of prophylaxis with clarithromycin, azithromycin, rifabutin, or other drugs among patients with MAC organisms at these sites and a negative blood culture. Therefore, routine screening of respiratory or gastrointestinal specimens for MAC cannot be recommended.

M. kansasii

The organism. Tap water is likely the major reservoir for *M. kansasii* causing human disease as environmental sources other than tap water have rarely been identified (323–326). Strains with the same phage type as those isolated from patients have been recovered from drinking-water distribution systems in the Netherlands and environmental isolates of the same genotype as clinical isolates have been identified in France (325, 327). DNA-based studies of *M. kansasii* isolates suggest five to seven subspecies or types are present among both environmental and human isolates (328–333). Subtype I is the predominant subspecies of *M. kansasii* among clinical isolates and is the major subtype responsible for human infection (328–336).

Epidemiology. *M. kansasii* is the second most common cause of NTM disease in the United States. Lung disease caused by *M. kansasii* occurs in geographic clusters in areas such as southeast England and Wales and the southern and central United States (334–337) In a study of NTM pulmonary disease in Texas, *M. kansasii* cases were significantly more likely to come from urban than rural areas (338). In geographic areas where HIV infection is common, even outside the areas endemic for *M. kansasii* lung disease, the prevalence of *M. kansasii* disease may be high (339).

M. kansasii primarily affects middle-aged white men, but it can affect adult patients of any sex, race, or age. Risk factors for *M. kansasii* infection include pneumoconiosis, chronic obstructive lung disease, previous mycobacterial disease, malignancy, and alcoholism (338). The combination of HIV infection and silicosis can result in profound susceptibility to *M. kansasii* (340).

Pulmonary disease. CLINICAL PRESENTATION. *M. kansasii* lung disease most closely parallels the clinical course of *M. tuberculosis*. Symptoms of *M. kansasii* lung disease are generally identical to those associated with pulmonary TB. The chest radiographic abnormalities are also very similar to reactivation pulmonary TB, including cavitary infiltrates with an upper lobe predilection. Noncavitary or nodular/bronchiectatic lung disease, similar to that seen with MAC, has also been recently described in patients with *M. kansasii* lung disease (95). The natural history of untreated *M. kansasii* lung disease includes progression of clinical, bacteriologic, and radiographic disease (341).

Treatment. Strains of *M. kansasii* are inhibited by rifampin, isoniazid, ethambutol, ethionamide, streptomycin, and clarithromycin at concentrations readily achievable in the serum with usual therapeutic doses (342–344). Because the concentrations of antituberculous drugs used in susceptibility testing were chosen for their usefulness with *M. tuberculosis*, and because *M. kansasii* is less susceptible to these drugs, some isolates of *M. kansasii* may be reported resistant to isoniazid at 0.2 or 1 μg/ml and to streptomycin at 2 μg/ml. These isolates are susceptible to slightly higher drug concentrations and laboratory reports of resistance to the low concentrations of these two drugs have no clinical or therapeutic significance as long as a regimen containing rifampin is used (342, 343, 345). Thus, in the absence of prior treatment with antimycobacterial drugs, isoniazid or streptomycin should be used against *M. kansasii*. *M. kansasii* is also susceptible *in vitro* to achievable serum levels of clarithromycin, sulfamethoxazole, amikacin, fluoroquinolones, and rifabutin, although there is limited information on the clinical usefulness of these drugs (56, 342, 347). Isolates are usually resistant to achievable serum levels of p-aminosalicylic acid, capreomycin, and pyrazinamide.

There have been no randomized trials of treatment for disease caused by *M. kansasii*. However, there have been several retrospective and prospective studies of various treatment regimens (341, 344, 345, 347–350). Earlier reports of treatment with antimycobacterial drugs in the prerifampin period were disappointing, with sputum conversion rates at 6 months ranging from 52 to 81%, and relapse rates of approximately 10% in patients achieving an initial response (344, 350).

With the availability of rifampin, outcomes of drug therapy for *M. kansasii* improved dramatically. Four-month sputum conversion rates with rifampin-containing regimens were 100% in 180 patients from three studies (344, 345, 347). Two patients failed therapy after initial sputum conversion and both failures were associated with the development of rifampin resistance (344). Long-term relapse rates with rifampin-containing regimens were very low, with only one relapse recorded among 134 patients (0.8%) who received long-term follow-up in three studies (344, 345, 348). Because of the excellent outcomes with antimycobacterial medications, surgery has no role in managing routine cases of pulmonary disease.

The 1997 ATS treatment recommendation for *M. kansasii* pulmonary disease in adults was the regimen consisting of isoniazid (300 mg), rifampin (600 mg), and ethambutol (25 mg/kg for the first 2 mo, then 15 mg/kg) given daily for 18 months with at least 12 months of negative sputum cultures (2). The recommendation for 2 months of ethambutol at 25 mg/kg/day has not been tested and was based on older studies of multidrug therapy for *M. kansasii* lung disease with very high initial microbiologic responses (344, 345, 347). Given that rifampin is the critical component for treatment success (344, 347, 347), that treatment success has been reported with rifampin-containing regimens without ethambutol, that 15 mg/kg of ethambutol has been used in successful treatment regimens, and that ocular toxicity is dose related with daily ethambutol administration, ethambutol can probably be given effectively at 15 mg/kg/day throughout the course of treatment (349, 350).

Similarly, there have been no prospective studies evaluating the efficacy of 18 months of therapy versus shorter (9 or 12 mo) treatment durations. The 18-month treatment recommendation was based on the very low relapse rate with that length of drug administration. Shorter, fixed treatment courses have been shown to be effective but higher relapse rates have been seen in recent studies compared with older studies. One study of 40 patients demonstrated that adding intermittent streptomycin

at 1 g twice weekly for the first 3 months to the previously recommended three-drug regimen given for 12 months resulted in apparent cure of all but one patient (347). The British Medical Research Council completed a trial of daily low-dose ethambutol (15 mg/kg) and daily rifampin given for 9 months in 155 adult patients (349). Sputum conversion was achieved in 99.4% of patients, but with a relapse rate of 10% with a 5-year follow-up. In a third study, 14 patients received rifampin, and isoniazid (INH) for 12 months with ethambutol (25 mg/kg) for the first 6 months (351). A second group of 14 patients were treated with the same regimen but for a total of 18 months. All patients in both regimens converted their sputum to negative. After 12 to 30 months of follow-up, only one patient in the 12-month treatment group and no patients in the 18-month group had relapsed after completing therapy. And finally, recent study of 15 patients receiving thrice-weekly therapy with rifampin (600 mg), ethambutol (25 mg/kg), and clarithromycin (500–1,000 mg) reported that 12 months of negative sputum cultures was associated with no disease relapses after 46 months of follow-up (95). As with MAC lung disease, a reasonable treatment endpoint for *M. kansasii* lung disease may be 12 months of negative sputum cultures, especially with a three-drug treatment regimen (352).

The recommended regimen for treating pulmonary *M. kansasii* disease includes rifampin (600 mg/d), isoniazid (300 mg/d), and ethambutol (15 mg/kg/d) for a duration that includes 12 months of negative sputum cultures. As noted previously, one study of 15 patients who received three-times-weekly rifampin, ethambutol, and clarithromycin suggests that intermittent therapy for *M. kansasii* disease can be successful (95).

Patients whose *M. kansasii* isolates have become resistant to rifampin as a result of previous therapy have been treated successfully with a regimen that consists of high-dose daily isoniazid (900 mg), pyridoxine (50 mg daily), high-dose ethambutol (25 mg/kg/d), and sulfamethoxazole (1.0 g three times/d) combined with daily or five times per week streptomycin or amikacin for the initial 2 to 3 months, followed by intermittent streptomycin or amikacin for a total of 6 months (342). The therapy was continued until the patient was sputum culture negative for 12 to 15 months. With this regimen, sputum conversion occurred in 18 of 20 patients (90%) after a mean of 11 weeks, with only one relapse (8%) among patients who were culture negative for at least 12 months on therapy (342). The excellent *in vitro* activity of clarithromycin and moxifloxacin against *M. kansasii* suggests that these agents may also be useful in re-treatment regimens (95). Multidrug regimens containing a macrolide (i.e., clarithromycin or azithromycin), moxifloxacin, and at least one other agent based on *in vitro* susceptibilities, such as ethambutol or sulfamethoxazole, are likely to be effective for treatment of a patient with rifampin-resistant *M. kansasii* disease.

***Context*:**

The following recommendations are for patients with rifampin-susceptible *M. kansasii* isolates unless noted otherwise.

***Recommendations*:**

1. Patients should receive a daily regimen including rifampin 10 mg/kg/day (maximum, 600 mg), ethambutol 15 mg/kg/day, isoniazid 5 mg/kg/day (maximum 300 mg), and pyridoxine (50 mg/day) (A, II). An initial 2 months of ethambutol at 25 mg/kg/day is no longer recommended (A, II).
2. Treatment duration for *M. kansasii* lung disease should include 12 months of negative sputum cultures (A, II).
3. For patients with rifampin-resistant *M. kansasii* disease, a three-drug regimen is recommended based on *in vitro* susceptibilities including clarithromycin or azithromycin, moxifloxacin, ethambutol, sulfamethoxazole, or streptomycin (A, II).
4. Patients undergoing therapy for *M. kansasii* lung disease should have close clinical monitoring with frequent sputum examinations for mycobacterial culture throughout therapy (C, III).

Disseminated* M. kansasii *disease. EPIDEMIOLOGY. *M. kansasii* is the second most common nontuberculous mycobacterium that produces disease in patients with AIDS (20). In contrast to MAC, pulmonary disease is seen in over half of patients (318, 319, 353). Bacteremia alone is far less common than for persons infected with MAC, occurring in fewer than 25% of individuals. The average $CD4^+$ T-cell count at diagnosis was under 50 cells/μl in most studies of persons with *M. kansasii* and HIV infection (319, 339, 353).

TREATMENT. The treatment regimen for disseminated disease should be the same as for pulmonary disease. Because of the critically important role of rifamycins in the treatment of *M. kansasii* disease, it is important to construct *M. kansasii* and antiretroviral treatment regimens that are compatible. Guidelines for the use of rifamycins in patients taking protease inhibitors and nonnucleoside reverse transcriptase inhibitors are published and updated by the CDC (http://www.cdc.gov/nchstp/tb/). An option for treating HIV-infected patients who receive an antiretroviral regimen not compatible with rifamycins is to substitute a macrolide or moxifloxacin for the rifamycin.

The recommendation for duration of therapy for disseminated *M. kansasii* disease in patients with AIDS or other immunocompromised patients are the same as the recommendation for duration of therapy for disseminated MAC infection. There is no recommended prophylaxis or suppressive regimen for disseminated *M. kansasii* disease.

M. abscessus (RGM)

Epidemiology. The southeastern United States from Florida to Texas appears to be the major endemic area for *M. abscessus* disease, although disease has been reported from all geographic areas of the United States (22).

Clinical presentation. SKIN, SOFT TISSUE, AND BONE DISEASES. Cutaneous disease caused by *M. abscessus* usually follows accidental trauma or surgery in a variety of clinical settings (173). Cutaneous lesions are usually purple nodules (*see* the online supplement). Some minor infections will resolve spontaneously or after surgical debridement. However, several studies of post-injection abscesses in which no therapy was given revealed disease that persisted in most patients for 8 to 12 months before spontaneously resolving. Several case studies and one clinical trial of patients with cutaneous disease due to other RGM treated on the basis of *in vitro* susceptibilities have shown good results (173, 354–357).

PULMONARY DISEASE. *M. abscessus* is the third most frequently recovered NTM respiratory pathogen in the United States and accounts for approximately 80% of RGM respiratory disease isolates (32). The largest group of patients with this lung disease are white, female nonsmokers, and older than 60 years, with no predisposing conditions or previously recognized lung disease. Underlying disorders that are associated with the disease include bronchiectasis and prior mycobacterial infection. As with MAC lung disease, the origin of bronchiectasis in these patients may be the *M. abscessus* infection, but this is not known with certainty. Other rare predisposing conditions include gastroesophageal disorders with chronic vomiting, lipoid pneumonia, CF, and AAT anomalies (32). The distinguishing feature of patients with a recognized underlying lung disease is that their *M. abscessus*

disease occurs at a younger age, usually in those younger than 50 years, and almost all patients younger than 40 years have one of the predisposing disorders (32).

The chest radiograph from patients with *M. abscessus* lung disease usually shows multilobar, patchy, reticulonodular, or mixed interstitial–alveolar opacities with an upper lobe predominance (*see* the online supplement). Cavitation occurs in only approximately 15% of cases (32). HRCT of the lung frequently shows associated cylindrical bronchiectasis and multiple small (< 5 mm) nodules (*see* the online supplement). Overall, the radiographic pattern is similar to the nodular bronchiectatic form of MAC lung disease (32). Approximately 15% of patients with *M. abscessus* lung disease will also have MAC isolated from their sputum, suggesting a close relationship of the disorders (32).

The usual presenting symptoms are similar to those for other NTM respiratory pathogens, especially MAC, including cough and easy fatigability. The natural history of this disease depends primarily on the presence or absence of underlying disorders. For most patients with *M. abscessus* and no underlying disorder other than bronchiectasis, the disease is indolent and slowly progressive. Some patients show little radiographic change over years. More fulminant, rapidly progressive disease can occur in association with gastroesophageal disorders and CF. In a study published in 1993, death occurred as a consequence of *M. abscessus* infection in 20% of cases, although current estimates are that death rates are lower (32).

Treatment. *M. abscessus* isolates are uniformly resistant to the standard antituberculous agents (358–360). Because of variable *in vitro* drug susceptibilities to some drugs, antibiotic susceptibility testing of all clinically significant isolates is recommended. Acquired mutational resistance to clarithromycin (23S rRNA gene) and amikacin (16S rRNA gene) can occur because isolates of *M. abscessus* have only a single copy of the gene. Untreated *M. abscessus* isolates generally have low or intermediate MICs, compared with achievable drug levels, to clarithromycin (100%), amikacin (90%), and cefoxitin (70%). Some isolates have low or intermediate MICs to linezolid. Some isolates (50%) also show low MICs to imipenem, although, as noted, this determination is not reliable (*see* Laboratory Procedures). Isolates also have low MICs to clofazimine, although methodology and MIC breakpoints have not yet been addressed by the CLSI for this agent.

For serious skin, soft tissue, and bone infections caused by *M. abscessus*, clarithromycin 1,000 mg/day or azithromycin 250 mg/day should be combined with parenteral medications (amikacin, cefoxitin, or imipenem). The macrolides are the only oral agents reliably active *in vitro* against *M. abscessus* (359, 361). The most active of the parenteral agents is amikacin. Intravenous amikacin is given at a dose of 10 to 15 mg/kg daily to adult patients with normal renal function to provide peak serum levels in the low 20-mg/ml range. Once-daily dosing is unproven clinically but appears reasonable. The lower dose (10 mg/kg) should be used in patients older than 50 years and/or in patients in whom long-term therapy (> 3 wk) is anticipated. The three-times-weekly amikacin dosing at 25 mg/kg is also reasonable, but may be difficult to tolerate over periods longer than 3 months (297). The amikacin combined with high-dose cefoxitin (up to 12 g/d given intravenously in divided doses) is recommended for initial therapy (minimum, 2 wk) until clinical improvement is evident. Limited cefoxitin availability may necessitate the choice of an alternative agent such as imipenem (500 mg two to four times daily), which is a reasonable alternative to cefoxitin (175, 359, 360). For serious disease, a minimum of 4 months of therapy is necessary to provide a high likelihood of cure. For bone infections, 6 months of therapy is recommended (354). Surgery is generally indicated with extensive disease, abscess formation, or where drug therapy is difficult. Removal of foreign bodies, such as breast implants or percutaneous catheters, is important and probably essential to recovery.

In contrast to the efficacy of medication regimens for nonpulmonary disease, no antibiotic regimens based on *in vitro* susceptibilities has been shown to produce long-term sputum conversion for patients with *M. abscessus* lung disease. The goal of 12 months of negative sputum cultures while on therapy may be reasonable, but there is no medication strategy to reliably achieve this goal. Alternative goals of therapy, such as symptomatic improvement, radiographic regression of infiltrates, or improvement in sputum culture positivity, short of conversion to negative culture, are more realistic at this point for *M. abscessus* lung disease. Monotherapy with macrolides is not sufficient to produce microbiologic cure for *M. abscessus* lung disease. Combination therapy (as outlined *above*) with amikacin plus cefoxitin or imipenem for 2 to 4 months usually produces clinical and microbiologic improvement, but cost and morbidity are significant impediments to a curative course of therapy. For patients with macrolide-resistant *M. abscessus* isolates or macrolide intolerance, most experts would recommend a combination of parenteral drugs based on *in vitro* susceptibilities. For some patients, symptoms can be controlled with intermittent periods of therapy with clarithromycin or azithromycin alone or in combination with one or more parenteral drugs. Suppressive therapy, including periodic parenteral antibiotic or oral macrolide therapy, may be all that can be realistically administered to control the symptoms and progression of *M. abscessus* lung disease. Because side effects and toxicities are common with aggressive parenteral therapy, expert consultation is recommended for these patients. Overall, with current antibiotic options, *M. abscessus* is a chronic incurable infection for most patients.

Curative therapy for *M. abscessus* lung disease is more likely to be obtained with limited disease and a combination of surgical resection of involved lung and chemotherapy (32). Patients with focal lung disease who can tolerate lung resection should be treated with surgery after an initial period on antimicrobial drug therapy to lessen the microbial burden. Caveats discussed for MAC lung disease surgery are pertinent for *M. abscessus* as well. For patients with underlying esophageal or other swallowing disorders, treatment of the underlying condition can result in improvement of the RGM lung disease.

Drugs that show some potential but are not extensively tested include three newer classes of drugs, the oxazolidinones, the glycylcyclines, and the ketolides, that all have some *in vitro* activity against *M. abscessus* (362). Approximately 50% of *M. abscessus* isolates are susceptible or intermediate in susceptibility *in vitro* to linezolid, the first FDA-approved oxazolidinone (363). A small number of patients with *M. abscessus* lung disease have been treated with linezolid and a companion drug, usually a macrolide, with mixed results. Long-term linezolid therapy at usually recommended antibacterial doses (600 mg twice daily) is often associated with severe side effects, such as anemia, peripheral neuropathy, nausea, and vomiting. A smaller dose, 600 mg/day, is associated with fewer gastrointestinal and hematologic side effects and may still have significant antimycobacterial activity (363). The tetracycline derivatives, glycylcyclines, especially tigecycline, also have *in vitro* activity against *M. abscessus*. This drug must be given intravenously and it is known to cause nausea and anorexia in some patients when given long term for mycobacterial disease. Telithromycin, a ketolide, in limited testing has *in vitro* activity against some *M. abscessus* isolates but has not been evaluated clinically.

***Context*:**

1. At present, there is no reliable or dependable antibiotic regimen, even based on *in vitro* susceptibilities and including parenteral agents, to produce cure for *M. abscessus* lung disease.

***Recommendations*:**

1. The only predictably curative therapy of limited (focal) *M. abscessus* lung disease is surgical resection of involved lung combined with multidrug chemotherapy (A, II).
2. Periodic administration of multidrug therapy, including a macrolide and one or more parenteral agents (amikacin, cefoxitin, or imipenem) or a combination of parenteral agents over several months may help control symptoms and progression of *M. abscessus* lung disease (C, III).

M. chelonae (RGM)

The organism. It is important to differentiate isolates identified as "*M. chelonae/abscessus*" to the species isolated since both species can cause skin, bone, and soft tissue infections, but therapy for *M. chelonae* is potentially easier than for *M. abscessus* infection (*see* Laboratory Procedures).

Clinical presentation. Skin, bone, and soft tissue disease are the most important clinical manifestations of *M. chelonae* infection. Disseminated *M. chelonae* disease can also occur in immunocompromised patients and presents with characteristic skin lesions (368). An example of cutaneous *M. chelonae* infection is provided in the online supplement.

Epidemic and sporadic cases of keratitis caused by NTM have been associated with contact lens wear and ocular surgery, particularly LASIK (217, 233, 234). Although both rapid and slow-growing NTM have been implicated in LASIK-associated infection, *M. chelonae* is the most frequently reported etiologic agent (233).

M. chelonae is a less common cause of pulmonary disease than *M. abscessus*. The symptoms and radiographic presentation are similar to *M. abscessus* and *M. fortuitum* (32).

Treatment. Isolates of *M. chelonae* are susceptible or intermediate in susceptibility to tobramycin (l00%), clarithromycin (l00%), linezolid (90%), imipenem (60%), amikacin (50%), clofazimine, doxycycline (25%), and ciprofloxacin (20%). For *M. chelonae*, tobramycin is more active *in vitro* than amikacin. Imipenem is preferred to cefoxitin because *M. chelonae* isolates are uniformly resistant to cefoxitin (359, 360, 364).

The only clinical treatment trial for *M. chelonae* skin disease, as a manifestation of disseminated *M. chelonae* infection, used clarithromycin alone. Of patients (all adults) treated with monotherapy at 500 mg twice a day for 6 months, all were cured except for one patient (8%) who relapsed with an isolate that developed mutational resistance to clarithromycin (356).

For serious skin, bone, and soft tissue disease, a minimum of 4 months of a combination drug therapy (at least initially to minimize the risk of macrolide resistance) is necessary to provide a high likelihood of cure. For bone infections, 6 months of therapy is recommended (354). Surgery is generally indicated with extensive disease, abscess formation, or where drug therapy is difficult. Removal of foreign bodies, such as breast implants and percutaneous catheters, is important, or even essential, to recovery.

For corneal infections, first-line treatment often involves topical and oral agents. Amikacin, fluoroquinolones, clarithromycin, and azithromycin are usually drugs of choice, depending on the *in vitro* susceptibility of the organism recovered from the infected tissue. The outcome for vision of such infections is typically poor, and many patients require corneal transplant for recovery of vision or for infection cure (231).

The optimal therapy for *M. chelonae* lung disease is unknown. On the basis of *in vitro* susceptibilitites, a regimen including clarithromycin with a second agent (on the basis of *in vitro* susceptibilities) would likely be successful with a treatment duration that includes 12 months of negative sputum cultures.

M. fortuitum (RGM)

The organism. Historically, the *M. fortuitum* group has included three species/taxa: *M. fortuitum*, *M. peregrinum*, and an unnamed third biovariant complex. Recently, additional species, including *M. houstonense* and *M. boenickei* and others, have been described with this group of organisms. Other established species, including *M. mageritense* and *M. senegalense*, have been proposed as members of this group. Separation of these species can only be accomplished by molecular testing.

Clinical presentation. Pulmonary disease due to *M. fortuitum* is clinically similar to lung disease caused by *M. abscessus* (32). Although *M. abscessus* is responsible for most lung disease caused by RGM, an important exception is the small group of patients who have gastroesophageal disorders with chronic vomiting and RGM lung disease, in whom *M. abscessus* and *M. fortuitum* occur with equal frequency (32). Other than in this specific setting, *M. fortuitum* lung disease is rare.

Skin, bone, and soft tissue are important sites of *M. fortuitum* infections as with other RGM. Recently, whirlpool footbaths commonly used during pedicure procedures in nail salons have been identified as a source of both sporadic and clustered outbreaks of furunculosis associated with *M. fortuitum* and other RGM (241–243). *M. fortuitum* nail salon furunculosis in most women either healed spontaneously or with oral antibiotic therapy, although disease lasted in most patients typically from several months to a year; one initially untreated person had lymphatic dissemination of disease that eventually required antibiotic therapy (241–243).

Treatment. *M. fortuitum* isolates are usually susceptible to multiple oral antimicrobial agents, including the newer macrolides and quinolones, doxycycline and minocycline, and sulfonamides (359–361). Isolates are susceptible to amikacin (100%), ciprofloxacin and ofloxacin (100%), sulfonamides (100%), cefoxitin (50%), imipenem (100%), clarithromycin (80%), and doxycycline (50%). Recent studies have shown that all isolates of *M. fortuitum* and the related species *M. smegmatis* and *M. houstonense* contain an inducible erythromycin methylase *erm* (39) gene that confers resistance to the macrolides (62, 63). Thus, despite the "susceptible" MICs seen in 80% of isolates for clarithromycin, macrolides should be used with caution. Drug susceptibilities for this species are important for guiding effective therapy.

For *M. fortuitum* lung disease, therapy with at least two agents with *in vitro* activity against the clinical isolate should be given for at least 12 months of negative sputum cultures. The optimal choice of agents is unknown, and would likely be dictated by patient tolerance; however, any two-drug combination based on *in vitro* susceptibility should be successful.

For serious skin, bone, and soft tissue *M fortuitum* disease, a minimum of 4 months of therapy with at least two agents with *in vitro* activity against the clinical isolate is necessary to provide a high likelihood of cure. For bone infections, 6 months of therapy is recommended (173). Surgery is generally indicated with extensive disease, abscess formation, or where drug therapy is difficult. Removal of foreign bodies, such as breast implants and percutaneous catheters, is important, and probably essential to recovery.

M. genavense

The organism. *M. genavense* has not been recovered from soil or water, but it has been recovered from a dog and a variety of pet birds, including psittacine birds (365). *M. genavense* requires supplemented media for growth (*see* LABORATORY PROCEDURES). Identification of this organism requires HPLC or molecular methods.

Clinical presentation. Most clinical *M. genavense* isolates have come from patients with AIDS (162, 366–369). Human isolates have been recovered from cultures of blood, bone marrow, liver, spleen, and other tissues. *M. genavense* should be considered in patients with AIDS who have suspected disseminated MAC, but whose routine AFB cultures are negative.

Treatment. *In vitro* susceptibility data are limited because of the extreme fastidiousness of the organism. Available data suggest that most isolates are susceptible to amikacin, rifamycins, fluoroquinolones, streptomycin, and macrolides (162, 366). Ethambutol has limited activity against *M. genavense* (366).

Optimal therapy is not determined, but multidrug therapies including clarithromycin appear to be more effective than those without clarithromycin (368–370).

M. gordonae

The organism. *M. gordonae* is a pigmented, slowly growing mycobacteria usually isolated as yellow/orange colonies after 3 weeks or more at 37°C.

Epidemiology. *M. gordonae* is frequently encountered in the environment and in clinical laboratories but is almost always considered nonpathogenic. *M. gordonae* is the most frequently isolated mycobacterial contaminant. It is readily recovered from freshwater, pipelines, and laboratory faucets (88, 203). With current technology, commercial DNA probes are available for confirmation of species identification, thus eliminating much of the delay in reporting.

Clinical presentation. In a recent study, only 23 confirmed clinically significant cases were found before 1992, and these cases antedated accurate molecular identification. However, occasionally, *M. gordonae* has been known to cause infections, especially in patients with an underlying predisposition or immunosuppression such as AIDS, steroid therapy, or carcinoma, or in patients undergoing peritoneal dialysis, in transplant recipients, and in children (371–376).

The isolation of *M. gordonae* in the absence of invasive disease may create diagnostic confusion and institution of inappropriate therapy. It is also problematic in the laboratory, causing unnecessary time and expense (377). In addition, reports of pseudo-outbreaks with *M. gordonae* have been reported. These outbreaks have implicated contaminated tap water or ice, topical anesthetics, and a commercial antibiotic solution used to suppress growth of nonmycobacterial species and facilitate the detection of mycobacteria in the laboratory (246, 377, 378). It has been hypothesized that *M. gordonae* is present in tap water ingested by patients before expectoration, tracheal suctioning, or bronchoscopy, and thus contaminates respiratory specimens (379, 380). Thus, it may be advantageous to avoid rinsing or drinking tap water or other beverages made from tap water for several hours before collection of respiratory samples (381). Similar suggestions have been made to avoid contamination with other tap-water species, such as *M. mucogenicum* and *M. simiae*, in the same document.

Treatment. Although few susceptibility data are available, antimicrobial agents most consistently active *in vitro* include ethambutol, rifabutin, clarithromycin, linezolid, and the fluoroquinolones (382, 383).

M. haemophilum

The organism. *M. haemophilum* has been recovered from patients in multiple locales around the world (194–197, 384, 385). *M. haemophilum* requires special medium with hemin or iron-containing compounds for growth. The optimal growth temperature of 28° to 30°C is compatible with the preference of *M. haemophilum* infection for cooler sites of the body, including the extremities (64, 160, 386, 387).

Clinical presentation. Because of the unusual culture requirements of *M. haemophilum*, some circumstances should dictate supplementation of media to recover the organism. Classically, *M. haemophilum* should be considered with an AFB smear–positive, draining skin lesion that has no growth on ordinary (routine) AFB media. Specimens from immunosuppressed patients (especially organ transplant recipients), such as skin lesions or ulcerations, lymph node aspiration, joint fluid, or other undiagnosed lesions, with a positive AFB smear result, should be cultured for *M. haemophilum*. Last, specimens obtained from adenitis in immunocompetent children should be cultured for *M. haemophilum*.

Disseminated infection with *M. haemophilum* is associated with immunosuppression with solid organ transplant, long-term steroid use, AIDS, and bone marrow transplant (64, 151, 160, 384–389).

M. haemophilum has also been recovered from immunologically intact children with lymphadenitis (194, 202).

Treatment. There are currently no standardized susceptibility methods for *M. haemophilum*. Agents that appear to be active *in vitro* include amikacin, clarithromycin, ciprofloxacin, rifampin, and rifabutin (160, 390–394). Doxycycline and sulfonamides have shown variable susceptibility but all isolates are resistant to ethambutol (160, 392). In the absence of standardized methodology, *in vitro* susceptibility data must be used with caution.

Optimal therapy for disseminated disease is unknown; however, successful therapy has been reported with multidrug regimens including clarithromycin, rifampin, rifabutin, and ciprofloxacin (64, 160, 391, 392). Surgical excision alone is usually adequate treatment for lymphadenitis in immunocompetent hosts.

M. immunogenum (RGM)

The organism. *M. immunogenum* is closely related to *M. abscessus* and *M. chelonae*. *M. immunogenum* grows poorly at routine temperatures for mycobacterial incubation. Because of overlap in HPLC pattern with other RGM, molecular techniques are necessary for confirmation of identification.

Clinical presentation. *M. immunogenum* isolates have been associated with multiple pseudo-outbreaks resulting from contaminated automated bronchoscope-cleaning machines and have been recovered from metalworking fluids (143, 206, 395, 396).

Clinically significant isolates have been recovered from skin lesions, corneal ulcers, joint fluid, central venous catheter sites, and blood (143). Pulmonary disease with this organism has also been reported (396).

Treatment. *M. immunogenum* isolates are susceptible to amikacin and clarithromycin but resistant to ciprofloxacin, doxycycline, cefoxitin, tobramycin, and sulfamethoxazole (143).

The optimal therapy for this organism is unknown; however, successful therapy is likely difficult due to the extensive antibiotic resistance of the organism.

M. malmoense

The organism. *M. malmoense* has been recovered from natural waters in Finland and soils in Zaire and Japan (397–399). In many areas of northern Europe, *M. malmoense* is the second

most common nontuberculous mycobacterium recovered from sputum and cervical lymph node specimens from children, surpassed only by MAC. *M. malmoense* has rarely been reported in the United States, with most isolates recovered from Florida, Texas, and Georgia (400, 401).

Clinical presentation. Most infections involving *M. malmoense* have been associated with pulmonary and lymph node diseases, but disseminated and extrapulmonary disease, including tenosynovitis and cutaneous infections, also has been reported (197, 402–404). To date, AIDS has not been a predisposing factor for *M. malmoense* infection.

Treatment. The results of susceptibility testing of *M. malmoense* are variable. The original isolates were reported as susceptible *in vitro* to ethambutol, ethionamide, kanamycin, and cycloserine, but resistant to INH, streptomycin, rifampin, and capreomycin (404). Several investigators have reported a lack of consistency and correlation between clinical response and *in vitro* antimicrobial susceptibilities among strains, which may be at least partially explained by differences in susceptibility techniques (197, 400, 402, 405, 406).

Pulmonary *M. malmoense* infection may be difficult to treat. The optimal chemotherapy is not known, but some microbiologic improvement has occurred with the use of combinations of INH, rifampin, and ethambutol, with and without quinolones and macrolides (400–402).

M. marinum

The organism. Isolates of *M. marinum* are pigmented, slowly growing organisms that grow optimally at temperatures of approximately 30 to 33°C.

Epidemiology. *M. marinum* is the cause of "swimming pool granuloma" or "fish tank granuloma" (407, 408). *M. marinum* is distributed widely in aquatic environments, in fresh- and saltwater, especially in relatively still or stagnant water, such as in fish tanks or nonchlorinated swimming pools (407). Adequate chlorination has, however, substantially reduced rates of colonization in swimming pools. Infection is typically acquired from a soft tissue injury to the hand in an aquatic environment.

Clinical presentation. *M. marinum* causes chronic granulomatous soft tissue infections involving skin and bone (218, 407–410). Cases occur in both healthy and immunocompromised hosts throughout the United States. The lesions usually appear as papules on an extremity, especially on the elbows, knees, feet, and hands, progressing subsequently to shallow ulceration and scar formation (*see* the online supplement). Most lesions are solitary, although occasional "ascending" lesions develop that resemble sporotrichosis. Clinical involvement of regional nodes is uncommon. The organisms may be introduced into the skin through previous abrasions contaminated while cleaning freshwater fish tanks ("fish tank granuloma") or by scratches or puncture wounds from saltwater fish, shrimp, or fins. In a recent report of 63 cases of *M. marinum* infection, 53 (84%) patients had inoculation related to fish-tank exposure. Infection involved the upper limb in 95% of patients, with involvement of deeper structures in 29%. Diagnosis is made from biopsy material, histologic examination, and culture (410).

Treatment. By standard susceptibility testing, *M. marinum* isolates are susceptible to rifampin, rifabutin, and ethambutol; intermediately susceptible to streptomycin; and resistant to isoniazid and pyrazinamide. Isolates are also susceptible to clarithromycin, sulfonamides, or trimethoprim sulfamethoxazole, and susceptible or intermediately susceptible to doxycycline and minocycline.

There have been no comparative trials of treatment regimens for skin and soft tissue infections due to *M. marinum* but a reasonable approach is to treat with two active agents for 1 to 2 months after resolution of symptoms, typically 3 to 4 months in total (410). Some experts believe that minimal disease can be treated with a single agent. In a study from France, 63 patients were treated for an average of 3.5 months, most commonly with the combination of clarithromycin and rifampin. Infection resolved in 42 (93%) of patients with localized infection and in 13 (72%) of those with deep structure involvement (e.g., osteomyelitis) (414). Treatment failure was related to deep structure involvement but not to any antibiotic regimen. Excellent outcomes have also been reported for the combination of clarithromycin and ethambutol and the combination of ethambutol and rifampin (408, 410). Clarithromycin and ethambutol are likely to provide the optimal balance of efficacy and tolerability for most patients, with the addition of rifampin in cases of osteomyelitis or other deep structure infection. Experience in treatment of other NTM suggests that azithromycin may be a reasonable alternative to clarithromycin. Susceptibility testing is not routinely recommended and should be reserved for cases of treatment failure. Surgical debridement may also be indicated, especially for disease involving the closed spaces of the hand, and for disease that has failed to respond to standard therapy.

M. mucogenicum (RGM)

The organism. *M. mucogenicum* was previously given the name *M. chelonae*–like organism or MCLO (411). The current name reflects the highly mucoid character of the isolates.

Clinical presentation. Central venous catheter infections are the most important clinical infection caused by this organism. In a series of 20 cases of clinical disease caused by *M. mucogenicum*, 9 (45%) were from blood and catheter sites in patients with infected central lines (412). *M. mucogenicum* has also been implicated in dialysis catheter–related peritonitis (411).

When isolated from respiratory specimens, this species is most often a contaminant. In one study that included 54 respiratory *M. mucogenicum* isolates, only 2 (4%) were found to be clinically significant (412).

Treatment. This species is susceptible to multiple antimicrobial agents including aminoglycosides, cefoxitin, clarithromycin, minocycline, doxycycline, quinolones, trimethoprim/sulfamethoxazole, and imipenem (412).

M. nonchromogenicum (*see M. terrae* complex)

M. scrofulaceum

The organism. Differentiation of *M. scrofulaceum* from other NTM may be difficult by conventional means and may require molecular methodology (DNA probes or 16S rRNA gene sequencing) (5, 413). Recent studies have shown the newly described species *M. parascrofulaceum* may account for many of the clinical isolates and for some infections attributed to *M. scrofulaceum* and will likely reduce the number of isolates of true *M. scrofulaceum* even more (5, 413, 414).

Epidemiology. *M. scrofulaceum* is found in the environment in house dust, soil, and water, and is an opportunistic pathogen that has been associated with lymphadenitis in children, disseminated infections, pulmonary disease, and skin infections (88, 415–417). In one study from 1982, it was estimated that *M. scrofulaceum* accounted for 2 to 3% of all mycobacterial isolates recovered from clinical samples in the United States (18). However, cases of clinical disease caused by this species were rarely documented except for childhood cervical lymphadenitis (88, 101, 340). In general, *M. scrofulaceum* has all but disappeared from many clinical laboratories for reasons that are unclear. Some have suggested that its most common reservoir was tap water, and changes in chlorination, have removed it from this source. Interestingly, in the early 1980s, *M. scrofulaceum* was replaced by

MAC as the most common cause of childhood cervical lymphadenitis; however, it is rarely recovered in this setting today.

Clinical presentation. In some circumstances, *M. scrofulaceum* continues to be seen clinically. In 1999, an unusually high incidence of *M. scrofulaceum* (14%) lung disease in HIV-negative South African gold miners was reported, suggesting an increased susceptibility to the organism among this population (340). The clinical presentation was indistinguishable from other mycobacterial pulmonary pathogens. Likewise, Swanson and colleagues stated that *M. scrofulaceum* accounts for approximately 2% of the mycobacterial infections in patients with AIDS (413).

Treatment. Susceptibility data are lacking and standard treatment regimens for *M. scrofulaceum* are controversial, emphasizing the need to perform susceptibility testing on confirmed disease-producing isolates of *M. scrofulaceum*.

M. simiae

The organism. The first isolates of *M. simiae* were recovered from monkeys and this association has led to speculation about the zoonotic epidemiology of disease caused by this species. *M. simiae* may produce pigmented or nonpigmented colonies similar to those of MAC. In the laboratory, the niacin test is sometimes positive, leading to possible confusion with *M. tuberculosis* among nonpigmented strains.

Epidemiology. Reports of recovery of *M. simiae* from clinical specimens have been clustered in three geographic areas: Israel, Cuba, and the southwestern United States, including Texas, Arizona, and New Mexico (418–421). Most recoveries have been single positive specimens that are smear negative and not associated with clinical disease, suggesting environmental contamination as a likely source (420, 421). For several clusters of isolates, organisms were also recovered from the local tap water, suggesting it as the likely organism source (420). A large pseudo-outbreak of *M. simiae* isolates from an urban hospital in Texas was recently reported (422). The source for most of the organisms was identified by RFLP analysis of the isolates as a hot-water holding area.

Clinical presentation. *M. simiae* is an uncommon cause of clinical disease. Early surveillance reports suggested that 21% of *M. simiae* patient isolates were believed to be indicative of underlying disease, but other studies have suggested a much lower incidence of clinical disease (419, 422). Most case reports involve immunocompromised groups, such as patients with AIDS or patients with underlying lung disease. Most reports describe pulmonary disease. There are also reports of intraabdominal infections, as well as reports of disseminated disease in immunocompromised patients. Recent pseudo-outbreaks involving contaminated water supplies have been described (108, 422).

Treatment. Treatment for *M. simiae* has proven difficult. *In vivo* response to therapy may not correlate with *in vitro* susceptibility. In previous ATS statements, regimens similar to those for MAC have been recommended for *M. simiae* (2). The optimal pharmacological management for *M. simiae* has yet to be defined, but likely should be clarithromycin based, because most reported favorable clinical outcomes with *M. simiae* involved the use of clarithromycin-based multiple drug regimens, many of which used a fluoroquinolone as well. The newer 8-methoxy fluoroquinolone, moxifloxacin, seems to have activity against *M. simiae* even with isolates resistant to ciprofloxacin. Some isolates are also susceptible *in vitro* to sulfamethoxazole and linezolid. Recent reports suggest a regimen including clarithromycin, moxifloxacin, and trimethoprim/sulfamethoxazole may be successful.

M. smegmatis (RGM)

The organism. The *M. smegmatis* group is currently composed of *M. smegmatis* and the recently described *M. wolinskyi* and *M. goodii*. The most accurate separation of the three species is achieved by molecular techniques including RFLP analysis of the *hsp* 65 gene. An important distinguishing feature of isolates of the *M. smegmatis* group, in contrast to other RGM such as *M. fortuitum*, *M. chelonae*, and *M. abscessus*, is their general lack of *in vitro* susceptibility to clarithromycin. Recent studies have shown this resistance to relate to the presence of a chromosomal erythromycin (macrolide) methylase gene.

Clinical presentation. *M. smegmatis* is rarely a cause of significant infection. *M. smegmatis* has been associated with lymphadenitis, cellulitis, osteomyelitis, or wound infections. It has also been associated with health care–associated infections, including sternal wound infections after cardiac surgery, bacteremia from intravenous catheter placement, and breast abscess after augmentation mammoplasty (423). *M. smegmatis* is a rare cause of mycobacterial lung disease, usually associated with exogenous lipoid pneumonia (32).

Treatment. Antituberculous medications are not active, with the exception of ethambutol, to which *M. smegmatis* is susceptible (423). *M. smegmatis* isolates are susceptible *in vitro* to sulfonamides, doxycycline, imipenem, and amikacin. They exhibit variable susceptibility to cefoxitin and the older fluoroquinolones and are usually resistant to the macrolides (423). Treatment of disease has generally involved the same drugs as for treatment of *M. fortuitum*, with doxycycline and trimethoprim–sulfamethoxazole being the most common oral agents used. For severe infections, amikacin or imipenem are the parenteral agents most often used.

M. szulgai

The organism. *M. szulgai* grows slowly and produces smooth or rough pigmented colonies after 2 to 4 weeks. Production of pigment may require a period of exposure to light in some strains. Using 16S rRNA gene sequences, *M. szulgai* is most closely related to *M. malmoense* but phenotypic distinction between the two species is not difficult.

Epidemiology. Recovery of *M. szulgai* from the environment is very unusual, and in only one case was this organism isolated from water (445). Because *M. szulgai* is rarely recovered from the environment, cultures yielding *M. szulgai* almost always have a pathological significance. *M. szulgai* has been reported from a small number of cases in the English-language literature as a human pathogen (424–428).

Clinical presentation. Pulmonary *M. szulgai* disease is indistinguishable from that caused by *M. tuberculosis*, with chronic cough, weight loss, and upper lobe cavitary infiltrates. The majority of patients are men older than 50 years with risk factors including alcohol abuse, smoking, COPD, and a history of pulmonary TB. The diagnosis of *M. szulgai* disease, similar to disease caused by *M. kansasii*, may be considered with just one positive culture, in the appropriate clinical circumstance.

Extrapulmonary infection due to *M. szulgai* includes cases of tenosynovitis of the hand, olecranon bursitis, osteomyelitis, keratitis, cervical lymphadenitis, and renal or cutaneous infection. Disseminated infection has been reported in immunocompromised patients.

Treatment. *M. szulgai* is susceptible *in vitro* to most anti-TB drugs. In previously reported cases, chemotherapy was successful when combinations of more than two drugs were used (425). Susceptibility of *M. szulgai* to quinolones and to the newer macrolides has also been reported (424–428). Although the optimal duration of treatment has not been established, a three- to four-drug regimen that includes 12 months of negative sputum cultures while on therapy is probably adequate. At least one patient has been reported to have been treated successfully with

a standard 6-month TB regimen including INH, rifampin, and pyrazinamide (425).

Therapy with combination antituberculous medication based on *in vitro* susceptibilities for 4 to 6 months should be successful for extrapulmonary *M. szulgai* disease.

M. terrae (complex)

The organism. *M. terrae* complex is currently composed of multiple species including *M. terrae*, *M. triviale*, *M. nonchromogenicum*, and *M. hiberniae* (5). Biochemically, the individual species within the complex have been difficult to distinguish and HPLC alone is not always adequate for identification of most isolates to the species level. Differentiation of the species usually requires molecular techniques so that most clinical laboratories still refer to the collective designation, *M. terrae* complex. Moreover, most of the isolates of this complex have previously been presumed to be nonpathogenic so that little attention has been focused on this group of organisms (429).

Clinical presentation. The one setting where *M. terrae* complex is generally accepted as a pathogen is chronic tenosynovitis of the hand. Ridderhof and colleagues reported six cases of *M. nonchromogenicum*, identified by HPLC, in patients with tenosynovitis (430). From this report, the authors concluded that *M. nonchromogenicum* was the primary pathogen in the *M. terrae* complex. However, more modern (molecular) methods have not been used to confirm this hypothesis, and separation of the species members by HPLC is difficult.

A review of 54 cases of the *M. terrae* complex disease was recently published (435). Of the cases cited, 59% involved tenosynovitis, and 26% were associated with pulmonary disease. Underlying medical problems were absent or not reported in 72% of the cases. One-half of the patients with tenosynovitis were treated with local or systemic corticosteroid and only one-half of the patients who were followed for 6 months showed clinical improvement. The other half of the patients required extensive debridement, and surgical intervention or amputation (431).

Some reports have also indicated potential pathogenicity of this organism for the lung. In 1983, a case of localized cavitary disease in the lung with multiple isolations of *M. terrae* complex in a patient with a diagnosis of pulmonary TB was described (432). Later, in 1991, a case of pulmonary *M. terrae* complex in a patient who had undergone an autologous bone marrow transplant and high-dose chemotherapy was described (433). An isolate of *M. terrae* complex in a patient with persistent urinary tract infections was also reported (434).

Treatment. The optimum antimicrobial therapy for *M. terrae* complex has not been established, although some investigators suggest the use of a macrolide plus ethambutol or other agent based on *in vitro* susceptibility results (431). In one report, all six of the isolates from a single center and 90% or more of an additional 22 isolates of *M. terrae* complex were susceptible to ciprofloxacin and sulfonamides. Recently, 11 isolates of *M. terrae* complex were also shown to be susceptible to linezolid (435).

M. ulcerans

The organism. *M. ulcerans* may require up to 6 to 12 weeks to grow at temperatures of 25° to 33°C. Many conventional decontamination methods may render the organism nonviable. Supplementation of media with egg yolk or reduction of oxygen tension enhances the recovery of this species. Molecular techniques have been developed that may lead to more rapid identification of the organism.

Epidemiology. *M. ulcerans* is not endemic in the United States but occurs in discrete but widely dispersed geographic areas in the watersheds of tropical rain forests, primarily in Africa, Southeast Asia, Australia, and South and Central America (436, 437). On a worldwide scale, *M. ulcerans* is now the third most prevalent mycobacterial species, after *M. tuberculosis* and *M. leprae*, in immunocompetent individuals (436).

Clinical presentation. *M. ulcerans* causes indolent, progressive necrotic lesions of the skin and underlying tissue with indeterminate scalloped edges known historically as "buruli ulcers" (87, 88, 438). Infection is believed to occur through abraded or compromised skin after contact with contaminated water or soil. The lesions occur most commonly in children and young adults and often result in severe scarring and deformities of the extremities (88).

Treatment. Medical treatment of large established ulcers is disappointing (436). Preulcerative lesions are often painless and can be treated effectively by excision and primary closure, rifampin monotherapy, or heat therapy. Postsurgical antimycobacterial treatment may prevent relapse or metastasis of infections. Most antimycobacterial agents are ineffective for the treatment of the ulcer. Clarithromyicn and rifampin may be the best choice for controlling complications of the ulcer. Drug treatment of the disease has been disappointing; surgical debridement combined with skin grafting is the usual treatment of choice (436).

M. xenopi

The organism. *M. xenopi* is an obligate thermophile with an optimum growth temperature of 45°C (*see* LABORATORY PROCEDURES).

Epidemiology. *M. xenopi* has been isolated from environmental water and soil, tap-water systems, and showerheads (439–441). Recovery from hot-water taps has been noted in areas that frequently recover *M. xenopi*, and suggests a likely source for contamination of clinical specimens during collection or laboratory processing (440–442). Colonization of the hot-water tank of an automated disinfection machine by *M. xenopi* resulted in a pseudoepidemic of infection with this organism by contamination of fiberoptic bronchoscopes (225).

Clusters of hospital isolates have been reported from the United States, the United Kingdom, and in other areas in Europe. In two studies, the clinical isolates and hospital-water isolates were shown to be identical by DNA genotyping (440, 441). It has been speculated that the organism enters the hospital from municipal water mains, then multiplies in the hospital heating tanks where the temperature is 43° to 45°C, the optimal temperature for growth of this organism (442).

Clinical presentation. *M. xenopi* is second to MAC as a cause of NTM lung disease in areas of Canada, the United Kingdom, and other areas of Europe (2). *M. xenopi* is infrequently isolated in the United States, although pulmonary infections caused by this organism have been recognized in patients residing in the northeastern and, more recently, the southeastern United States. The organism has also been reported from Japan and Israel.

M. xenopi lung disease typically occurs in patients with obstructive pulmonary disease. Symptoms from *M. xenopi* pulmonary infection are typical of NTM pulmonary disease and insidious in onset. The radiographic appearance of *M. xenopi* pulmonary infection is usually an apical cavitary process, although most patients develop minimal disease. Lymphadenopathy and pleural effusions are rare roentgenographic findings.

Extrapulmonary cases are rare but have been reported. Nosocomial spinal infections caused by *M. xenopi* have also been reported as the result of tap water contamination of surgical instruments (451). Joint and soft tissue infections have also been reported (440, 442).

Treatment. The optimal treatment regimen and duration of treatment for *M. xenopi* pulmonary disease have not been established. In addition, the response of this organism to therapy is variable and does not always correlate well with the results of *in vitro* susceptibility. Susceptibility testing of *M. xenopi* can be difficult to interpret. Some reports have shown the isolates to

be susceptible to most first-line antituberculous agents; however, some isolates have been reported to have variable resistance to rifampin, ethambutol, and low levels of INH. The cornerstone of therapy for *M. xenopi* is a combination of clarithromycin, rifampin, and ethambutol. Therapy should be continued until the patient has maintained negative sputum cultures while on therapy for 12 months. It has been observed that sputum conversion occurs readily, but relapse rates are high even with macrolide-containing regimens. Surgical resection of the affected lung may be appropriate in selected patients who have sufficient lung function and fail to respond to chemotherapy.

Therapeutic response may be enhanced with the addition of quinolones and clarithromycin to the standard antituberculous therapy (443–446). A reasonable regimen might consist of INH, rifabutin or rifampin, ethambutol, and clarithromycin, with or without an initial course of streptomycin. A quinolone, preferably the 8-methoxy quinolone moxifloxacin, could be substituted for one of the antituberculous drugs.

In one previous report, the mortality rate from *M. xenopi* pulmonary infection was 57%, possibly reflecting severe underlying pulmonary disease (445).

Therapy for extrapulmonary disease would include the same agents as for pulmonary disease. Surgical debridement is also frequently important for soft tissue infections.

Other NTM Species/Pathogens

For other NTM species and pathogens, *see* the online supplement.

RESEARCH AGENDA FOR NTM DISEASE

More fundamental information is needed to improve understanding in essentially all areas of NTM disease. There is little information about the incidence or prevalence of NTM diseases. There are multiple reasons for a lack of progress in this area but the major problems remain that NTM diseases occur sporadically and are not reportable to state public health authorities. Perhaps the highest priority and one that would facilitate most of the other NTM research questions and goals is a mechanism for reporting or collecting data on all patients diagnosed with NTM diseases. Important issues to be answered include prevalence and incidence rates, including geographic differences in those rates, and potential risk factors. A national effort, perhaps spearheaded by the CDC or National Institutes of Health will be necessary to answer the important questions about the epidemiology of NTM diseases. Recognition of NTM as an "emerging pathogen" would perhaps elevate NTM as a priority for funding.

With better understanding of disease epidemiology, clues will likely emerge that will also direct research in NTM disease pathogenesis. Through identification and evaluation of mutations and polymorphisms in components of the IFN-γ/IL-12 synthesis and response pathways, we have gained a better understanding of the mechanisms and risk factors influencing the development of mycobacterial disease. Although significant progress has been made in understanding NTM disease pathogenesis in some narrow areas of immune dysfunction, the role of immune factors in disease development for most patients with NTM disease remains to be elucidated. However, greater awareness of factors at the molecular level, such as mutations and polymorphisms, and at the morphologic level, such as the roles of sex and chest shape, will gradually improve our understanding of susceptibility to mycobacterial diseases of individual patients. An animal model of NTM disease, other than disseminated MAC disease, would also likely accelerate our understanding of NTM disease pathogenesis.

As important as identifying predisposing factors for NTM disease is identifying the source(s) of infection both for newly infected and for reinfected patients. Investigation of nosocomial infections is beginning to provide clues about the acquisition of NTM infection in selected vulnerable patients. Although NTM exposure appears to be ubiquitous, it may be possible to identify a role for disease avoidance and prevention for at least some patients with NTM lung disease, perhaps those identified with predisposing immune-related susceptibility.

A rapidly emerging area of NTM disease is in the area of CF. Understanding of the natural history of NTM infection in this setting and how it affects the progression of bronchiectasis and CF disease, how and if patients respond to drug treatment for NTM, and the role of measuring serum drug levels for determining optimal drug dosages are important questions that remain unanswered. *M. abscessus* is perhaps the most virulent NTM pathogen in CF, and as with other CF pathogens, the source of infection for these patients also remains unknown.

Advances are needed in the treatment of virtually all NTM infections but the chronicity and indolence of NTM pulmonary disease make clinical trials expensive and difficult. Nevertheless, multicenter, controlled trials are desperately needed for answering the many important questions about optimal therapy that remain unanswered. In contrast to TB, basic information, such as the efficacy of many individual agents in the treatment of NTM disease, is not available. There is a need for a disease treatment model that will allow agents to be tested without significantly long monotherapy exposure. As noted above, an animal model for evaluating drugs in NTM diseases other than disseminated diseases would also likely accelerate drug development and evaluation. New antimicrobial agents are urgently needed to shorten or simplify therapy, provide more effective therapy, and diminish drug side effects. With the recent unprecedented introduction of several promising agents for the treatment of TB, there is some hope that there will be collateral benefit for the therapy of NTM disease as well (447). In the laboratory, identifying MICs that predict clinical outcome, especially for MAC, whether for individual drugs or combinations of drugs, would greatly facilitate the treatment of these patients. The identification of specific immune defect(s) might prove the essential element for the development of new therapeutic approaches.

Interest in developing new drugs with mycobacterial disease activity is limited by the lack of economic return for these relatively rare diseases. The cost/benefit considerations may be more difficult than with a communicable disease threat such as TB. Perhaps recognition of NTM infections in populations such as CF or, even more importantly, as an expanding public health problem will spur further development of new treatment approaches and stimulate the release of funds for multicenter studies and trials.

SUMMARY OF RECOMMENDATIONS

The recommendations are rated on the basis of a system developed by the U.S. Public Health Service and the IDSA (3). The rating system includes a letter indicating the strength of the recommendation, and a roman numeral indicating the quality of the evidence supporting the recommendation (3) (Table 1). Ratings pertain to all points within the numbered recommendation.

Laboratory Procedures

Collection, digestion, staining, decontamination, and culturing of specimens.

***Recommendations*:**

1. As much material as possible for NTM culture should be provided with clear instructions to the laboratory to culture for mycobacteria (C, III).

2. All cultures for NTM should include both a rapid detection broth (liquid) media technique and solid media cultures (C, III).
3. Quantitation of the number of colonies on plated culture media should be performed to aid clinical diagnosis (C, III).
4. Supplemented culture media and special culture conditions (lower incubation temperatures) should be used for material cultured from skin lesions, joints, and bone (A, II).
5. The time (in days) to detection of mycobacterial growth should be stated on the laboratory report (C, III).

NTM identification.

***Recommendations*:**

1. Clinically significant NTM isolates should be routinely identified to the species level. An important exception is MAC because the differentiation between *M. avium* and *M. intracellulare* is not yet clinically significant. Although not routinely recommended, this differentiation may be important epidemiologically and, in the future, therapeutically (C, III).
2. The RGM (especially *M. chelonae*, *M. abscessus*, and *M. fortuitum*) should be identified to species level using a recognized acceptable methodology, such as PRA or biochemical testing, not HPLC alone (A, II).
3. Susceptibility of RGM for eight agents, including amikacin, cefoxitin, clarithromycin, ciprofloxacin, doxycycline, linezolid, sulfamethoxazole, and tobramycin, can also be used to facilitate identification of *M. abscessus*, *M. chelonae*, and *M. fortuitum* (C, III).
4. Communication between the clinician and laboratorian is essential for determining the importance and extent of the identification analysis for a clinical NTM isolate (C, III).

Antimicrobial susceptibility testing.

***Recommendations*:**

1. Clarithromycin susceptibility testing is recommended for new, previously untreated MAC isolates. Clarithromycin is recommended as the "class agent" for testing of the newer macrolides because clarithromycin and azithromycin share cross-resistance and susceptibility. No other drugs are recommended for susceptibility testing of new, previously untreated MAC isolates. There is no recognized value for testing of first-line antituberculous agents with MAC using current methodology (A, II).
2. Clarithromycin susceptibility testing should be performed for MAC isolates from patients who fail macrolide treatment or prophylaxis regimens (A, II).
3. Previously untreated *M. kansasii* strains should be tested *in vitro* only to rifampin. Isolates of *M. kansasii* that show susceptibility to rifampin will also be susceptible to rifabutin (A, II).
4. *M. kansasii* isolates resistant to rifampin, should be tested against a panel of secondary agents, including rifabutin, ethambutol, isoniazid, clarithromycin, fluorquinolones, amikacin, and sulfonamides (A, II).
5. *M. marinum* isolates do not require susceptibility testing unless the patient fails treatment after several months (A, II).
6. There are no current recommendations for one specific method of *in vitro* susceptibility testing for fastidious NTM species and some less commonly isolated NTM species (C, III).
7. Validation and quality control should be in place for susceptibility testing of antimicrobial agents with all species of NTM (C, III).

Clinical presentations and diagnostic criteria.

***Recommendations*:**

1. The minimum evaluation of a patient suspected of NTM lung disease should include (*1*) chest radiograph or, in the absence of cavitation, chest HRCT scan; (*2*) three or more sputum specimens for AFB analysis; and (*3*) exclusion of other disorders, such as TB and lung malignancy. In most patients, a diagnosis can be made without bronchoscopy or lung biopsy (A, II).
2. Disease caused by *M. tuberculosis* is often in the differential diagnosis for patients with NTM lung disease. Empiric therapy for TB, especially with positive AFB smears and results of nucleic acid amplification testing, may be necessary pending confirmation of the diagnosis of NTM lung disease (C, III).
3. *See* Table 3 for diagnostic criteria of nontuberculous mycobacterial lung disease.

Cystic Fibrosis

***Recommendations*:**

1. Adult and adolescent patients with CF should have periodic, at least yearly, screening cultures for NTM. During periods of clinical decline unresponsive to treatment for non-NTM pathogens, all patients with CF, including children, should be evaluated for NTM (A, II)
2. Patients being considered for macrolide monotherapy as immunotherapy for CF should have sputum cultured for NTM before starting therapy and periodically thereafter, and those with repeated isolation of NTM should not receive macrolide monotherapy (C, III).
3. The diagnostic criteria and treatment regimens for NTM pulmonary infection in patients with CF are the same as for patients without CF, although they may be more difficult to apply because of underlying disease and concomitant infections (C, III).

Hypersensitivity-like Disease

***Recommendations*:**

1. For indoor pools and hot tubs, manufacturers universally recommend following regular maintenance procedures (including draining and thorough cleaning of the tub and filtering system) and bathing before hot-tub use (C, III).
2. For any patient with documented hypersensitivity pneumonitis (hot-tub lung)–related disease, complete avoidance of mycobacterial antigen is paramount. For hot-tub lung, avoidance of MAC antigen, including avoidance of indoor hot-tub use, and for metal grinders, avoidance of *M. immunogenum* antigen, including avoidance of metalworking fluid, is recommended (A, II).
3. Patients with severe disease or respiratory failure should receive prednisone at 1 to 2 mg/kg/day tapered over 4 to 8 weeks (C, III).
4. For immunocompromised patients, patients with persistent disease after removal from MAC antigen exposure (with or without corticosteroids) or patients with bronchiectasis, begin antimicrobial drugs with activity against MAC as recommended elsewhere in this document, with

consideration given to shorter (3–6 mo) duration of therapy (C, III).

Health Care– and Hygiene-associated Disease and Disease Prevention

***Recommendations*:**

1. Prevention of health care–associated NTM outbreaks and pseudo-outbreaks:
   a. Intravenous catheters: Patients with indwelling central catheters, especially bone marrow transplant recipients, should avoid contact or contamination of their catheter with tap water (B, II).
   b. Fiberoptic endoscopes: The use of tap water should be avoided in automated endoscopic washing machines as well as in manual cleaning. The instruments should have a terminal alcohol rinse. The reader should consult the "Association for Professionals in Infection Control (APIC) Guidelines for Infection Prevention and Control in Flexible Endoscopy" at www.apic.org for a detailed discussion of cleaning and disinfection of endoscopic equipment (A, II).
   c. Local injections: Avoid benzalkonium chloride (e.g., Zephiran) as a skin disinfectant as it allows growth of mycobacteria such as *M. abscessus.* Avoid use of multidose vials (A, II).
   d. Recognize and avoid the risk of alternative medicine practices that provide injections of unknown or unapproved substances (C, III).
   e. Surgery: (*1*) Do not use tap water and/or ice prepared from tap water in the operating room, especially during cardiac surgery or augmentation mammoplasty (A, II). (*2*) Do not wash or contaminate open wounds with tap water (A, II). (*3*) Outpatient facilities performing plastic surgery procedures such as liposuction or augmentation mammoplasty must carefully follow recommended sterilization guidelines (C, III).
   f. Sputum collection: Do not allow a patient to drink or rinse the mouth with tap water before collecting an expectorated specimen (C, III).
2. Recognition of outbreaks: Be familiar with the settings for health care–associated outbreaks and pseudo-outbreaks and the organisms (usually RGM) most frequently involved, and intervene as soon as possible to interrupt this transmission (C, III).

NTM Species: Clinical Aspects and Treatment Guidelines

***Context and General Recommendations*:**

1. NTM are uncommonly encountered clinical pathogens; some species, in fact, are much more likely to be isolated as a result of specimen contamination than as a result of disease. However, even these species can, under some circumstances, cause clinical disease. The clinician, therefore, must always know the context in which an NTM isolate was obtained to assess accurately the clinical significance of that isolate. When questions about the clinical significance of an NTM isolate arise, expert consultation is strongly encouraged (C, III).
2. Treatment recommendations for infrequently encountered NTM are made on the basis of only a few reported cases. With that limitation in mind, unless otherwise stated, the duration of therapy for most pulmonary NTM pathogens is based on treatment recommendations for more frequently encountered species such as MAC and *M. kansasii* (e.g., 12 mo of negative sputum cultures while on therapy). For disseminated disease, treatment duration for most NTM pathogens is the same as for disseminated MAC infection (C, III).
3. The treatment of NTM disease is generally not directly analogous to the treatment of TB. *In vitro* susceptibilities for many NTM do not correlate well with clinical response to antimycobacterial drugs. Recommendations for routine *in vitro* susceptibility testing of NTM isolates are limited (*see* Laboratory Procedures). The clinician should use *in vitro* susceptibility data with an appreciation for its limitations. *See* an expanded discussion of *in vitro* susceptibilities in Laboratory Procedures (B, II).
4. Empiric therapy for suspected NTM lung disease is not recommended (C, III).
5. There are no widely accepted criteria for choosing patients with NTM lung disease for resectional surgery. In general, the more difficult an NTM pathogen is to treat medically, the more likely surgery should be considered from a risk/benefit perspective. Expert consultation is strongly encouraged (C, III).

MAC Lung Disease

***Recommendations*:**

1. The recommended initial regimen for most patients with nodular/bronchiectatic MAC lung disease is a three-times-weekly regimen including clarithromycin 1,000 mg or azithromycin 500 mg, ethambutol 25 mg/kg, and rifampin 600 mg administered three times per week (A, II).
2. The recommended initial regimen for fibrocavitary or severe nodular/bronchiectatic MAC lung disease includes clarithromycin 500–1,000 mg/day or azithromycin 250 mg/day, ethambutol 15 mg/kg/day, and rifampin 10 mg/kg/day (maximum, 600 mg). An initial 2 months of ethambutol at 25 mg/kg/day is no longer recommended (A, II). Alternative treatment recommendations, including the use of parenteral agents, are illustrated in Table 5 (B, II).
3. Intermittent drug therapy is not recommended for patients who have cavitary disease, patients who have been previously treated, or for patients who have moderate or severe disease (C, III).
4. The primary microbiologic goal of therapy is 12 months of negative sputum cultures while on therapy; therefore, sputum must be collected from patients for AFB examination throughout treatment (A, II).
5. Macrolides should not be used as montherapy for MAC because of the risk for developing macrolide-resistant MAC isolates (A, II).
6. A macrolide with a single companion drug, ethambutol, may be adequate for nodular/bronchiectatic MAC disease but should not be used in patients with fibrocavitary disease because of the risk of emergence of macrolide resistance (A, II).
7. Patients respond best to MAC treatment regimens the first time they are administered; therefore, it is very important that patients receive recommended multidrug therapy the first time they are treated for MAC lung disease (A, II).
8. Expert consultation should be sought for patients who have difficulty tolerating MAC treatment regimens or who do not respond to therapy (C, III).

See Tables 5, 6, and 7.

Surgical Treatment For MAC Lung Disease

***Recommendations*:**

1. Surgical resection of limited (focal) disease in a patient with adequate cardiopulmonary reserve to withstand partial or complete lung resection can be successful in combination with multidrug treatment regimens for treating MAC lung disease (B, II).
2. Surgical resection of a solitary pulmonary nodule due to MAC is considered curative (C, III).
3. Mycobacterial lung disease surgery should be performed in centers with expertise in both medical and surgical management of mycobacterial diseases (C, III).

M. kansasii

***Recommendations*:**

1. Patients should receive a daily regimen including rifampin 10 mg/kg/day (maximum, 600 mg), ethambutol 15 mg/kg/day, isoniazid 5 mg/kg/day (maximum, 300 mg), and pyridoxine 50 mg/day (A, II). An initial 2 months of ethambutol at 25 mg/kg/day is no longer recommended (A, II).
2. Treatment duration for *M. kansasii* lung disease should include 12 months of negative sputum cultures (A, II).
3. For patients with rifampin-resistant *M. kansasii* disease, a three-drug regimen is recommended based on *in vitro* susceptibilities including clarithromycin or azithromycin, moxifloxacin, ethambutol, sulfamethoxazole, or streptomycin (A, II).
4. Patients undergoing therapy for *M. kansasii* lung disease should have close clinical monitoring with frequent sputum examinations for mycobacterial culture throughout therapy (C, III).

M. abscessus

***Recommendations*:**

1. The only predictably curative therapy of limited (focal) *M. abscessus* lung disease is surgical resection of involved lung combined with multidrug chemotherapy (A, II).
2. Periodic administration of multidrug therapy, including a macrolide and one or more parenteral agents (amikacin, cefoxitin, or imipenem) or a combination of parenteral agents over several months may help control symptoms and progression of *M. abscessus* lung disease (C, III).

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