

ATYPICAL MYCOBACTERIA



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Learning Objectives

1. Classify the atypical mycobacteria by microbiological characteristics, epidemiology, pathogenesis, sites of infection, and general pharmacotherapy
2. Given a specific history of present illness, devise a diagnostic strategy for a suspected atypical mycobacterial infection.
3. Distinguish between infection control measures necessary for atypical mycobacterial infections and tuberculosis.
4. Evaluate the potential for successful outcomes associated with various pharmacotherapeutic strategies for infections due to atypical mycobacteria.
5. Given pertinent clinical and laboratory data, construct a pharmacotherapy plan for a patient with an infection due to atypical mycobacteria.
6. Develop a treatment monitoring plan for a patient with an atypical mycobacterial infection.
7. Justify the patient populations that may benefit from preventive measures.

Introduction

Infections from *Mycobacterium* species have a variety of clinical presentations. The most notorious species of this genus is *Mycobacterium tuberculosis*, which is responsible for millions of cases of tuberculosis worldwide each year (about 4 million cases were reported to the World Health Organization in 2001). *Mycobacterium tuberculosis* overshadows most other mycobacterial species, termed “atypical mycobacteria”. The most common atypical mycobacteria that cause disease in the United States are *Mycobacterium avium* complex (MAC), *Mycobacterium fortuitum* complex, and *Mycobacterium kansasii*.

The epidemiology of mycobacterial infections has been dynamic over the past several decades. In the developed world, tuberculosis has been on the decline because of the maturation of infection control measures and the development of effective antituberculosis pharmacotherapy. Atypical mycobacteria, although recognized soon after the discovery of *M. tuberculosis* in the 19th century, were not deemed significant pathogens until the mid-20th century with the emergence of pulmonary infection in patients with preexisting lung disease. Subsequently, the acquired immune deficiency syndrome (AIDS) epidemic brought forth drastic increases in the occurrence of certain opportunistic infections. One of the most common systemic opportunistic infections was disseminated disease due to MAC. Many established atypical mycobacterial infections also grew in prevalence over the past few decades, and several new species emerged with variable ability to cause human disease.

Atypical mycobacteria have caused many types of infections, including pneumonia, lung abscess, pleural space infection, lymphadenitis, skin and soft tissue infection (including postoperative wound infection), meningitis, gastrointestinal infection, joint space infection, osteomyelitis, disseminated infection, and even intravenous catheter-related infection. Although most mycobacterial infections are community acquired, nosocomial infection and nosocomial outbreaks have occurred, most often originating from contaminated water supplies that led to central venous catheter, wound, or pulmonary infections. Infections with atypical mycobacteria are not limited to immunocompromised patients. Before AIDS-associated disseminated MAC disease, the most common presentation of atypical mycobacteria in the developed world was lung infection in relatively immunocompetent individuals with chronic lung diseases.

This chapter focuses on the bacteriology, pathophysiology, epidemiology, common disease states, diagnostic principles, and pharmacotherapeutic

Abbreviations in this Chapter

AFB	Acid-fast bacilli
AIDS	Acquired immune deficiency syndrome
ATS	American Thoracic Society
CYP	Cytochrome P450
HIV	Human immunodeficiency virus
MAC	<i>Mycobacterium avium</i> complex

management of atypical mycobacteria. The chapter highlights recent advancements, though relatively few, in the understanding of these concepts.

Pathophysiology

Bacteriology

The genus *Mycobacterium* contains several species, many of which have caused human illness. *Mycobacterium tuberculosis* and three closely related mycobacterial species (*M. bovis*, *M. africanum*, and *M. microti*) cause tuberculous disease, composing what is known as the *M. tuberculosis* complex. In the United States, tuberculosis cases are predominantly caused by *M. tuberculosis*. *Mycobacterium bovis* and *M. africanum* are rare causes of disease in the United States; *M. microti* does not cause disease in humans. Mycobacteria other than those that make up the *M. tuberculosis* complex are called nontuberculous or atypical mycobacteria.

Atypical mycobacteria that historically have been recognized as causing human disease include MAC, *M. kansasii*, *M. fortuitum*, *Mycobacterium chelonae*, *Mycobacterium abscessus*, *M. gordonae*, *M. terrae*, *M. leprae*, *M. szulgae*, *Mycobacterium ulcerans*, *Mycobacterium marinum*, and *Mycobacterium scrofulaceum*. More than 100 species of atypical mycobacteria have been described. Most have been implicated in human infection, including more than 20 newly described species since the 1990s (see Table 1-1).

Classification of atypical mycobacteria usually is described by the Runyon criteria. The four groups, distinguished by in vitro growth characteristics on agar plates, include photochromogens, scotochromogens, nonchromogens, and rapid growers. Photochromogens are mycobacteria that produce a yellow pigment after being exposed to light. These include the potential pathogens *M. kansasii* and *M. marinum*. Scotochromogens are those that produce a pigment without exposure to light. These mycobacteria include *M. scrofulaceum*, *Mycobacterium xenopi*, *M. gordonae*, and *M. szulgae*. Nonchromogens usually produce no pigment and include MAC, *M. ulcerans*, and *Mycobacterium malmoense*. *Mycobacterium fortuitum*, *M. chelonae*, and *M. abscessus* are classified as rapidly growing mycobacteria, or “rapid growers,” because of their ability to produce visible growth on standard agar used for mycobacterial culture within 1 week. In contrast to

M. tuberculosis, atypical mycobacteria typically take 2 or more weeks to grow on standard agar. Some confusion exists regarding the taxonomy of rapid-growing mycobacteria. *Mycobacterium chelonae* and *M. abscessus* often are referred together as the *M. chelonae/abscessus* complex, although not because they often are present in the same infection (in contrast to MAC). In addition, *M. fortuitum* and *M. fortuitum* group often are referred to interchangeably. *Mycobacterium fortuitum* has several common morphological characteristics with other rapid-growing mycobacteria (e.g., *Mycobacterium peregrinum*, *M. fortuitum* third biovariant, and *Mycobacterium mucogenicum*), and these organisms are referred to as the *M. fortuitum* group. Some clinical laboratories and research reports do not pursue the procedures necessary to identify these organisms more specifically than “*M. fortuitum* group.” For this review, references refer to the specific species, *M. fortuitum*, *M. chelonae*, and *M. abscessus*, unless noted otherwise.

Identification of mycobacteria is made with several microbiological techniques that differ from methodologies used for standard bacteria, so clinicians should notify their microbiology laboratory that tests other than those for routine bacteria are required. Despite several limitations, staining procedures are still of critical importance in mycobacterial infections. Staining procedures for mycobacteria take advantage of the low permeability of the lipid-rich and mycolic acid-containing cell wall for basic dyes. Permeability is enhanced by heat or prolonged exposure, allowing colorization by the basic dyes. When stained, mycobacteria retain color despite decolorization techniques that use acids with or without alcohol (i.e., “acid-fast”). Concentrating the specimen before staining typically is recommended to increase sensitivity. The Ziehl-Neelson method is a commonly used staining technique using basic fuchsin and phenol for colorization, hydrochloric acid and ethanol for acid decolorization, and then counterstaining with methylene blue. Against a blue background, the acid-fast bacilli (AFB) appear as slender red rods under microscopy. The Kinyoun stain is similar, although it typically is thought to be less effective. Another method used is fluorescent microscopy, which uses prolonged exposure to auramine-rhodamine dye (without heating), decolorization with hydrochloric acid and ethanol, and brief treatment with a potassium permanganate solution. Fluorescent microscopy reveals bright yellow rods against a dark background. Fluorescent microscopy is thought to be more sensitive than the Ziehl-Neelson stain, but this characteristic is countered by a greater potential for a false-positive result.

Acid-fast smears are important to rapidly detect the potential presence of a mycobacterial infection, allowing for proper infection control measures to be initiated or continued (such as respiratory isolation in patients suspected of having pulmonary tuberculosis). Other positive aspects of the acid-fast smear include ease of preparation and the low expense relative to other identification techniques, a relatively high specificity (some other bacteria, most notably *Nocardia* species, also can

appear acid-fast), the provision of a crude quantitative estimate, and usefulness in following the success of antimycobacterial therapy. However, there are limitations of acid-fast smears. Among these, the smear cannot determine the species of mycobacteria detected on microscopic examination, has low sensitivity (high false-negative rate), and requires expertise and viewing more than several hundred microscopic fields to adequately confirm a negative result.

Special solid agar or egg-based media are required for successful culture of *Mycobacterium* species. This process requires 2–8 weeks to obtain viable growth of most mycobacteria. Liquid broth culture procedures have the benefit of producing viable growth between 1 and 3 weeks. The Centers for Disease Control and Prevention recommends both culture methods be used for clinical specimens suspected of harboring mycobacteria. Certain *Mycobacterium* species, such as *Mycobacterium haemophilum*, do not grow particularly well in broth. In addition, some mycobacteria have great difficulty growing on any culture media, such as *M. ulcerans* or *M. leprae*. Some species require unique supplementation or techniques for successful culture.

Even after viable growth has been achieved on solid agar media, traditional phenotypic identification procedures may take several more days for adequate species identification. However, nucleic acid probes (e.g., AccuProbe by Gen-Probe, San Diego, CA) can now be used commercially for the identification of *M. tuberculosis* complex, MAC, *M. kansasii*, and *M. goodii* in isolates that have sufficient

growth on solid agar or certain broth media. When the growth on culture is sufficient, results from each assay are available within a few hours.

Other applications are rapidly advancing the sensitivity, specificity, and most dramatically, timeliness to successful identification even without the need for visible growth on culture. Nucleic acid amplification techniques (e.g., Amplicor polymerase chain reaction assay, Roche Molecular Systems, Branchburg, NJ; Amplified *Mycobacterium tuberculosis* Direct Test, Gen-Probe, San Diego, CA; and BDProbeTec, Becton-Dickinson Diagnostic Systems, Sparks, MD) are commercially available and are becoming widely used applications within the United States for detecting *M. tuberculosis*. The technologies are similar to nucleic acid probes that identify specific sequences of nucleic acids with the added ability to amplify those nucleic acids for rapid detection. The sensitivity and specificity for detecting *M. tuberculosis* by nucleic acid amplification on direct acid-fast smear-positive sputum samples is excellent, but the sensitivity suffers for acid-fast smear-negative sputum samples. Nucleic acid amplification techniques for atypical mycobacteria are in development. However, in a smear-positive pulmonary specimen with a negative nucleic acid amplification test for *M. tuberculosis*, the patient may presumptively be considered to harbor nontuberculous mycobacteria.

Pathogenesis and Epidemiology

Atypical mycobacteria are found in natural soil and water environments; they can be transferred to individuals from

Table 1-1. Atypical *Mycobacterium* Species

Slow Growing ^a	Rapid Growing
Established pathogens	Established pathogens
<i>M. avium-intracellulare</i> complex	<i>M. abscessus</i>
<i>M. haemophilum</i>	<i>M. chelonae</i>
<i>M. kansasii</i>	<i>M. fortuitum</i>
<i>M. leprae</i>	
<i>M. malmoense</i>	
<i>M. marinum</i>	
<i>M. scrofulaceum</i>	
<i>M. simiae</i>	
<i>M. szulgae</i>	
<i>M. ulcerans</i>	
<i>M. xenopi</i>	
Newly discovered or emerging mycobacteria	Newly discovered or emerging mycobacteria
<i>M. bohemicum</i>	<i>M. agri</i>
<i>M. branderi</i>	<i>M. alvei</i>
<i>M. celatum</i>	<i>M. bonickei</i>
<i>M. conspicuum</i>	<i>M. brumae</i>
<i>M. genavense</i>	<i>M. chitae</i>
<i>M. heckeshornense</i>	<i>M. confluentis</i>
<i>M. heidelbergense</i>	<i>M. fortuitum</i> biovariant subtypes
<i>M. interjectum</i>	<i>M. hassiacum</i>
<i>M. intermedium</i>	<i>M. houstonense</i>
<i>M. kubiaca</i>	<i>M. immunogenum</i>
<i>M. lentiflavum</i>	<i>M. mageritense</i>
<i>M. triplex</i>	<i>M. mucogenicum</i>
<i>M. tusciae</i>	<i>M. novocastrense</i>
	<i>M. porcinum</i>
	<i>M. senegalense</i>
	<i>M. septicum</i>
	<i>M. smegmatis</i> group
	<i>M. goodii</i>
	<i>M. peregrinum</i>
	<i>M. smegmatis</i> (<i>sensu stricto</i>)
	<i>M. wolinskyi</i>

^aOther notable slow-growing mycobacteria, such as *M. goodii* and *M. terrae*, are questionable pathogens.

Somaskovi A, Mester J, Hale YM, Parsons LM, Salfinger M. Laboratory diagnosis of nontuberculous mycobacteria. Clin Chest Med 2002;23:585–97.

Table 1-2. Common Atypical *Mycobacterium* Species and Notable Sites of Infection

Organism	Sites of Infection	
	Common	Less Common
Slow Growing		
<i>M. avium</i> complex	Pulmonary Dissemination ^a Lymphadenitis	Skin
<i>M. genavense</i>	Dissemination ^a Gastrointestinal ^a	Pulmonary ^a
<i>M. haemophilum</i>	Lymphadenitis (cervical) Skin Pulmonary Dissemination ^a Bone and joint	Intraocular
<i>M. kansasii</i>	Pulmonary Dissemination ^a	Lymphadenitis Skin
<i>M. leprae</i>	Skin Lymphadenitis	
<i>M. malmoense</i>	Pulmonary	Lymphadenitis Skin Bone and joint Dissemination ^a
<i>M. marinum</i>	Skin	Joint space Lymphadenitis Dissemination ^a
<i>M. scrofulaceum</i>	Lymphadenitis (cervical)	Pulmonary Skin Dissemination ^a
<i>M. ulcerans</i>	Skin	Dissemination ^a
<i>M. xenopi</i>	Pulmonary	Dissemination ^a Joint space Lymphadenitis
Rapid growing		
<i>M. abscessus</i>	Pulmonary	Skin Catheter-related Dissemination ^a
<i>M. chelonae</i>	Skin Dissemination ^a Bone and joint Catheter-related	Pulmonary
<i>M. fortuitum</i>	Skin Catheter-related	Pulmonary Lymphadenitis Ophthalmological Bone and joint

^aPrimarily opportunistic infection in patients with severe immunocompromise (i.e., HIV, hematological malignancy, and bone marrow transplantation).

HIV = human immunodeficiency virus.

such environments and establish colonization at various sites. Some mycobacteria, such as MAC, are quite ubiquitous, whereas others, such as *M. kansasii*, *M. xenopi*, and *M. marinum*, have significant regional variation. Atypical mycobacteria differ from *M. tuberculosis* in that they typically are not transferred from patient to patient through airborne contact (with the exception of *M. leprae*). Thus, atypical mycobacteria either colonizing or infecting the pulmonary tract are not considered contagious.

Atypical mycobacteria have a variety of virulence properties that assist in causing infection. These properties allow the microorganisms to establish infection in a variety of sites in immunocompromised and immunocompetent patients. Table 1-2 summarizes the most important pathogens with common and less common sites of infection. For the majority of atypical mycobacteria, the most common single organ system affected is the lung. Most atypical mycobacteria elicit granulomatous inflammation, and many establish cavitory disease that often is difficult to distinguish from tuberculosis based on clinical and radiological findings. The key to understanding how colonization or infection is established in the lung by atypical mycobacteria appears to be their interplay with alveolar macrophages, which in many ways also is similar to *M. tuberculosis*. The most extensively studied organism is MAC, for which several mechanisms for invading macrophages and monocytes have been demonstrated. When within the macrophage, MAC is able to survive within a vacuole and may ultimately use the macrophage as a launching pad for infection if the host's defenses weaken. Within the pulmonary setting, chronic obstructive pulmonary disease and other chronic pulmonary disorders may impair the host's natural defenses (e.g., cilia and alveolar macrophages). The demise of these local defenses, or other systemic insults to the immune system, may lead to activation of mycobacterial disease.

In the setting of human immunodeficiency virus (HIV) infection, MAC becomes a major threat once the patient's disease state has progressed to AIDS, especially as the CD4 cell count falls below 50–75 cells/mm³. It is ironic that the pulmonary tract is not a major site of infection for MAC in patients with AIDS. Disseminated disease is the most common presentation in these patients, involving the bloodstream and bone marrow. Other sites of infection, such as gastrointestinal, intra-abdominal, skin and soft tissue, bone, and lung occur relatively infrequently. *Mycobacterium avium* complex can colonize the respiratory tract in patients with AIDS and also may colonize the gastrointestinal tract of these patients, where it is able to withstand the acidic gastric environment. Using various genetic elements not found in most other atypical mycobacteria, MAC is able to adhere to, gain entry, suppress inflammatory host response, and successfully translocate through the intestinal tract wall.

Mycobacterium kansasii is most noted for causing respiratory tract infection in patients with chronic preexisting pulmonary disease, malignancy, HIV infection, alcoholism, or certain occupational exposures. In the United States, *M. kansasii* is behind only MAC in the incidence of pulmonary infection due to atypical mycobacteria. *Mycobacterium kansasii* is widespread but

more predominant in central (Illinois, Kansas, and Nebraska) and southern (Texas, Louisiana, and Florida) states than other regions. Its primary environmental source of exposure appears to be aerosolization from water sources, and its pathogenic and virulence properties are similar to MAC. The organism is known for causing thin-walled cavitation within the lung, although clinical and radiological presentations are considered indistinguishable from tuberculosis because of significant overlap. Other sites of infection of *M. kansasii* include disseminated infection (primarily in patients with HIV, and often in the presence of coexisting lung infection), pleural space, skin and skin structure, bone and joint space, meninges, and pericardium.

Mycobacterium marinum, as the name implies, also is most often transferred to humans by contact with water sources. It often is direct contact with skin and, more important, abrasions of or trauma to the skin, that lead to infection. Individuals with the greatest exposure to nonchlorinated water, such as commercial or avid fisherman and water hobbyists, are at most risk. In the United States, the southern coastal saltwater areas of the Gulf of Mexico and Atlantic Ocean are areas of common infection. Infection with *M. marinum* often is referred to as “swimming pool” or “fish tank” granuloma because exposure to these environments also often can be the source for the establishment of infection, especially if inadequate chlorination exists. Infection typically is delayed for up to 2–6 months, and often only manifests as a solitary nodule at the portal of entry, which persists for some time and eventually often is self-limiting. One rationale for *M. marinum*’s predilection for skin infection is that optimal growth for the organism occurs at about 30–32°C, well below core body temperature. Nodular spread occurs in a minority of patients, after a lymphatic spread similar to lymphocutaneous sporotrichosis. Treatment is necessary at this point, although some clinicians recommend treatment in patients with a singular nodule to potentially prevent spread and to advance healing. Systemic disease is rare and usually occurs only in the severely immunocompromised, although contiguous spread from skin infection can lead to adenopathy, joint space infection, or tenosynovitis.

Skin infection also is the most common clinical presentation of *M. ulcerans*. Although *M. marinum* is a widespread organism in water environments, *M. ulcerans* is limited primarily to warmer climates in Africa, Central America, Southeast Asia, and Australia. Skin infection with *M. ulcerans* is called “Buruli ulcer” and is distinctive with severe, sometimes necrotic, ulcerative plaques. Similar to *M. marinum*, the microorganism gains entry after an abrasion or trauma to the skin, and has a 3-month incubation period. A painless nodule develops, which opens, ulcerates, and eventually necroses. Although the disease may not be eliciting many systemic symptoms, the organism often invades deeper tissues aggressively. Although *M. marinum* usually infects upper extremity sites, *M. ulcerans* infects primarily the lower extremities. Successful therapy usually requires significant surgical intervention including amputation if necessary.

Mycobacterium scrofulaceum is associated primarily with cervical lymphadenitis in immunocompetent or immunocompromised children, usually between 1 and 10

years of age. Until the past couple of decades, *M. scrofulaceum* was the leading cause of cervical lymphadenitis in children, but MAC has become the predominant etiological organism in this infection. Many cases are self-limiting and may not require intervention. However, if progressive disease occurs, this organism is highly resistant to most antibacterial drugs, and treatment often is surgical excision. Despite intervention, lesions occasionally progress to form fistulous tracts and deeper infection.

Mycobacterium haemophilum causes a wide range of infections, although it potentially has been overlooked as a pathogen in the past because of its fastidious nature. *Mycobacterium haemophilum* grows well only on solid agar media, and only if the media is supplemented with iron sources. The organism most commonly causes cervical adenitis in otherwise healthy children, and skin and skin structure infection and disseminated infection in primarily immunocompromised adults. Skin infections most commonly appear as sporadic nodules, but can have a wide range of presentations, often as a result of dissemination. Joint space infection and osteomyelitis are common manifestations of disseminated disease as well.

Mycobacterium leprae causes leprosy, or Hansen’s disease. Leprosy has been on the decline worldwide in recent decades because of effective pharmacotherapy and prevention programs, but the disease remains a large problem in Southeast Asia and South America. This ancient disease causes a slowly progressive infection that first presents as a few skin lesions after a prolonged incubation. The infection progresses through a delicate interplay between the organism and the host immune system’s response to infection. In susceptible patients, the disease progresses to several skin lesions and attacks peripheral nerves. Lesions appear primarily on the cooler aspects of skin, including distal extremities, knees, cheekbone, earlobes, and chin. Susceptibility to disease appears to be in part genetic, but transmission can occur through aerosolized droplets or direct skin contact. Natural progression of disease leads to irregular anesthetic areas and numerous thickened skin lesions with atrophy. Patients also can experience periodic acute inflammatory reactions at any time during the disease, when skin lesions become erythematous and swollen, and are accompanied by an acute, painful peripheral neuritis that can produce irreversible damage. A complete description of the complicated progressive stages of disease and transmission potential is not within the scope of this chapter.

Mycobacterium xenopi is a leading cause of pulmonary disease from atypical mycobacteria in western Europe. The organism also occasionally causes disseminated disease, joint space infection, and lymphadenitis, especially in immunocompromised individuals. Another atypical *mycobacterium* that is a common but less frequent cause of pulmonary infection in Europe (particularly northern Europe and British Isles) is *M. malmoeense*. Lymphadenitis and skin, bone, and joint infection rarely occur, and dissemination primarily is in severely immunocompromised populations. Other infrequent causes of pulmonary infection include *M. szulgae* and *Mycobacterium simiae*.

Of the newly discovered, or emerging, slow-growing atypical mycobacteria, *Mycobacterium genavense* may garner the most interest, presenting almost exclusively in patients with AIDS and CD4 cell counts of less than 100 cells/mm³. Disseminated disease predominates and often includes gastrointestinal sites such as liver, spleen, and intestine. Other slow-growing, emerging atypical mycobacteria are listed in Table 1-1 and have been implicated sporadically in a variety of infections.

Rapid-growing atypical mycobacteria are unique not only in their in vitro cultivation characteristics, but also in clinical presentation. Predominant types of infections include postoperative, postinjection, or post-trauma wound infection and catheter-associated sepsis, along with more classic atypical mycobacterial diseases, such as pulmonary infection, skin and skin structure infection, and disseminated disease in immunocompromised individuals. Three species are responsible for the vast majority of disease due to rapid-growing atypical mycobacteria: *M. fortuitum*, *M. abscessus*, and *M. chelonae*. Along with *Mycobacterium smegmatis*, *M. fortuitum* group members *M. mucogenicum*, *M. peregrinum*, and two *M. fortuitum* biovariant subtypes have emerged recently and are the etiologies of most of the remaining small number of infections by this group of atypical mycobacteria.

Mycobacterium fortuitum most commonly presents as a skin or soft tissue infection, and less commonly as catheter-associated infection or pulmonary infection. Nodular ulcers or abscesses due to *M. fortuitum* can present about a month after trauma to the skin, including abrasions, injections, or surgical procedures. Postsurgical infection often requires aggressive surgical intervention in addition to pharmacotherapy. Removal of foreign bodies placed at the time of surgery often is necessary. Catheter-associated infection requires removal of the affected catheter, debridement of the area when indicated, and a relatively short treatment course. Pulmonary infection due to *M. fortuitum* occurs less commonly than other atypical mycobacteria in the United States, falling below MAC, *M. kansasii*, and another rapid grower, *M. abscessus*. Disseminated disease most commonly is seen in immunocompromised individuals, including patients with AIDS.

Mycobacterium abscessus is an organism most noted for its ability to produce cases or outbreaks in various health care-related settings, including after injections, surgical procedures, or such procedures as hemodialysis or bronchoscopy. Cutaneous infection presents as erythematous nodules or abscesses. Similar to *M. fortuitum*, postsurgical infection requires aggressive surgical correction and removal of any foreign bodies. Disseminated disease can occur after hemodialysis; otherwise dissemination primarily occurs in immunocompromised patients. *Mycobacterium abscessus* is the most common rapid grower causing pulmonary disease. Pharmacotherapy is extremely limited against this microorganism, and surgical intervention often is the only hope for a successful outcome.

In contrast to most of the other cutaneous infections caused by atypical mycobacteria, where the presentation is most often at a site of trauma and often is fairly localized,

M. chelonae most commonly presents as disseminated cutaneous disease with multiple erythematous nodular lesions in no particular pattern. Patients usually are immunosuppressed through medical therapy (corticosteroids or antirejection therapy) or primary disease state (e.g., hematological malignancy or HIV infection). Drainage occurs spontaneously from the lesions, or with a moderate amount of pressure. Drainage often is purulent with necrotic debris. Fistulous drainage also often is present.

Mycobacterium chelonae also presents in a localized cutaneous form after trauma, including after injection or surgical procedure, similar to other rapid-growing atypical mycobacteria. These infections can commonly progress to involve bone and joint infection. In addition, catheter-associated infection occurs similar to *M. fortuitum*, most often in hemodialysis settings.

Diagnosis

General Principles

Diagnosis of infection due to atypical mycobacterial differs depending on the site of infection. However, certain general principles apply to most atypical mycobacterial infections. Patients with atypical mycobacterial infections usually present with indolent or subacute courses, and fever is the most common symptom. Suspicion of infection should be heightened in immunosuppressed individuals, or individuals with other comorbidities that damage host defenses (e.g., chronic obstructive pulmonary disease). Atypical mycobacteria are variably reactive to purified protein derivative tuberculin skin tests, but will stain positive on acid-fast smears assuming adequacy of the specimen and disease significant enough to produce a positive acid-fast smear. Pathology closely resembles the pathology seen with *M. tuberculosis* infections in the form of granulomatous inflammatory changes, but not often including necrotizing or caseating granulomas.

For proper microbiological evaluation, optimal etiological discovery requires collecting high-quality clinical specimens. As with most microbial etiological evaluations, cultures taken from biopsy or fluid aspiration from otherwise normally sterile body sites are essential for definitive diagnosis of atypical mycobacterial infection. In the absence of such cultures, clinicians must rely on cultures taken from suboptimal specimens, such as expectorated sputum, bronchoalveolar lavage, or wound swabs. High-quality specimens are difficult to obtain from lung or skin/skin structure infection. However, dissemination, septic arthritis, osteomyelitis, lymphadenitis, and intravenous catheter-associated infection involve sites that are normally sterile; these sites should be biopsied or aspirated for culture specimens. Adequate specimen collection also entails placing the specimen in correct containers and rapidly transporting it to the microbiology laboratory.

Routine culture and staining techniques by clinical microbiology laboratories rarely include an AFB smear and AFB culture media. Therefore, clinicians must clearly order the proper procedures to be done on the specimens sent to

the clinical microbiology laboratory, and do so at a time when the laboratory is properly staffed. Some laboratories are set up for routine AFB smear and culture of bronchoalveolar lavage or bronchial biopsy specimens, or cerebrospinal fluid collected from lumbar puncture, in addition to routine bacterial and fungal stains and cultures. Clinicians should become familiar with the policies and procedures of the clinical microbiology laboratories within their medical centers to facilitate rapid and appropriate detection of atypical mycobacterial infection. Clinicians in some medical centers also need to become familiar with any off-site clinical microbiology laboratories that provide these services for their medical center through contractual relationships. Culture methods in clinical microbiology laboratories in medical centers with little experience in processing AFB cultures may have lower sensitivity and accuracy.

When the atypical mycobacteria have grown in sufficient quantities, susceptibility testing usually is undertaken. Testing has been standardized for *M. tuberculosis*, and much of the standardization has been applied to atypical mycobacteria. Considerations for susceptibility testing of atypical mycobacteria are: 1) standardization is not uniformly established for most species, 2) correlation of susceptibility results with clinical outcomes is sparse, and 3) results are reported in a different format than “typical” bacteria and are confusing to many clinicians. It is advisable to send isolates to clinical reference laboratories that are familiar with mycobacterial susceptibility testing and do them routinely. Susceptibilities of individual organisms are discussed further in the Quality Patient Care section.

The following sections discuss some specific diagnostic characteristics for the common manifestations: pulmonary infection, skin and skin structure infection, lymphadenitis, and disseminated disease.

Pulmonary Infection

Diagnostic criteria for pulmonary infection caused by atypical mycobacteria have been standardized through guidelines published by the American Thoracic Society (ATS). Key criteria include having a clinical course and radiological findings consistent with atypical mycobacterial infection, and having significant growth from microbiological cultures. There is great overlap in clinical and radiological features among all mycobacterial pulmonary infections, including *M. tuberculosis*, and identification at the species level by the clinical microbiology laboratory is necessary to establish prognostic implications and guide proper management. Table 1-3 summarizes the features necessary to diagnose atypical mycobacteria pulmonary infection.

Patients presenting from the community with acute signs and symptoms consistent with lower respiratory tract infection most often have routine bacterial or viral etiologies and should be evaluated and managed as such. Suspicion for uncommon microbial etiologies, such as mycobacterial or fungal infection, should be heightened when patients present with more subacute or chronic processes. Other noninfectious etiologies, such as malignancy or other chronic pulmonary diseases should be ruled out when

Table 1-3. Summary of the American Thoracic Society Guidelines for the Diagnosis of Pulmonary Atypical Mycobacterial Infection

Clinical criteria

- Combination of the following symptoms:
Cough, fever, shortness of breath, fatigue, weight loss, hemoptysis

PLUS

Radiological criteria

- Chest radiography or computerized axial tomography demonstrating persistent, progressive nodular infiltrate usually with cavitation

PLUS

Bacteriological criteria

- Minimum of three adequate samples from expectorated sputum or bronchoalveolar lavage demonstrating:
 - Three positive cultures with negative AFB smears OR
 - Two positive cultures with one positive AFB smear
- Bronchoalveolar lavage
 - Positive culture with at least 2+ growth
 - Any positive culture with at least 2+ AFB smear
- Tissue biopsy by transbronchial, percutaneous, or thoracotomy
 - Any positive culture
 - Pathology indicative of granuloma or AFB smear positive
- Includes any growth from a normally sterile extrapulmonary site if clinical and radiologic criteria for pulmonary infection are met

AFB = acid-fast bacilli.

appropriate. Severely immunosuppressed patients may have more rapidly developing courses of infection, occasionally mimicking the time course of a typical community-acquired bacterial pneumonia episode. A thorough medical history including a patient’s current comorbid conditions, medical history, immune status, history of exposure to animals or ill human contacts, and travel exposure may give clues to the microbial etiology. Exposure to people with active tuberculosis recently or in the past places tuberculosis at or near the top of the diagnostic differential. Some geographic areas may have a predilection for certain atypical mycobacteria (such as the epidemiological characteristics of *M. kansasii*), but otherwise, findings on history do not specifically point a clinician toward mycobacterial infection, much less differentiate between active tuberculosis and atypical mycobacterial infection. Signs and symptoms of atypical mycobacterial infection most often include fever, chills, night sweats, chronic cough, sputum production, progressive dyspnea, weight loss, fatigue, malaise, and hemoptysis. This presentation often is indistinguishable from tuberculosis. Concomitant comorbidities usually include chronic lung diseases, such as chronic obstructive pulmonary disease, pulmonary fibrosis, bronchiectasis, pneumoconiosis, or cystic fibrosis. Physical examination reveals typical pulmonary findings for pneumonia (e.g., rales, decreased breath sounds, and egophony changes). With the exception of certain parameters that establish

levels of immunosuppression, general laboratory results at presentation are of little assistance in providing differentiation of the etiology for disease.

Radiographic findings may help differentiate among malignancy, fungal infection, and mycobacterial infection. Tuberculosis is notorious for causing cavitory lesions in the apices of the lung, but other atypical mycobacteria and certain fungal infections may be able to produce a similar appearance on chest radiographs or computer-assisted tomography scan. Cavitation with associated infiltration is a classic characteristic of slow-growing atypical mycobacterial pulmonary infection, and other than the trend of causing a thin-walled cavitation, it typically is indistinguishable from that caused by tuberculosis. Presentation may be in the form of nodular infiltrates with or without cavitation, especially with MAC in severely immunosuppressed individuals or in patients with rapid-growing atypical mycobacterial infection.

The etiological evaluation in a patient suspected of having an atypical mycobacterial infection is similar to the evaluation for tuberculosis. A patient should be placed in respiratory isolation until active tuberculosis is ruled out. Skin testing should be conducted to help identify exposure to *M. tuberculosis*. A clinician should be aware that infection due to atypical mycobacteria may produce a positive skin test as well. A patient who has AFB-positive smears should be deemed to have active tuberculosis and therapy should commence until further confirmation is available.

If three adequately collected sputum specimens collected on 3 separate days are AFB-smear negative, then a patient may be taken out of respiratory isolation, even though the patient may subsequently prove to have active tuberculosis. In a patient whose sputum specimen smears are AFB-negative, antimycobacterial therapy usually is deferred until further microbiological evaluation identifies potential mycobacterial infection. The chronic, indolent course most patients experience allows the clinician to have patience to establish a diagnosis. In the interim, a patient often is placed on antibiotic drugs for the empiric treatment of community-acquired pneumonia in case the patient simply has community-acquired pneumonia or is potentially superinfected with a community-acquired pneumonia pathogen in addition to the mycobacterial infection.

In a patient whose sputum specimen smears are AFB-positive, antitubercular therapy usually is begun empirically with isoniazid, rifampin, ethambutol, and pyrazinamide. Treatment may convert the sputum specimen smears to AFB-negative, accelerating the removal of the patient from respiratory isolation. In select patients whose clinical presentations also are consistent with MAC pulmonary infection, some clinicians may add clarithromycin to the empiric regimen. This decision is made most commonly when the patient is clinically deteriorating, and more broad-spectrum empiric treatment may reverse the clinical course.

After adequate growth on culture occurs, nucleic acid probes may be able to identify the pathogen within hours, reducing the traditional lag time for identification by several days. Nucleic acid amplification processes for the identification of *M. tuberculosis* may be placed on smear-

positive sputum specimens as discussed in the Bacteriology section, and this technology should rapidly progress to include many atypical mycobacteria. When available, it may be recommended that clinicians heed the results of such techniques with some caution because of potential concerns over sensitivity (especially in AFB-negative smear specimens); however, specificity should be high. When the use of these tests is proven, the time required to direct therapy at a specific atypical mycobacterial pathogen will be reduced from a few weeks to several hours.

Although the detection of *M. tuberculosis* on any pulmonary culture is considered diagnostic for active pulmonary tuberculosis, such is not the case when atypical mycobacteria are detected. Colonization and contamination are well-established entities for several atypical mycobacteria, even occasionally in patients with clinical courses consistent for mycobacterial disease. Because of the potential for misdiagnosis, the ATS guidelines include specific recommendations to improve the accuracy in diagnosing mycobacterial disease (see Table 1-3). Criteria vary somewhat given the type of immunosuppression the patient may have. For the patient with chronic pulmonary disease without specific systemic immunosuppression, three expectorated or induced sputum or bronchial wash specimens with three positive cultures despite AFB-negative smears, or two positive cultures with at least one AFB-positive smear are considered to be consistent with probable atypical mycobacterial disease. If no adequate sputum specimen is available, a bronchial wash must have a significant quantity of growth to provide a diagnosis. Growth on a biopsy culture provides a more definitive diagnosis, as do pathological findings consistent with mycobacterial disease (e.g., granulomatous inflammation) combined with any positive culture from sputum or bronchial wash, or culture from a normally sterile site (e.g., pleural fluid). Other than allowing less quantitative growth from a bronchial washing specimen, diagnostic criteria for patients with severe immunosuppression, including patients with AIDS, are similar to patients without significant immunosuppression.

Bacteriological criteria set by the ATS for diagnosing pulmonary infection due to atypical mycobacteria center on those that most commonly cause disease in the United States: MAC, *M. kansasii*, and *M. abscessus*. The criteria also may apply to those that commonly cause pulmonary disease in other parts of the world (e.g., *M. xenopi* and *M. malmoense*). The accuracy of diagnosis may lessen if other, less common, pulmonary pathogens are found on culture. For example, *M. gordonae* is found broadly in the environment and is commonly a contaminant or colonizer of the respiratory tract. It rarely may cause disease in immunocompromised individuals. Clinical courses of patients with sputum or bronchoalveolar lavage cultures positive for this species must be highly scrutinized, and the clinician should have a relative skepticism over the pathogenic role of the species.

Skin and Skin Structure Infection

Atypical mycobacteria that commonly cause skin and skin structure infections are diverse in clinical presentation and geographic prevalence. Therefore, presumptive

diagnosis is made primarily through signs and symptoms, physical examination findings, clinical history, geographic location, and if available, any preliminary evidence of the presence of AFB by pathology, smear, or early culture reports. Probable or definitive diagnosis is made by adequate culture of any drainage or biopsy specimen. The species most commonly encountered include *M. marinum*, *M. ulcerans*, *M. haemophilum*, *M. leprae*, and the rapid-growing organisms *M. fortuitum*, *M. chelonae*, and *M. abscessus*. Each organism has a fairly unique clinical presentation that allows clinicians to have suspicion for not only the presence of an atypical mycobacterial infection, but also the specific organism involved. The clinical presentations of these organisms were summarized in the Pathogenesis and Epidemiology section.

Lymphadenitis

Lymphadenitis due to atypical mycobacteria primarily occurs in children, including the immunocompetent. Lymphadenitis also can occur in adults with immunosuppression, primarily in patients with HIV. Areas affected usually are the cervical, submandibular, submaxillary, and preauricular lymph nodes. Lymphadenitis tends to develop slowly, usually involves a unilateral distribution, and typically produces no systemic symptoms as long as there is no further tracking into the soft tissue structures. On occasion, infection spontaneously resolves, but more often the affected lymph nodes can enlarge and eventually produce suppurative drainage. Most cases of mycobacterial lymphadenitis in children are caused by MAC or *M. scrofulaceum* in the United States (*M. malmoense* is the predominant pathogen in northern Europe, including England). However, about 10% of cases in children are due to *M. tuberculosis*, and cat-scratch disease also should be in the differential diagnosis. The diagnosis of an atypical mycobacteria infection is most often based on pathological and culture findings of surgically excised diseased tissue. Culture-negative specimens may indicate the presence of a fastidious atypical mycobacteria, such as *M. haemophilum* or *M. genavense*. Mycobacterial culture is important to rule out *M. tuberculosis* because antimycobacterial therapy is always indicated for this pathogen. Surgical excision is not without complications, as fistulous tracts may develop or lymphatic spread may occur. Routine biopsy or limited incision and drainage are not recommended because of such complications.

Disseminated Infection

Disseminated infection due to atypical mycobacteria should be suspected in immunosuppressed individuals. Those at risk include patients with AIDS or hematological malignancy, recipients of immunosuppressive drugs, solid organ or hematopoietic stem cell transplantation recipients, and occasionally patients undergoing hemodialysis. Almost all of the pathogenic atypical mycobacteria have caused disseminated infection, and with the advent of AIDS, the most common by far is MAC. *Mycobacterium kansasii* is the second most common pathogen causing disseminated disease in the United States. Disseminated disease in patients without AIDS typically presents with nonspecific

signs and symptoms, such as persistent fever, fatigue, malaise, weight loss, and anemia. Gastrointestinal symptoms of nausea, vomiting, and diarrhea may be present and indicate gastrointestinal involvement. Multiple organ systems can be involved, most often including bone marrow, lymph nodes, spleen, liver, and bowel. Overt pulmonary infection is not commonly present. There may be evidence of dissemination through diffuse subcutaneous nodules or abscesses. *Mycobacterium kansasii*, *M. haemophilum*, *M. chelonae*, and *M. abscessus* often have skin involvement, whereas MAC does not. The differential diagnosis in these patients varies depending on severity of the underlying immunosuppression, but includes disseminated tuberculosis; chronic fungal infection, such as histoplasmosis; viral illness; and noninfectious phenomena, such as graft-versus-host disease in transplant patients. Diagnosis is made by culturing the offending organism from normally sterile sites such as blood, affected lymph nodes, nodular aspiration, and bone marrow; however, isolation of the organism from other sites, such as stool or sputum, also may aid in the diagnosis.

Diagnosis of disseminated MAC disease in patients with AIDS is somewhat easier given its common occurrence. These patients have similar signs and symptoms as previously discussed, and also have CD4 cell counts of less than 75 cells/mm³. The absence of preventive drugs (i.e., azithromycin, clarithromycin, or rifabutin) also should raise the clinician's suspicion for disseminated MAC. Several opportunistic infections in patients with AIDS can present in a similar fashion, most notably tuberculosis; cytomegalovirus infection; other atypical mycobacterial infection; and disseminated fungal infections, such as histoplasmosis, cryptococcosis, blastomycosis, and coccidioidomycosis. Diagnosis often is most made by lysis centrifugation or BACTEC blood cultures, which may take several days to grow MAC. Using polymerase chain reaction methods with culture may speed recovery and identification of MAC. Bone marrow biopsy or other more invasive diagnostic techniques occasionally are required.

Quality Patient Care

General Principles

Therapy of infection due to atypical mycobacteria may involve pharmacotherapy, surgical care, and supportive care. Supportive care entails providing symptomatic relief, ensuring adequate nutrition and hydration, and maintaining end-organ function. Maintaining or reestablishing adequate nutritional status is of utmost importance, as many patients with atypical mycobacterial infections (most notably pulmonary and disseminated disease) present with moderate to severe weight loss.

The importance of the extent of patient compliance, as it relates to potential outcome, has not been addressed for atypical mycobacterial infections, with the exception of *M. leprae* infection, where strict compliance leads to less resistance and better outcomes. Directly observed therapy is not a practical option for most of the atypical mycobacterial infections because of lack of data linking strict compliance to outcomes, the lack of data demonstrating rapid ability for

the organisms to become resistant on substandard therapy, and the lack of a significant public health threat because of respiratory transmission (or other mode of transmission). The World Health Organization promotes a “multidrug therapy” program to treat leprosy in developing countries. Because there are potentially significant issues with *M. leprae* in terms of resistance and transmission capabilities, the World Health Organization recommends dispensing intermittent drug dosage regimens that come in specific blister packaging to aid with compliance.

Patients with AIDS and CD4 cell depletion often experience atypical mycobacterial infections when not receiving effective antiretroviral therapy. These patients often will be placed on effective antiretroviral therapy and antimycobacterial therapy at the same time. Two problems that may arise with this approach are the complicated drug interactions that may be introduced and immune reconstitution syndrome. This syndrome is characterized by an aggressive inflammatory response when virological control is established by effective antiretroviral therapy. The response may exacerbate the severity of the mycobacterial infection during the first 1–2 months of therapy. This response can be misconstrued as failure of antimycobacterial therapy.

Surgical therapy includes excision of involved lymph tissue with lymphadenitis, partial lung resection in patients with recalcitrant severe disease, or incision and drainage of abscess cavities. Surgical therapy for pulmonary disease is rarely required now given advancements in antimicrobial therapy.

Pharmacotherapy for most atypical mycobacterial infections includes multiple drugs for several months. The standard first-line antituberculous drugs, such as isoniazid, ethambutol, streptomycin, and rifampin, often are used. Other drugs used include clarithromycin, azithromycin, fluoroquinolones, amikacin, cefoxitin, and imipenem-cilastatin. Many of these drugs have activity against many mycobacterial species. Table 1-4 presents a summary of the characteristics associated with drugs used to treat atypical mycobacterial infections. The following section discusses these drugs in more depth.

Pharmacotherapy—Drug Class Overviews

Traditional Antimycobacterial Drugs

Isoniazid

Isoniazid has maintained its status as the cornerstone of treatment for latent tuberculous infection and tuberculosis. Although isoniazid is part of the first-line therapy of *M. kansasii*, its overall use for treating most other atypical mycobacteria is limited. The drug typically is bactericidal for rapidly dividing mycobacteria and is thought to work by inhibiting cell wall mycolic acid synthesis. Isoniazid’s most important pharmacokinetic attribute is its metabolic fate. Isoniazid primarily is metabolized by acetylation. In rapid and slow acetylators, the half-lives for isoniazid are about 1 and 3 hours, respectively. Genetic predisposition for rapid acetylation exists primarily in people from Japan and China, and in native Alaskans (accounting for 80–90% of the population in each group). In most other populations, a slight majority are slow acetylators. Acetylator phenotype has not been a significant factor in determining outcomes

for treating tuberculosis when isoniazid is given either 1 or 2 times/day in directly observed therapy. It is less clear if this is true for treating infections due to atypical mycobacteria. For treating atypical mycobacterial infections, the usual dose of isoniazid is 300 mg/day orally, or up to 5 mg/kg/day.

Monitoring parameters during treatment with isoniazid center on assessing hepatotoxicity and neurotoxicity. Assessment of hepatic function, specifically serum aspartate aminotransferase and alanine aminotransferase enzyme concentrations, should occur before therapy. Hepatotoxicity is rare in patients with no previous history of hepatic dysfunction, the young, and in those who do not receive concomitant hepatotoxic drugs (such as rifampin or pyrazinamide). Monitoring of aspartate aminotransferase and alanine aminotransferase should be done within a month of starting therapy and continued if asymptomatic serum enzyme concentration elevation not requiring discontinuation occurs. More intensive monitoring of aspartate aminotransferase and alanine aminotransferase during therapy is warranted in patients with preexisting liver disease: monthly for the first few months, then every 3–4 months thereafter. Some authorities recommend monthly monitoring of liver function tests for at least the initial few months of therapy in any patient receiving isoniazid with other hepatotoxic drugs. Alternatives should be considered if a patient has severe liver disease, and therapy should be stopped and reevaluated if a patient develops symptomatic enzyme elevation with greater than 3 times the upper limits of normal serum concentrations of aspartate aminotransferase or alanine aminotransferase, or asymptomatic elevation with greater than 5 times the upper limits of normal.

Peripheral neuropathy and optic neuritis are rare complications of isoniazid therapy, but the incidence of these complications may be increased in alcoholism, pregnancy, nutritional deficiencies, diabetes mellitus, kidney failure, concomitant ethambutol (for optic neuritis), and those with HIV infection. In these patients, minimizing the risk of neurotoxicity with supplemental pyridoxine in doses of at least 25 mg/day is recommended. Alcohol ingestion during isoniazid therapy should be strictly avoided because of hepatic and neuropathic effects. Patients should be counseled to avoid food high in tyramine content, such as certain cheeses and wines, to avoid tyramine toxicity. Drug interactions with isoniazid are numerous. Antacids should be given at least 2 hours after isoniazid administration. Isoniazid may increase serum concentrations of carbamazepine, phenytoin, theophylline, and warfarin primarily through inhibition of cytochrome P450 (CYP) enzyme system metabolism. Isoniazid also can act as a monoamine oxidase inhibitor, necessitating careful monitoring of potentially affected drugs.

Rifampin and Rifabutin

Rifampin and rifabutin are rifamycin derivatives that are potent antimycobacterial drugs used to treat several mycobacterial infections, including *M. tuberculosis*, *M. kansasii*, MAC, *M. malmoense*, and *M. xenopi*. Bioavailability can be an issue with rifabutin; it is variably absorbed, with mean bioavailability of about 50% in

HIV-negative patients and as low as 20% in HIV-positive patients. Rifabutin and rifampin are eliminated primarily through hepatic metabolism, but rifabutin has a longer half-life (about 40 hours) than rifampin. For most mycobacterial infections, the dose of rifampin is 600 mg/day orally, up to 10 mg/kg/day. For rifabutin, treatment of active infection requires a dose of 300 mg/day orally.

Rifampin typically is well tolerated, and most adverse effects are either rare or of mild significance. The most common adverse effect is an orange discoloration of bodily fluids, most notably urine and perspiration (which may stain clothing). This should be explained to the patient before initiating treatment. Patients should be told that soft contact lenses may become permanently stained. Moderate adverse effects include gastrointestinal intolerance, flu-like symptoms, and rash with or without pruritis. Hepatic cholestasis commonly is mentioned but of low potential, and often exhibits as an asymptomatic hyperbilirubinemia. The most common adverse effects of rifabutin include rash, bodily fluid discoloration similar to rifampin, and gastrointestinal intolerance. More serious but less common adverse effects of rifabutin include uveitis, neutropenia, thrombocytopenia, and arthralgia. Rifabutin-associated uveitis involves a retinal abnormality that may include vitreous opacity, and may occur at any time during therapy. These adverse effects may be increased if drugs are given that increase the serum concentrations of rifabutin by inhibiting metabolism. Common interacting drugs that are encountered include clarithromycin, protease inhibitors, and azole antifungals. Specific dose adjustments for rifabutin are recommended in these cases.

Monitoring rifamycin therapy includes careful observation for drug interactions. Rifampin is one of the most potent inducers of CYP enzyme systems, affecting a wide range of isoforms, including CYP3A4, CYP2B6, CYP2C8, CYP2C19, CYP2C9, and CYP2D6. Of recent concern has been the effect of concomitant rifampin on antiretroviral therapy for patients with HIV. Rifampin is clearly contraindicated with all protease inhibitors in the absence of “ritonavir boosting”. Ritonavir boosting refers to the use of low doses of ritonavir, typically 100–200 mg 1–2 times/day, which provides subtherapeutic antiretroviral activity, but dramatically decreases the rate of hepatic metabolism of a concomitant protease inhibitor. Therefore, the concomitant protease inhibitor can either achieve higher serum concentrations and/or be given in a simplified regimen. Rifampin may be given with saquinavir if ritonavir boosting is present. Ritonavir boosting of either indinavir or lopinavir should not be coadministered with rifampin. For non-nucleoside reverse transcriptase inhibitors, the combination of rifampin and nevirapine should be avoided if possible, and delavirdine use is contraindicated with rifampin. Efavirenz should be dose-adjusted from 600 mg/day to 800 mg/day when given with rifampin. Rifabutin, with the exception of a contraindication with delavirdine, is an alternative in most cases for patients with HIV as long as recommended dose adjustments occur. Rifabutin is a modest inducer of CYP3A4 and can be given with certain protease inhibitors with appropriate dose adjustment of either drug. As

previously discussed, rifabutin also is a substrate of CYP3A4 and can be affected by drugs that inhibit or induce that isoform.

Ethambutol

Ethambutol represents an integral component of combination therapy against *M. tuberculosis*, *M. kansasii*, *M. xenopi*, and MAC. Ethambutol interferes with protein metabolism through inhibition of ribonucleic acid synthesis. The bioavailability of ethambutol is excellent and is unaffected by food. Ethambutol primarily is eliminated by the kidney with a half-life of 2.5–4 hours in patients with normal kidney function. The usual dose of ethambutol is 15–20 mg/kg/day orally with dose reduction required in kidney dysfunction.

The most common serious adverse effect of ethambutol is optic neuritis that occurs with varying intensity in about 1% of patients taking 15 mg/kg/day and up to 6% of patients taking 25 mg/kg/day. Patients should receive baseline ophthalmological evaluation for red/green color discrimination and visual acuity. Clinicians should counsel patients to contact a health care provider if any changes in vision, most often manifested as blurring, color blindness, or decreased visual acuity occur. Such visual changes should prompt discontinuation of ethambutol in the vast majority of cases. Monthly visual acuity testing should occur during treatment in patients receiving more than 15–20 mg/kg/day, in those receiving prolonged treatment duration (more than 2 months, which is common in nontuberculous mycobacterial infection), and in those with kidney dysfunction. Optic neuritis commonly is reversible, but irreversible toxicity has occurred, primarily in the elderly or those who did not receive frequent ophthalmological examinations for detection of early disease. It typically is recommended that children younger than 5–6 years of age not be treated with ethambutol because of the presumption that they are too young to undergo accurate visual acuity testing. Other common adverse effects include hyperuricemia; rash; central nervous system effects, such as dizziness, confusion, and mania; and gastrointestinal intolerance. In contrast to isoniazid and rifampin, ethambutol appears to be free of clinically significant pharmacokinetic drug interactions.

New Macrolides

The new macrolides, in particular clarithromycin, have been welcome additions in treatment of several atypical mycobacterial infections. Clarithromycin revolutionized the treatment of disseminated MAC infection in patients with HIV, and azithromycin is a convenient drug to prevent such disease. Before clarithromycin, five- or six-drug regimens were commonly used to treat disseminated MAC infection, often with disappointing outcomes. Clarithromycin allowed MAC regimens to be reduced to two- to three-drug regimens with superior outcomes. Preventive azithromycin therapy greatly reduced the incidence of MAC infection in patients with AIDS, and its prolonged half-life allows once-a-week regimens. These drugs have growing roles in treating other atypical mycobacterial infections, including those caused by *M. kansasii*, *M. chelonae*, *M. fortuitum*, *M. abscessus*,

Table 1-4. Characteristics of Commonly Used Drugs for Treating Atypical Mycobacterial Infections

Drug	First-line Therapy	Alternative Therapy	Dosage Regimen ^a	Toxicities
Isoniazid	<i>M. kansasii</i> <i>M. scrofulaceum</i>	MAC <i>M. malmoense</i>	5 mg/kg/day up to 300 mg/day	Hepatotoxicity Peripheral neuritis
Rifampin	<i>M. kansasii</i> <i>M. haemophilum</i> <i>M. leprae</i> <i>M. malmoense</i> <i>M. marinum</i> <i>M. scrofulaceum</i> <i>M. ulcerans</i> <i>M. xenopi</i>	MAC	10 mg/kg/day up to 600 mg/day	Fluid discoloration (red/orange) Rash Hepatic cholestasis
Ethambutol	MAC <i>M. genavense</i> <i>M. kansasii</i> <i>M. malmoense</i> <i>M. marinum</i> <i>M. ulcerans</i> <i>M. xenopi</i>		15–25 mg/kg/day	Optic neuritis Hyperuricemia
Rifabutin	MAC	<i>M. genavense</i> <i>M. haemophilum</i> <i>M. kansasii</i>	300 mg/day	Uveitis Fluid discoloration (red/orange) Rash
Tobramycin	<i>M. chelonae</i>		3–5 IV mg/kg/day	Nephrotoxicity Ototoxicity
Streptomycin	<i>M. scrofulaceum</i>	MAC <i>M. kansasii</i> <i>M. xenopi</i>	15 mg/kg IM or IV 3–5 times/week	Ototoxicity Nephrotoxicity
Amikacin	<i>M. abscessus</i>	MAC <i>M. fortuitum</i> <i>M. haemophilum</i> <i>M. kansasii</i> <i>M. xenopi</i>	6.0–7.5 mg/kg IM or IV 1–2 times/day	Nephrotoxicity Ototoxicity

M. malmoense, *M. simiae*, *M. xenopi*, and *M. marinum*. It is ironic that *M. tuberculosis* represents the few species that are not readily susceptible to the newer macrolides.

Clarithromycin and azithromycin share relatively similar pharmacokinetic properties, differing the most in elimination. Both are variably absorbed, with clarithromycin minimally affected by food and azithromycin optimally taken without food, if tolerable. Both have huge volumes of distribution. Clarithromycin primarily is metabolized in the liver into an active metabolite, with a half-life of 5–7 hours. Azithromycin also primarily is metabolized in the liver, and its half-life is about 40 hours. Gastrointestinal intolerance remains the most common adverse effect of clarithromycin and azithromycin, although the overall incidence is greatly reduced in comparison to erythromycin.

The same severe drug interactions that plague erythromycin are present for clarithromycin. Clarithromycin is a potent inhibitor of CYP3A4 and other isoforms, affecting several drugs (including warfarin, theophylline, anticonvulsants, benzodiazepines, protease inhibitors, estrogens, and certain hydroxymethylglutaryl coenzyme A reductase inhibitors). Pimozide and terfenadine are

contraindicated with clarithromycin. Of importance, the effect of clarithromycin on increasing the area under the curve of protease inhibitors may be desirable. It is common practice to add low-dose ritonavir to protease inhibitor therapy to significantly increase the protease inhibitor area under the curve. This “ritonavir-boosting” effect often is much more pronounced than the effect by clarithromycin. Azithromycin has little to no significant drug interactions.

Fluoroquinolones

Ciprofloxacin and levofloxacin have excellent in vitro activity and/or have been used successfully (most reports involve ciprofloxacin) in regimens for treating MAC, *M. fortuitum*, *M. kansasii*, *M. malmoense*, *M. marinum*, *M. simiae*, and *M. szulgae*. Moxifloxacin and gatifloxacin have activity against many of these species as well, but clinical experience is not available for either drug to compare to the vast experience with ciprofloxacin. Comparative in vitro activities among the fluoroquinolones are difficult to ascertain because of sparse reports, variability of methods, and variability of results. Fluoroquinolone’s clinical use in mycobacterial infections is best documented in regimens containing ciprofloxacin or levofloxacin for multidrug-

Table 1-4. Characteristics of Commonly Used Drugs for Treating Atypical Mycobacterial Infections (Continued)

Drug	First-line Therapy	Alternative Therapy	Dosage Regimen ^a	Toxicities
Clarithromycin	MAC <i>M. abscessus</i> <i>M. chelonae</i> <i>M. fortuitum</i> <i>M. genavense</i> <i>M. haemophilum</i> <i>M. marinum</i> <i>M. ulcerans</i> <i>M. xenopi</i>	<i>M. kansasii</i> <i>M. malmoense</i> <i>M. scrofulaceum</i>	500 mg 2 times/day	GI toxicity
Azithromycin		Alternative to clarithromycin	500 mg/day	GI toxicity
Ciprofloxacin	MAC <i>M. fortuitum</i> <i>M. haemophilum</i>	<i>M. chelonae</i> <i>M. kansasii</i> <i>M. malmoense</i> <i>M. xenopi</i>	500–750 mg 2 times/day	Hypersensitivity GI toxicity
Levofloxacin	Same as ciprofloxacin		500 mg/day	Hypersensitivity Dizziness GI toxicity
Cefoxitin	<i>M. abscessus</i> <i>M. fortuitum</i>	<i>M. chelonae</i> <i>M. haemophilum</i>	2 g IV every 4–6 hours	Hypersensitivity
Imipenem/ Cilastatin	<i>M. chelonae</i> <i>M. fortuitum</i>	<i>M. abscessus</i>	500 mg IV every 6 hours	Neurologic toxicity
Doxycycline	<i>M. fortuitum</i>	<i>M. chelonae</i>	100–200 mg 2 times/day	GI toxicity Photosensitivity
Clofazimine	<i>M. leprae</i>	MAC	50–100 mg/day	GI toxicity Orange discoloration
TMP-SMX ^a	<i>M. fortuitum</i> <i>M. marinum</i>	<i>M. chelonae</i> <i>M. haemophilum</i> <i>M. kansasii</i>	800–1600 mg (sulfamethoxazole component) 2 times/day	Bone marrow suppression Hypersensitivity

^aDoses listed are adult dosages based on normal kidney function and oral administration unless otherwise noted.

GI = gastrointestinal; IM = intramuscularly; IV = intravenously; MAC = *Mycobacterium avium* complex; TMP-SMX = trimethoprim-sulfamethoxazole.

resistant tuberculosis and MAC infections. Fluoroquinolones are attractive drugs given their unique primary mechanism of action of inhibiting deoxyribonucleic acid-gyrase and topoisomerase IV, their excellent bioavailability, distribution, and other favorable pharmacokinetic characteristics. Levofloxacin is given once daily, has an elimination half-life of 5–7 hours, and is excreted primarily unchanged through the kidney. Ciprofloxacin is given 2 times/day, has an elimination half-life of 3–5 hours, and is excreted significantly both by kidney and hepatic mechanisms.

Most of the safety data gathered for the fluoroquinolones has been after short-term treatment for acute bacterial infections. However, increasing use for extended periods to treat infections such as bacterial osteomyelitis or mycobacterial infection has confirmed that long-term use of fluoroquinolones is not associated with a large increase in toxicity. Fluoroquinolones have low rates of gastrointestinal intolerance and hypersensitivity. Central nervous system effects such as headache, dizziness, and agitation are observed in less than 10% of patients taking fluoroquinolones. Fluoroquinolones are relatively

contraindicated in children because animal data demonstrate adverse effects on joint and cartilage development; however, in some patient populations, such as those with cystic fibrosis, the benefit may outweigh the potential risk. Tendon inflammation and tendon rupture have rarely been reported in adults. Other rare events include the potential for corrected QT interval prolongation, hepatotoxicity, and disturbances of glucose control.

Ciprofloxacin has variable CYP enzyme inhibition that affects drugs, such as warfarin, theophylline, sulfonyleureas, and anticonvulsants. Newer fluoroquinolones have been implicated only rarely in affecting the disposition of these drugs. Another mechanism of drug interaction is chelation, by divalent metal cations such as aluminum, magnesium, zinc, iron, and calcium, resulting in moderate to severe decreased bioavailability of the fluoroquinolone. This chelation occurs with all available fluoroquinolones. Antacids, multivitamins, sucralate, and other drugs containing these metal cations should not be given with fluoroquinolones, unless the dosages are separated by at least 4–6 hours.

Aminoglycosides

Even though streptomycin and amikacin have a broad spectrum of activity against mycobacteria, they are only occasionally used to treat mycobacterial infections. The use of these drugs is now commonly reserved for treating resistant or severe infection, and the duration of use often is limited to only a few weeks. The expanded availability of oral drugs active against mycobacteria with favorable safety profiles has in large part supplanted the use and toxicities of intravenous or intramuscular administration routes of aminoglycosides.

The dosage regimens for streptomycin and amikacin are quite different from those suggested for treating gram-positive or gram-negative acute bacterial infections. In general, to treat mycobacterial infections, 15 mg/kg of streptomycin is recommended to be given by intramuscular injection 2–3 times/week, with doses dependent on kidney function and body weight. Targeted peak concentrations are about 20 mcg/ml, and trough concentrations should be undetectable well before the next 2 or 3 times/week dose is repeated. Amikacin usually is recommended to be given 1–2 times/day for “low-dose” therapy to achieve peak concentrations of 20 mcg/ml and trough concentrations of 5 mcg/ml or lower. As with any aminoglycoside therapy of more than a few days duration, therapeutic drug monitoring typically should be used to ensure targeted serum concentrations, thereby maximizing efficacy while minimizing toxicity. However, therapy duration and total aminoglycoside exposure are risk factors for toxicity in addition to supratherapeutic serum concentrations. The degree of aggressiveness for monitoring serum concentrations is debated, although it appears reasonable to provide a “stepped” approach to therapeutic drug monitoring; monitoring can be conducted throughout the first few weeks of therapy until the clinician is reasonably comfortable that the dosage regimen is providing targeted serum concentrations and the patient’s kidney function is stable. Thereafter, therapeutic drug monitoring can be reduced to every few weeks as necessary. If therapy duration is to be longer than 2 months, clinically stable patients should require therapeutic drug monitoring only periodically. For streptomycin, therapeutic drug monitoring may not be necessary if recommended dosage adjustments are made according to changes in kidney function.

The primary toxicity of streptomycin is vestibular/auditory toxicity. These effects may result in symptoms such as dizziness, vertigo, ataxia, tinnitus, and hearing impairment. Nephrotoxicity also is a concern with streptomycin therapy. For amikacin and other aminoglycosides, both nephrotoxicity and ototoxicity are of high importance. Monitoring should include 1–2 times/week assessment of kidney function for the first 2 months of therapy, then weekly to every 2 weeks thereafter. More aggressive monitoring may be appropriate with concomitant use of other nephrotoxic drugs, especially amphotericin B, and including drugs such as cyclosporine or tacrolimus.

Clinicians should encourage patients to note any changes in hearing, tinnitus, dizziness, or feelings of fullness within the ears. Vestibular function testing and audiometric testing should occur at baseline if the plan for therapy is 4 weeks or

more, and these tests should be repeated during therapy if any minor symptoms consistent with the toxicities are noticed. Irreversible damage can occur with prolonged therapy; therefore, if ototoxicity or nephrotoxicity progresses, aminoglycoside therapy should be discontinued and alternative therapy given where appropriate. Aminoglycosides disrupt neuromuscular transmission through acetylcholine receptor interference; but clinically, this is not a common adverse effect. Patients at high risk for this adverse effect are those with conditions such as myasthenia gravis (weigh risk versus benefit), and those receiving other drugs associated with neuromuscular blockade such as muscle relaxants, anesthesia, or corticosteroid therapy. Aminoglycoside use is not absolutely contraindicated in these situations, and the clinician should be attentive to signs and symptoms of neuromuscular blockade such as respiratory paresis, decreased tendon reflexes, and flaccid tetraparesis (incomplete paralysis of the four limbs). Clinicians also should carefully weigh the risk versus benefit of aminoglycoside therapy in patients with severe hepatic disease because of the increased possibility of hepatorenal syndrome.

β-Lactams and Carbapenems

Cefoxitin and imipenem-cilastatin are used to treat *M. abscessus*, *M. fortuitum*, and *M. chelonae*. Their use is limited to severe cases and often for short initial durations, because of their need for intravenous administration every 6–8 hours. Imipenem-cilastatin has emerged as most clinicians’ drug of choice of the two, although neither drug has been proven clinically superior in an adequate comparative trial. Cefoxitin typically is given at a dose of 2 g intravenously every 6 hours, and imipenem-cilastatin is most often given either 500 mg intravenously every 6 hours or 1 g every 8 hours. Both drugs share a modest volume of distribution, short half-life, and both primarily are excreted unchanged in the urine. Cefoxitin use may be associated with uncommon adverse effects, such as gastrointestinal intolerance, hypersensitivity reactions, interstitial nephritis, liver function enzyme elevation, and blood dyscrasias. Imipenem-cilastatin is most notorious for causing neurological toxicity, including seizures. Appropriate dose adjustment for kidney dysfunction is critical to prevent neurotoxicity. There are no significant pharmacokinetic interactions for either drug.

Miscellaneous Drugs

Doxycycline and minocycline have variable clinical use against *M. chelonae*, *M. fortuitum*, and *M. marinum*. These drugs can be taken orally 2 times/day with food, with good bioavailability. Adverse effects include photosensitivity, rash, nausea and vomiting, diarrhea, and some central nervous system toxicity. Gastrointestinal toxicities include esophageal irritation and ulceration, and patients should be instructed to drink plenty of water to help minimize such toxicity. Photosensitivity may be an added concern when these drugs are given for extended durations. Phenytoin, carbamazepine, and barbiturates may decrease the half-life of doxycycline through enzyme induction.

Trimethoprim-sulfamethoxazole is an option for treating infections due to *M. marinum*, *M. fortuitum*, *M. chelonae*, and *M. abscessus*. This oral drug has good bioavailability and 2 times/day dosing; its primary drawbacks are hypersensitivity reactions, initial gastrointestinal intolerance, and the potential for bone marrow suppression, especially with long therapy. Monitoring serum chemistries and complete blood cell counts is recommended every 1–2 months for the doses used to treat atypical mycobacteria.

Clofazimine is a second-line antituberculosis drug that has been used to treat infections due to *M. abscessus*, *M. chelonae*, *M. leprae*, and MAC. Its primary adverse effects include aggressive gastrointestinal intolerance with nausea, vomiting, cramping, and diarrhea, and an orange/brown discoloration of bodily fluids and tissues (including skin). Resolution of the discoloration can be slow after discontinuation of the drug because of its long terminal half-life of about 10 weeks.

Treatment

Pulmonary Infection

When the organism is identified, pharmacotherapy is tailored based on the recommended regimen for treating that specific organism. Therapy may need further adjustment if susceptibilities subsequently become available or if the patient's clinical status deteriorates. The goals of therapy are eventual cure in most cases, and this can commonly be accomplished with patient compliance, a reasonable immune system response, and adequate non-pharmacological care. Some organisms, such as *M. abscessus*, are recalcitrant to pharmacotherapy, and cure often is attainable only with surgical resection. In addition, underlying lung disease may affect the ability to cure the infection, requiring even lifelong therapy in some instances. The ATS guidelines provide a basis for pharmacotherapy of the most common atypical mycobacteria encountered in lung disease. Table 1-5 lists the most common regimens for each infection. The most common pulmonary pathogens are reviewed below. In most cases, pulmonary infection primarily occurs in the HIV-negative population; thus, recommendations below typically are reflective of treatment of pulmonary disease in the HIV-negative population. Treatment for patients with HIV and pulmonary infection is similar in most cases, with the exception of a possible need for maintenance therapy after initial therapy is completed.

Mycobacterium avium Complex

For MAC pulmonary infection, a regimen of clarithromycin plus ethambutol, with or without a third drug (usually either ciprofloxacin or rifabutin), is recommended. Recommendations for treating MAC pulmonary infection often are partially derived from studies in disseminated MAC disease in patients with AIDS. Recent trials in this population provide conflicting data regarding improved outcomes if a third drug is given (see the *Mycobacterium*

avium Complex section of the Disseminated Infection section for treatment of disseminated MAC disease). Azithromycin can be substituted for clarithromycin if patients are unable to tolerate clarithromycin. Susceptibility testing should at least include the new macrolides, ethambutol, rifamycins, ciprofloxacin or levofloxacin, clofazimine, and amikacin or streptomycin.

The efficacy of regimens containing clarithromycin and ethambutol is superior to the premacrolide era regimens consisting often of five or six drugs for treating MAC pulmonary infection. Extensive disease may prompt the clinician to add a third drug, such as ciprofloxacin or rifabutin, as well as a short duration of streptomycin or amikacin. Overall therapy duration is recommended to be 18–24 months, or at least 12 months after sputum conversion.

If productive cough continues, patients should have monthly sputum specimens tested until sputum conversion is documented. Clinical improvement should be seen within 6 months, including improvements in respiratory function, disappearance of fever, increased stamina, improved appetite, and weight gain. Patients should be monitored for drug toxicity consistent with the regimen that they are receiving. Evidence of clinical failure should prompt the clinician to add more drugs to the regimen, which can often total up to four to five drugs.

Mycobacterium kansasii

First-line therapy for *M. kansasii* mirrors that of *M. tuberculosis* (with the exception of pyrazinamide, which has no useful activity against *M. kansasii*), which makes empiric decisions relatively easy. Although clarithromycin is the cornerstone for treating MAC disease, rifampin appears to be the crucial component for *M. kansasii* therapy. The initial regimen for treating *M. kansasii* pulmonary infection should be isoniazid, rifampin, and ethambutol. Clarithromycin, ciprofloxacin, levofloxacin, and trimethoprim-sulfamethoxazole may have clinical use and can be used as alternatives to isoniazid or ethambutol, especially in settings of resistance or apparent clinical failure. Susceptibility testing should include at least rifampin, isoniazid, ethambutol, aminoglycosides, ciprofloxacin or levofloxacin, and clarithromycin. Clinical outcomes in compliant patients receiving rifampin-based regimens are extremely high, with failure rates of only about 1% in large studies. Therapy duration is recommended to be at least 18 months, and extended if necessary to obtain 12 months of therapy after sputum conversion. Preliminary results from a recent open-label trial described 14 patients treated successfully with a regimen of clarithromycin, ethambutol, and rifampin 3 times/week. Monitoring for response is similar to that for MAC therapy as previously discussed.

Mycobacterium xenopi

Case series evaluating various regimens containing traditional antituberculous drugs have observed variable

Bloch KC, Zwerling L, Pletcher MJ, et al. Incidence and clinical implications of isolation of *Mycobacterium kansasii* results of a 5-year, population-based study. *Ann Intern Med* 1998;129:698–704.

Griffith DE, Brown-Elliott BA, Wallace RJ. Thrice-weekly clarithromycin-containing regimen for treatment of *Mycobacterium kansasii* lung disease: results of a preliminary study. *Clin Infect Dis* 2003;37:1178–82.

Table 1-5. General Recommendations for Pharmacotherapy of Common Atypical Mycobacterial Infection

<i>Mycobacterium</i> species	Regimens of Choice	Comments
MAC	Clarithromycin plus ethambutol with or without rifabutin, ciprofloxacin, or levofloxacin ^a	Third drug most likely required with disseminated disease
<i>M. kansasii</i>	Isoniazid plus rifampin plus ethambutol	Clarithromycin and fluoroquinolone roles emerging
<i>M. haemophilum</i>	Rifampin plus clarithromycin plus ciprofloxacin	Amikacin or doxycycline may be added in serious infection
<i>M. marinum</i>	Superficial infection: Ethambutol plus rifampin, or one or two of the following: Clarithromycin, mino/doxycycline, or TMP-SMX Deep infection: Clarithromycin plus ethambutol plus rifampin	Superficial infection may not require pharmacotherapy
<i>M. genavense</i>	Clarithromycin plus ethambutol with or without rifabutin	
<i>M. malmoense</i>	Rifampin plus ethambutol	Additional drugs have been controversial, but clarithromycin or ciprofloxacin may be of benefit
<i>M. ulcerans</i>	Clarithromycin plus rifampin plus ethambutol	Very recalcitrant to pharmacotherapy
<i>M. scrofulaceum</i>	Isoniazid plus rifampin plus streptomycin	Cycloserine, clarithromycin, or ciprofloxacin may be added
<i>M. xenopi</i>	Ethambutol plus rifampin with or without clarithromycin	Clarithromycin should be added in patients with HIV Ciprofloxacin may be substituted into regimen if ethambutol or rifampin cannot be used
<i>M. leprae</i>	Paucibacillary disease: Dapsone plus rifampin Multibacillary disease: Dapsone plus rifampin plus clofazimine	See the Cutaneous subsection of the Treatment section for details
<i>M. fortuitum</i>	Pulmonary disease: Clarithromycin plus doxycycline, TMP-SMX, or levofloxacin Catheter-related infection: Cefoxitin plus amikacin with or without clarithromycin	Numerous alternative options
<i>M. chelonae</i>	Mild to moderate cutaneous disease: Clarithromycin plus ciprofloxacin Systemic disease: Clarithromycin plus imipenem plus tobramycin	See the Disseminated Infection subsection of the Treatment section for oral conversion options
<i>M. abscessus</i>	Clarithromycin plus amikacin plus cefoxitin	Imipenem may substitute cefoxitin

HIV = human immunodeficiency virus; MAC = *Mycobacterium avium* complex; TMP-SMX = trimethoprim-sulfamethoxazole.

responses to therapy. A randomized study conducted by the British Thoracic Society compared rifampin and ethambutol with or without isoniazid. Isoniazid did not add any beneficial outcomes in this small study population of 42 patients. A few case reports and case series describe successful outcomes of clarithromycin-containing regimens, often combined with rifampin and ethambutol. The ATS guidelines recommend clarithromycin, rifampin, and ethambutol for initial therapy of pulmonary *M. xenopi* infection. In Europe, where this infection presents more commonly, the British Thoracic Society recommends rifampin and ethambutol. The society currently is evaluating clarithromycin- and/or ciprofloxacin-containing regimens in a randomized study. For patients with HIV infection, the British Thoracic Society suggests adding clarithromycin. Susceptibility testing should include clarithromycin, ethambutol, rifampin, aminoglycosides, ciprofloxacin, and isoniazid.

Treatment outcomes for individuals with pulmonary infection due to *M. xenopi* are poorer than most other slow-growing atypical mycobacteria. A separate British Thoracic Society report found the 5-year follow-up all-cause mortality rate in the randomized trial of 42 patients to be 69%. If disease is unilateral, surgical resection followed by pharmacotherapy may improve outcomes. Therapy for most patients is recommended for 18–24 months, or at least 18 months after surgical resection or sputum conversion.

Mycobacterium malmoense

Mycobacterium malmoense pulmonary infection is similar to that caused by *M. xenopi* in epidemiology, presentation, and treatment modes. Outcomes of therapy are somewhat better than infections due to *M. xenopi* based on a couple of retrospective reviews and a randomized trial. Clinical improvement was noted in 90% of patients treated in a randomized trial (n=106) comparing rifampin plus ethambutol, with or without isoniazid; however, cure was noted in only 42% of patients, and all-cause mortality reached 34%. Initial therapy is anchored with rifampin and ethambutol, and the addition of a third or fourth drug is debated. Some early evidence suggested therapy with the four or five traditional antituberculous drugs led to poorer outcomes, including safety. The newer macrolides and fluoroquinolones may be able to improve outcomes provided by rifampin-ethambutol regimens, but evidence is scant to date. Drugs included for susceptibility testing should be similar to those recommended for *M. xenopi*.

Recommendations for therapy duration are similar to those for *M. xenopi* pulmonary infection.

Rapid-growing Atypical Mycobacteria

Besides the unique in vitro growth characteristics,

epidemiology, and sites of infection, rapid-growing mycobacteria also greatly differ from their slow-growing counterparts in antimicrobial susceptibilities. These organisms routinely are resistant to all first-line antituberculosis drugs, susceptible to some second-line antituberculosis drugs (fluoroquinolones and amikacin), and susceptible to certain β -lactam and carbapenem antimicrobials (cefoxitin and imipenem). Ciprofloxacin and gatifloxacin should be tested against these isolates (gatifloxacin may have more activity against *M. fortuitum* and *M. chelonae*). The one constant is the activity of clarithromycin. Susceptibility testing for rapid-growing mycobacteria also should include linezolid, sulfamethoxazole, and doxycycline or minocycline.

Mycobacterium abscessus causes about four out of every five cases of pulmonary infection due to rapid-growing mycobacteria. Unfortunately, *M. abscessus* is arguably the toughest mycobacteria to treat. Only a few antibiotic drugs demonstrate activity against the organism, and their activity often is inconsistent. The three antibiotics with the most consistent activity include clarithromycin, amikacin, and cefoxitin. Variable activity is seen with imipenem and linezolid. There are no studies available to adequately evaluate the optimal initial regimen. Case series of monotherapy with clarithromycin and azithromycin exist, but because of the potential for resistance, monotherapy cannot be recommended routinely. An initial regimen has been suggested that includes clarithromycin, amikacin, and cefoxitin (or imipenem). Given concerns over drug administration difficulty and toxicity, and often the futility of curing the disease, it may be appropriate to give abbreviated intermittent courses of therapy in some cases to simply control the rate or suppress the progression of disease. Surgical resection may be of benefit when appropriate.

Mycobacterium fortuitum is responsible for most of the remaining (20%) pulmonary infections due to rapid-growing mycobacteria. It is much more susceptible and amenable to therapy than *M. abscessus*. In the absence of adequate trials, recommendations for an initial regimen include clarithromycin plus one other usually active drug, including doxycycline, trimethoprim-sulfamethoxazole, or levofloxacin. Treatment often is curative with compliance, and the duration can be a “relatively short” 6–12 months.

Mycobacterium chelonae, *M. smegmatis*, *M. mucogenicum*, and the two biovariants of *M. fortuitum* may rarely cause pulmonary infection, and one or two drugs added to clarithromycin may be appropriate initial therapy. These mycobacteria rarely cause pulmonary disease, and the treatment principles used with *M. fortuitum* can be used as general guidance if the patient appears to be responding.

Research Committee of the British Thoracic Society. First randomised trial of treatments for pulmonary disease caused by *M. avium* intracellulare, *M. malmoense*, and *M. xenopi* in HIV negative patients: rifampicin, ethambutol, and isoniazid versus rifampicin and ethambutol. *Thorax* 2001;56:167–72.

Jenkins PA, Campbell IA; Research Committee of the British Thoracic Society. Pulmonary disease caused by *Mycobacterium xenopi* in HIV negative patients: five year follow-up of patients receiving standardized treatment. *Respir Med* 2003;97:439–44.

Research Committee of the British Thoracic Society. Pulmonary disease caused by *M. malmoense* in HIV negative patients: 5-yr. follow-up of patients receiving standardized treatment. *Eur Respir J* 2003;21:478–82.

Extrapulmonary Infection Sites

As with treating extrapulmonary tuberculosis, treatment recommendations of most extrapulmonary atypical mycobacterial infections are similar to those for treating pulmonary infection. A few of the more common infection sites are discussed in the following sections, including cutaneous disease, lymphadenitis, catheter-related infection, and infections involving deep tissues such as bone and joint disease.

Cutaneous Infection

The primary atypical mycobacteria responsible for cutaneous infection include *M. marinum*, *M. ulcerans*, *M. haemophilum*, *M. leprae*, and rapid-growing mycobacteria. Non-pharmacological management of disease includes observation for potential resolution with time or surgical treatment. For some mycobacterial cutaneous infections, pharmacotherapy can be adequately delivered with fewer drugs and shorter treatment duration compared to other infection sites.

***Mycobacterium marinum*.** Most reports of disease due to *M. marinum* were from exposures to inadequately chlorinated fish aquariums, pools, or southern United States coastal areas. Most of the patients for whom therapy was described had relatively superficial skin and skin structure infection of an upper extremity. Although infections in immunocompetent patients often resolve without treatment in about 2 years, therapy may be able to resolve the infection more rapidly. For such patients, optimal therapy may be 3–6 months of monotherapy or dual therapy with drugs, such as clarithromycin, minocycline, doxycycline, or trimethoprim-sulfamethoxazole, or with combination therapy of ethambutol plus rifampin. These are the drugs that should be selected for susceptibility testing. In a recent French national survey, 42 of 45 superficial infections with *M. marinum* were treated successfully with a mean duration of 4 months; monotherapy was successful in all 20 attempts. Deeper infections were treated primarily with combination therapy using clarithromycin, a tetracycline, and rifampin, which was effective in 13 of 18 cases, with a mean therapy duration of 7 months. Ethambutol plus rifampin was considered the regimen of choice before the availability of clarithromycin, but now clarithromycin plus either ethambutol or rifampin is considered the regimen of choice.

***Mycobacterium ulcerans*.** *Mycobacterium ulcerans* infections are not amenable to pharmacotherapy, and extensive surgical management is the primary treatment in almost all cases. Early disease may respond to a regimen including clarithromycin, rifampin, and ethambutol. Optimal therapy durations is not known.

***Mycobacterium haemophilum*.** This organism is responsible for skin and skin structure infection primarily in immunocompromised adult patients. No trials exist to establish a firm recommendation for pharmacotherapy, but

articles have described therapy in case series of infections at various sites. The largest and most recent case series review described two- to three-drug regimens of rifampin, clarithromycin, and ciprofloxacin. Amikacin, trimethoprim-sulfamethoxazole, rifabutin, levofloxacin, cefoxitin, and doxycycline also may have a role in therapy. The organism typically is resistant to isoniazid, ethambutol, and streptomycin. Therapy duration in immunosuppressed individuals may need to be indefinite, although a course of at least 6–9 months is recommended in immunocompetent individuals or individuals who have had their immunosuppression reversed. Response rates are variable.

***Mycobacterium leprae*.** Multidrug therapy against *M. leprae* has improved clinical outcomes and has helped prevent spread to others. Rifampin is the most rapidly bactericidal drug against the organism, to the extent that some recommended regimens have rifampin being given once a month. For mild disease or “paucibacillary disease,” the World Health Organization recommends rifampin 600 mg orally each month and dapsone 100 mg/day orally for a total of 6 months. Patients with only one skin lesion and virtually no other signs of disease or immunosuppression can be treated effectively with a one-time dose of rifampin 600 mg, ofloxacin 400 mg, and minocycline 100 mg, although microbiological outcomes and rates of recurrence with this regimen have not been fully addressed. For more serious disease or “multibacillary disease”, the World Health Organization recommends rifampin 600 mg orally each month, dapsone 100 mg/day orally, and clofazimine 100 mg/day orally for a total duration of 12 months. The United States Department of Health and Human Services recommends a more conservative approach to treatment. For paucibacillary disease, dapsone 100 mg/day and rifampin 600 mg/day are recommended for 12 months, and multibacillary disease should be treated for 24 months with those two drugs plus clofazimine 50 mg/day. For disease that does not properly respond to therapy, the duration should be lengthened until skin smear negativity occurs, which can exceed 5 years. Clinical outcomes can be assessed by observation of the skin lesions, patient symptoms, and occasional skin smear examination to quantify the number of organisms. Relapse after successful therapy is extremely low. Prophylaxis of household contacts has been investigated but is not recommended currently.

Rapid-growing Mycobacteria. In vitro susceptibilities of rapid-growing mycobacteria were discussed previously. Mild skin infections due to *M. fortuitum* should be treated with clarithromycin plus one other active oral antibiotic drug, such as doxycycline, trimethoprim-sulfamethoxazole, or ciprofloxacin. For more serious infections involving large areas or deep tissues, including extension into bony structures, intravenous therapy with amikacin, cefoxitin, or imipenem is recommended. Some experts recommend

Aubry A, Chosidow O, Caumes E, et al. Sixty-three cases of *Mycobacterium marinum* infection: clinical features, treatment, and antibiotic susceptibility of causative isolates. Arch Intern Med 2002;162:1746–52.

Shah KS, Sebti A, Kiehn TE, Massarella SA, Sepkowitz KA. *Mycobacterium haemophilum* in immunocompromised patients. Clin Infect Dis 2001;33:330–7.

Straus WL, Ostroff SM, Jernigan DB, et al. Clinical and epidemiologic characteristics of *Mycobacterium haemophilum*, an emerging pathogen in immunocompromised patients. Ann Intern Med 1994;120:118–25.

adding oral clarithromycin to the regimen. Surgical debridement often is necessary for adequate control of infections involving deeper tissues. Because this infection can occur with surgical procedures, removal of any surgically placed hardware is important for cure. Therapy duration often is recommended from as few as 2 months for mild disease to 4–6 months for more serious disease.

Similar pharmacotherapy is recommended for serious disease due to *M. abscessus*, although the prognosis may be worse. Oral therapeutic options for mild disease may include only clarithromycin, clofazimine, and potentially linezolid. Fortunately, localized skin infection in immunocompetent individuals can resolve without pharmacotherapy over 6–12 months. Pharmacotherapy should be given to patients with local skin infection for about 3–6 months. Empiric pharmacotherapy in serious disease should include clarithromycin, intravenous cefoxitin (or imipenem), and amikacin, with adjustment once susceptibilities are available. Serious disease often necessitates treatment for a minimum of 6 months.

For *M. chelonae* cutaneous infections, a recent small noncomparative, open trial reported clarithromycin alone to be effective without relapse. The addition of ciprofloxacin may be reasonable, assuming the organism is susceptible, if a clinician has concerns about the potential of resistance with monotherapy. For more serious, deep tissue involvement, empiric therapy with clarithromycin, imipenem, and tobramycin is recommended. Treatment usually lasts at least 6 months.

Lymphadenitis

When mycobacterial lymphadenitis is suspected, empiric therapy with a four-drug regimen directed at *M. tuberculosis* may be warranted until the microbial etiology is confirmed with pathological findings from surgical excision or biopsy. In many circumstances, particularly in children and immunocompetent adults, confirmed atypical mycobacterial infection requires surgical excision alone. If excision is contraindicated, the patient is immunosuppressed, or recurrence occurs, pharmacotherapy typically is recommended, but there are no adequate trials to assess the optimal therapy (drug regimens or therapy duration). For the common atypical mycobacterial species encountered in lymphadenitis, suggested pharmacotherapy includes clarithromycin plus ethambutol with or without rifabutin, which probably should be given for 1–2 years. *Mycobacterium scrofulaceum* requires several drug therapy (3–4 drugs, including isoniazid, rifampin, streptomycin, cycloserine, and potentially clarithromycin or ciprofloxacin) for at least 12 months, but the most common situation of childhood lymphadenitis rarely requires therapy other than surgical excision. *Mycobacterium malmoense* should be treated with rifampin and ethambutol if necessary.

Bone and Joint Infection

Virtually any of the atypical mycobacteria can cause infection involving bone and joint spaces, primarily through direct inoculation by trauma, injection, or surgical

procedures. The most commonly encountered species include *M. kansasii*, MAC, rapid-growing atypical mycobacteria, *M. ulcerans*, and *M. marinum*. The therapeutic recommendations for these infections are not based on adequate trials because of the sporadic nature of the disease, but are extrapolated from recommendations for treating more common sites of infection (e.g., pulmonary and cutaneous infection as previously discussed). Surgical incision and drainage may be necessary in some cases. Pharmacotherapy duration approaches the more extended lengths that are typically recommended. Monitoring parameters to assess clinical response are murky, but may include periodic imaging studies or periodic assessment of markers of inflammation such as the erythrocyte sedimentation rate.

Catheter-related Infections

Catheter-related infection is a relatively common presentation of rapid-growing atypical mycobacteria and the primary health care-associated mycobacterial disease. *Mycobacterium fortuitum*, *M. chelonae*, and *M. abscessus* are the most common mycobacteria involved. Infections include exit-site infections, tunnel infections, and/or bacteremia. Hematogenous spread to organ systems can occur occasionally. These infections can cause outbreaks within hospital settings. Immunosuppression and the presence of long-term central indwelling catheters (including those associated with hemodialysis or peritoneal dialysis) may be risk factors for the disease. Therapy should include removal of the catheter, surgical excision and drainage when appropriate, and a relatively short antibiotic drug course of 2–4 months. For *M. fortuitum*, initial therapy of cefoxitin and amikacin with or without clarithromycin should be given for at least 2–4 weeks, with potential conversion to an oral regimen of clarithromycin and a fluoroquinolone (ciprofloxacin or gatifloxacin) to complete the course. For *M. chelonae*, treatment with imipenem-cilastatin or cefoxitin plus tobramycin should be initiated. After initial intravenous therapy, oral therapy may be possible with clarithromycin, ciprofloxacin, gatifloxacin, trimethoprim-sulfamethoxazole, or doxycycline. Therapy duration is similar to treatment of *M. fortuitum* infections. Treatment of *M. abscessus* is similar to *M. chelonae*, with a poorer response to therapy.

Disseminated Infection

Disseminated infection with atypical mycobacteria occurs most often in immunosuppressed patients, particularly with cell-mediated defects seen in patients with AIDS, with hematological malignancy, patients receiving corticosteroid therapy, or transplant recipients (particularly bone marrow transplantation). Patients with disseminated disease may present severely ill, and may require initial intravenous therapy if the gastrointestinal tract is not accessible or is not functioning. Fortunately, several drugs can be used intravenously for empiric or initial atypical mycobacterial infection, including rifampin, azithromycin, fluoroquinolones, aminoglycosides, doxycycline,

Wallace RJ, Tanner D, Brennan PJ, Brown BA. Clinical trial of clarithromycin for cutaneous (disseminated) infection due to *Mycobacterium chelonae*. *Ann Intern Med* 1993;119:482–6.

trimethoprim-sulfamethoxazole, cefoxitin, or imipenem-cilastatin.

Disseminated mycobacterial infections due to different species often have similar clinical presentations, including fever, weight loss, anorexia, weakness, and anemia. Monitoring of therapy includes observing for the reversal of these problems. In addition, documentation of the clearing of bacteremia or sterilization of other normally sterile sites that were initially culture-positive is indicative of a good response and may assist in determining therapy duration. In general, the prognosis is poorer if immune recovery cannot be accomplished, and in some cases (particularly in patients with AIDS), indefinite therapy will be necessary.

Mycobacterium avium Complex

Treating MAC infection in patients with AIDS has evolved from four- to six-drug regimens with little effectiveness to two- to three-drug regimens with much-improved effectiveness. Traditional antituberculous drugs commonly used in the past have little to modest activity against MAC, with the exception of the potent in vitro activity of ethambutol. The introduction of the newer macrolides represented a major advancement in the treatment of disseminated MAC infection, and the usefulness of a two- to three-drug regimen was rapidly recognized after several studies in the 1990s. Clarithromycin (or, as demonstrated recently, azithromycin) and ethambutol are considered essential for treatment, and the primary question remains whether a third drug provides additional benefit. Candidates for the third drug include ciprofloxacin, rifabutin, clofazimine, and amikacin. Trials adding clofazimine or amikacin as a third drug to treat disseminated MAC infections have been disappointing and one study even demonstrated higher mortality with the inclusion of clofazimine. Outcomes associated with the addition of a fluoroquinolone have not been adequately addressed. Two well-conducted trials comparing the two-drug regimen with a three-drug regimen containing rifabutin have had conflicting results. The first trial published was a randomized, placebo-controlled trial that included 198 patients and found no difference in outcome between the two groups. The second study was an open-label trial where 160 patients were randomly divided among three arms (clarithromycin plus ethambutol, clarithromycin plus rifabutin, or all three drugs). The primary end points (microbiological and clinical response by week 12 of therapy) were not different among these groups. Survival was listed as one of the secondary end points, and the triple-drug therapy arm was superior in overall survival at 48 weeks (72% vs. 47% and 50% in the ethambutol and rifabutin arms, respectively). Because most trials to assess

treatment outcomes of disseminated MAC infection occurred before the advent of highly active antiretroviral therapy, practitioners are left with unresolved questions in the era of highly active antiretroviral therapy. For instance, the potential for effective highly active antiretroviral therapy to boost CD4 cell counts to more than 100 cells/mm³ may remove any difference in outcome that a third drug may be able to provide, which is especially important if the regimen is affecting or being affected through drug interactions or additive toxicity with a patient's antiretroviral regimen. Another question involves appropriate therapy duration, which in the era before highly active antiretroviral therapy was presumed to be lifelong; however, with the potential for immune recovery with effective highly active antiretroviral therapy, could therapy potentially be stopped at some point? Results of a few trials indicate that therapy could be reasonably stopped after 12 months if the patient has had a rapid response to highly active antiretroviral therapy with a sustained CD4 cell count more than 100 cells/mm³.

Clarithromycin plus ethambutol should be initial therapy for disseminated MAC infections, with or without a third drug. Rifabutin or ciprofloxacin is recommended to be the third drug. The addition of rifabutin must be done with caution in patients receiving antiretroviral therapy, given rifabutin's CYP3A4 induction properties and the potential for antiretroviral drugs to affect rifabutin's metabolism. Patients should be placed on effective highly active antiretroviral therapy if possible to improve immune function and obtain control of their HIV infection. Symptoms, including weakness, anorexia, weight loss, and gastrointestinal distress, should be monitored for improvement. If patients have significant gastrointestinal adverse effects, clarithromycin often is the etiology and clinicians should consider replacing it with azithromycin if these problems do not resolve. If immune recovery does not occur, the patient will receive therapy lifelong.

Mycobacterium kansasii

As previously discussed, susceptibility testing for *M. kansasii* should include rifampin, isoniazid, ethambutol, amikacin, streptomycin, ciprofloxacin, levofloxacin, gatifloxacin, and clarithromycin. Therapy for disseminated *M. kansasii* is recommended to be similar to therapy for pulmonary infection: isoniazid, rifampin, plus ethambutol. However, disseminated disease most often is encountered in immunosuppressed patients. Rifampin is contraindicated in many patients with HIV taking antiretroviral regimens because of its potent CYP enzyme system induction. In addition, certain immunosuppressives may be contraindicated with rifampin in transplant recipients. In

Gordin FM, Sullam PM, Shafran SD, et al. A randomized, placebo-controlled study of rifabutin added to a regimen of clarithromycin and ethambutol for treatment of disseminated infection with *Mycobacterium avium* complex. *Clin Infect Dis* 1999;28:1080-5.

Benson CA, Williams PL, Currier JS, et al. A prospective, randomized trial examining the efficacy and safety of clarithromycin in combination with ethambutol, rifabutin, or both for the treatment of disseminated *Mycobacterium avium* complex disease in people with acquired immune deficiency syndrome. *Clin Infect Dis* 2003;37:1234-43.

Aberg JA, Williams PL, Liu T, et al; AIDS Clinical Trial Group 393 Study Team. A study of discontinuing maintenance therapy in human immunodeficiency virus-infected subjects with disseminated *Mycobacterium avium* complex. *J Infect Dis* 2003;187:1046-52.

Dunne M, Fessel J, Kumar P, et al. A randomized, double-blind trial comparing azithromycin and clarithromycin in the treatment of disseminated *Mycobacterium avium* infection in patients with human immunodeficiency virus. *Clin Infect Dis* 2000;31:1245-52.

these instances, options may include the substitution of rifampin with rifabutin (assuming rifabutin is not contraindicated and dose is properly adjusted) or with clarithromycin (whose CYP3A4 inhibitory effects also may pose a problem, especially with immunosuppressive drugs in transplant recipients). These nonrifampin-containing regimens have not been formally evaluated. If these options are not possible or are not providing an adequate response, the addition of amikacin, ciprofloxacin, or trimethoprim-sulfamethoxazole may be useful, but these measures also have not been properly evaluated.

The decision regarding therapy duration probably should be more conservative than that of *M. kansasii* pulmonary infection, realizing that response to therapy may not be as rapid or consistent, and ongoing immunosuppression may not allow for discontinuation of therapy. No data exist to provide clear recommendations.

Mycobacterium haemophilum

Recommendations for treating disseminated infection due to *M. haemophilum* are similar to those recommended for cutaneous disease. Rifampin plus clarithromycin and ciprofloxacin appear to be a reasonable initial regimen pending susceptibility test results. Once again, these drugs must be used with caution and in some circumstances will be contraindicated with drugs used for the patient's comorbidities. Alternative drugs, such as rifabutin, can be used to ameliorate or remove potentially dangerous drug interactions. For serious infections, intravenous amikacin and/or doxycycline may be added. Unlike cutaneous disease, treatment of disseminated disease often has been continued for 12–24 months, and if adequate immune recovery does not occur, therapy may be indefinite.

Mycobacterium genavense

Therapy for *M. genavense* infection is based on scattered cases in the literature. A regimen of clarithromycin and ethambutol, with or without rifabutin has been recommended. This disease primarily affects patients with AIDS whose CD4 cell count is below 50 cells/mm³, so immune recovery is expected to improve prognosis.

Mycobacterium chelonae

Mycobacterium chelonae disseminated infection should initially be treated with imipenem, tobramycin, and clarithromycin. Conversion to an oral regimen is difficult because of the high levels of resistance, but if susceptibility tests allow, clarithromycin may be combined with one or two other drugs, such as ciprofloxacin, doxycycline, or clofazimine, to complete a course of at least 6 months. *Mycobacterium chelonae* as a disseminated disease predominates in transplantation patients and patients receiving corticosteroids, and it often is characterized by

dozens of erythematous subcutaneous nodules in the extremities. Monitoring of therapy includes observing for resolution of these lesions, as well as any other constitutional symptoms the patient may have. Prognosis is good if the patient is able to be placed on at least two active drugs.

Prevention of Disease

Mycobacterium avium complex is the primary atypical mycobacteria species that has been demonstrated to be effectively prevented with pharmacotherapy in selected populations. It has been clearly demonstrated through prospective, randomized trials that pharmacotherapy with rifabutin, clarithromycin, or azithromycin can provide primary prevention of MAC disseminated infection in patients with AIDS whose CD4 cell count has fallen below 50 cells/mm³. Some of these trials have demonstrated that clarithromycin or azithromycin is superior to rifabutin in preventing disease. Furthermore, the CYP3A4 induction effects of rifabutin may complicate a patient's antiretroviral regimen. The United States Public Health Service recommends primary prophylaxis begin in patients with AIDS with CD4 cell counts of less than 50 cells/mm³ with either azithromycin 1200 mg orally each week or clarithromycin 500 mg orally 2 times/day. Alternatives include rifabutin 300 mg/day orally or a combination of azithromycin plus rifabutin in the same dosage stated. The weekly azithromycin regimen is clearly the preferred mode of prevention by most clinicians given the ease of administration and lack of significant drug interactions. Primary prevention can be discontinued if patients experience sustained immune recovery with CD4 cell counts greater than 100 cells/mm³ with highly active antiretroviral therapy. Primary prevention should be reinstated if the CD4 cell count again falls below 100 cells/mm³.

Conclusions

Although the pathogenesis, epidemiology, disease states, and clinical presentations of atypical mycobacterial infections are quite diverse, a common characteristic is their challenging pharmacotherapeutic management. The prolonged duration of antimicrobial therapy, variable response rates to therapy, and the pharmacological characteristics of the drugs involved place tremendous responsibilities on the clinician to manage compliance, adverse effects, and drug interactions while ensuring that the patient's condition is improving and the infection is being effectively treated.

United States Public Health Service and Infectious Diseases Society of America. 2001 USPHS/IDSA guidelines for the prevention of opportunistic infections in people infected with human immunodeficiency virus. 2001:1–64. Available at http://www.aidsinfo.nih.gov/guidelines/op_infections/OI_112801.pdf. Accessed June 1, 2004.

Oldfield EC, Fessel WF, Dunne MW, et al. Once weekly azithromycin therapy for prevention of *Mycobacterium avium* complex infection in patients with AIDS: a randomized, double-blind, placebo-controlled multicenter trial. Clin Infect Dis 1998;26:611–9.

Currier JS, Williams PL, Koletar SL, Cohn SE, Murphy RL, Heald AE. Discontinuation of *Mycobacterium avium* complex prophylaxis in patients with antiretroviral therapy-induced increases in CD4 cell count: a randomized, double-blind, placebo-controlled trial. Ann Intern Med 2000;133:493–503.

Annotated Bibliography

1. Wallace RJ, Glassworth J, Griffith DE, Olivier KN, Cook JL, Gordin F. Diagnosis and treatment of disease caused by nontuberculous mycobacteria. *Am J Respir Crit Care Med* 1997;156(suppl):S1–S25.

These guidelines were published by the American Thoracic Society (ATS) to serve as the authoritative source for information on diagnosing and managing atypical mycobacterial infection. Although focused on pulmonary infection, the guidelines include a fairly comprehensive overview of extrapulmonary infection. The committee members authoring the guidelines are the preeminent bench and clinical researchers for mycobacterial disease in North America. Although the guidelines have not been updated, most of the content remains relevant. Subsequent to publication, the most important new information has been produced for disseminated *Mycobacterium avium* complex (MAC) disease, particularly trials assessing the potential for discontinuation of therapy for active disease or prophylaxis.

2. Management of opportunist mycobacterial infections: Joint Tuberculosis Committee Guidelines 1999. Subcommittee of the Joint Tuberculosis Committee of the British Thoracic Society. *Thorax* 2000;55:210–18.

The guidelines published by the British Thoracic Society are the European counterpart to the ATS guidelines. The guidelines are not as comprehensive or exhaustive as the ATS guidelines. In general, the recommendations of the British Thoracic Society guidelines where possible are based on published clinical trials, whereas the ATS attempts to extrapolate data derived from susceptibility testing, case series, and the like to provide updated recommendations for mycobacterial diseases where clinical trial data are lacking. An example includes the approach each guideline takes with regard to the inclusion of clarithromycin into drug regimens for MAC or *Mycobacterium kansasii*. The 1997 ATS guidelines include clarithromycin as a first-line drug for MAC, regardless of disease presentation, and a favorable alternative for *M. kansasii* infection. The 1999 British Thoracic Society guidelines neither include clarithromycin as a first-line therapy for pulmonary infection in an HIV-negative patient, nor endorse clarithromycin as an alternative for *M. kansasii* infection. Information presented by the British Thoracic Society for mycobacterial diseases that are more prominent in Europe, such as pulmonary infection due to *Mycobacterium xenopi*, is of great value.

3. Horsburgh CR Jr. Disseminated *Mycobacterium avium* complex disease in patients infected with human immunodeficiency virus, 1985–2000. *Clin Infect Dis* 2001;33:1938–43.

This study clearly demonstrates the dramatic effect of clarithromycin and highly active antiretroviral therapy on outcomes of patients with acquired immune deficiency syndrome (AIDS) who developed disseminated MAC infection. This investigation included 1458 patients in Georgia to determine prognosis of patients with AIDS and disseminated MAC infection throughout much of the first 2 decades of the AIDS epidemic. The article chronicles the outcomes of these patients stratified by time frame of disease: before or after highly active antiretroviral therapy. Treatment with clarithromycin and highly active antiretroviral therapy were associated with a superior prognosis, using multivariate analysis.

4. Ustianowski AP, Lockwood DN. Leprosy: current diagnostic and treatment approaches. *Curr Opin Infect Dis* 2003;16:421–7.

This article provides an up-to-date, critical review of leprosy management. Discussion includes recent advances made in understanding therapeutic, socioepidemiological, and human immunodeficiency virus (HIV) coinfection roles. Drug regimens are critiqued thoroughly based on available data. The most valuable information presented for the clinical pharmacist includes concise recommendations for managing nerve damage, lepromatous reactions, and patient education.

5. Shafran SD, Mashinter LD, Phillips P, et al. Successful discontinuation of therapy for disseminated *Mycobacterium avium* complex infection after effective antiretroviral therapy. *Ann Intern Med* 2002;137:734–7.

The most recent advance in managing disseminated MAC infection in patients with AIDS is the demonstration by the authors that it is possible to discontinue therapy after at least 12–18 months if the patient demonstrates a sustained immune recovery after treatment with highly active antiretroviral therapy.

The study was a retrospective chart review in 13 Canadian HIV clinics, including 52 patients who received a median of 32 months of macrolide-based antimycobacterial therapy. At the time of diagnosis of disseminated MAC infection, the median CD4 cell count was 16 cells/mm³. When antimycobacterial therapy was discontinued, the median CD4 cell count was 230 cells/mm³. A median of 20 months after discontinuation of antimycobacterial therapy, only one patient had developed recurrent MAC disease. The other 51 were presumably free of MAC disease, and most continued to be virologically suppressed on highly active antiretroviral therapy with a median CD4 cell count of 288 cells/mm³.

SELF-ASSESSMENT QUESTIONS

Questions 1–5 pertain to the following case.

A 68-year-old man with a history of steroid-dependent chronic obstructive pulmonary disease and type 2 diabetes mellitus, comes to the emergency department with worsening shortness of breath for 5 weeks. He also complains of intermittent fevers, chills, and night sweats, and weight loss of 30 pounds over the past month (current weight 53 kg). His temperature in the emergency department is 38.4°C. Within the past 5 weeks, he has been treated twice with antibiotic drugs (first with cefuroxime axetil for 7 days, then azithromycin for 5 days) for presumed upper respiratory tract infections. Pertinent laboratory information available in the emergency department reveals a peripheral white blood cell count of 17,000 cells/mm³, with 78% neutrophils, 20% lymphocytes, and serum creatinine of 1.2 mg/dl. Chest radiography indicates severe bullous disease and patchy consolidation of the right upper lobe.

The patient is begun on ceftriaxone and azithromycin intravenously for possible community-acquired pneumonia and oxygen supplementation and a full evaluation for tuberculosis was performed. On day 3 of hospitalization, the second sputum specimen sent to the laboratory is positive by acid-fast smear. The patient is still febrile, still requiring the same amount of oxygen supplementation since admission, and has a white blood cell count of 19,000 cells/mm³.

1. Which one of the following mycobacteria, other than tuberculosis, should be highest on the differential of etiologies in this patient?
 - A. *Mycobacterium kansasii*.
 - B. *Mycobacterium genavense*.
 - C. *Mycobacterium avium* complex (MAC).
 - D. *Mycobacterium chelonae*.
2. Which one of the following tests can potentially confirm the diagnosis of *Mycobacterium tuberculosis* with excellent sensitivity and specificity from an acid-fast positive sputum smear within a few hours?
 - A. Nitrate reduction test.
 - B. Presence of yellow pigment.
 - C. Fluorescent microscopy.
 - D. Nucleic acid amplification.
3. Which one of the following infection control measures should be implemented at this point in the patient's treatment course?
 - A. Standard universal precautions.
 - B. "Gown and glove" procedures and standard respiratory isolation procedures.
 - C. Standard universal precautions and standard respiratory isolation procedures.
 - D. Standard universal precautions and standard contact isolation procedures.
4. The patient remained stable through 10 days of hospitalization, when a deoxyribonucleic acid probe of a sputum specimen with sufficient growth on culture revealed *M. kansasii*. Knowing this information, which one of following regimens should be initiated?
 - A. Isoniazid, rifampin, ethambutol, and pyrazinamide.
 - B. Isoniazid, rifampin, and ethambutol.
 - C. Cefoxitin and amikacin.
 - D. Clarithromycin, ethambutol, and rifabutin.
5. Which one of the following monitoring parameters is most important for this patient?
 - A. Periodic assessment of visual acuity.
 - B. Weekly metabolic profiles to monitor liver function.
 - C. Monthly complete blood cell counts to monitor platelet cell counts.
 - D. Compliance through directly observed therapy.

Questions 6–8 pertain to the following case.

A 35-year-old Hispanic man with history of acquired immune deficiency syndrome (AIDS) has just been diagnosed with disseminated disease due to MAC after presenting with complaints of 6–8 weeks of persistent fever, 20-pound weight loss, and generalized weakness. A blood culture obtained 10 days before at admission was reported with acid-fast bacilli (AFB), deoxyribonucleic acid probes confirmed identification the next day. Recent laboratory values include a white blood cell count of 3000 cells/mm³ with 42% neutrophils, serum creatinine of 1.0 mg/dl, and most recent CD4 count of 29 cells/mm³. The patient's most recent ultrasensitive human immunodeficiency virus (HIV) viral load test result was undetectable. The patient's current antiretroviral therapy consists of tenofovir 300 mg/day, lamivudine 300 mg/day, and lopinavir/ritonavir 3 tablets 2 times/day. The patient currently is receiving no MAC preventive therapy.

6. Which one of the following regimens is the best initial treatment of disseminated MAC in this patient?
 - A. Clarithromycin and rifabutin.
 - B. Isoniazid, rifabutin, and ethambutol.
 - C. Clarithromycin, ethambutol, and rifampin.
 - D. Clarithromycin and ethambutol.
7. Assuming a rapid clinical response to antimycobacterial therapy, which one of the following attitudes regarding therapy duration is most accurate?
 - A. Therapy should last indefinitely, unless the patient's CD4 cell count is persistently higher than 100 cells/mm³ (immune reconstitution) after 12 months of therapy.
 - B. Therapy should last indefinitely whether or not immune reconstitution occurs.
 - C. Therapy duration should be 12–18 months with or without immune reconstitution.
 - D. Therapy duration should be 12–18 months with or without immune reconstitution, then clarithromycin 500 mg/day alone indefinitely.
8. This patient was at risk for MAC infection, but was not receiving preventive pharmacotherapy. Which one of the following preventive regimens is considered among the “regimens of choice”?
 - A. Rifampin 300 mg/day.
 - B. Clarithromycin 500 mg/day.
 - C. Trimethoprim-sulfamethoxazole one double-strength tablet daily.
 - D. Azithromycin 1200 mg once weekly.

Questions 9–11 pertain to the following case.

A 70-year-old woman goes to the thoracic surgery clinic for follow-up after having a coronary artery bypass graft procedure several weeks ago. Two weeks before this clinic visit, a 7-day course of amoxicillin-clavulanate failed to resolve an apparent thoracic incision site surgical wound infection. After the unsuccessful antibiotic drug course, the

surgeon sent drainage from a dehiscence area for culture. Six days after the culture was sent, colonies visible to the naked eye were present on standard mycobacteria agar media.

9. An organism that produces colonies visible to the naked eye on standard mycobacteria agar media routinely in less than 1 week includes which one of the following?
 - A. *Mycobacterium tuberculosis*.
 - B. *Mycobacterium chelonae*.
 - C. *Mycobacterium ulcerans*.
 - D. *Mycobacterium marinum*.
10. It subsequently is determined that the organism is *Mycobacterium fortuitum*. The patient is taken to the operating room for an incision and drainage procedure. On entering the infected area, minimal purulence is noted, but a 1-cm inferior portion of the sternum appeared soft and malleable. Involved areas are appropriately resected. When the patient is transferred from the operating room to the intensive care unit, she is hemodynamically stable with a normal metabolic profile and complete blood cell count. Infectious diseases service is consulted. Which one of the following antimicrobial regimens is recommended?
 - A. Clarithromycin 500 mg/day plus trimethoprim-sulfamethoxazole one double-strength tablet 2 times/day.
 - B. Imipenem 500 mg intravenously every 6 hours plus amikacin 7.5 mg/kg intravenously every 24 hours.
 - C. Isoniazid 300 mg/day, rifampin 600 mg/day, and ethambutol 15 mg/kg/day.
 - D. Imipenem 500 mg intravenously every 6 hours plus ethambutol 15 mg/kg/day.
11. Which one of the following statements regarding clinical outcomes in disease caused by rapidly-growing mycobacteria is true?
 - A. *Mycobacterium abscessus* is the most difficult species to treat.
 - B. Disseminated infection due to *M. chelonae* is fatal in a majority of patients.
 - C. A regimen of isoniazid and rifampin is recommended for serious infections due to *M. abscessus*.
 - D. Mild cutaneous infection due to *M. fortuitum* can be routinely treated with doxycycline monotherapy.

Questions 12–14 pertain to the following case.

A 42-year-old woman who immigrated to North America 3 months ago from Southeast Asia goes to the emergency department with numerous skin lesions suspected to be due to *Mycobacterium leprae*. She recently developed anesthetic symptoms at some involved areas. Most noticeable are dime-sized necrotic lesions on three of her fingers on the left hand.

12. Which one of the following antimicrobial regimens should be recommended, based on United States

- Department of Health and Human Services recommendations?
- Dapsone 100 mg/day, rifampin 600 mg/day, and clofazimine 50 mg/day.
 - Dapsone 100 mg/day and rifampin 600 mg/day.
 - Dapsone 100 mg/day, minocycline 100 mg/day, and clofazimine 50 mg/day.
 - Rifampin 600 mg/day and clofazimine 50 mg/day.
- A member of the patient's health care team remembers reading about a one-time dose therapy consisting of rifampin, ofloxacin, and minocycline and asks about the applicability to this case. Which one of the following responses is most accurate?
 - This regimen has been evaluated for multibacillary disease but is not considered a regimen of choice to date.
 - This regimen has only been evaluated for paucibacillary disease and, thus, is not relevant to this case.
 - This regimen has been ineffective for treating any form of *M. leprae* infection.
 - This regimen has been effective for treating multibacillary disease, but resistance rates to ofloxacin are high in Southeast Asia.
 - The leprosy treatment recommendations of the World Health Organization primarily differ from those of the United States Department of Health and Human Services in which one of the following manners?
 - Antimicrobial drugs used.
 - Therapy duration.
 - Monitoring parameters.
 - Prophylaxis of contacts.
 - A 4-year-old child, otherwise healthy, is taken to the family medicine clinic with a swollen cheek as the only symptomatology. He has a cervical lymph node excised because of lymphadenitis. Nucleic acid amplification is negative for *M. tuberculosis*. Cultures are pending. Which one of the following options should be the next course of action?
 - Clarithromycin, ethambutol, and rifampin.
 - Isoniazid, ethambutol, and rifampin.
 - No drug therapy should be initiated.
 - Isoniazid, rifampin, streptomycin, and levofloxacin.
 - A 45-year-old man, who receives chronic prednisone (20 mg orally every day) and sirolimus therapy after lung transplantation 1 year ago, is diagnosed with disseminated *M. kansasii* infection. He goes to the clinic with progressive fatigue and a hemoglobin level that has fallen from 11.7 g/dl 2 months before presentation to 9.2 g/dl at presentation. The patient is otherwise stable. Which one of the following regimens should be initiated?
 - Isoniazid, rifabutin, and ethambutol.
 - Isoniazid, rifampin, and ethambutol.
 - Isoniazid and clarithromycin.
 - Ethambutol, rifampin, and clarithromycin.
 - A 62-year-old kidney transplantation patient goes to the emergency department with a 3-month history of progressive shortness of breath, which has been progressing more rapidly for the past week. He is placed on ceftriaxone and azithromycin for community-acquired pneumonia. His respiratory status worsens over the next 48 hours to the point of requiring intubation. The patient is placed empirically on isoniazid, ethambutol, rifampin, and pyrazinamide. Six days after intubation, his respiratory status has not changed, and a bronchoscopy is performed. The microbiology laboratory reports a few hours later that a bronchoalveolar lavage specimen is positive for 1+ AFB on a Ziehl-Neelson stain. Infectious diseases service is asked to provide a differential diagnosis. Which one of the following microbial etiologies is effectively ruled out at this point?
 - Mycobacterium tuberculosis*.
 - Mycobacterium avium* complex.
 - Nocardia asteroides*.
 - Mycobacterium goodii*.
 - A 45-year-old commercial fisherman with no significant medical history has been diagnosed with *M. marinum* infection presenting as several nodular skin lesions in his right hand and arm, after a lymphatic spread. Which one of the following treatments is best?
 - Surgical excision.
 - Clarithromycin plus rifampin.
 - Doxycycline alone.
 - Clarithromycin alone.
 - A patient has been in respiratory isolation for a right upper lobe cavitary lesion on chest radiography that is suspicious for active tuberculosis. The patient has remained on 6 L of oxygen by nasal cannula with poor appetite and intermittent low-grade fever for almost a week. Microbiology reports that a rapid-growing mycobacteria has appeared on a sputum culture that is 4 days old. Which one of the following considerations is the best therapy option at this point?
 - The lung is a rare site of infection for rapid-growing mycobacteria; this laboratory report should be noted but no action should be taken.
 - Continue respiratory isolation at this point, and begin clarithromycin, isoniazid, rifampin, and ethambutol.
 - Remove respiratory isolation and begin empiric therapy with imipenem, clarithromycin, and amikacin.
 - Remove respiratory isolation at this point, but withhold therapy until identification of the organism is available.

20. Which one of the following cases can be treated with just 2–4 months of antimycobacterial therapy in an immunocompetent individual?
- A 52-year-old man with chronic obstructive pulmonary disease and pulmonary infection due to MAC.
 - A 45-year-old abdominal gunshot wound victim receiving total parenteral nutrition with a catheter-related infection due to *M. fortuitum*.
 - A 32-year-old Brazilian woman from a remote, underdeveloped village with multibacillary leprosy.
 - A 60-year-old Scandinavian man with bronchiectasis and pulmonary infection due to *Mycobacterium xenopi*.

Questions 21 and 22 pertain to the following case.

A 56-year-old woman taking warfarin and etanercept for recent-onset atrial fibrillation and rheumatoid arthritis, respectively, has been treated for 4 weeks with clarithromycin, rifampin, levofloxacin, and amikacin for right knee septic arthritis determined to be because of *Mycobacterium haemophilum*. Throughout the course of antibiotics, the patient's primary care team has been having difficulty keeping her warfarin therapy therapeutic, and the patient's international normalized ratios have been 1.1–1.3.

21. Which one of the following therapy recommendations is best to continue throughout the remainder of the course?
- Continue current therapy and adjust warfarin therapy accordingly with increased doses.
 - Discontinue rifampin and amikacin therapy and continue with clarithromycin, levofloxacin, and rifabutin for the course duration.
 - Replace rifampin with rifabutin to presumably reduce the severity of metabolic induction of warfarin.
 - Replace clarithromycin with azithromycin to presumably improve control of warfarin's effect on the patient's international normalized ratio.
22. The patient is seen in orthopedic surgery clinic 2 months into treatment with an apparent good response. Normalization of the Westergren erythrocyte sedimentation rate has occurred, and a repeat culture of synovial fluid aspirate is still negative after 2 weeks. The orthopedic surgeon requests clarification regarding duration of antimycobacterial therapy. Which one of the following recommendations is best?
- Therapy can be discontinued if the repeat culture of the synovial fluid aspirate remains negative after 4 weeks.
 - Septic arthritis typically is treated for 4–6 weeks, so treatment should be stopped at this point.
 - Therapy should continue for a total of 12–18 months.
 - Therapy may need to be indefinite if the patient's level of immunosuppression remains similar.
23. A 38-year-old woman with HIV infection has been receiving antiretroviral drug therapy consisting of

zidovudine, lamivudine, and efavirenz since her initial diagnosis 1 year ago. At that time, she had *Pneumocystis carinii* pneumonia, a CD4 cell count of 42 cells/mm³, and an HIV viral load of 46,000 copies/ml. In addition to her antiretroviral drug therapy, she receives trimethoprim-sulfamethoxazole daily and azithromycin weekly. Her CD4 cell counts have been 45, 52, 80, and 98 cells/mm³ at 3, 6, 9, and 12 months, respectively, of antiretroviral drug therapy with an undetectable HIV viral load until the most recent measurement, which was a low but detectable level of 2290 copies/ml. Which one of the following suggestions regarding azithromycin therapy is best for this patient?

- Azithromycin should be changed to clarithromycin to optimize prevention of disseminated MAC infection.
 - Azithromycin therapy should be discontinued with her sustained virological and immunological response.
 - Azithromycin should continue until the patient's CD4 cell count achieves a persistent level of more than 100 cells/mm³.
 - Azithromycin should continue indefinitely regardless of the effect of antiretroviral drug therapy.
24. A 52-year-old man with chronic obstructive pulmonary disease and alcoholic liver disease has been treated for *M. kansasii* pulmonary infection for 2 months when he goes to the clinic for follow-up. His antimycobacterial regimen has been isoniazid, rifampin, and ethambutol. At this visit, serum aspartate aminotransferase has risen from a baseline of 63 mmol/ml to 438 mmol/ml (upper limit of normal is 50 mmol/ml), serum alanine aminotransferase has risen from a baseline of 25 mmol/ml to 162 mmol/ml (upper limit of normal is 30 mmol/ml), and the patient's prothrombin time has increased from a baseline of 19 to 28 seconds. The patient is relatively asymptomatic, reporting no noticeable abdominal pain or distension. He notes that his previous breathing difficulties have improved with therapy and it appears that he has returned to his baseline. Which one of the following actions should be undertaken?
- No change should be made to the regimen as the patient is asymptomatic.
 - Therapy should continue, with a reduction of rifampin from 600 mg/day to 300 mg/day.
 - Isoniazid should be replaced by clarithromycin for the remainder of treatment.
 - Rifampin should be replaced by levofloxacin for the remainder of treatment.
25. A pulmonologist requests consultation on the necessity of ordering susceptibility testing for a patient with pulmonary infection due to *M. kansasii*. The most accurate statement regarding the current status on susceptibility testing of atypical mycobacteria to

convey to the pulmonologist is which one of the following?

- A. Testing has been standardized for most of the clinically relevant atypical mycobacteria but has not been linked to clinical outcomes.
- B. Testing has been linked to clinical outcomes for most of the clinically relevant atypical mycobacteria.
- C. Testing has not been standardized for most of the clinically relevant atypical mycobacteria.
- D. Testing has been standardized for most of the clinically relevant atypical mycobacteria but for only first-line antituberculous drugs.

