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Caused by Nontuberculous Mycobacteria

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American Thoracic Society

MEDICAL SECTION OF THE AMERICAN LUNG ASSOCIATION

Diagnosis and Treatment of Disease Caused by Nontuberculous Mycobacteria

THE OFFICIAL STATEMENT OF THE AMERICAN THORACIC SOCIETY WAS APPROVED BY THE BOARD OF DIRECTORS, MARCH 1997

SUMMARY

Diagnostic Criteria of Nontuberculous Mycobacterial Lung Disease in HIV-Seropositive and -Seronegative Hosts

The following criteria apply to symptomatic patients with infiltrate, nodular or cavitary disease, or a high resolution computed tomography scan that shows multifocal bronchiectasis and/or multiple small nodules.

- A. If three sputum/bronchial wash results are available from the previous 12 mo:
 1. three positive cultures with negative AFB smear results or
 2. two positive cultures and one positive AFB smear
- B. If only one bronchial wash is available:
 1. positive culture with a 2+, 3+, or 4+ AFB smear or 2+, 3+, or 4+ growth on solid media
- C. If sputum/bronchial wash evaluations are nondiagnostic or another disease cannot be excluded:
 1. transbronchial or lung biopsy yielding a NTM or
 2. biopsy showing mycobacterial histopathologic features (granulomatous inflammation and/or AFB) and one or more sputums or bronchial washings are positive for an NTM even in low numbers

Comments:

These criteria fit best with *M. avium* complex, *M. abscessus*, and *M. kansasii*. Too little is known of other NTM to be certain how applicable these criteria will be.

At least three respiratory samples should be evaluated from each patient. Other reasonable causes for the disease should be excluded. Expert consultation should be sought when diagnostic difficulties are encountered.

KEY LABORATORY FEATURES OF THE NONTUBERCULOUS MYCOBACTERIA

1. *Staining and culture.* Current methods of specimen staining and culture used for *M. tuberculosis* are acceptable for most NTM species. The preferred methodology includes fluorochrome staining and culture in a liquid medium as well as on Middlebrook 7H10 or 7H11 agar. Species for which special growth conditions are needed include those responsible for cutaneous disease, which need lower incubation temperatures, and the relatively fastidious species *M. haemophilum*, *M. genavense*, and *M. conspicuum*.
2. *Species identification.* Methods of rapid species identifica-

tion including commercial DNA probes (*M. avium* complex, *M. kansasii*, *M. goodii*) and high-pressure liquid chromatography are preferred over the slower traditional biochemical methods.

3. *Susceptibility testing of M. avium complex.* Susceptibility testing with rifabutin and the antituberculosis drugs is not recommended. Routine testing against clarithromycin should not be performed, but that test should be performed on isolates from patients who have failed prior macrolide therapy or prophylaxis. Minimal inhibitory concentration (MIC) of $> 32 \mu\text{g/ml}$ is the recommended resistance breakpoint.
4. *Susceptibility testing of M. kansasii.* Routine susceptibility testing of *M. kansasii* should include only rifampin, because currently used resistance breakpoints for isoniazid and streptomycin often give misleading results and methods for the other drugs have not been established.
5. *Susceptibility testing of the rapid growers.* Susceptibility testing of clinically significant rapidly growing mycobacteria (*M. fortuitum*, *M. abscessus*, *M. chelonae*) should not be performed with the antituberculosis agents. They should be tested against antibacterial drugs including amikacin, doxycycline, imipenem, the fluorinated quinolones, a sulfonamide, cefoxitin, and clarithromycin.

PROPHYLAXIS AND TREATMENT OF NONTUBERCULOUS MYCOBACTERIA DISEASE

1. *Treatment of M. kansasii pulmonary disease.* A regimen of daily isoniazid (300 mg), rifampin (600 mg), and ethambutol (25 mg/kg for 2 mo, then 15 mg/kg) for 18 mo with a minimum of 12 mo culture negativity is recommended for pulmonary disease in adults caused by *M. kansasii*. Clarithromycin or rifabutin will need to be substituted for rifampin in HIV-positive patients who take protease inhibitors.
2. *Treatment of M. avium complex pulmonary disease.* A regimen of daily clarithromycin (500 mg twice a day) or azithromycin (250 mg), rifampin (600 mg) or rifabutin (300 mg), and ethambutol (25 mg/kg for 2 mo, then 15 mg/kg) is recommended for therapy of adults not infected with the HIV virus. Streptomycin two to three times per week should be considered for the first 8 wk as tolerated. Patients should be treated until culture-negative on therapy for 1 yr.
3. *Treatment of disseminated M. avium complex disease.* Therapy in adults should include daily clarithromycin (500 mg twice a day) or azithromycin (250 to 500 mg), plus ethambutol 15 mg/kg per day. Consideration should be given to the addition of a third drug (preferably rifabutin at a dose of 300 mg/d). Therapy should be continued for life until more data becomes available.

4. **Prophylaxis of disseminated *M. avium* complex disease.** Prophylaxis should be given to adults with AIDS with CD4 counts < 50 cells, especially with a history of a prior opportunistic infection. Rifabutin 300 mg/d, clarithromycin 500 mg twice daily, azithromycin 1,200 mg once weekly, and azithromycin 1,200 mg once weekly plus rifabutin 300 mg daily are all proven effective regimens.
5. **Treatment of nontuberculous mycobacteria cervical lymphadenitis.** Nontuberculous mycobacteria cervical lymphadenitis is still treated primarily by surgical excision alone, with a 95% cure rate. A clarithromycin-containing regimen should be considered for patients with extensive disease or a poor response to surgery.
6. **Treatment of nonpulmonary rapidly growing mycobacteria.** Therapy of nonpulmonary disease caused by *M. fortuitum*, *M. abscessus*, and *M. chelonae* should include drugs such as amikacin and clarithromycin, based on *in vitro* susceptibility tests.

INTRODUCTION

The continued growth in the number and prevalence of mycobacteria species other than the *Mycobacterium tuberculosis* complex, and recent advances in diagnostic methods and drug therapies for disease caused by these agents, has prompted us to put forth this second, updated diagnostic and therapeutic standard that deals exclusively with the nontuberculous mycobacteria. As in the first statement (1), we refer to these mycobacterial species collectively as the nontuberculous mycobacteria (NTM). The principles of therapy and diagnosis of disease caused by *M. tuberculosis* have been dealt with separately and appear in two ATS statements published most recently in 1990 and 1994 (2, 3). Like the previous NTM statement published in 1990 (1), this statement is designed as a basic guide for professionals involved in the diagnosis and management of disease caused by NTM. Although not all-inclusive, the areas of discussion are referenced in enough detail to allow the reader to assess the scientific basis for ideas and recommendations that are put forth. Included within this statement are revised recommendations for diagnostic criteria that apply primarily to the NTM and updated recommendations of specific therapeutic drug regimens for disease caused by *M. avium* complex and other species of NTM, recognizing the major impact of the newer macrolides and rifabutin, which have become available since 1990. Unless otherwise stated, these drug dosages are for adults. Pediatric doses are described where available.

EPIDEMIOLOGY AND PATHOGENESIS

Sources of Infection

Most NTM organisms have been isolated from water and soil (4-6). The best studied of these has been *M. avium* complex. Extensive environmental studies in the United States have shown that *M. avium* complex grows well in natural waters, particularly in the Southeast (7). *Mycobacterium avium* complex strains with plasmids, possibly associated with virulence, have been shown to be preferentially aerosolized, providing a possible mechanism for airborne acquisition of these organisms (8). Although *M. avium* is an important cause of disease in poultry and swine, serologic studies have suggested that animal-to-human transmission is not important in human infection (Y), and recent molecular studies involving IS901-IS902 and IS1245 have shown that strains infecting humans and animals (especially swine) are different (10, 11). It is now generally accepted that environmental sources, especially natural waters, are the reservoir for most human infections caused by

M. avium complex. The reservoir of *M. avium* for most patients with disseminated disease has not been identified, but it is assumed to be the same as or similar to that for patients with non-HIV-related *M. avium* complex lung disease. *Mycobacterium avium* complex is present in tap water, and one study of disseminated *M. avium* complex disease in AIDS demonstrated that some cases are likely acquired from hospital tap water (12). Interestingly, there does not appear to be a geographic predilection with disseminated disease in the United States, as there is with skin test reactivity and with chronic lung disease.

Water is also the likely source of infection for numerous other NTM species including *M. marinum*, *M. kansasii*, nosocomial outbreaks or pseudo-outbreaks due to rapidly growing mycobacteria, *M. xenopi*, and *M. simiae*. *Mycobacterium marinum* has been commonly associated with salt water, fresh water, fish tanks, and swimming pools (13). *Mycobacterium kansasii* has not been recovered from soil or natural water supplies (5). It has been isolated repeatedly, however, from tap water (14, 15) in the same communities where *M. kansasii* disease exists. Interestingly, it has been shown to survive up to 12 mo in tap water but not in soil.

Rapidly growing mycobacteria such as *M. fortuitum*, *M. chelonae*, and *M. abscessus* can be recovered from soil and natural water supplies, and are the most common NTM associated with nosocomial disease (16-24). Investigations of nosocomial outbreaks or pseudo-outbreaks caused by these species including the use of DNA fingerprinting with pulsed-field gel electrophoresis (25, 26) have demonstrated that tap water (18, 19), ice prepared from tap water (20, 21), processed tap water used for dialysis (22), and distilled water used for preparing solutions such as gentian violet (23, 24) are the usual nosocomial sources of the organisms.

Mycobacterium xenopi is an obligate thermophile that requires temperatures of 28°C or above to grow (4). It has been recovered almost exclusively from hot water and hot water taps within hospitals (15, 27-29), where it has been associated with multiple positive (i.e., probably contaminated) clinical samples and a few cases of clinical pulmonary and soft tissue disease (28-30). These clusters of hospital isolates have been reported from the United States, the United Kingdom, and other areas in Europe. In two studies, the clinical isolates and hospital water isolates have been shown to be identical by DNA fingerprinting (28, 29). 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 43-45°C, the optimal temperature for growth of this organism (30).

Reports of recovery of *M. simiae* from clinical specimens have been clustered in three geographic areas: Israel (31), Cuba, and the southwestern United States-Texas, Arizona, and New Mexico (32-34). Most recoveries have been single positive specimens that are smear-negative (32, 33) and not associated with clinical disease (33), suggesting environmental contamination as a likely source. For several clusters of isolates, organisms were also recovered from the local tap water (34, M. Yakrus, personal communication, 35), suggesting it as the likely organism source.

Mycobacterium mageritense, which has emerged as a major NTM pathogen in northern Europe, has been recovered from natural waters in Finland (36) and soils in Zaire (37) and Japan (38). The recently recognized pathogen *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 (39, 40). *Mycobacterium ulcerans* disease 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 (35).

Much less is known about the environmental epidemiology and sources of infection for the other NTM. A number of NTM species have yet to be recovered from the environment, including *M. ulcerans*, *M. haemophilum*, *M. szulgai*, *M. celatum*, *M. genavense*, and *M. conspicuum*. Despite this, environmental sources of infection are highly likely. Good reviews of environmental studies have been provided by Wolinsky and Rynearson (5), Portaels (35), and Falkinham (41).

Much remains to be understood about the pathogenesis of NTM infection and disease in humans. Epidemiologic studies, skin test surveys, and more recently DNA fingerprinting studies suggest that person-to-person transmission of infection is rare. It is assumed that most persons are infected by environmental NTM. Of the likely sources of infection, airborne NTM may play an important role in respiratory disease, whereas ingestion may be the source of infection for children with NTM cervical lymphadenitis and for most patients with AIDS whose disseminated *M. avium* or *M. genavense* begins as gastrointestinal colonization. Bacteremic spread of the organism in patients with AIDS then involves multiple organ systems, including bone marrow, lymph nodes, liver, and spleen. Direct inoculation with NTM organisms from water or other material is likely the source of infection for patients with soft tissue infections. It is not known whether NTM disease (especially pulmonary disease) develops soon after infection or, like tuberculosis, develops after a period of latency.

Prevalence in Humans

Although first observed soon after Koch's discovery of the tubercle bacillus, NTM were not widely recognized as human pathogens until the 1950s, when several large series of patients with NTM lung disease were reported (42-44). These patients were epidemiologically distinct from patients with tuberculosis, being older, more commonly white, and quite often having underlying chronic lung disease such as bronchiectasis, silicosis, and healed tuberculosis. Positive reactions of 10 mm or more to purified protein derivative (PPD) tuberculin were less common than among tuberculous patients, and family contacts tended to be tuberculin-negative.

As reports of patients with NTM disease increased, it became apparent there was marked geographic variability both in the prevalence of disease and in the mycobacterial species responsible for disease. Most patients in the southeastern United States with NTM lung disease were from rural areas and had isolates of *M. avium* complex, whereas those in the central United States more commonly had disease caused by *M. kansasii* (45).

In addition, patients with NTM disease tended to react more strongly to skin test antigens prepared from the infecting mycobacterial species than to standard PPD-S or PPD-T, antigens prepared from *M. tuberculosis* (46). Skin test surveys using NTM antigens suggested that infection by NTM was common, especially in rural areas and in the Southeast (47).

NTM disease is not reportable in the United States, and reliable estimates of its incidence or prevalence have been limited. Two national surveys in the early 1980s were the first to try to define the extent of NTM infection in the United States. The initial study, based on state laboratory reports from 1979-1980, indicated that NTM comprised approximately one-third of the 32,000 mycobacterial isolates (48). Of these, 61% were *M. avium* complex, 19% were *M. fortuitum* complex, and 10% were *M. kansasii*.

A second surveillance study based on reports from tuberculosis control officers on isolates of NTM recovered between

1981 and 1983 showed higher rates of NTM disease among nonwhites, women, and patients residing in urban areas when compared with the initial study. White males, however, continued to serve as the major diseased population (49). Using combinations of national surveillance data, the prevalence of NTM (pulmonary) disease at that time was estimated to be 1.8 cases per 100,000 population for the entire United States. Of this, *M. avium* complex represented 1.1/100,000.

A more recent Centers for Disease Control (CDC) study from 1991 to 1992 (50) that included results from 33 state laboratories demonstrated a dramatic change in the prevalence of NTM. Despite the increases in isolates of *M. tuberculosis* noted in the United States since 1985, there were now more isolates of *M. avium* complex than *M. tuberculosis*, with the latter representing only 26% of the total mycobacterial isolates. The reasons for this dramatic increase in numbers for NTM is unknown, but better clinical recognition and more culturing for both pulmonary and disseminated disease are felt to play important roles.

One category of people with NTM disease not represented in the two earliest studies but almost certainly represented in the 1993 study were patients with AIDS and disseminated NTM disease. HIV-infected patients were at especially high risk of disease due to NTM. The majority of disease in this population (> 95%) is due to *M. avium* (51). Disseminated *M. avium* infection is the most common bacterial infection in patients with AIDS, occurring in 20 to 40% of all patients in several reported series (52-55). Disease in these patients is highly correlated with severe immunosuppression, with the average CD4 cell count at the time of dissemination in the 25 to 30 range (53-55). Patients with < 100 CD4 cells, not receiving prophylaxis, develop disseminated *M. avium* at the rate of approximately 20% per year (53). The overall incidence of *M. avium* as an initial diagnosis has increased among AIDS patients while other complications of AIDS, such as *Pneumocystis* pneumonia, have decreased (56). Disseminated *M. avium* occurs in similar rates in all geographic regions and various HIV risk groups (57). Localized pulmonary disease in AIDS due to *M. avium* occurs in less than 5% of patients (58).

Other NTM species, including *M. kansasii* (51, 59-61), *M. scrofulaceum* (51), *M. goodii* (51), *M. haemophilum* (60, 61), *M. genavense* (39), *M. celatum* (62), *M. conspicuum* (63), *M. xenopi* (64), *M. fortuitum* (51, 65), *M. marinum* (66), *M. malmoense* (67), and *M. simiae* (68) have also been described as a cause of pulmonary and/or disseminated NTM disease in AIDS. Some of these, especially *M. haemophilum*, *M. kansasii*, and *M. genavense*, have occurred in localized geographic areas. More than 95% of cases of disseminated disease, however, are due to isolates of *M. avium* (51).

CLINICAL PRESENTATION AND DIAGNOSTIC CRITERIA

Pulmonary Disease

Chronic pulmonary disease is the most common localized clinical manifestation of NTM (41, 69). *Mycobacterium avium* complex, followed by *M. kansasii*, is the most frequent pathogen causing lung disease in the United States. Other pathogens occasionally causing pulmonary disease include *M. abscessus*, *M. fortuitum*, *M. szulgai*, *M. simiae*, *M. xenopi*, *M. malmoense*, *M. celatum*, *M. asiaticum*, and *M. shimoii*. *Mycobacterium xenopi* is second to *M. avium* complex as a cause of NTM lung disease in areas of Canada, the United Kingdom, and other areas of Europe, while *M. malmoense* is second to *M. avium* complex in Scandinavia and areas of northern Europe (70). The patients with chronic lung disease due to NTM are generally older adults. Except for patients with cystic fibrosis, chil-

dren rarely develop this form of NTM disease (69). Although some NTM patients have a history of underlying chronic lung disease, not all do. The interpretation of NTM in the sputum of HIV-positive patients presents a particular problem, as these patients are frequently infected with NTM without evidence of pulmonary disease. Such infection may be transient, but it may also reflect disseminated NTM disease or subclinical NTM pulmonary disease. In addition, some NTM species that are generally considered nonpathogenic have been associated with pulmonary disease in the HIV-infected host.

Signs and symptoms of NTM pulmonary disease are variable and nonspecific. They include chronic cough, sputum production, and fatigue. Less commonly, malaise, dyspnea, fever, hemoptysis, and weight loss can also occur, usually with advanced NTM disease. Evaluation is often complicated by the symptoms caused by co-existing lung diseases. These conditions include chronic obstructive airway disease associated with smoking, bronchiectasis, previous mycobacterial diseases, cystic fibrosis, and pneumoconiosis.

There are some differences in the radiographic features of NTM lung disease compared with those produced by *M. tuberculosis* with regard to conventional radiographic studies. Nontuberculous mycobacteria tend to cause thin-walled cavities with less surrounding parenchymal infiltrate, have less bronchogenic but more contiguous spread of disease, and produce more marked involvement of pleura over the involved areas of the lungs. Occasionally, they may produce dense pneumonic disease or a solitary pulmonary nodule without cavitation. Basal pleural disease is not often found, and pleural effusion is rare. Recent studies with high-resolution computed tomography (HRCT) of the chest have shown that up to 90% of patients with mid and lower lung field noncavitary disease with *M. avium* complex have associated multifocal bronchiectasis, with many patients having clusters of small (< 5 mm) nodules in associated areas of the lung (71-74).

There has been a great deal of interest in the availability of species-specific skin test antigens. Unfortunately, many antigens are shared by different mycobacterial species for which there are previously tested NTM skin test antigen preparations, and extensive cross-reactions were observed with PPDs. However, recent studies provide hope for increased specificity of a preparation for *M. avium* complex testing, although it is not yet FDA approved (75). Specific skin test reagents for other NTM infections are not standardized and are neither available nor undergoing clinical trials at this time.

In the absence of specific diagnostic features in the history and physical examination, the chest roentgenogram, and differential skin testing, isolation of the NTM in a culture is essential for diagnosis. However, as these organisms are commonly found in nature, contamination of culture material or transient infection does occur. Thus, a single positive sputum culture, especially with small numbers of organisms, does not always suffice to diagnose NTM disease. Some previous authors suggested that the respiratory tract may be infected with the organism without disease, particularly in patients with chronic respiratory disease (48, 49, 69). This condition was often referred to as "colonization," and was described most often with *M. avium* complex. It was characterized by the presence of noncavitary, stable, and usually minimal radiographic disease in women, and was associated with sporadic excretion of organisms from the respiratory tract. No pathologic studies were 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 (71-74), with the latter or both now felt to be due to mycobacterial disease. "Coloniza-

tion" in the true sense (i.e., no tissue invasion) is probably quite rare. In addition, not all patients with this disease have a benign prognosis, a point first emphasized by Prince and colleagues in a landmark 1989 paper (76).

Given these observations, the diagnosis of lung disease caused by NTM is usually not difficult if a combination of clinical, radiographic, and bacteriologic criteria are used. AFB smear, culture results, and clinical status suggest a close correlation among the three. Minimal evaluation should include three or more sputums for AFB and efforts to exclude other confounding disorders such as tuberculosis and lung malignancy. In most patients, a diagnosis can be made without a lung biopsy. Although criteria are based on experience with *M. avium* complex, there is no reason to believe these criteria would not be applicable to other species. The diagnostic criteria are presented in Table 1.

Clinical studies have established the validity of bronchial washings as a culture source for *M. tuberculosis*. Although similar studies have not been done for NTM, bronchial washings are considered to be more sensitive than routine expectorated sputums; however, their relative specificity for clinical disease is unknown. Approximately 90% of patients with disease caused by *M. kansasii* and most patients with disease caused by *M. avium* complex have cavitary infiltrates (77) and can be readily identified. Among patients without cavities, the presence of clinical symptoms and HRCT abnormalities are important adjuncts to defining the presence of NTM disease. Bacteriologic criteria have been best analyzed with cavitary disease for *M. avium* complex and *M. kansasii*, and the HRCT abnormalities, with *M. avium* complex. Although these are reasonable criteria for diagnosing other NTM, their use with other species has not been studied in detail.

In the patient with nondiagnostic cultures and radiographic studies, or concern about the presence of another disease producing radiographic abnormalities, a lung biopsy is often required for diagnosis. If a tissue sample from a transbronchial, percutaneous, or open-lung biopsy yields an NTM organism and shows mycobacterial histopathologic changes (i.e., granulomatous inflammation with or without AFB), this by itself is sufficient to establish the diagnosis of NTM lung disease. If the lung biopsy has a negative culture (something that often happens 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 sputums or bronchial washes are culture-positive for NTM, even if they are negative for AFB on smear and result in light growth on culture.

Lymphadenitis

Infection of the submandibular, submaxillary, cervical, or preauricular lymph nodes in children between 1 and 5 yr old is the most common presentation of NTM lymphadenitis (78-81). It is the most common disease manifestation of NTM in children and, in the absence of HIV infection, rarely affects adults. The disease occurs insidiously, with only rare associated 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 (80). There is typically no history of exposure to tuberculosis, screening PPD skin test of family members are usually negative, and the chest radiograph is normal.

TABLE 1
CRITERIA FOR DIAGNOSIS OF NONTUBERCULOUS MYCOBACTERIA PULMONARY DISEASE

Presumed or Confirmed HIV Seronegative Potential Risk Factors		Presumed or Confirmed HIV Seropositive Potential Risk Factors
I. Local immune suppression	II. General severe immune suppression	
Alcoholism (<i>M. avium</i> complex)	Leukemia	CD4 count < 200
Bronchiectasis	Lymphoma	
Cyanotic heart disease	Organ transplantation	
Cystic fibrosis	Other immunosuppressive therapy	
Prior mycobacterial disease		
Pulmonary fibrosis		
Smoking/chronic obstructive lung disease		
None		
1. Clinical criteria	a. Same	a. Same
a. Compatible signs/symptoms (cough, fatigue most common; fever, weight loss, hemoptysis, dyspnea may be present, particularly in advanced disease) with documented deterioration in clinical status if an underlying condition is present and		
b. Reasonable exclusion of other disease (e.g., tuberculosis, cancer, histoplasmosis) to explain condition, or adequate treatment of other condition with increasing signs/symptoms	b. Same	b. Same
2. Radiographic criteria	a. Same	a. Same
a. Any of the following chest X-ray abnormalities; if baseline films are more than 1 yr old, should be evidence of progression		
• Infiltrates with or without nodules (persistent \geq 2 mo or progressive)		
• Cavitation		
• Nodules alone (multiple)		
b. Any of these HRCT abnormalities	b. Same	b. Same
• Multiple small nodules		
• Multifocal bronchiectasis with or without small lung nodules		
3. Bacteriologic criteria	a. Same	a. Same
a. At least three available sputum/bronchial wash samples within 1 yr		
• Three positive cultures with negative AFB smears		
or		
• Two positive cultures and one positive AFB smear		
or		
b. Single available bronchial wash and inability to obtain sputum samples	b. Same except	b. Same except
• Positive culture with 2+, 3+, or 4+ growth	• Culture positive with 1 + or greater growth	• Culture positive with 1 + or greater growth
or		
• Positive culture with a 2+, 3+, or 4+ AFB smear		(excludes <i>M. avium</i> complex)
or		
c. Tissue biopsy	c. Same	c. Same
• Any growth bronchopulmonary tissue biopsy		
• Granuloma and/or AFB on lung biopsy with one or more positive cultures from sputum/bronchial wash		
• Any growth from usually sterile extrapulmonary site		

For a diagnosis of pulmonary disease, all three criteria—(1) clinical, (2) radiographic, and (3) bacteriologic—must be satisfied.

Most **children** with NTM lymphadenitis will react to skin test antigens prepared from *M. avium* complex, such as PPD-B (79, X2, 83). A 1991 multicenter study of NTM antigens from the CDC that used PPD-B, however, was terminated early, due to a blistering reaction in several of the children (82). More recent studies using a less potent, protein weight-standardized *M. avium* skin-test material called “sensitin” and a dual skin-test technique to determine *M. avium*-dominant versus PPD-dominant reactions have suggested improved specificity with this antigen preparation in study populations with known disease (75). Although these antigens may prove beneficial for future evaluation of cervical lymphadenitis, no commercial NTM skin-test material is currently available for clinical use in the United States, and this procedure is not recommended for diagnosis of NTM. All children in this setting should be tested using PPD tuberculin. Most children tested with intermediate strength (5 tuberculin unit [TU]) PPD tuberculin will have a weakly reactive skin test (S-9 mm) due to cross-reactivity with NTM, but some children may be negative, and as many as one-third will have reactions with 10 mm or more induration (80).

Distinguishing tuberculous from nontuberculous lymphadenitis is key, because the former requires drug therapy and public health tracking, whereas the latter does not. The presumptive diagnosis of NTM lymphadenitis is based on the histopathologic appearance of the lymph node showing caseating granulomata with or without AFB and a negative tuberculin skin test. Failure of the node to **yield *M. tuberculosis*** provides stronger presumptive evidence for the diagnosis of NTM lymphadenitis.

The utility of fine needle aspiration in obtaining diagnostic material is controversial (X4-86). However, granulomata or other compatible cytopathology such as a mixture of degenerating granulocytes, lymphocytes, and epithelioid histiocytes are seen in most cases. A positive culture may be obtained in up to 50% of HIV-seronegative patients and in even higher proportions of HIV-positive patients with tuberculous adenitis.

A definite diagnosis of NTM lymphadenitis is made by recovery of the causative organism from lymph node cultures. A simple diagnostic biopsy or incision and drainage of the involved lymph nodes should be avoided, since most of these

procedures will be followed by fistulae formation with chronic drainage (79). However, even with excised nodes with compatible histopathology, only about 50% will yield positive cultures (79), although the recovery rate may be as high as 82% in some centers (80). Some of these smear-positive, culture-negative cases may be due to fastidious species such as *M. haemophilum* (87) or *M. genavense* (39). Currently, approximately 80% of culture-proven cases of NTM lymphadenitis are due to *M. avium* complex (88). In the United States and Australia the remaining cases are caused by *M. scrofulaceum* (79, 80, 88), while in Scandinavia, the United Kingdom, and other areas of northern Europe, *M. malmoense* has recently emerged as the major pathogen after *M. avium* complex (70, 89, 90). The predominance of *M. avium* complex is a change from 20 years ago, when most geographic areas reported *M. scrofulaceum* as the most common etiologic agent (78, 80). Now in the United States, only about 10% of the culture-proved mycobacterial cervical lymphadenitis in children is due to *M. tuberculosis*; the remainder is due to *M. avium* complex and *M. scrofulaceum* (88). In contrast, in adults more than 90% of the culture-proven mycobacterial lymphadenitis is due to *M. tuberculosis*.

Localized Skin, Soft Tissue, and Skeletal Infection

The NTM species that most commonly cause localized infections of the skin and subcutaneous tissue are *M. fortuitum*, *M. abscessus*, *M. murinum*, and *M. ulcerans* (5). However, virtually all species of NTM have been described as a cause of cutaneous disease (41, 69). 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 rapidly growing mycobacterial species *M. fortuitum*, *M. abscessus*, or *M. chelonae* (91). Nosocomial skin and soft-tissue disease caused by these three species is also seen (16-26). These include infections of long-term intravenous or peritoneal catheters (91, 92), postinjection abscesses, or surgical wound infections such as those occurring after augmentation mammoplasty (23, 93) or cardiac-bypass surgery (16, 17, 21, 94). Diagnosis is made by culture of the specific pathogen from drainage material or tissue biopsy.

Mycobacterium murinum is the cause of "swimming pool granuloma" or "fish tank granuloma" (69). The lesions usually appear as papules on an extremity, especially on the elbows, knees, and dorsum of feet and hands, progressing subsequently to shallow ulceration and scar formation. 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 fresh-water fish tanks ("fish tank granuloma") or by scratches or puncture wounds from salt water fish, shrimp, fins, etc. Diagnosis is made from biopsy material, histologic examination, and culture.

Mycobacterium ulcerans causes indolent necrotic lesions of the skin and underlying tissue in Australia and tropical areas of the world (34, 69, 95). It is not endemic in the United States. The lesions occur most commonly in children and young adults and often result in severe deformities of the extremities (95). Drug treatment of the disease has been disappointing; surgical debridement combined with skin grafting is the usual treatment of choice.

Infection of Bursae, Joints, Tendon Sheaths, and Bones

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. *Mycobacterium*

murinum (41, 69) and *M. avium* complex (96) are particularly prone to causing tenosynovitis of the hand, although *M. fortuitum*, *M. abscessus*, *M. chelonae*, and *M. kansasii* have also been implicated (41, 69). *Mycobacterium terrae* complex (especially *M. nonchromogenicum*) has also been isolated from synovial tissue of the hand or wrist, and it tends to be associated with a very indolent, chronic type of disease. Occasionally, axial bones and extremities have been infected without apparent trauma and are due presumably 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 (16, 17, 21, 94).

Disseminated Disease in Patients without AIDS

Dissemination of NTM in adult patients with immunosuppression but without AIDS (e.g., those with renal or cardiac transplantation, chronic corticosteroid use, leukemia, etc.) has been observed. *Mycobacterium avium* complex (69, 97), *M. kansasii* (98), *M. chelonae* (91, 99-101), *M. scrofulaceum* (69), *M. abscessus* (69), and *M. haemophilum* (60) have all been reported to cause disease in this setting. In general, the disease caused by *M. avium* complex presents as a fever of unknown origin (97), whereas disease caused by *M. kansasii*, *M. chelonae*, *M. abscessus*, and *M. haemophilum* generally presents as multiple subcutaneous nodules or abscesses that drain spontaneously (60, 69, 99-101). The mortality relates directly to the type and severity of underlying disease (101). Lincoln and Gilbert (78) reviewed 12 cases, all fatal, of disseminated NTM disease in children. Most of the children were infected with *M. avium* complex, were less than 3 yr old, and had no apparent underlying disease. A recent review of disseminated *M. avium* complex disease in children noted its occurrence, rarely, in the setting of severe combined immunodeficiency syndrome or chemotherapy for malignancy (102). The isolation of organisms from sterile, closed sites such as bone marrow or blood or from a skin biopsy (in the setting of multiple lesions) is diagnostic of the disease.

Disseminated Disease in Patients with AIDS

Disseminated disease due to NTM in patients with HIV infection usually occurs only in those with very advanced immunosuppression (51-57). Because these patients frequently have other complications, the diagnosis of mycobacterial infection may be confused or delayed. The diagnosis is exceedingly rare in person with > 100 CD4 cells, and it should usually be suspected only in persons with < 50 CD4 cells (53-55). Most patients (> 90%) have prolonged fevers, which may be as high as 103-104° F, frequently accompanied by night sweats. Weight loss is common, and some patients complain of abdominal pain and diarrhea. Physical findings may be only those of advanced HIV disease, although abdominal or retroperitoneal adenopathy and hepatosplenomegaly may be present. Anemia is the most striking laboratory abnormality, with many patients having a hematocrit of < 25%. Alkaline phosphatase is elevated in approximately one-third of patients and may be indicative of hepatic disease due to *M. avium*. Thus, the diagnosis of disseminated *M. avium* should be aggressively pursued in any person with < 50 CD4 cells who has a history of fever, weight loss, anemia, diarrhea, or elevated alkaline phosphatase, especially in one with a history of other opportunistic infections.

The diagnosis of disseminated *M. avium* is most commonly confirmed by isolation of *M. avium* in blood, using any of the culture techniques described in the laboratory section. The bacteremia in *M. avium* is ongoing, and a single culture has a sensitivity of approximately 90%. It is recommended that a single culture be drawn, with repeat cultures only if the first is

negative. Routine blood cultures of asymptomatic patients has a very low yield and is not recommended. In a prospective study of HIV-infected patients with < 50 CD4 cells, approximately 67% of patients with *M. avium* in sputum or stool had disseminated disease within 1 yr, although most did not develop pulmonary disease. However, only one-third of all patients with disseminated disease had a prior positive stool or sputum. Therefore, routine screening of stool or sputum is not indicated, but a positive culture of one of these sites needs to raise concern about future dissemination. Sputums that are smear-positive for AFB in the setting of HIV should always be regarded as tuberculosis until proven otherwise, since *M. tuberculosis* is a common cause of pulmonary disease in HIV-infected patients and is more likely than *M. avium* complex to produce positive AFB smears.

Nontuberculous mycobacteria other than *M. avium* may present as disseminated disease. Disseminated *M. kansasii* is usually associated with pulmonary disease (51, 59). *Mycobacterium genavense* has been isolated from the blood of patients with AIDS and requires extensive laboratory analyses for isolation and identification (39). *Mycobacterium haemophilum* has been associated with infections of the skin, soft tissue, bones, and joints (60, 61). Disseminated disease has rarely been reported with other species, including *M. fortuitum* (51), *M. marinum*, *M. simiae*, *M. scrofulaceum*, *M. celatum*, and *M. malmoense* (41).

LABORATORY METHODS

Digestion, Decontamination, and Staining Procedures

Methods used for digestion and decontamination of clinical samples to recover *M. tuberculosis* have also proved useful for the NTM. In general, however, NTM are more susceptible to killing by NaOH, and for this reason, care must be taken not to exceed the recommended concentration and time guidelines. Because of the frequent presence of bronchiectasis in patients with *M. avium* complex and *M. abscessus* lung disease, *Pseudomonas aeruginosa* overgrowth in specimens from these patients is a more frequent problem than with tuberculosis. Growth of *P. aeruginosa* can be minimized by processing the specimens with the conventional *N*-acetyl-L-cysteine-sodium hydroxide (NALC-NaOH) solution followed by 5% oxalic acid, a procedure that should be considered when one or more specimens are contaminated in this setting (103).

Staining and microscopy of the NTM also follows the guidelines used for *M. tuberculosis*. Both conventional basic fuchsin method (Kinyoun stain) and the fluorochrome method (auramine stain) are effective in recognizing NTM in clinical material, with the fluorochrome method being preferred (104). The appearance of NTM by microscopy is generally indistinguishable from *M. tuberculosis*.

Culture Techniques for Nontuberculous Mycobacteria

The principles and practices of culturing *M. tuberculosis* were updated in 1993 by the CDC (104), with these methods having proved very effective for NTM species. At least three respiratory (sputum) cultures should be used for the initial evaluation. Cultures should be inoculated onto one or more solid medias and into a liquid medium. Use of solid media as the primary or sole culture is no longer recommended by us or by the CDC (104), given the greater recovery rate and more rapid recovery of all mycobacteria, including *M. tuberculosis*, in rapid broth systems (104-107). Mycobacterial blood cultures may use a single medium, with the BACTEC 13A broth (105) or the lysis centrifugation method with plating on 7H10

or 7H11 (Isolator; Wampole Laboratories, Cranbury, New Jersey) being the recommended methods. Two general types of solid media are available: egg-potato-base media (commonly, Lowenstein-Jensen agar) and a clear agar-base media (commonly, Middlebrook 7H10 or 7H11 agar). Quantitation of growth on agar plates (generally 0 to 4+) is important to estimates of clinical significance and responses to therapy, and it is recommended for all samples other than blood cultures. Blood cultures using the Isolator System can also be quantitated, which may be useful for similar reasons. Because of its greater recovery rate for *M. avium* complex and ease of quantitation, Middlebrook 7H10 or 7H11 agars are the preferred solid media. Lowenstein-Jensen is an excellent medium for recovery of *M. tuberculosis*, but is generally inferior to Middlebrook agar as an all-purpose medium for both *M. tuberculosis* and NTM (105,106).

The broth medium can involve one of several automated commercial systems, including radiolabeled BACTEC 12B broth used in the BACTEC TB 460 radiometric system (Becton Dickinson Instruments Systems, Sparks, Maryland), and the nonradiolabeled ESP Culture System II (Difco Laboratories, Detroit, Michigan) (107). For lower volume laboratories, the recently introduced mycobacterial growth indicator tubes with a fluorescent detection system (MGIT; Becton Dickinson Microbiology Systems, Cockeysville, Maryland) or biphasic agar/broth (Septi-Chek AFB System; Becton Dickinson Microbiology Systems) may prove more practical.

Most slowly growing NTM produce detectable growth in 2 to 4 wk on the solid media and in 1 to 2 wk with the BACTEC system. Cultures are generally incubated at 35–37° C for 6 wk. All of the currently recognized NTM pathogens will grow on these media in this time except *M. haemophilum*, *M. genavense*, and *M. conspicuum*. If *M. haemophilum* is suspected, a commercial paper surface containing hemin (X factor) used to identify *Haemophilus influenzae* should be added to the surface of the 7H10 or 7H11 plate (108), or hemin or ferric ammonium citrate should be incorporated into the medium. *Mycobacterium genavense* often grows only from the blood in BACTEC 13A medium or comparable broth media, and requires incubation for at least 8 wk (109). Some authors have identified better growth in the slightly acidic (pH 6) radiometric Middlebrook 7H12 broth (pyrazinamide test medium). *Mycobacterium conspicuum* will grow in BACTEC media at 35–37° C but will only grow on solid media at lower temperatures, 22–31° C (63). The presence of an AFB smear-positive sample with no growth on solid media should immediately bring to mind *M. haemophilum*, *M. conspicuum*, or *M. genavense*. Because of the relatively poor growth of *M. genavense* (only approximately 50% of autopsy-proven cases are culture-positive [39]), molecular techniques such as polymerase chain reaction are the optimal method of identification (39).

The major modification of culture techniques for recovering NTM species is the need to incubate all skin or soft tissue samples at two temperatures: 35° C and 28–32° C. This is because a number of the common pathogens of these tissues, including *M. haemophilum*, *M. ulcerans*, *M. marinum*, and *M. chelonae*, may grow only at the lower temperatures, especially on primary isolation. Five to ten percent CO₂ enhances the growth of some NTM species, such as *M. haemophilum*, and should be used for primary isolation because of its definite growth enhancement for *M. tuberculosis*.

Identification of Nontuberculous Mycobacteria

Traditional identification of NTM, as well as *M. tuberculosis*, has relied upon statistical probabilities of presenting a charac-

teristic reaction pattern in a battery of biochemical tests. The niacin test was the most useful for separating NTM and *M. tuberculosis* because the former is usually negative, whereas isolates of *M. tuberculosis* are positive. Runyon devised the first good scheme for grouping NTM based on growth rates and colony pigmentation (69). Species identification has become more sophisticated and the number of potential pathogens has increased since this scheme was introduced.

A more appropriate grouping currently for these organisms is based on the type of clinical disease they produce: lymphadenitis, cutaneous disease, disseminated disease, and pulmonary disease. Grouping of the NTM by this scheme is shown in Table 2.

Because of the extremely slow nature of traditional biochemical tests, most clinical and public health laboratories now use one or more rapid diagnostic methods for species identification (110, 111). These rapid methods are recommended for identification of the NTM when possible; they include HPLC, the BACTEC NAP test, and commercial DNA probes. The HPLC examines the mycolic acid fingerprint patterns that differ among most species or complexes of mycobacteria (112). Recent increased sensitivity of this technique using fluorescence detection has allowed identification directly from the sputum sample in approximately 50% of AFB smear-positive samples of *M. tuberculosis* and 33% of *M. avium* complex (113). A small number of species (complexes) are not separable by HPLC, including most of the pathogenic rapidly growing mycobacterial species. Two additional techniques for

rapid identification of NTM are currently in use. These are the species-specific DNA probes and the BACTEC NAP test. Commercial nonradiolabeled DNA probes complementary to ribosomal RNA are available for identifying isolates of *M. tuberculosis*, *M. gordonae*, *M. kansasii*, *M. avium*, and *M. intracellulare*. They are highly sensitive and specific, providing species identification using a culture directly from BACTEC broth within 2–4 h. The presence or absence of serpentine cording on AFB smear of the BACTEC 12B bottle (114) and the time required for the bottle to turn positive (115) will help the laboratory decide which probe (*M. tuberculosis* or *M. avium* complex) should be used initially.

The BACTEC TB 460 system can be used to differentiate between *M. tuberculosis* and the NTM using a selective growth inhibitor called NAP (*p*-nitro- α -acetylaminobenzophenone) (116). This compound, at a concentration of 5 μ g/ml, inhibits the growth of *M. tuberculosis* complex but not NTM (with the exception of *M. genavense*). The average time for the NAP test is 5 d. However, a species identification schema other than the use of DNA probes for NTM has not been worked out for use with the BACTEC, and such identification must depend on one of the previously discussed methods.

Because of its generally poor growth, identification of *M. genavense* can be difficult (43, 109). A presumptive identification can be made on the basis of organism morphology (small, coccobacillary forms on AFB smear), failure to grow on subculture to solid media, a negative nucleic acid probe for *M. avium* complex, and a positive NAP test (39). *Mycobacte-*

TABLE 2
CLASSIFICATION OF THE NONTUBERCULOUS MYCOBACTERIA RECOVERED FROM HUMANS

Clinical Disease	Features of the Common Species			Unusual Etiologic Species
	Common Etiologic Species	Geography	Morphologic Features*	
Pulmonary disease	1. <i>M. avium</i> complex	Worldwide	Usually not pigmented; slow growth (> 7 d)	1. <i>M. simiae</i>
	2. <i>M. kansasii</i>	USA, coal mining regions, Europe	Pigmented; often large and beaded on acid-fast stain	2. <i>M. szulgai</i>
	3. <i>M. abscessus</i>	Worldwide but mostly USA	Rapid growth (< 7 d); not pigmented	3. <i>M. fortuitum</i>
	4. <i>M. xenopi</i>	Europe, Canada	Slow growth; pigmented	4. <i>M. celatum</i>
	5. <i>M. malmoense</i>	UK, northern Europe	Slow growth, not pigmented	5. <i>M. asiaticum</i>
Lymphadenitis	1. <i>M. avium</i> complex	Worldwide	Usually not pigmented	6. <i>M. shimodii</i>
	2. <i>M. scrofulaceum</i>	Worldwide	Pigmented	7. <i>M. haemophilum</i>
	3. <i>M. malmoense</i>	UK, northern Europe (especially Scandinavia)	Slow growth	8. <i>M. smegmatis</i>
Cutaneous disease	1. <i>M. marinum</i>	Worldwide	Photochromogen; requires low temperatures (28–30° C) for isolation	1. <i>M. fortuitum</i>
	2. <i>M. fortuitum</i>	Worldwide, mostly USA	Rapid growth; not pigmented	2. <i>M. chelonae</i>
	3. <i>M. chelonae</i>			3. <i>M. abscessus</i>
	4. <i>M. abscessus</i>			4. <i>M. kansasii</i>
	5. <i>M. ulcerans</i>	Australia, tropics, Africa, SE Asia	Grows slowly, pigmented	5. <i>M. haemophilum</i>
Disseminated disease	1. <i>M. avium</i> complex	Worldwide	Isolates from patients with AIDS usually pigmented (80%)	1. <i>M. abscessus</i>
	2. <i>M. kansasii</i>	USA	Photochromogen	2. <i>M. xenopi</i>
	3. <i>M. chelonae</i>	USA	Not pigmented	3. <i>M. malmoense</i>
	4. <i>M. haemophilum</i>	USA, Australia	Not pigmented; requires hemin, often low temperatures, and CO ₂ to grow	4. <i>M. genavense</i>
				5. <i>M. simiae</i>
				6. <i>M. conspicuum</i>
				7. <i>M. marinum</i>
				8. <i>M. fortuitum</i>

* Photochromogen: isolate is buff-colored in the dark but turns yellow with brief exposure to light.

rium genavense is one of the few mycobacteria, other than the *M. tuberculosis* complex, which is inhibited by NAP.

Antimicrobial Susceptibility Testing

Although there are specific recommendations from the CDC, ATS, and the National Committee for Clinical Laboratory Standards (NCCLS) regarding which isolates of *M. tuberculosis* should have antimicrobial susceptibility tests, which test methods to use, and which antimicrobial agents to test, the same is not true for the NTM. There are however, sufficient data now available to make temporary recommendations regarding when, how, and to which agents the NTM should be tested. Recommendations will differ for different groups or species of the NTM (Table 3). Although routine testing of all NTM is discouraged, there are circumstances where susceptibility testing is warranted, including having baseline data available if the patient does not respond to therapy, or when relapses occur.

Slow-growing Mycobacteria

Antimicrobial susceptibility testing of the slow-growing mycobacteria can be performed using either the agar proportion or the radiometric (BACTEC) methods used for testing *M. tuberculosis* (117–125). However, the two methods give varying results between some NTM and antimicrobial agents, with the radiometric broth method tending to give lower minimal in-

hibitory concentrations (MICs) than the agar method (118, 119). Too little experience is available with the antibiotic gradient strip method (E-test; AB Biodisk, Piscataway, NJ) to make any general recommendations on its use.

The agar proportion method uses Middlebrook 7H10 or 7H11 agar and the modified method of proportions, defining resistance as growth on the drug-containing medium of 1% or more of the number of colonies that grow on the drug-free control medium. Details of the agar proportion method are included in the 1990 ATS statement "Diagnostic Standards and Classification of Tuberculosis" (3), and a more detailed description is now available as a tentative standard (for *M. tuberculosis*) by the NCCLS (126).

The radiometric BACTEC method is a more rapid method combining antimicrobial agents, the mycobacterium, and a C^{14} -labeled substrate in a broth medium. Resistance is determined by the rate and amount of labeled CO_2 produced, which is directly proportional to the rate and amount of growth that occurs in the broth medium. The BACTEC method has been widely used by some laboratories for testing all drugs for the NTM, but at present no universally agreed-upon method has been developed.

Mycobacterium avium complex. When and how isolates of the *M. avium* complex should be tested remains controversial (127). Recent data suggest that the radiometric broth method is more reliable than the agar method for testing the *M. avium*

TABLE 3
ANTIMYCOBACTERIAL AGENTS TO CONSIDER FOR SUSCEPTIBILITY TESTING
OF NONTUBERCULOUS MYCOBACTERIA

Mycobacterium Species or Group	Proven Utility	Uncertain Relevance	Susceptibility Testing Results of No Benefit
	Clinically Relevant		
Slowly growing NTM			
<i>M. avium</i> complex	Clarithromycin*	Amikacin Ciprofloxacin Ethambutol Ethionamide Rifabutin Rifampin Streptomycin	Isoniazid Pyrazinamide
<i>M. kansasii</i>	Rifampin	Amikacin Ciprofloxacin Clarithromycin* Ethambutol Isoniazid Rifabutin Streptomycin Sulfonamide	Pyrazinamide
<i>M. marinum</i>	Doxycycline or Minocycline Ethambutol Rifampin Sulfonamide	Amikacin Ciprofloxacin Clarithromycin* Rifabutin	Isoniazid Pyrazinamide
Other slowly growing NTM			
<i>M. haemophilum</i>	Clarithromycin*†	Amikacin	Pyrazinamide
<i>M. malmoense</i>	Ethambutol†	Ciprofloxacin	
<i>M. simiae</i>	Rifampin†	Isoniazid	
<i>M. szulgai</i>		Rifabutin	
<i>M. xenopi</i>		Streptomycin	
Rapidly growing NTM			
<i>M. abscessus</i>	Amikacin	Cefmetazole	Clofazimine
<i>M. chelonae</i>	Cefoxitin	Imipenem	Ethambutol†
<i>M. fortuitum</i>	Ciprofloxacin	Ofloxacin	Isoniazid
<i>M. mucogenicum</i>	Clarithromycin*	Tobramycin (<i>M. chelonae</i> only)	Pyrazinamide
<i>M. smegmatis</i>	Doxycycline or Minocycline Sulfonamides		Rifampin Streptomycin

* Class drug for macrolides (clarithromycin, azithromycin, roxithromycin).

† Ethambutol is clinically useful for *M. smegmatis*.

‡ Proven utility/clinically relevant for some but not all species.

complex. There is, however, considerable controversy regarding the size of the inoculum, the drug concentrations to use, and interpretation of the BACTEC results. Strains of the complex are almost always resistant to the relatively low drug concentrations of isoniazid, rifampin, streptomycin, and ethambutol used for defining susceptibility of *M. tuberculosis*. Using higher concentrations of the antituberculous agents with specific NTM breakpoints for susceptibility and resistance, determination of MICs, or determination of the activity of combined drugs are some of the newer approaches that may be helpful in predicting clinical response (118, 120, 121, 128). Such a benefit has not yet been shown by clinical trials, so susceptibility testing of *M. avium* complex isolates to the antituberculosis drugs is not recommended.

Other drugs have also been tested, including amikacin, rifabutin (118, 122, 123), ciprofloxacin (124, 125), clofazimine (129), azithromycin (127), and clarithromycin (127). Changes in MICs of the antituberculosis drugs following unsuccessful therapy of *M. avium* complex disease have been difficult to demonstrate. Such changes have been readily demonstrable with microbiologic relapses following monotherapy with clarithromycin, however (130). Pretreatment isolates with this drug have MICs ≤ 4.0 $\mu\text{g/ml}$ when done in media with a pH of 7.4. Post-therapy or relapse isolates following macrolide therapy have MICs to clarithromycin of > 32 $\mu\text{g/ml}$ (105, 130–132) and a point mutation involving one of two base pairs in the 23S ribosomal macrolide binding site (131, 132).

Susceptibility testing should not be performed on pretreatment or initial isolates against clarithromycin, but it should be performed with clarithromycin for all isolates from patients on prior macrolide therapy, including those on macrolide prophylaxis for disseminated disease. The recommended clarithromycin resistance breakpoint is > 32 $\mu\text{g/ml}$ for broth or agar with pH corrected to 7.4 (105). Until more data are available, patients on azithromycin should have their isolates characterized as susceptible or resistant based on clarithromycin susceptibility values.

Alterations or changes in MICs following treatment or prophylaxis failure have also been difficult to demonstrate with rifabutin. For this reason, testing of susceptibility to rifabutin even after therapy is not recommended. Because of lack of standardization, results of testing other nontuberculous drugs such as amikacin, clofazimine, and ciprofloxacin should be used with caution.

Mycobacterium kansasii. Although wild strains of *M. kansasii* are initially susceptible to rifampin, acquired resistance does develop during therapy (133, 134). Since the correct history of therapy may not be known, all initial isolates of *M. kansasii* should be tested against rifampin, using the agar proportion method and the interpretive criteria for *M. tuberculosis* (resistance breakpoint of 1 $\mu\text{g/ml}$) (134). Also, testing should be performed when the patient's sputum fails to convert from smear- and/or culture-positive or when a relapse occurs during therapy. Treatment for rifampin-susceptible isolates is empiric and is not influenced by susceptibility to drugs other than rifampin (i.e., ethambutol and isoniazid); hence their routine testing is not recommended. A rifampin-resistant isolate could be tested against ciprofloxacin or ofloxacin, clarithromycin, ethambutol, streptomycin and a sulfonamide (e.g., sulfamethoxazole) (133, 134).

Other slow-growing nontuberculous mycobacteria. Susceptibility testing of infrequently isolated species of NTM may be helpful, since knowledge of susceptibility patterns is limited. Pulmonary infections caused by *M. malmoense*, *M. xenopi*, and *M. szulgai* have been successfully treated with combinations of ethambutol, isoniazid, rifampin, and most recently

clarithromycin (70, 135–137), whereas ciprofloxacin, clarithromycin, and rifampin are suggested for treating *M. haemophilum* infection (60, 61). Thus, susceptibility tests for these slow-growing NTM might include these five drugs. The agar proportion and broth methods have usually been used for testing. For *M. marinum*, several methods have been used (138), with the desired test drugs being rifampin, ethambutol, doxycycline or minocycline, clarithromycin, and a sulfonamide.

Rapidly Growing Nontuberculous Mycobacteria

Because of differences in susceptibilities among species of rapidly growing mycobacteria and even within species, susceptibility testing should be performed on all clinically significant isolates as well as isolates that have been recovered after treatment failure or relapse. Antimicrobial susceptibility testing of the rapidly growing mycobacteria differs from the other NTM. Most drugs are different, although the methods are similar to those used to test other bacteria (138–142). Most infections are caused by three species; *M. abscessus*, *M. chelonae*, and *M. fortuitum* (91). A primary panel of drugs for these species could include amikacin, cefoxitin, ciprofloxacin, clarithromycin, doxycycline, imipenem, and a sulfonamide. The most convenient method for susceptibility testing is to use microtiter MIC trays containing cation-supplemented Mueller-Hinton broth. Agar dilution, agar disk elution, and disk diffusion methods have also been used. Details of these methods can be found in several laboratory handbooks, including the American Society for Microbiology's *Manual of Clinical Microbiology* (142).

TREATMENT OF *Mycobacterium kansasii* DISEASE

Disease caused by *M. kansasii* is the second most common NTM pulmonary disease in the United States. It occurs in geographic clusters and affects primarily adult white men, but it can affect patients of any sex, race, or age. Pulmonary disease is the most frequent clinical presentation. The organism frequently exhibits a beaded or cross-barred appearance on acid-fast stain, and produces rough buff-colored colonies that develop a yellowish pigmentation because of the deposition of beta-carotene crystals after exposure to light. Disease-producing strains are usually highly catalase-positive. Recent DNA-based studies suggest that up to five taxonomic groups or subspecies are present among both environmental and human isolates (143).

Untreated 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 (134, 144, 145). 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 the latter species may be reported resistant to isoniazid at 0.2 or 1 $\mu\text{g/ml}$ and to streptomycin at 2 $\mu\text{g/ml}$. These isolates are susceptible to slightly higher drug concentrations (134, 144) and laboratory reports of resistance to the low concentrations of these two drugs have no clinical or therapeutic significance as long as a rifampin regimen is being used (146). Thus, when clinically indicated, isoniazid and/or streptomycin should be used against *M. kansasii* regardless of their *in vitro* susceptibility results. *Mycobacterium kansasii* is also susceptible *in vitro* to clarithromycin (134), sulfamethoxazole (133), amikacin (133), the newer quinolones (125), and rifabutin (134), although there is limited information on the clinical usefulness of these drugs (133, 134). Isolates are usually resistant to achiev-

able serum levels of *p*-aminosalicylic acid, capreomycin, and pyrazinamide. Acquired resistance to rifampin, ethambutol, and isoniazid has been demonstrated in isolates from treatment failure cases (133, 134, 145), and resistance to the first two agents is reliably demonstrated by current *M. tuberculosis* susceptibility test methods (134).

Treatment

The natural history of pulmonary disease caused by *M. kansasii* in patients receiving no drug treatment has been assessed (147). In general, the history has shown persistence of sputum positivity and progression of clinical and radiographic disease. On this basis, patients with pulmonary disease should receive drug therapy.

There have been no randomized comparative trials of treatment for disease caused by *M. kansasii*, comparing one drug regimen with another or with no drug treatment at all. There have been, however, several retrospective and prospective studies of various treatment regimens (145-151) that have given us a good basis for drug therapy recommendations. Earlier reports of treatment with antimycobacterial drugs in the prrifampin period were disappointing when compared with the much higher success rates achieved in treating tuberculosis with these same drugs. The sputum conversion rates at 6 mo ranged from 52 to 81%, and relapse rates of approximately 10% were seen in patients achieving an initial response (145, 148). Surgical resection was often recommended to achieve better initial control and prevent relapse. The advantage of adding surgery was never established, however (148).

With the advent of rifampin, the picture changed considerably for the better. Four-month sputum conversion rates with rifampin-containing regimens were 100% in 180 patients from three studies (145, 146, 149). There were two treatment failure cases, however (an incidence of 1.1%). These patients converted their sputa but then became culture-positive again while still receiving therapy. Both had been treated with isoniazid, rifampin, and ethambutol, and both failures were associated with the development of rifampin resistance (145). Long-term relapse rates with rifampin-containing regimens also appear to be very low, with only one relapse recorded among 134 patients (0.8%) who received long-term follow-up in three studies (145, 146, 150). Surgery is now considered to have no role in managing routine cases of pulmonary disease.

The current recommendation for treatment of pulmonary disease caused by *M. kansasii* in adults is the regimen 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 mo with at least 12 mo of negative sputum cultures. In patients who are unable to tolerate one of these three drugs, clarithromycin would seem a reasonable alternative, but its effectiveness has not been established by clinical trials (see **below**). Pyrazinamide is **unacceptable** as an alternate or third drug for *M. kansasii* because all isolates are resistant.

The use of intermittent drug regimens or short-course treatment for *M. kansasii* has not been studied enough to recommend it. One study of 40 patients did demonstrate that adding intermittent streptomycin at 1 g twice weekly for the first 3 mo to the previously recommended three-drug regimen given for 12 mo resulted in apparent cure of all but one patient (149). A trial of daily low-dose ethambutol (15 mg/kg) and daily rifampin given for 9 mo sponsored by the British Medical Research Council was completed in 155 adult patients (151). Sputum conversion was achieved in 99.4% of patients, but with a relapse rate of 10% with a 5 year follow-up. This suggests that isoniazid does not contribute greatly to the treat-

ment of *M. kansasii*; however, 9 mo is not a long enough treatment period for the studied two-drug regimen.

In adult patients whose organisms have become resistant to rifampin as a result of previous therapy, a regimen consisting of high-dose daily isoniazid (900 mg), pyridoxine (50 mg daily), high-dose ethambutol (25 mg/kg per day), and sulfamethoxazole (1.0 gm three times per day) until the patient is culture-negative for 12 to 15 mo has been under investigation (133, 134). The oral therapy has been combined with daily or five times per week streptomycin or amikacin for the initial 2 to 3 mo, followed by intermittent streptomycin or amikacin for a total of 6 mo. Results with this regimen described sputum conversion in 18 of 20 patients (90%) after a mean of 11 wk, with only one relapse (8%) among patients who were culture-negative for at least 12 mo on therapy (134). The excellent *in vitro* activity of clarithromycin against *M. kansasii* (134) suggests this agent will also be highly useful in retreatment regimens, perhaps allowing for omission of the aminoglycoside. The newer quinolones may also be potentially useful in this setting but have not been studied.

For treatment of extrapulmonary disease in adults, the regimen of antimycobacterial drugs should be the same as for pulmonary disease. Pulmonary disseminated disease has been described in patients with AIDS (59), and it is the second most common NTM that produces disease in this setting (51). Of the cases detailed in the literature, most have been fatal (59). In the treatment of lymph node disease in children, excision of all accessible nodes at the time of the initial biopsy should be done, since the etiologic agent is probably an NTM other than *M. kansasii*, for which excision is the indicated treatment.

The use of protease inhibitors for the treatment of HIV disease complicates the management of *M. kansasii* disease because rifampin dramatically enhances the metabolism of these drugs and cannot be used with them concurrently. Options for treating HIV-infected patients who receive a protease inhibitor are to substitute clarithromycin for rifampin in the standard regimen, or to substitute rifabutin 150 mg/d for rifampin if the patient is receiving indinavir. None of these regimens have been studied clinically; however, they appear likely to be successful.

TREATMENT OF PULMONARY *Mycobacterium avium* COMPLEX DISEASE (*M. avium*, *M. intracellulare*)

Medical treatment of *M. avium* complex pulmonary disease in HIV-negative patients has historically been frustrating and disappointing. In the few studies in which initial sputum conversion rates have been high (> 50%), long-term follow-up to establish continued sputum conversion is rarely documented (152-156). Relapses after medical therapy with premarolide treatment regimens are common, and the best outcomes have frequently been in those patients subjected to resectional surgery (157,158). Recent significant advances in the drugs available for treatment of *M. avium* complex have been made, however, and there is now greater expectation that pulmonary *M. avium* complex disease can be effectively treated (defined as high rates of sputum conversion with long-term culture negativity) with medications alone.

The major limitations for effective therapy have been the absence of antimicrobial agents with low toxicity and good *in vivo* activity against the organism. Most first-line antituberculosis drugs have 10-100 times less *in vitro* activity against *M. avium* complex isolates than against *M. tuberculosis*. This diminished activity may be due to the lipophilic cell wall of *M. avium* complex, which prevents drug penetration (159).

The major therapeutic advances in the treatment of pulmonary *M. avium* complex disease have come as a result of prog-

ress in treating disseminated *M. avium* complex in the setting of HIV disease. Recent studies have shown excellent *in vivo* and clinical activity against *M. avium* complex by the newer macrolides, clarithromycin and azithromycin, presumably due to the high phagocyte and tissue levels achieved by these agents. (The structure of azithromycin is technically an azalide; however, because of the close similarity of azalides to macrolides, the term macrolide will be used to refer to both in subsequent discussion.) Human trials of patients with disseminated *M. avium* complex disease and AIDS have shown both newer macrolides to have clinical and microbiologic activity as monotherapy (160–163) and clarithromycin to have clinical and microbiologic activity in drug combinations (162). Studies have also demonstrated significant sterilizing activity of both azithromycin and clarithromycin with short-term initial treatment as single agents in pulmonary *M. avium* complex disease (164, 165). Although it is not appropriate to treat patients with disease (outside of clinical trials) with single agents, these are the first studies demonstrating significant *in vivo* activity of any single agent for pulmonary *M. avium* complex disease.

Rifabutin, a derivative of rifamycin S, has been shown to be more active *in vitro* than rifampin against isolates of *M. avium* complex (117). Peak serum rifabutin concentrations are much lower than those of rifampin and exceed the MICs for only approximately 70% of *M. avium* complex strains (123). The relevance of this finding is uncertain, given higher levels of the drug in tissue than in serum. Rifabutin has demonstrated effectiveness as a prophylactic agent against disseminated *M. avium* complex disease in AIDS (54), and there is some evidence of improved clinical response of pulmonary *M. avium* complex disease in HIV-negative patients when rifabutin is added to multidrug regimens (166). The newer macrolides and rifabutin form the basis of improved treatment regimens for pulmonary *M. avium* complex disease.

Clinical Presentations

The natural history of *M. avium* complex lung disease is unpredictable in HIV-negative patients. Some patients maintain a stable clinical and radiographic picture for years, whereas others have a relatively rapid progression of their disease. The variability in the natural history of *M. avium* complex lung disease appears to relate in part to the presence of two types of clinical disease and presentation. The traditional presentation of *M. avium* complex lung disease has been as apical fibrocavitary lung disease, sometimes with huge cavities, in males in their late 40s and early 50s who have a history of heavy cigarette smoking and, frequently, alcohol abuse. This form of disease is generally progressive within 1 to 2 yr if left untreated. More recently, it has become apparent that *M. avium* complex lung disease also presents as bilateral nodular and interstitial/nodular disease or as isolated right middle lobe or lingular disease, predominantly in elderly nonsmoking females (71–74, 167). These syndromes were often referred to as *M. avium* complex “colonization,” with bronchiectasis considered to be the only real disease. This form of disease (nodular bronchiectasis) tended to have a much slower progression, such that long term follow-up (5–10 yr) was often needed to show clinical or radiographic changes. For the nodular bronchiectatic forms of *M. avium* complex lung disease, sputum submission for AFB analysis was often delayed months to years as the patient had radiographic and symptomatic progression.

In the past, many patients with nodular bronchiectatic *M. avium* complex disease received a variety of nonspecific measures (“pulmonary toilet”) rather than specific antimycobacterial therapy for their pulmonary disease. These nonspe-

cific therapies included bronchodilators, postural drainage, smoking cessation, and broad spectrum antibiotics (77). Clearly, these measures may be appropriate and can be associated with symptomatic improvement in bronchiectasis unrelated to any effect on *M. avium* complex. Before the development of newer, more active agents against *M. avium* complex, it had been proposed that patients in this group with a stable clinical picture (usually over 3–6 mo) and minimal symptoms, and those whose sputum “cleared” with nonspecific therapy, should not be treated. However, based on recent studies using chest HRCT scans, these patients have specific radiographic features of parenchymal disease in addition to their multifocal bronchiectasis (71–74). The term “colonization” is, therefore, incorrect. The appropriate distinction is not between colonization and invasive disease but between those patients with the disease of nodular bronchiectasis who require immediate therapy directed at *M. avium* complex 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 medical problems), it is incumbent upon the treating physician to continue collecting respiratory specimens for AFB analysis as well as follow-up chest radiographs and/or CTs over a relatively long period of time (perhaps the patient’s entire lifetime), as the *M. avium* complex 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 *M. avium* complex isolate in the context of the patient’s overall status. In general, almost any patient with two or three positive respiratory cultures for *M. avium* complex has *M. avium* complex lung disease. Although not all patients with an *M. avium* complex respiratory isolate will require immediate therapy, the clinician must resist the temptation to make facile clinical decisions, particularly if that decision is to not treat a patient with a *M. avium* complex respiratory isolate. As treatment regimens improve both in effectiveness and the ability of the patient to tolerate the medications, there should be less reluctance to treat *M. avium* complex lung disease at an earlier stage. For patients with substantial symptoms and/or advanced or progressive radiographic abnormalities, an observation period is not needed to establish the need for therapy.

Drug Treatment

Drug therapy for *M. avium* complex disease involves multiple drugs; therefore, the risk of drug toxicities is relatively high. Additionally, the optimal therapeutic regimen has yet to be established. For these reasons, the treatment of *M. avium* complex disease may best be served by physicians experienced in pulmonary or mycobacterial diseases.

With empiric combination regimens that include clarithromycin and usually ethambutol and a rifamycin (rifampin or rifabutin), sputum conversion rates for pulmonary *M. avium* complex disease in adult patients able to tolerate the medications are about 90% (164, 168, 169). Rifabutin is the preferred rifamycin because it is more active *in vivo* than rifampin against *M. avium* complex, but it may also produce more problematic adverse events (uveitis, leukopenia). All untreated strains of *M. avium* complex are macrolide susceptible (clarithromycin MICs of 0.25 to 4.0 µg/ml), while microbiologic relapses associated with symptom recurrence reveal isolates with MICs of > 32 µg/ml (170). Patients with either pulmonary or disseminated *M. avium* complex do not respond to macrolide-containing regimens in which the macrolide is the sole or principle agent if the patient’s isolate is macrolide resistant *in vitro* (161,

164, 168, 160). Isolates of *M. avium* complex resistant to clarithromycin are cross-resistant to azithromycin (170).

The newer macrolides are the cornerstone of contemporary therapy for pulmonary *M. avium* complex disease, as they are for disseminated *M. avium* complex disease. Initial therapy for adult HIV-negative patients with *M. avium* complex disease needing treatment should consist of a minimum three-drug regimen of clarithromycin (500 mg twice a day) or azithromycin (250 mg/d or 500 mg three times a week), rifabutin (300 mg/d) or rifampin (600 mg/d), and ethambutol (25 mg/kg per day for 2 mo followed by 1.5 mg/kg per day). For patients of small body mass and/or an age over 70, clarithromycin at 250 mg twice a day or azithromycin 250 mg three times a week may be better tolerated. Studies are currently ongoing to determine the feasibility and efficacy of both azithromycin- and clarithromycin-containing regimens with all drugs given intermittently (three times weekly) for pulmonary *M. avium* complex disease.

The potential and method for treating pediatric patients (e.g., those with underlying cystic fibrosis) with the above regimen has not been studied, nor have drug doses for the newer agents such as clarithromycin and rifabutin.

Intermittent streptomycin for the first 2 to 3 mo of therapy may be considered, in addition to the above regimen, for extensive disease. The exact dose of streptomycin in this multi-drug regimen will depend on the patient's age and weight. For extensive disease, we recommend at least 2 mo of intermittent (twice or three times weekly) streptomycin, although longer therapy with streptomycin may be desirable in patients with very extensive disease or for those who do not tolerate other agents. There are no data, however, comparing clarithromycin-containing regimens with and without an aminoglycoside. The patient and physician should be alert to signs and symptoms of streptomycin toxicity, and these may prevent completion of the full course of therapy. Because ototoxicity due to streptomycin is often irreversible, patients receiving streptomycin 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 suggestive signs of toxicity occur. Suggested doses of streptomycin based on patient age and weight are shown in Table 4.

The optimal length of drug therapy for *M. avium* complex lung disease has not been established. Recommendations in the premacrolide era were that patients be treated for 18 to 24 mo without considering how long the sputum culture results were negative. This recommendation was based on empiric data, in part, drawing from the early experience in treating tuberculosis. With macrolides, a shorter length of therapy seems acceptable. Only two long-term studies of *M. avium* complex

lung disease have been reported to date, both investigating clarithromycin (168, 169). One study using 12 mo of culture negativity as the treatment endpoint observed no pulmonary disease relapses with a mean follow-up of 18 mo (168), while the second study, which used 7 to 9 mo of culture negativity, resulted in no early pulmonary disease relapses with a mean follow-up of 7 mo (169). Early relapses with less than 10 mo of culture negativity were seen in the first study. These initial studies suggest that culture negativity of 10 to 12 mo while on a clarithromycin-containing regimen is adequate for most patients.

Acid-fast bacilli smears and cultures of sputum should be obtained monthly during therapy for pulmonary *M. avium* complex disease to assess response, then periodically after completion of therapy to evaluate possible relapse. The desired endpoint is negative sputum cultures; patients who respond to therapy should develop negative AFB smears and cultures. One or more cultures containing small numbers of *M. avium* complex organisms (single colonies on solid media or positive liquid media cultures only) may occur after sputum conversion and should not necessarily be interpreted as indicative of treatment failure or relapse. Rather, these culture results should be interpreted in light of the patient's overall clinical status.

All patients should show clinical improvement within 3 to 6 mo and should convert their sputum to negative within 12 mo on macrolide-containing regimens (168). Thus, patience is required in evaluating response to therapy. However, failure to respond in these time periods should prompt investigation for possible noncompliance or macrolide resistance.

For patients whose disease has failed to respond to a macrolide-containing regimen (usually as a consequence of *in vitro* macrolide resistance, noncompliance, or drug intolerance) and have progressive, symptomatic disease, an alternative drug regimen will be necessary. The treatment for pulmonary *M. avium* complex disease in HIV-negative adult patients as recommended in the first ATS NTM statement published in 1990, consisted of the four-drug regimen of isoniazid (300 mg/d), rifampin (600 mg/d), ethambutol (25 mg/kg per day for the first 2 mo, then 1.5 mg/kg per day) with streptomycin for the initial 3 to 6 mo of therapy (1). With the use of rifabutin instead of rifampin, this may be a reasonable regimen for patients who are macrolide resistant or intolerant. Which drugs are most useful in treating macrolide-resistant strains is a major issue to be addressed in future studies as resistant strains become more prevalent. Although there are no trials comparing regimens with and without a macrolide for treating pulmonary *M. avium* complex, most experts consider the regimen without a macrolide to be inferior, and one such regimen (rifampin, ethambutol, ciprofloxacin, and clofazimine) has been shown to be inferior to a clarithromycin-containing regimen for disseminated *M. avium* (171).

A number of other drugs have been used in multidrug regimens in the past, but they are limited by toxicity (e.g., cycloserine and ethionamide) or little or no evidence of clinical efficacy (e.g., clofazimine, newer quinolones, capreomycin). Some experts feel that clofazimine 100 mg/d and ciprofloxacin 750 mg twice daily or ofloxacin 400 mg twice daily are useful in the setting of *M. avium* complex lung diseases, although there are no data corroborating their efficacy. Therapy with only two drugs, especially isoniazid and rifampin only, is strongly discouraged and not likely to be effective. Antituberculosis drugs are generally well tolerated, even by the elderly population with *M. avium* complex lung disease.

If patients are unable to tolerate or fail first-line antituberculosis medications, an alternative "salvage" regimen should

TABLE 4
SUGGESTED DOSES OF STREPTOMYCIN RELATIVE
TO AGE AND WEIGHT IN PATIENTS WITH
NORMAL SERUM CREATININE*

Weight and Age	Initial Therapy [†]	Maintenance Therapy [‡]
≥ 50 kg and ≤ 50 yr	1 g 5×/wk	1 g 3×/wk
< 50 kg and ≤ 50 yr	500 mg 5×/wk	750 mg 2×/wk
> 50 kg and 50-70 yr	500 mg 5×/wk	750 mg 2×/wk
> 70 yr	750 mg 2×/wk	750 mg 2×/wk

*. These doses have not been established as optimal by clinical trials. The reduced doses with age reflect the reduced renal function and increased risk of toxicity with streptomycin seen in patients older than 50 yr.

[†] For the first 6 to 12 wk of therapy as tolerated.

[‡] For subsequent therapy as tolerated.

be considered with potential agents including ciprofloxacin 750 mg twice daily or ofloxacin 400 mg twice daily, clofazimine 100 mg daily, ethionamide (2.50 mg twice a day, then increased to three times a day as tolerated), and prolonged use of streptomycin or amikacin (three to five times per week). A multiple drug regimen including these potentially toxic drugs can also be associated with at least short-term conversion of the sputum to AFB-negative. The long-term success rate for salvage regimens is unknown but is likely very low.

The role of immune therapy in patients who fail drug therapy has not been established. Interleukin and gamma interferon have been used in selected patients, and some investigation in this area continues.

Surgical Treatment

Patients whose disease is localized to one lung and who can tolerate resectional surgery might also be considered for surgery, if there has been poor response to drug therapy or if the patient's isolate has become macrolide resistant. For some patients successfully treated by surgical resection, the prognosis has been better than for patients treated medically, although these results predated the use of macrolide-containing regimens (157, 158). Lung resectional surgery for mycobacterial disease is associated with significant morbidity and mortality (172, 173). In one recent series from a thoracic surgeon experienced in mycobacterial surgery, 8 of 38 (21%) of patients undergoing surgery and 8 of 17 (47%) of patients undergoing pneumonectomy developed postoperative bronchopleural fistulae, especially following a right pneumonectomy (172). Whenever possible, this surgery should be performed at centers with thoracic surgeons who have considerable experience with this type of surgery. Overall, the bilateral nature of *M. avium* complex lung disease, the advanced age of the patients, and the frequency of underlying chronic lung disease have limited the number of patients who are good candidates for surgery.

Toxicity Monitoring

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) (174), auditory and vestibular function (streptomycin, amikacin, clarithromycin, azithromycin), renal function (streptomycin and amikacin), leukocyte and platelet counts (rifabutin) (175, 176), and the central nervous system (cycloserine). Patients who receive both a macrolide and rifabutin must be monitored for the development of toxicity related to the interaction of these drugs (175, 176). Clarithromycin enhances rifabutin toxicity (especially uveitis) while the rifamycins, rifampin more than rifabutin, lower clarithromycin serum drug levels. Details are provided in the section on monitoring for drug toxicity.

TREATMENT OF LOCALIZED EXTRAPULMONARY *Mycobacterium avium* COMPLEX DISEASE

Lymphadenitis

Excisional surgery without chemotherapy is the recommended treatment for children with NTM cervical lymphadenitis, including those with disease caused by *M. avium* complex and *M. scrofulaceum* (79, 80, 177, 178). The success rate with this procedure is about 95% (79). Incisional biopsy or the use of antituberculosis drugs alone (without a macrolide) has frequently been followed by persistent clinical disease, including

sinus tract formation and chronic drainage, and should be avoided (79, 80, 177, 178). 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) may be the use of a clarithromycin multidrug regimen such as that used for pulmonary disease (80, 179, 180). Experience with such an approach is limited (179–182), but the proven activity of clarithromycin against *M. avium* complex in other clinical settings and preliminary reports makes this approach appear promising.

A special problem is created by the child who has granulomatous disease with or without AFB on examination of the excised lymph nodes, and whose PPD tuberculin skin test is strongly positive (e.g., more than 15 mm). A course of antituberculosis therapy while awaiting the results of the lymph node culture is reasonable, especially when there are any risk factors for tuberculosis (positive family history, foreign-born child, etc.). If the cultures fail to yield any mycobacteria, antituberculosis therapy should be discontinued unless there are significant risk factors for tuberculosis.

Skin, Tissue, and Skeletal Disease

For adult patients with extrapulmonary, localized *M. avium* complex disease involving skin, soft tissue, tendons and joints, and occasionally bone, a combination of excisional surgery (or surgical debridement) and chemotherapy is usually performed. Whether a three-drug regimen alone in this setting would be adequate is not known. The optimal duration of treatment is also unknown, but drug treatment usually lasts 6 to 12 mo.

TREATMENT OF DISSEMINATED *Mycobacterium avium* DISEASE

Disseminated *M. avium* is associated with an increased mortality in patients with AIDS. In one natural history study, the median survival was 134 d after the first positive blood culture, and only 13% of patients were alive at 1 yr (53). Initially, some clinicians questioned whether *M. avium* was a direct cause of death or only present in persons who were dying of other reasons. Several controlled studies have shown shortened survival in patients with disseminated *M. avium* when compared to cohorts of patients without *M. avium* (183). Based on the increased morbidity and mortality associated with disseminated *M. avium*, prophylaxis should be strongly considered in high-risk patients and therapy should be offered to all patients with established disease.

Early (premacrolide) studies of the treatment of *M. avium* in patients with AIDS demonstrated the ability of multidrug regimens to lower the burden of mycobacteria in the blood and improve symptoms (184, 185). The drugs used in these studies such as ethambutol, clofazimine, rifampin, and ciprofloxacin have been shown to have modest activity *in vitro*, and two of the agents (ethambutol and rifabutin) to have modest activity in single-drug therapy studies of patients with AIDS and *M. avium* (186, 187). A major advance in therapy came with the recognition that clarithromycin and azithromycin were potent agents against *M. avium* complex. Both clarithromycin and azithromycin were shown to markedly reduce the number of bacteria in the blood of patients in small pilot studies (160, 163). In a larger study of 154 adult patients with AIDS and *M. avium* bacteremia, clarithromycin was given as single-drug therapy in doses of 500, 1,000 or 2,000 mg twice daily. All three groups had clearance of bacteremia and reduction in symptoms, although the groups receiving the higher doses had greater toxicity and a higher mortality (161). It was also noted, however, that resistance was a problem, as clinical

relapse and in *vitro* resistance developed in approximately 20% of individuals by 12 wk.

Rifabutin has also been demonstrated to be effective in several small studies of patients with AIDS who had disseminated *M. avium* (184, 188). As monotherapy, it was shown to reduce colony counts in the blood (187). Clearance of bacteremia occurred in 7 of 11 patients receiving rifabutin, clofazimine, and ethambutol, compared to 0 of 13 patients with clofazimine alone in another study (188).

Due to problems with drug resistance, as well as the need to eradicate large numbers of organisms, multidrug therapy is considered essential in the treatment of patients with disseminated *M. avium*. There are currently few well done comparative trials of the many possible multidrug regimens. A Canadian HIV Trials Network study (171) involving 229 patients did demonstrate the combination of clarithromycin, rifabutin, and ethambutol to be superior to rifampin, ethambutol, clofazimine, and ciprofloxacin at both reducing bacteremia (69% versus 29%, $p < 0.001$) and prolonging median survival (8.6 mo versus 5.2 mo, $p = 0.001$).

Based on currently available data, it would be advisable to always use a minimum of three drugs—one of which should be clarithromycin (500 mg twice daily) or azithromycin (250 mg or 500 mg daily). Most investigators would use ethambutol as the second agent at a dose of 15 mg/kg per day, although consideration should be given to an initial course of 25 mg/kg for the first 2 mo. Rifabutin has the best potential as the third agent. Use of rifabutin will be problematic, however, in patients also on protease inhibitors, given its induction of the cytochrome P-450 system that metabolizes all currently approved members of this drug class. Clofazimine has also been used, as has a quinolone, but neither seems to contribute much to the regimen, and clofazimine has been associated with a higher mortality in two comparative treatment trials (189). Amikacin (191) and streptomycin are both active, and one or the other should be considered for use in patients with severe symptoms due to *M. avium* complex, especially as part of initial therapy.

It should be noted that drugs used to treat mycobacterial diseases in patients with AIDS are associated with frequent adverse effects, and changes to therapeutic regimens may often be required. Of particular note has been the frequent occurrence of uveitis when doses of clarithromycin higher than 500 mg twice daily have been used in combination with rifabutin doses of 600 mg daily (175). This incidence fell to only 6% (3 of 53 patients) in the Canadian HIV trial when the rifabutin dose was reduced to 300 mg daily, the currently recommended dose (171).

Another problem is the interaction of rifamycins with the recently introduced protease inhibitors (saquinavir, zidovudine, and zalcitabine) for treatment of AIDS. Rifampin, and to a lesser degree rifabutin, enhances hepatic metabolism of the protease inhibitors, which may result in subtherapeutic levels of these agents and promote the emergence of resistant HIV strains. The protease inhibitors inhibit metabolism, and therefore promote dose-related adverse effects, of the rifamycins (especially rifabutin). Recent recommendations, made in the context of tuberculosis therapy, suggest that rifampin should not be used with the protease inhibitors, but that rifabutin can be used at modified doses with at least one of these agents, zidovudine (190). This recommendation would have little impact on the treatment or prophylaxis of disseminated *M. avium* disease since rifabutin is the preferred rifamycin. The impact on the treatment of other NTM such as *M. kansasii*, where rifampin has traditionally been used, is less clear. Alternative strategies include treatment of NTM infections without a rifa-

mycin or withholding the protease inhibitor until the mycobacterial infection has been treated. The improved immune function resulting from aggressive antiretroviral therapy, including a protease inhibitor, might ultimately be the most important factor for clearance of disseminated NTM infection in AIDS patients; therefore, continuing a protease inhibitor is a high priority. Optimal therapy for disseminated NTM disease, especially *M. avium*, requires a multidrug treatment regimen including a rifamycin. Overall, in a patient on protease inhibitors with proven disseminated *M. avium*, it still seems prudent to include rifabutin in the treatment regimen, even if the dose is attenuated. For other NTM, the importance of the rifamycin should be evaluated based on the specific organism being treated.

PROPHYLAXIS OF DISSEMINATED DISEASE IN AIDS

The incidence of disseminated *M. avium* can be reduced by prophylactic antimicrobials. Rifabutin was demonstrated to be effective in two placebo-controlled, double-blind studies. *Mycobacterium avium* bacteremia developed in 8% of adult patients receiving 300 mg of rifabutin daily and in 17% of patients on placebo (54). Because rifabutin is highly active against *M. tuberculosis*, it is probable that daily use of rifabutin would also provide prophylaxis against tuberculosis. Active tuberculosis must be ruled out before initiating rifabutin prophylaxis in order to prevent the development of drug-resistant tuberculosis. Clarithromycin in a dose of 500 mg twice daily was effective in a controlled trial of 667 adult patients in reducing the incidence of *M. avium* complex bacteremia from 16% in the placebo group to 6% in the treatment group (192, 193), while in a related trial it was shown to be more effective than rifabutin (193). Azithromycin at a dose of 1,200 mg once weekly, either alone or in combination with rifabutin, has also been shown to be effective in a published clinical trial involving 693 adult patients (194). The final selection of agents may depend on cost, tolerability, and potential drug interactions of the agents. Rifabutin should generally be avoided in patients on protease inhibitors because it markedly enhances their metabolism and reduces serum levels of the protease inhibitors. Some clinicians and the United States Public Health Service have advocated use of zidovudine but not other currently available protease inhibitors (zalcitabine, saquinavir) with reduced-dose rifabutin if both drugs are deemed essential.

The development of drug resistance during prophylaxis is a concern, and it has already been noted to occur with the use of clarithromycin (192, 193) or azithromycin (194) as monotherapy, but not the rifabutin monotherapy (54) or azithromycin when combined with rifabutin (194). Because of the very high risk of disseminated *M. avium* in persons with advanced HIV infection, prophylaxis should be offered to all patients with < 50 CD4 cells, especially in patients with a history of opportunistic infection (195,196).

TREATMENT OF RAPIDLY GROWING MYCOBACTERIAL DISEASE

Disease caused by the rapidly growing mycobacteria, especially cutaneous disease, has come to be recognized as relatively common in selected areas of the United States. The southeastern United States from Georgia to Texas appears to be the major endemic area, although disease has been reported from all over the United States. Most clinical disease is sporadic and community acquired, although nosocomial outbreaks or clustered cases have been reported (16–26), and the association of rapidly growing mycobacteria wound infections

with augmentation mammoplasty (23, 93) and cardiac surgery (16, 17, 21, 94) is well recognized.

Most clinical disease (more than 90%) is due to three species of rapidly growing mycobacteria: *M. fortuitum*, *M. abscessus*, and *M. chelonae* (91). Two taxa originally identified as biovariants within *M. fortuitum* (*M. fortuitum* third biovariant complex, sorbitol-positive and sorbitol-negative) are still undergoing taxonomic evaluation. Both groups may eventually attain species status. *Mycobacterium smegmatis* (197), *M. peregrinum* (91), *M. mucogenicum* (formerly known as the "*M. chelonae*-like organisms" or MCLO) (198), and rarely, chromogenic rapidly growing mycobacteria (199-201) may also occasionally be responsible for human disease.

Mycobacterium fortuitum, *M. abscessus*, and *M. chelonae* are resistant to the antituberculous agents, but they are susceptible (especially *M. fortuitum*) to a number of traditional antibacterial agents (100, 138-141). Isolates of *M. fortuitum* treatment are susceptible to amikacin (100%), ciprofloxacin and ofloxacin (100%), sulfonamides (100%) cefoxitin (SO%), imipenem (100%), clarithromycin (80%), and doxycycline (50%). Isolates of *M. abscessus* are susceptible to clarithromycin (100%), clofazimine, amikacin (90%), and cefoxitin (70%) and imipenem (SO%). Isolates of *M. chelonae* are susceptible to amikacin (80%), tobramycin (100%), clarithromycin (100%), imipenem (60%), clofazimine, doxycycline (25%), and ciprofloxacin (20%).

Cutaneous Diseases

Clinical disease caused by the rapidly growing mycobacteria usually follows accidental trauma or surgery in a variety of clinical settings (91). Some minor infections will resolve spontaneously or after surgical debridement. However, several studies of postinjection abscesses in which no therapy was given revealed disease that persisted in most patients for 8 to 12 mo before spontaneously resolving. In two outbreaks of *M. abscessus* in the era

should be used in patients over the age of 50; once-daily dosing is unproven clinically but appears reasonable. The amikacin combined with high-dose cefoxitin (1.2 g/d given intravenously) is recommended for initial therapy (minimum 2 wk) until clinical improvement is evident. For *M. chelonae*, tobramycin is more active *in vitro* than amikacin. Imipenem appears to be a reasonable alternative to cefoxitin for these two species, and it should be used with isolates of *M. smegmatis* and *M. chelonae* that are resistant to cefoxitin (100, 139, 197). Monitoring of renal function, eighth nerve function, and white blood cell counts (for the beta lactams) should be done on patients receiving this regimen. If organisms are susceptible to oral agents, therapy can be switched to one or more of these agents. For *M. abscessus*, the only oral agents available for therapy are clofazimine and clarithromycin (140). For *M. chelonae*, clarithromycin, clofazimine, and (for approximately 20% of strains) ciprofloxacin and doxycycline are the only oral drugs susceptible *in vitro* (100, 140). The only clinical trial for *M. chelonae* skin disease was done with clarithromycin. Of patients (all adults) treated with monotherapy at 500 mg twice a day for 6 mo, all were cured except one patient (8%) who relapsed with an isolate that developed resistance to clarithromycin (204). For serious disease, a minimum of 4 mo of therapy is necessary to provide a high likelihood of cure. For bone infections, 6 mo of therapy is recommended (202).

Surgery is generally indicated with extensive disease, abscess formation, or where drug therapy is difficult. Removal of foreign bodies such as breast implants, percutaneous catheters, etc., is important, or even essential, to recovery.

Pulmonary Disease

The prevalence of lung disease caused by rapidly growing mycobacteria is unknown; however, it is likely more common than early estimates as these organisms have gained increasing recognition as pathogens. The largest group of patients with this lung disease are elderly (older than 60), Caucasian, female nonsmokers with no predisposing conditions or known lung disease. Underlying disorders that are associated with the disease include lung damage produced by prior mycobacterial infection (usually tuberculosis or *M. avium* complex), gastroesophageal disorders with chronic vomiting, lipoid pneumonia, cystic fibrosis, and bronchiectasis due to a prior respiratory infection (206). The distinguishing feature of patients with a recognized underlying disease is that their rapidly growing mycobacteria lung disease occurs at a younger age, usually less than 50, and almost all patients under 40 have one of these disorders (206).

Although early studies identified most respiratory isolates of rapidly growing mycobacteria as *M. fortuitum*, use of modern identification schemes have shown that *M. abscessus* (formerly *M. chelonae* subspecies *abscessus*) accounts for approximately 80% of rapidly growing mycobacterial respiratory disease isolates, while *M. fortuitum* (formerly *M. fortuitum* biovariant *fortuitum*) accounts for approximately 15% of these isolates (206). An important exception is the small group of patients who have gastroesophageal disorders with chronic vomiting and rapidly growing mycobacterial lung disease, in whom *M. abscessus* and *M. fortuitum* occur with equal frequency. Overall, *M. abscessus* appears to be a more virulent respiratory pathogen than *M. fortuitum*. Obtaining a single respiratory isolate of *M. abscessus* is more likely to indicate significant disease than a single isolate of *M. fortuitum*, although careful clinical evaluation and follow-up is always necessary to determine the significance of an NTM respiratory isolate.

In lung disease due to rapidly growing mycobacteria in patients with no apparent risk factors, the chest radiograph usu-

M. fortuitum, *M. abscessus*, or *M. chelonae*, comparing one form of treatment with another or with no drug treatment at all, have been performed. However, susceptibility studies (139-141) have demonstrated excellent *in vitro* activity of drugs such as clarithromycin, imipenem, cefoxitin, cefmetazole, and amikacin. Several case studies (197, 202, 203) and one clinical trial (204) of patients with cutaneous disease treated on the basis of *in vitro* susceptibilities have shown good results.

On the basis of these studies, guidelines have been suggested for drug therapy of nonpulmonary disease caused by rapidly growing mycobacteria (205). Because of variable drug susceptibility among species and even within species and subgroups, susceptibility testing of all clinically significant isolates is essential for good patient management. The first-line antituberculosis drugs (isoniazid, rifampin, pyrazinamide, etc.) have no role in the therapy of rapidly growing mycobacterial disease, with the exception of ethambutol, to which *M. smegmatis* is susceptible (197).

For serious disease caused by *M. fortuitum* and *M. abscessus*, intravenous amikacin is given at a dose of 10 to 15 mg/kg in two divided doses to adult patients with normal renal function (average 400 mg twice a day) to provide peak serum levels in the low 20 µg/ml range. The lower dose (10 mg/kg)

ally shows multilobar, patchy, reticulonodular or mixed interstitial-alveolar infiltrates with an upper lobe predominance. Cavitation occurs in only approximately 15% of cases (206). The chest radiograph is usually not typical for or suggestive of reactivation pulmonary tuberculosis, which likely accounts for a delay in ordering sputum for AFB analysis and therefore a delay in diagnosis. High resolution computed tomography of the lung frequently shows associated cylindrical bronchiectasis and multiple small (<5 mm) nodules, a pattern also seen in nonsmokers with *M. avium* complex lung disease (65-68). Interestingly, approximately 15% of patients with *M. abscessus* will also have *M. avium* complex, suggesting the close relationship of the disorders (206). Some patients have positive sputum cultures for *Pseudomonas aeruginosa*, further evidence of bronchiectasis. The radiographic features of this disease in cystic fibrosis are still under investigation.

The usual presenting symptoms are cough and easy fatigability, often attributed for months or years to bronchitis or bronchiectasis. Fever, night sweats, and weight loss occur, but they are much less common and less severe than with *M. tuberculosis*. The constellation of typical presenting symptoms in an elderly nonsmoking patient with no underlying lung disease, a compatible chest radiograph, and multiple positive sputa is sufficient to make a diagnosis. The presence of other diseases or unusual features may necessitate obtaining a lung biopsy (bronchoscopy with transbronchial biopsy) to be certain of the diagnosis.

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, the disease is indolent and slowly progressive. Some patients show little radiographic change over years. More fulminant, rapidly progressive disease can occur, particularly in association with gastroesophageal disorders. Death occurs as a consequence of *M. abscessus* in 20% of cases (206).

Mycobacterium fortuitum isolates, when they do occur, are usually susceptible to multiple oral antimicrobial agents including the newer macrolides and quinolones, doxycycline and minocycline, and sulfonamides (139-141). Drug susceptibilities for this species are essential for effective therapy. Six to twelve months of therapy with two oral agents to which the *M. fortuitum* isolate is susceptible *in vitro* usually results in clinical cure. Unfortunately, the *M. fortuitum* group produces less than 20% of lung disease due to rapidly growing mycobacteria.

Mycobacterium abscessus isolates are usually susceptible *in vitro* only to the parenteral agents amikacin, cefoxitin, and imipenem, and to the newer oral macrolides (clarithromycin and azithromycin). Preliminary studies suggest that monotherapy with the newer macrolides is not sufficient to produce microbiologic cure for *M. abscessus*. Combination therapy of low-dose amikacin plus high-dose cefoxitin for 2-4 wk almost invariably produces clinical and microbiologic improvement, but cost and morbidity prohibit potentially curative courses of treatment (probably 4-6 mo). Surgical resection for limited disease related to prior localized lung disease can also be curative (206). Unfortunately, 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.

TREATMENT OF *Mycobacterium marinum* DISEASE

A number of treatment modalities have been used for cutaneous disease caused by *M. marinum* (69, 13). These include simple observation for minor lesions, surgical excision, the use of

antituberculous agents, and the use of single antibiotic agents. By standard susceptibility testing, these isolates are susceptible to rifampin 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.

Acceptable treatment regimens in adults include clarithromycin 500 mg twice a day, minocycline or doxycycline at 100 mg twice a day (207-209), trimethoprim-sulfamethoxazole at 160/800 mg twice a day (210), or rifampin (600 mg) plus ethambutol (15 mg/kg) daily (208, 211), with each regimen being given for at least 3 mo. Rifampin alone has also been recommended, but little experience with this regimen has been reported (212). The rate of clinical response is quite variable, and a minimum of 4 to 6 wk of therapy should be given before considering that the patient may not be responding. Surgical debridement may also be important, especially for disease involving the closed spaces of the hand or disease that responds poorly to drug therapy (13, 211). If a lesion is excised surgically, many clinicians provide drug coverage during the perioperative period. It is not clear if longer durations of drug treatment after surgery offer any additional advantage.

TREATMENT OF PULMONARY DISEASE DUE TO OTHER NONTUBERCULOUS MYCOBACTERIA

Although most species of NTM have been reported to cause pulmonary disease, there are only four additional species that merit consideration. Because of the small number of reported cases and the absence of therapeutic trials or treatment of disease caused by these species, only limited recommendations on drug therapy can be made now. In most cases, if there has been satisfactory clinical and bacteriologic response to chemotherapy, a treatment period of 18 to 24 mo is recommended.

Mycobacterium malmoense is a slowly growing, nonpigmented NTM species that causes pulmonary disease. Although rare in the United States, it has been increasingly recognized in England, Wales, and northern Europe. Most isolates are susceptible to ethambutol, and many are susceptible to rifampin and streptomycin. The four-drug regimen recommended for treating *M. avium* complex (before the availability of macrolides and rifabutin) has resulted in clinical and bacteriologic responses in most cases (70, 213). Potential improvements in therapeutic response with the macrolides and rifabutin has not been assessed.

Mycobacterium simiae is a slowly growing, nonpigmented *Mycobacterium* that may be confused with *M. tuberculosis*, as it is the only NTM that is niacin-positive. It is an uncommon cause of pulmonary and disseminated infection, and many patients with respiratory isolates of this species do not have disease. Most isolates are resistant to all first-line antimycobacterial drugs, and response to chemotherapy has been variable (32, 214). For patients with disseminated or progressive pulmonary disease in need of treatment, initial therapy may be started with the four-drug regimen recommended for *M. avium* complex (clarithromycin, ethambutol, rifabutin, and streptomycin), modified as needed using results of susceptibility tests.

Mycobacterium szulgai is a slowly growing *Mycobacterium* that has been associated with skin, joint, lymphatic, pulmonary, and disseminated disease (135). When isolated from humans, it should be considered pathogenic. Through 1986, only 24 cases of disease had been reported in the English literature. The organism is usually susceptible to rifampin and higher concentrations of isoniazid, streptomycin, and ethambutol. Enhanced activity of rifampin, ethambutol, and streptomycin

TABLE 5
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 alanine aminotransferase (ALT) or aspartate aminotransferase (AST) determinations, especially in first 3 mo of therapy
	Increased serum levels of phenytoin (Dilantin™)	Monitor serum levels
Ethambutol	Peripheral neuropathy related to pyridoxine deficiency	Clinical symptoms
	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 per day); 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
Rifabutin only	Hepatitis	Clinical symptoms; AST or ALT determinations based on symptoms
	Increased hepatic metabolism of numerous agents, including birth control pills, ketoconazole, quinidine, 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
Streptomycin amikacin, tobramycin	Polymyalgia, polyarthralgia, leukopenia, granulocytopenia, anterior uveitis (rifabutin with clarithromycin)	Clinical symptoms, periodic WBC counts
	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
	Renal toxicity	Periodic serum creatinines; periodic amikacin or tobramycin serum levels
Ethionamide	Hypersensitivity (fever, rash, eosinophilia) (streptomycin)	Clinical symptoms
	Gastrointestinal disturbance (anorexia, nausea, vomiting, abdominal pain, diarrhea)	Clinical symptoms
	Hepatitis	Clinical symptoms; periodic AST or ALT determinations
Cycloserine	Central nervous system (anxiety, depression, altered behavior)	Clinical symptoms
	Peripheral neuropathy	Clinical symptoms
	Central nervous system (depression, altered behavior, confusion, anxiety, psychosis, seizures)	Clinical symptoms, assessment of mental status; serum levels weekly for first month if timely testing available
Azithromycin, clarithromycin	Gastrointestinal disturbance (nausea, vomiting, diarrhea)	Clinical symptoms
	Decreased hearing	Clinical symptoms
	Hepatitis	Clinical symptoms
Clarithromycin only	Inhibited hepatic metabolism of several agents, including rifabutin, some protease inhibitors, Seldane™	Periodic alkaline phosphatase, AST and gamma glutamyl transpeptidase (GGT) for first 3 mo
		Monitor clinical status and appropriate serum levels when possible; avoid use of Seldane

(continued)

TABLE 5
CONTINUED

Drug	Major Side Effects/Toxicity	Monitoring Procedures
Ciprofloxacin ofloxacin	Gastrointestinal disturbance (nausea, vomiting, diarrhea)	Clinical symptoms
	Central nervous system (headache, insomnia)	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

when used in combination has been shown *in vitro* (215). Most patients treated with these drugs respond to therapy.

Relatively uncommon in the United States, *M. xenopi* has been reported as a common cause of slowly progressive NTM pulmonary disease in western Europe. In southeast England, it is the most common NTM recovered in the laboratory and has been since 1977 (216). Disseminated disease and joint disease caused by this organism have also been reported. *In vitro* susceptibility to antituberculosis agents is variable, although enhanced drug activity has been shown with the combination of rifampin and streptomycin (215). Although some investigators have reported success with surgical therapy similar to that used for selected patients with *M. avium* complex disease, others have had disappointing results (136, 173). Results with drug therapy alone in the premacrolide era have also shown variable results. One recent study of clarithromycin-containing regimens (137) demonstrated an excellent sputum conversion rate compared to these older studies. For most patients, initial therapy should consist of a macrolide, rifampin or rifabutin, and ethambutol with or without initial streptomycin. Patients who fail therapy or who relapse after treatment might be considered for surgery (30, 136, 173).

MONITORING FOR DRUG TOXICITY

Monitoring for drug toxicity of patients who are being treated for NTM disease is important, given the number and type of drugs used and the older age of these patients. It should include monitoring of the visual system including visual acuity (ethambutol), the presence of eye pain and decreased visual acuity or uveitis (rifabutin) (175, 176), and red-green color discrimination (ethambutol); the central nervous system (cycloserine, ciprofloxacin, ofloxacin, ethionamide); the liver (isoniazid, rifampin, ethionamide, clarithromycin, rifabutin) (174, 176); the kidney (streptomycin, amikacin); auditory and vestibular function (streptomycin, amikacin, azithromycin); and hematologic indices (sulfonamides, cefoxitin, rifabutin) (176). Major side effects and monitoring procedures are listed in Table 5.

For the aminoglycosides, this monitoring should include routine questioning about balance, ability to walk (especially in the dark), tinnitus, dizziness, and difficulty hearing. Baseline blood urea nitrogen and creatinine measurements should be obtained, with reduction of the streptomycin dose and/or frequency of administration if these are abnormal. Periodic monitoring of renal function is recommended for high-risk patients receiving drugs daily or five times a week, especially with patients older than 50 yr or who have impairment of renal function. A baseline hearing test should be considered, especially in high-risk patients, and then repeated if signs or symptoms of seventh nerve toxicity appear.

For cycloserine, careful attention should be given to signs of central nervous system toxicity, which may include seizures, lethargy, depression, alterations in personality, and even suicidal ideations. Because toxicity with this drug relates primarily to excessive serum levels ($> 40 \mu\text{g/ml}$), patients with central nervous system symptoms or abnormal baseline renal function should have serum level determinations. Unfortunately, such tests are not available in most clinics and are rarely available in a timely fashion to help with decisions on dosing. If serum levels are not available, physicians should remember that the drug is excreted by the kidney, and high serum levels tend to occur in the elderly or in the presence of renal failure. A lower dose (e.g., 250 mg twice a day) is often given in such cases, and discontinuation of the drug may be necessary if central nervous system symptoms occur and one cannot monitor serum levels.

Given that isoniazid hepatotoxicity is higher in the older population, some physicians obtain a baseline measurement of aspartate aminotransferase (AST), then repeat this determination at 2, 4, and 8 wk and thereafter during therapy as clinically indicated. Other monitoring considerations are the same as those for patients with tuberculosis (see the ATS Statement "Treatment of Tuberculosis and Tuberculosis Infections in Children and Adults" (2,217)).

The incidence of gastrointestinal side effects such as nausea, vomiting, abdominal pain, and cramping is almost prohibitive with ethionamide. These symptoms can be minimized by

starting with a 250 mg single dose, slowly increasing the dose, and administering it with food. In the older patient, limiting the total dose to 500 mg may help reduce toxicity. A good review of side effects and toxicities experienced at the National Jewish Hospital with ethionamide and cycloserine is provided in a study by Lester (218).

Some adverse events with rifabutin are comparable to those seen with rifampin. These include rash, fever, nausea, vomiting, and hepatitis. Several adverse events are unique to rifabutin, including anterior uveitis, skin hyperpigmentation or pseudojaundice, and a polymyalgia/polyarthralgia syndrome (175, 176). The last three adverse events are seen almost exclusively in patients concurrently receiving clarithromycin. These effects can be minimized by giving no more than 300 mg/d of rifabutin when combined with clarithromycin. Leukopenia is also seen with rifampin, but it is much more common with rifabutin. Periodic white blood cell counts should be performed on all patients taking rifabutin, perhaps at monthly intervals. Mild leukopenia is common (8 of 26 or 31% of patients in one series of HIV-negative patients on 600 mg/d developed WBC counts below 4,000 cells/mm³) (176), and the drug should be discontinued only if cell counts fall below a comfortable range (perhaps 2,500 cells/mm³ or an absolute granulocyte count of 1,500 or less in HIV-negative patients).

This statement was prepared by an ad hoc committee of the Scientific Assembly on Microbiology, Tuberculosis, and Pulmonary Infections. Members of the committee were:

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