Nontuberculous Mycobacterial Infections in Children

Jyotsna Bhattacharya, MD,* Sindhu Mohandas, MBBS,* David L. Goldman, MD†
*Department of Pediatric Infectious Diseases and †Department of Pediatrics and Microbiology and Immunology, Children’s Hospital at Montefiore/Albert Einstein College of Medicine, Bronx, NY

Education Gaps

1. Outbreaks of nontuberculous mycobacterial infections have been increasingly reported following cosmetic procedures performed abroad. Failure to recognize this association can lead to inappropriate or delayed therapy. (1)

2. The emergence of drug resistance in specific species of nontuberculous mycobacteria infections (especially Mycobacterium abscessus) complicates medical therapy. Appropriate treatment of these infections involves the identification of a specific species and drug resistance testing. (2)

Objectives

After completing this article, readers should be able to:

1. Recognize the major clinical features associated with nontuberculous mycobacteria (NTM) infections in children.

2. Recognize that NTM infections are a potential risk related to medical tourism for cosmetic surgery.

3. Understand the strengths and weaknesses of currently available diagnostic methods.

4. Plan the appropriate management of NTM infections based on the specific clinical presentation and mycobacterial species.

INTRODUCTION

Nontuberculous mycobacteria (NTM) include all mycobacteria other than Mycobacterium tuberculosis, Mycobacterium bovis, and Mycobacterium leprae. Children are constantly exposed to NTM, yet clinical signs of infection are unusual. NTM exist primarily in the environment, causing human disease as opportunistic pathogens in the appropriate clinical context. Lymphadenitis is far and away the most common manifestation of NTM disease in children. Other, less common, manifestations include skin and soft tissue infections (SSTIs), lung infections, and disseminated disease. Since the last review of NTM disease in Pediatrics in Review, (3) several important developments have occurred,
including changes in the epidemiology and treatment, which are reviewed herein.

**MICROBIOLOGY AND CLASSIFICATION**

Currently there are more than 170 recognized NTM species, although a limited number of species cause human disease. It survives inside amoeba, and the traits that promote this process may also allow for successful macrophage infection. (4) Several characteristics promote both persistence in the environment and human disease. The lipid mycolic acid outer membrane is responsible for the acid-fast bacillus (AFB) staining feature of NTM (Fig 1). It confers a hydrophobic nature to the organism, which has been linked to changes in organism aggregation and enhanced aerosolization. (5) The hydrophobic NTM membrane also promotes surface adherence and helps restrict entry of antibiotics and disinfectants into the cell. NTM form biofilms that promote surface attachment and persistence of the organism in water systems (ie, pipes, showerheads) and catheters. (6) Other traits that have been linked with the NTM persistence in the environment include the ability to grow in a variety of hostile conditions, such as low oxygen concentrations, low organic matter concentrations, high temperatures, and low pH. (7)(8)(9)

Typically, NTM are categorized by their growth characteristics into 2 categories: slowly growing (SGM) and rapidly growing (RGM) mycobacteria species. RGM demonstrate visible growth in culture media within 7 days, whereas SGM take weeks to exhibit growth. Certain species are particularly slow growers (eg, *Mycobacterium ulcerans* and *Mycobacterium genavense*) and may take 8 to 12 weeks to grow. (10) The NTM species commonly implicated in human disease are listed in Tables 1 and 2. Growth characteristics along with colony pigmentation are used to sort NTM into groups using the Runyon classification system. Definitive speciation of NTM isolates using standard microbiological techniques is often not possible. As a result, species with similar phenotypic characteristics have historically been grouped into complexes (ie, *Mycobacterium avium* and *Mycobacterium abscessus* complex). Newer molecular assays (see later herein) have led to improved discrimination of NTM at the species and subspecies levels.

**EPIDEMIOLOGY**

NTM are found in a wide range of environmental sites, and disease is acquired primarily through exposure to these sites, including soil and water (ie, drinking water, household plumbing, drainage waters, and natural waters). (6)(11) These organisms are easily aerosolized in droplets and also survive in dust particles, both of which serve as a source for pulmonary infection. Aerosols containing high densities of NTM are found around areas with splashing water, including sinks and showers. Human-to-human and animal-to-human transmissions are thought not to occur or to occur rarely. A recent whole genome sequencing study of respiratory NTM isolates indicates the possibility of human-to-human transmission, although more study is needed in this area. (12) Health-care–associated transmission can also occur after dental, surgical, and cosmetic procedures. (13)(14)

Pediatric studies during the past decade show NTM disease incidence rates ranging from 0.84 per 100,000 in Australia to 3.1 per 100,000 in Germany. (15)(16) Many but not all studies report an increasing incidence of NTM disease, although it is unclear whether this reflects a true increase in disease or a result of improved diagnostics. (17)(18)(19) An increase in the number of susceptible children due to new immunomodulatory therapies may have also contributed to this increased incidence. Seasonal variation in the incidence of NTM lymphadenitis and SSTIs with a higher incidence in the late winter and early spring has been reported. (20) Outbreaks of NTM disease can occur in both cystic fibrosis (CF) centers and in the context of contaminated medical equipment. (14)(21)

Severe NTM disease occurs with immunodeficiency and chronic lung disease. In immunocompromised children, NTM infections may present in both localized and nonlocalized forms. Effective immunity against

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**Figure 1.** Acid-fast bacillus stain of tissue from a patient that subsequently grew *Mycobacterium chelonae*. (Image provided by Dr Michael Levi [Montefiore Hospital, Bronx, NY]).
NTM involves a coordinated response among T cells, natural killer cells, and macrophages. Macrophage infection with NTM results in interleukin-12 production that stimulates interferon-\(\gamma\) (IFN-\(\gamma\)) by T cells and natural killer cells. In turn, IFN-\(\gamma\) activates macrophages to limit organism growth. Children with defects in T-cell immunity (ie, AIDS) or the interleukin-12/IFN-\(\gamma\) pathway are, therefore, at risk for severe disease. (22) An increased incidence of NTM infections has been observed in both hematopoietic stem cell and solid organ transplant recipients. Lung transplant recipients are disproportionately affected by NTM-associated pneumonia, presumably due to previous colonization of the donor lung and augmented immunosuppression. Similar to \(M\) \(tuberculosis\) infections, tumor necrosis factor–blocking agents seem to increase the risk of NTM infections, although additional studies are needed.

### TABLE 1. Slowly Growing Mycobacteria

<table>
<thead>
<tr>
<th>SPECIES</th>
<th>PULMONARY DISEASE</th>
<th>SSTI</th>
<th>PHYSICAL EXAMINATION</th>
<th>OTHER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mycobacterium avium complex</td>
<td>• Frequently isolated in patients with cystic fibrosis</td>
<td>• Most common cause of cervical adenitis</td>
<td>• Nodules, pustules, or plaques</td>
<td>• Nodules, pustules, ulcers, and abscesses</td>
</tr>
<tr>
<td>Mycobacterium kansasii</td>
<td>• More frequent in patients with HIV and older individuals with COPD</td>
<td>• Infrequent</td>
<td>• Nodules, pustules, ulcers, and abscesses</td>
<td>• May resemble sporotrichosis</td>
</tr>
<tr>
<td>Mycobacterium marinum</td>
<td>• Exposure to fresh or salt water and marine animals</td>
<td>• Swimming pool granuloma</td>
<td>• Solitary, red to violaceous papule or nodule that progresses to a shallow ulceration</td>
<td>• Occasionally in a sporotrichotic distribution</td>
</tr>
<tr>
<td>Mycobacterium ulcerans</td>
<td>• Buruli ulcer</td>
<td>• Endemic in Africa, Southeast Asia, Australia, and South and Central America</td>
<td>• Chronic ulcerative skin disease</td>
<td></td>
</tr>
</tbody>
</table>

COPD=chronic obstructive pulmonary disease; HIV=human immunodeficiency virus; SSTI=skin and soft tissue infection.

### TABLE 2. Rapidly Growing Mycobacteria

<table>
<thead>
<tr>
<th>SPECIES</th>
<th>PULMONARY</th>
<th>SSTI</th>
<th>PHYSICAL EXAMINATION</th>
<th>OTHER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mycobacterium abscessus complex</td>
<td>• Severe pneumonia in children with cystic fibrosis</td>
<td>• Commonly implicated</td>
<td>• Multiple lesions that may be purple, persistent-drainage abscesses</td>
<td>• Three subspecies with different susceptibility patterns, especially to macrolides</td>
</tr>
<tr>
<td>Mycobacterium chelonae</td>
<td>• Colonization common</td>
<td>• Disease rare</td>
<td>• Tattooing</td>
<td>• Catheter-related infections</td>
</tr>
<tr>
<td>Mycobacterium fortuitum</td>
<td>• Colonization common</td>
<td>• Less frequent cause of disease</td>
<td>• Surgical procedures</td>
<td>• More likely to present as a single lesion</td>
</tr>
</tbody>
</table>

SSTI=skin and soft tissue infection.
to better characterize this association. (10) In addition to immunodeficiency, children with chronic lung disease, especially those with cystic fibrosis (CF)– and non-CF–related bronchiectasis are at increased risk for NTM pulmonary disease. (23) The basis for this enhanced susceptibility is poorly understood but may be related to damage to the respiratory mucosa, which allows for increased adhesion by the organism and changes in the local microbiota. (24) (25) Because of the close association between NTM and non-CF bronchiectasis, some have hypothesized that NTM infection may actually cause bronchiectasis (reviewed in the article by Bonaiti et al [26]). Other forms of chronic respiratory disease that have been associated with NTM infection include conditions that are more common in adults, such as α₁-antitrypsin deficiency chronic obstructive pulmonary disease, α₁-antitrypsin anomalies, Lady Windermere syndrome, and pneumoconiosis (reviewed in the article by Chan and Iseman [27]). Risk factors for NTM disease are shown in Table 3.

NTM INFECTIONS

Lymphadenitis
Chronic cervicofacial adenitis (affecting the superior anterior cervical or submandibular nodes) is the most common manifestation of NTM adenitis. Less commonly, posterior cervical nodes may also be involved. (28) NTM adenitis outside the cervicofacial region (ie, axillary and inguinal nodes) is described but is relatively uncommon (1.6% of all cases in 1 study). (29) The precise mechanism by which the organism is acquired from the environment and comes to infect the lymph node is poorly understood. Infection typically occurs in children aged 1 to 5 years and progresses over weeks to months in a subacute manner. NTM adenitis is generally unilateral and not associated with fever or systemic symptoms. (20)(30) This contrasts with M. tuberculosis adenitis, which tends to occur in older children and adolescents and is often associated with systemic symptoms. Local signs and symptoms of NTM adenitis include firmness, erythema, fluctuance with a violaceous skin discoloration, and even fistula formation. Typically, NTM adenitis is less painful than bacterial adenitis. Suppuration with the development of chronic sinus tracts may complicate NTM adenitis and also cause damage to the facial nerve, especially with preauricular disease. (28) The diagnosis (see later herein) is usually made in the context of children who are initially treated with antistaphylococcal antibiotics but who do not respond appropriately. The most common species of NTM causing adenitis in the United States belong to the MAC group, which includes M. avium and Mycobacterium intracellulare. A variety of other species have been reported to cause adenitis, including but not limited to Mycobacterium scrofulaceum, Mycobacterium haemophilum, Mycobacterium malmoense, and Mycobacterium kansasii. (20)

NTM Skin and Soft Tissue Infections
The next most common form of pediatric NTM disease, SSTIs, occur in both healthy and immunocompromised children. SSTIs secondary to NTM typically exhibit less erythema and tenderness compared with pyogenic infections. Both RGM and SGM cause skin and subcutaneous tissue infections (Fig 2). NTM SSTIs usually result from direct inoculation of the organism into soft tissue. The most common portals of entry are skin abrasions, open injuries, fractures, surgical or injection sites, puncture wounds (stepping on a nail), and even combat-related injuries (ie, high-impact blast) with environmental wound contamination. (31) Abscess formation, which may be painful, and drainage can occur at the affected site, especially with infections due to RGM species. Importantly, skin involvement may be a

### TABLE 3. Risk Factors for NTM Disease

<table>
<thead>
<tr>
<th>LUNG CONDITION</th>
<th>IMMUNOLOGIC DEFECTS</th>
<th>EXPOSURE TO HIGH NTM CONCENTRATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystic fibrosis</td>
<td>HIV/AIDS</td>
<td>Nosocomial exposures (medical equipment)</td>
</tr>
<tr>
<td>Non–cystic fibrosis</td>
<td>Common variable immunoglobulin deficiency syndrome</td>
<td>Showerheads, indoor hot tubs, water heater temperatures ≤122°F (≤50°C)</td>
</tr>
<tr>
<td>α₁-antitrypsin deficiency</td>
<td>Genetic defects in interferon-γ receptors or interleukin-12</td>
<td>Potting soils, particularly those enriched with peat</td>
</tr>
<tr>
<td>Pulmonary alveolar proteinosis</td>
<td>Biological anti-inflammatory agents</td>
<td>Livestock, seawater</td>
</tr>
</tbody>
</table>

HIV = human immunodeficiency virus; NTM = nontuberculous mycobacteria.
representation of disseminated disease in immunocompromised hosts.

Direct inoculation may result in localized infections at other sites, including tendon sheaths, bursae, joints, and bones. *Mycobacterium marinum* is the most common NTM that causes tenosynovitis, with infection usually involving the hands and wrists. (32) Other NTM that cause tenosynovitis include *Mycobacterium fortuitum, M abscessus, Mycobacterium chelonae,* and *M kansasii.* Deep tissue infections have been reported after cardiac surgery, including osteomyelitis of the sternum. (33)

**Cosmetic Procedures.** Recently, RGM infections have increasingly been reported after cosmetic procedures performed abroad in developing countries. (34) In these instances, infection is likely acquired as a result of a breeched sterile procedure and exposure to nonsterile water. A multistate US outbreak was reported in 2013 with 21 cases of NTM infections after cosmetic procedures performed in the Dominican Republic. The procedures included liposuction, breast surgery, buttock augmentation, and abdominoplasty. Thirteen of the 21 patients had the procedures performed at the same clinic. The most common cause of the infection was *M abscessus,* followed by *M fortuitum.* (34) Patients with these types of infection can present with deep-seated or superficial wound infections with tender erythematous nodules, pustules, and abscesses. Systemic signs and symptoms are usually less prominent. The wounds usually involve the incision sites with raised granulomatous tissue. Erythema, wound dehiscence, and purulence may be present (Fig 3).

Affected patients are often unsuccessfully treated for other bacterial disease before a diagnosis of RGM SSTI is considered. These infections have nonspecific clinical features, and a high index of suspicion is necessary to correctly diagnose, treat, and limit the spread of disease. When clinicians suspect RGM infection in medical tourists, adequate specimens should be collected in addition to notifying the laboratory so that special techniques can be used for optimal recovery of these organisms: *M chelonae, M fortuitum,* and *M abscessus.* Also, SSTIs have been reported in association with nonsurgical cosmetic procedures. *M chelonae* and *M abscessus* infections have been described with tattooing. *M haemophilum* infection has been described with permanent eyebrow makeup. (37)

**Buruli Ulcer.** *M ulcerans* is an extremely common mycobacterial disease worldwide and is the cause of Buruli ulcer. This diagnosis should be considered in travelers, especially to tropical regions. Most cases are reported from West and Central Africa and Australia. (39) *M ulcerans* infection usually begins as a painless nodule or papule on an

![Figure 2. A 17-year-old girl with systemic lupus erythematosus receiving immunosuppressive therapy presented with erythematous palpable nodules of the lower extremity. Pathology was significant for necrotizing granuloma. A tissue block was sent to the Centers for Disease Control and Prevention (CDC) and was confirmed by polymerase chain reaction and sequencing to be *Mycobacterium chelonae* infection. (Image provided by Dr Diana H. Lee [Children’s Hospital at Montefiore, Bronx, NY]).](http://pedsinreview.aappublications.org/)

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extremity that goes on to ulcerate. Primary involvement of the head, neck, and genitals also occurs. The hallmark of this disease is extensive ulceration leading to scarring, limb contractures, and disfigurement. Antimicrobial drug treatment for *M ulcerans* infection may produce an initial clinical worsening before a positive response. (40)

Pulmonary Infections

**CF- and Non-CF–Associated Bronchiectasis.** NTM pulmonary disease most often occurs in children with preexisting lung disease, especially CF, and children with non-CF–related bronchiectasis or immunodeficiency. Infections in lung transplant recipients are also well described. (41) Pulmonary NTM infection is rare in otherwise healthy children. The potential for outbreaks of NTM pulmonary disease in CF centers has been highlighted in recent studies. (12)(42) Most children have fever, weight loss, and fatigue. In children with underlying lung disease, increasing cough, sputum production, waning exercise intolerance, and deterioration in pulmonary function may be indications of pulmonary NTM disease. (43)(44) The most frequently isolated NTM in patients with CF is MAC, followed by *M abscessus* complex, although the relative proportions of these isolates vary by geographic area. (43)(44) In general, *M abscessus* pulmonary infections tend to be more virulent than MAC infections and are more likely to be associated with invasive disease and deterioration of pulmonary function. A range of radiologic features has been reported in association with pulmonary NTM disease. In children with CF, small pulmonary nodules with bronchiectasis is the most common radiologic presentation. (45) A tree-and-bud pattern may also be present on computed tomographic scans, reflecting bronchiolar disease. Importantly, these features are not specific for NTM and can be seen with infections secondary to a variety of pathogens. Other radiologic presentations of NTM lung disease include fibrocavitary lesions (indistinguishable from *M tuberculosis* disease) and large nodules that can be confused with malignancy. (45)(46)

**Hot Tub Lung.** A hypersensitivity pneumonitis, also known as hot tub lung, occurs in immunocompetent adults and children after bathing in hot tubs, where NTM are well suited to grow. Aerosolization of NTM by water jets can result in high inocula exposures, and in some individuals, an overexuberant inflammatory response ensues. (47)(48) The radiologic appearance of hot tub lung is extensive ground glass opacification or consolidation along with centrilobular nodularity.

**Disseminated Disease**

Disseminated NTM infections typically occur in immunocompromised children, including those with a defect in
cellular immunity and in the gamma interferon pathway. Other conditions associated with disseminated NTM infection include hematologic malignancy and the immunosuppression used for organ transplant recipients. During the AIDS epidemic, the incidence of disseminated disease dramatically increased in both children and adults. (49) However, with the introduction of highly active antiretroviral therapy (HAART), the incidence has greatly decreased.

The most common NTM associated with disseminated disease is MAC (>90%). (10)(50) In children with human immunodeficiency virus (HIV) infections, disseminated MAC occurs in the context of extremely depressed T-cell numbers. Disseminated disease may occur in the context of SSTIs and pulmonary infections, especially those secondary to NTM rapid growers. Skin lesions may be the earliest manifestation of disseminated disease in immunocompromised patients.

**NTM-Associated Immune Reconstitution Inflammatory Syndrome.** NTM-associated immune reconstitution inflammatory syndrome (IRIS) occurs in immunosuppressed individuals and results from an enhanced immune response (in the context of HAART or reduction of immunosuppression in organ transplant recipients) against residual NTM organisms or antigens. NTM-related IRIS should be considered in the first few weeks to months after starting antiretroviral therapy. (51) Affected individuals may or may not have a previous diagnosis of NTM infection. Common presentations include lymphadenitis (peripheral, intrathoracic, or intra-abdominal), fever, and night sweats. IRIS may also present as pulmonary infiltrates and hepatosplenomegaly. (52)

**Catheter-Associated Infections.** Biofilm formation along with environmental contamination and inadequate sterilization procedures promote catheter- and medical device-associated infections. A systematic breakdown in infection control procedures can lead to outbreaks of disease. (53)(54) This situation must be carefully distinguished from pseudo-outbreaks, in which laboratory contamination of specimens results in repeated positive cultures. (55) Catheter-associated bloodstream infections secondary to NTM occur in both immunocompetent and immunocompromised patients (especially those with hematologic malignancies). (56) These infections are often due to RGM (ie, *Mycobacterium mucogenicum*, *M fortuitum*, and *M abscessus*). (10)(57) Most patients are febrile but not necessarily neutropenic. (58) Catheter-associated infections may also result in peritonitis and exit site infections in children receiving peritoneal dialysis. (59)(60) In patients with ventriculoperitoneal shunts, meningitis can occur. (61) Recently, invasive NTM disease has been reported in association with the use of heater-cooler devices during cardiothoracic surgery. (62)

**DIAGNOSIS**

AFB (Ziehl-Neelsen or Kinyoun methods) and fluorochrome staining are used to detect mycobacterial organisms in tissue, with the latter technique being more sensitive. Tuberculin skin testing has been reported to have a wide range of sensitivity (30%–60%) in the diagnosis of NTM disease (reviewed in the study by Zimmermann et al [63]). This assay has limited utility in distinguishing between NTM and *M tuberculosis* infections. An interferon-γ release assay (IGRA) is more specific than tuberculin skin testing and is useful in differentiating tuberculous and NTM infections, especially in areas with a low prevalence of tuberculosis. (64)(65) For most NTM infections, including MAC, the results of the QuantiFERON test (Qiagen, Hilden, Germany) should be negative. However, false-positive results have been described for specific strains of NTM that express specific antigens with substantial homology to those expressed by *M tuberculosis*. (66)(67)(68) Furthermore, interpretation of both tuberculin skin testing and IGRA assays is not possible in the context of simultaneous infections with both pathogens, which occurs more frequently in areas of high tuberculosis prevalence. (66) For children younger than 5 years, who are most likely to have NTM lymphadenitis, there are limited data on the utility of IGRA.

Specimens for NTM isolation are cultured using both solid and liquid media. For nonsterile specimens, decontamination should be performed to prevent bacterial or fungal overgrowth. Certain NTM species may be difficult to grow in the laboratory because they have specific nutritional requirements, requiring media supplementation. In addition, individual species may grow very slowly. Thus, the laboratory should be alerted when NTM disease is being considered. Strict adherence to laboratory protocols is necessary for processing culture specimens because laboratory contamination (especially with tap water) is a well-recognized cause of pseudo-outbreaks. (55)(69)

The gold standard for diagnosis is the isolation of the organism in culture, which also allows for drug susceptibility testing. However, a negative culture does not exclude disease (Table 4). Multiple molecular methods have been developed to detect NTM. Polymerase chain reaction probes that allow for detection of organisms in fixed and unfixed tissue specimens are commercially available for some species (eg, MAC, *M kansasii*, and

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Mycobacterium gordonae), but not all. Matrix-assisted laser desorption/ionization–time of flight (MALDI-TOF) has been studied for the diagnosis and differentiation of NTM species, although specific species and subspecies identification is limited. (70)(71) 16S rRNA gene sequencing is useful in these circumstances, but occasionally multigene (ie, hsp65, rpoB, and secA) or whole genome sequencing is needed for definitive identification of certain species and subspecies. (71)(72)(73) Species/subspecies identification can be critical in guiding initial treatment. For example, among Mycobacterium abscessus complex organisms, M. abscessus subsp. abscessus and subsp. bolletii are notable for resistance to multiple antibiotic agents, including inducible resistance to macrolides, coded by an erythromycin methylase gene.

Adenitis and SSTI
The preferred approach to the diagnosis of NTM adenitis is excision of the affected node, because incision and drainage can be complicated by fistula formation. Pathologic examination of affected tissue often reveals AFB with caseating or noncaseating granulomas. However, staining and pathology studies do not distinguish between disease due to NTM and M. tuberculosis. In a 10-year review of NTM cases, the greatest diagnostic yield was observed with polymerase chain reaction testing of lymph node material (91.3% sensitivity), followed by culture (64.8% sensitivity) and microscopy for AFB (30.3% sensitivity). (20)

Pulmonary Disease
The US Cystic Fibrosis Foundation and the European Cystic Fibrosis Society, along with the Infectious Diseases Society of America and the American Thoracic Society, have developed recommendations for the diagnosis and treatment of NTM pneumonia. (10)(74) In contrast to M. tuberculosis, the isolation of NTM from a nonsterile specimen (nasopharyngeal or gastric aspiration) may not imply respiratory disease and should be interpreted within a broader clinical context. The diagnosis of NTM-associated pulmonary disease requires clinical, radiologic, and microbiological evidence indicative of (or consistent with) NTM infection. Alternative diagnoses that could account for these findings should be excluded. For adults and older children, multiple (≥3) early morning sputum samples should be obtained for NTM culture. This approach improves the specificity and sensitivity of culture results. Because airway NTM colonization is common in children with CF, 2 positive sputum sample culture results are generally required to establish a diagnosis. Alternatively, culture of bronchoalveolar lavage fluid and induced sputum samples can be used to establish a diagnosis. In making the diagnosis of NTM-associated lung disease, the species of the isolated organisms should be taken into account because some species are unlikely to cause lung disease and more likely represent contamination.

<table>
<thead>
<tr>
<th>TOOL</th>
<th>UTILITY</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFB smear</td>
<td>Rapid identification of mycobacteria in the specimen</td>
<td>AFB staining cannot distinguish among NTM species or between NTM species and Mycobacterium tuberculosis</td>
</tr>
<tr>
<td>Mycobacterial culture</td>
<td>Obtain an isolate for subsequent identification and possible susceptibility testing</td>
<td>Culture remains the gold standard for laboratory confirmation of NTM and is required for genotypic identification and drug susceptibility tests</td>
</tr>
<tr>
<td>DNA probes</td>
<td>Rapid identification/commercially available</td>
<td>Available for only certain species; cross-reactivity may occur</td>
</tr>
<tr>
<td>MALDI-TOF</td>
<td>Identification of organism</td>
<td>Accurate, rapid, and cost-effective system for identification of NTM species; discrimination power largely depends on the quality of the databases and cannot accurately differentiate Mycobacterium abscessus complex to the subspecies level</td>
</tr>
<tr>
<td>Gene sequencing (eg, 16S)</td>
<td>Identification of organisms to the species level</td>
<td>Multiple gene sequencing (erm, 23S rRNA, hsp65, and rpoB) can discriminate species</td>
</tr>
</tbody>
</table>

AFB=acid-fast bacillus; MALDI-TOF=matrix-assisted laser desorption/ionization–time of flight; NTM=nontuberculous mycobacteria.
Disseminated Disease
The diagnosis of disseminated disease is based on a positive AFB blood culture using bottles specifically intended for mycobacteria isolation. Bacteremia may be intermittent, so multiple cultures should be obtained. Cultures of other sites, including bone marrow and lymph nodes, may also be beneficial in making a diagnosis.

TREATMENT
The Infectious Diseases Society of America and the American Thoracic Society guidelines provide specific recommendations for the treatment of NTM infections. (10)(74) The Clinical and Laboratory Standards Institute has established standardized testing methods and cutoff values for susceptibility testing that can be used for RGM and SGM. This method allows for detection of macrolide resistance for certain NTM species (eg, MAC, M abscessus, and M chelonae) and rifampin resistance in M kansasii, which is invaluable for devising treatment regimens. Susceptibility testing can also be used to monitor for increasing resistance during antimicrobial drug therapy and for recurrent disease. Nonetheless, the value of in vitro testing is significantly limited by the lack of known cutoff values for certain species of NTM (especially fastidious organisms) and the clear lack of correlation between susceptibility results and clinical response. (10)

Lymphadenitis
The treatment of choice for NTM lymphadenitis is generally considered to be complete surgical excision of the infected lymph node. This recommendation, however, is based on somewhat limited data. The largest prospective study to date was a multicenter randomized controlled trial that compared surgical excision with antibiotic drug therapy in 100 children with NTM adenitis. A significantly higher success rate was found for surgical excision (96%) compared with antibiotic drug therapy (66%), although several methodological issues with this study exist. (28)(63) A meta-analysis conducted in 2015, which included almost 2,000 children, provides further support for the superiority of complete surgical excision compared with medical therapy, with cure rates of 98% and 73%, respectively. (75) Interestingly, watchful waiting alone was associated with a cure rate of 70.4%, which was not significantly different from medical therapy. Of note, facial nerve palsy occurred in approximately 10% of children who underwent surgical excision, with 2% of these cases being permanent. Furthermore, incomplete surgical excision was frequently associated with fistula formation.

Medical therapy may be used in children for whom surgical options are limited due to anatomical considerations (ie, close proximity of an infected lymph node to the facial nerve). Antimycobacterial regimens typically use more than 1 agent to prevent the emergence of resistance. Most cases (70%–90%) of NTM lymphadenitis in the United States are secondary to MAC (20), and M scrofulaceum accounts for much of the remaining disease. MAC adenitis has traditionally been treated with a macrolide (azithromycin or clarithromycin) combined with either rifabutin/rifampin or ethambutol. (76) (77) Compared with clarithromycin (7.5–15.0 mg/kg per dose orally twice daily; maximum dose, 500 mg), azithromycin has the advantage of once-daily dosing (10-mg/kg dose; maximum dose, 500 mg). For lymphadenitis caused by non-MAC species of NTM, therapy regimens should be tailored to historical data until results of susceptibility testing are available. The optimal duration of therapy is not known, but patients are often treated for a minimum of 12 weeks. (28) Because treatment failures with medical therapy are not infrequent, the clinician should always be alert to the possibility of drug resistance.

Skin and Soft Tissue Infections. A combination of surgery and lengthy medical treatment is usually required for the treatment of NTM-associated SSTIs. Medical therapy should be directed at the specific NTM species isolated. M abscessus infections are often difficult to treat secondary to drug resistance. Depending on the subspecies, clarithromycin, amikacin, and tigecycline have been demonstrated to have excellent in vitro activity against M abscessus. Suggested treatment includes a combination of macrolide, amikacin, and cefoxitin/imipenem in conjunction with surgical debridement. At least 4 months of antibiotic drug therapy with at least 2 weeks of intravenous therapy is recommended. (10)(20) Species-specific treatment considerations are provided in Table 5 for RGM infections.

Pulmonary Disease. Due to issues of drug resistance and toxicities, treatment of NTM pulmonary infection should be done in consultation with an infectious diseases specialist with expertise in this area. M abscessus complex lung disease requires an individualized treatment approach based on drug susceptibility test results. (74) Adjunctive surgery, including lobectomy, may be necessary to contain pulmonary disease. Treatment recommendations consist of an oral macrolide with 2 parenteral agents for several months. Parenteral choices include amikacin, cefoxitin, imipenem, and tigecycline. This is followed by a continuation phase of therapy, which consists of 2 to 3 oral...
drugs. The total suggested duration of therapy is 1 year after the development of negative sputum cultures. (10) The emergence of macrolide resistance in certain *M. abscessus* subspecies complicates the management of these patients. Recently, there has been increased interest in the use of clofazimine as an oral agent to treat pulmonary NTM. (78) Unfortunately, patients with previous structural or immunologic derangement (ie, CF, AIDS) may fail to fully respond to this therapy. Surveillance for the emergence of increasing antimicrobial drug resistance and drug toxicity is indicated.

**Disseminated Disease.** Treatment of disseminated MAC disease should include antimicrobial management along with optimization of immune status. Initial treatment of disseminated MAC disease should consist of at least 2 or more antimycobacterial drugs to which the isolate is or is likely susceptible. (10)(79) The preferred first agent for MAC treatment is a macrolide (azithromycin or clarithromycin). The recommended second drug is ethambutol. (10)(79) Some clinicians add rifabutin as a third drug. For disseminated MAC disease, testing for macrolide susceptibility should be considered for all isolates, especially in patients who have persistent disease despite macrolide therapy or who develop disease while receiving macrolide prophylaxis. Without immune reconstitution, patients will require lifelong chronic maintenance therapy. (10) Primary prophylaxis (ie, before the advent of disease) with a macrolide should be given in children with severe immunosuppression secondary to advanced HIV infection, according to age-specific CD4⁺T-cell counts. Recommended macrolide primary prophylaxis doses are as follows: clarithromycin 7.5 mg/kg body weight (maximum, 500 mg) by mouth orally twice daily, or azithromycin 20 mg/kg body weight (maximum, 1,200 mg) orally once weekly. Treatment of catheter-associated infections has not been standardized. Most recommendations include removal of the affected catheter along with a course of antitymbacical therapy directed at the specific species involved. (57)

**Summary**

- Based on strong evidence from independent gold standard studies of independent populations, nontuberculous mycobacteria (NTM) disease is acquired from environmental exposures and affects both immunocompetent and immunocompromised children. (15)(20)
- Based on strong evidence from independent gold standard studies of independent populations, rapidly growing NTM, which are resistant to a variety of antimycobacterial agents, have become an important cause of skin and soft tissue infections, and outbreaks of disease have been reported in association with medical tourism. Likewise, pulmonary infections due to resistant NTM have become increasingly problematic for patients with CF. (2)(34)(37)
- Based on strong evidence from independent gold standard studies of independent populations, advances in molecular biology have led to improved diagnostics, which provide for a timelier diagnosis and allow for differentiation of organisms at the species and subspecies levels. Depending on the host and type of disease, this differentiation may be important in guiding initial therapy before susceptibilities are available. (10)(72)(74)
- Based on strong evidence from independent gold standard studies of independent populations, treatment of NTM-associated disease is site specific and should also take into account the immune status of the host and organism susceptibility testing results. (2)(10)(75)

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**TABLE 5. Species-Specific Treatment Considerations**

<table>
<thead>
<tr>
<th>RGM</th>
<th>RESISTANCE PATTERNS</th>
<th>TREATMENT CONSIDERATIONS</th>
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<tbody>
<tr>
<td><em>Mycobacterium abscessus</em> complex</td>
<td>• Subspecies dependent</td>
<td>• Combination therapy with parenteral agents plus ≥1 oral agents have often been used in severe disease</td>
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<tr>
<td></td>
<td>• Frequently resistant to clarithromycin</td>
<td>• Consider linezolid as a part of combination therapy</td>
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<tr>
<td></td>
<td></td>
<td>• Clofazimine as a possible oral agent</td>
</tr>
<tr>
<td><em>Mycobacterium chelonae</em></td>
<td>• Uniformly resistant to cefoxitin</td>
<td>• Demonstrates frequent susceptibility to clarithromycin and linezolid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Intermediate susceptibility to imipenem, amikacin</td>
</tr>
<tr>
<td><em>Mycobacterium fortuitum</em></td>
<td>• Can also be resistant to macrolides</td>
<td>• Demonstrates frequent susceptibility to amikacin, ciprofloxacin, sulfonamides, and imipenem</td>
</tr>
<tr>
<td></td>
<td>• Generally less resistant to antimicrobial agents than other RGM</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Considered easier to treat than other RGM</td>
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RGM = rapidly growing mycobacteria.
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1. A 2-year-old otherwise healthy boy is brought to the clinic with a 3-week history of slowly progressive left neck swelling. The parents report that he has been afebrile and had normal appetite and activity. His vaccinations are up-to-date. He was born in the United States and his growth and development up to this point have been normal. The paternal grandmother is originally from India but has lived with them for the past 3 years. There are no recent sick contacts or travel outside the United States. Three months ago, he visited his cousin’s house with his parents. The cousin has 2 older cats. He was seen in an urgent care center 1 week earlier and was prescribed oral cephalaxin, which he has been taking with no improvement in the appearance of the swelling. On physical examination today he is nontoxic appearing, playful, and interactive. He is afebrile with normal vital signs. There is a swollen, firm, fluctuant, and minimally tender left anterior cervical lymph node with the overlying skin appearing thin and violaceous. The node measures approximately 2 cm. A small sinus tract appears to be forming in the center of the node. There is no other adenopathy appreciated and no hepatosplenomegaly. The rest of the physical examination is normal. Which of the following is the most likely diagnosis in this patient?
   A. Cat-scratch disease.
   B. Infectious mononucleosis.
   C. Lymphoma.
   D. Nontuberculous mycobacterium (NTM).
   E. Tuberculosis.

2. An 18-year-old girl presents to the emergency department with bilateral breast pain and left breast drainage. She had undergone bilateral breast reduction surgery in the Dominican Republic 5 weeks before presentation. Three weeks postoperatively she complained of fevers, chills, and purulent discharge from the left breast. At that time, the discharge was cultured by her primary care provider, and Gram-stain of the fluid showed gram-positive cocci in clusters. She was sent home on a 2-week course of oral trimethoprim-sulfamethoxazole. Four days before presentation she had an increase in her breast pain, wound dehiscence of the left breast, and temperatures to 103°F (39.4°C). Which of the following organisms is most likely to be the cause of her infection?
   A. Mycobacterium abscessus.
   B. Mycobacterium haemophilum.
   C. Mycobacterium marinum.
   D. Mycobacterium tuberculosis.
   E. Mycobacterium ulcerans.

3. The patient in the previous vignette underwent ultrasonography of the left breast that showed a 1.4-cm loculated fluid collection. You suspect an NTB to be the cause of her illness. Which of the following is the gold standard laboratory test for making the diagnosis of NTB in this patient?
   A. Acid-fast bacillus or fluorochrome staining of sputum.
   B. Interferon-γ release assay.
   C. Isolation of the organism in culture.
   D. Matrix-assisted laser desorption/ionization–time of flight (MALDI-TOF) testing.
   E. Tuberculin skin testing.

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4. A 4-year-old girl is brought to the clinic with a 5-week history of a progressive, unilateral, nontender lymph node swelling on the right side of her neck. She was seen 2 weeks earlier, diagnosed as having cervical lymphadenitis, and prescribed a 10-day course of oral clindamycin, which she completed without improvement. Her parents deny any fevers, chills, weight loss, or cough. She has no known sick contacts and no international travel history. A complete blood cell count and erythrocyte sedimentation rate are obtained and they are both normal. NTM lymphadenitis is suspected. Which of the following is the next best step in management?
   A. Antimicrobial therapy against NTM.
   B. Blood culture for mycobacteria isolation.
   C. Incision and drainage of the node.
   D. Surgical excision of the node.
   E. Throat swab for culture.

5. A 15-year-old boy with a history of congenital human immunodeficiency virus (HIV) infection and herpes simplex virus esophagitis 1 year earlier presents for routine follow-up. He reports increasing fatigue, poor appetite, and weight loss but denies fevers, diarrhea, cough, sore throat, or night sweats. On examination, his vital signs are within normal limits. He has lost 2 kg since his last visit 3 months earlier. On oropharyngeal examination he is noted to have oral thrush. The rest of his examination findings are normal. He admits that he is not always compliant with his antiretroviral therapy. His CD4 count is 44 cells/μL. In addition to close clinical monitoring and optimization of his antiretroviral therapy, the clinician decided to begin him on prophylaxis for *Mycobacterium avium* complex (MAC). Which of the following antimicrobial agents is recommended for primary MAC prophylaxis of patients with severe immunosuppression secondary to advanced HIV infection?
   A. Amikacin.
   B. Azithromycin.
   C. Doxycycline.
   D. Pyrazinamide.
   E. Rifampin.
# Nontuberculous Mycobacterial Infections in Children

Jyotsna Bhattacharya, Sindhu Mohandas and David L. Goldman

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