Common Presentations of Nontuberculous Mycobacterial Infections

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Nontuberculous mycobacteria (NTM) are acid-fast bacteria (AFB) that are ubiquitous in the environment. They colonize soil, water sources, dust particles, animals and the food supply. There is no evidence to support human-human or animal-human transmission.

There are over 160 species of NTM, and improved cultivation and molecular identification techniques have identified new species. For example, closely related species, previously classified as part of the *Mycobacterium avium* complex (MAC), have been reclassified as *Mycobacterium lentiflavum, Mycobacterium celatum* and *Mycobacterium conspicuum*.[1] The categorization of NTM organisms can be generalized into slowly growing species (eg, MAC, *Mycobacterium kansasii, Mycobacterium marinum* and *Mycobacterium ulcerans*), and rapid growing species (RGM) with growth in <1 week (eg *Mycobacterium fortuitum* group, *Mycobacterium abscessus* and *Mycobacterium chelonae*).[1]

COMMON PRESENTATIONS OF NTM INFECTIONS

The most common NTM presentations in immunocompetent children are skin, soft tissue, deep tissue, pulmonary infections and lymphadenitis. Disseminated disease is rare and is limited to immunocompromized hosts, particularly those with: HIV (highest risk with CD4 count <50/mm^3); hematopoietic stem cell transplant; disorders of cell-mediated immunity and genetic mutations including interleukin-12 deficiency, INF-γ receptor 1 and 2 mutations, signal transducer and activator of transcription 1 mutations and nuclear factor-kappa-B essential modulator mutation.[1] Specific presentation of and treatment recommendations for NTM disease in immunocompromized hosts is beyond the scope of this review.

NTM Lymphadenitis

Lymphadenitis is the most common manifestation of NTM infection in children. Infection of the anterior cervical and submandibular nodes is most common, followed by the preauricular, postauricular and submental nodes. The oral mucosa is likely the portal of entry following exposure to soil or contaminated water. MAC accounts for over 80% of cases in most reports. Other NTM associated with lymphadenitis include *M. kansasii, Mycobacterium haemophilum, Mycobacterium szulgai, Mycobacterium malmoense*, nonculturable NTM species (eg, *Mycobacterium genavense*) and RGM.[2,3]

Fifty percentage of NTM lymphadenitis occurs in children <3 years of age and 80% in children <5 years of age. There is no predilection for disease by race or gender.[2–5] Most children are diagnosed after several weeks of illness and after unsuccessful treatment for common bacterial pathogens. The disease is usually unilateral; lymph nodes are minimally tender, matted, firm and fixed with an erythematous or violaceous appearance of the overlying skin. Subsequently, the lymph nodes often suppurate and form draining sinus tracts.[2] Most children lack fever and other systemic symptoms and have normal chest radiographs. Ultrasound and computed tomography imaging of the neck often reveals more extensive disease than apparent on physical examination.

An important differential diagnosis for NTM lymphadenitis is tuberculosis. In low tuberculosis prevalence areas, tuberculosis accounts for approximately 10% of culture-proven mycobacterial cervical adenitis cases in children, while it accounts for over 90% of adult cases.[1] These infections can be clinically indistinguishable and culture is often required to determine the cause of the chronic lymphadenitis. Other Important differential diagnoses include: *Bartonella henselae*, Epstein-Barr virus, *Toxoplasma gondii*, malignancy, infected branchial cleft cyst and cystic hygroma.

Skin and Soft Tissue NTM Infections

Skin and soft tissue infections are most often caused by the RGM, MAC, *M. marinum* and *M. ulcerans*. Most infections caused by the RGM organisms are healthcare-associated, presenting as a postsurgical or posttraumatic cellulitis, parenteral or peritoneal catheter site infection or postinjection complication. These are usually isolated tissue infections, but associated bacteremia can occur. Clusters of NTM disease have been associated with healthcare-associated outbreaks occurring in association with cardiac surgery (mediastinal wound infections), joint injections (most often those using multidose vials), dialysis catheter use and middle ear tympanostomy tube insertion.[6]

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M. marinum is known to cause infections after skin trauma followed by contact with marine life, contaminated open bodies of water or (most commonly) tropical fish tanks. The incidence of these infections has decreased with chlorination of swimming pools. Most infections occur in adolescents and typically involve the elbows, hands, knees and ankles. The incubation period is approximately 3 weeks, and disease begins with a small papule which ulcerates and crusts over as a granuloma. Usually, there is no associated regional lymphadenopathy. The tuberculin skin test (TST) and/or interferon-gamma release assay test result is often positive.[1]

M. ulcerans infections are usually reported in tropical areas of the world. Infection occurs most often on the extremities following a skin scrape and contact with foliage. The disease manifests in 3 stages: preulcerative stage (hard, mobile, pruritic nodule) which may spontaneously resolve; ulcerative stage which is protracted (6–9 months) with extensive necrosis of the subcutaneous tissue and finally healing in the form of extensive tissue fibrosis.[1]

NTM Infections Children/ Adolescents with Cystic Fibrosis (CF)

The incidence of NTM disease in patients with CF appears to be increasing, which is attributed to improved diagnostic techniques, increased surveillance, and the increased lifespan of patients with CF. NTM infection is rare in CF patients <5 years of age, and most cases occur in patients >14 years of age. Thirteen percentage of a cohort of approximately 1000 CF patients > 10 years of age were found to have 3 positive serial cultures for NTM. MAC and *M. abscessus* were the primary pathogens followed by *M. kansasii, M. fortuitum* and *M. chelonae*.[7,8] Other studies have shown an NTM prevalence of 11–24% in the sputum of patients with CF. Additional risk factors for NTM disease in CF patients include: severe lung disease, use of corticosteroids, tenacious sputum, diabetes mellitus and, based on in vitro data, potentially azithromycin that is used frequently in CF patients with chronic *Pseudomonas aeruginosa* lung infection.

The key issue in CF patients lies in the distinction between contamination/colonization and NTM disease. As NTM species are found widely in nature, it is common for a single sputum sample from a CF patient to have small numbers of NTM organisms. It is difficult to distinguish radiographic changes caused by NTM infection from chronic bronchiectatic changes that occur as a natural progression of CF. The American Thoracic Society has published guidelines to assist in the diagnosis of NTM lung disease in CF patients.[1,7,8] Diagnostic criteria include: isolation of multiple colonies of the same NTM species on 3 serial sputum cultures or a positive AFB stain and 2 positive cultures; isolation of NTM from a bronchioalveolar wash or lavage; unexplained pulmonary decline (a change in high-resolution computed tomography imaging may be a more sensitive measure than spirometry testing)[8]; compatible radiographic changes; histopathologic changes consistent with mycobacterial infection on transbronchial or lung tissue biopsy and exclusion of other pathogens. Suggestive findings on high-resolution computed tomography include: cystic lesions or cavitations in the lung parenchyma; subsegmental parenchymal consolidation; pulmonary nodules and tree-in-bud opacities.[1] CF patients with *M. abscessus* infection are more likely to meet the American Thoracic Society guidelines for diagnosis than those with MAC.[8,9]

DIAGNOSIS OF NTM INFECTIONS

The diagnosis of NTM infection requires a high level of clinical suspicion, proper collection of specimens and isolation of a clinically relevant organism. The isolation of a single, clinically relevant NTM species from a sterile site, including blood, cerebrospinal fluid, pleural fluid, bone marrow, lymph node, middle ear or mastoid space or excised tissue, should be considered pathogenic until proven otherwise. The isolation of an NTM organism from blood or multiple sites should prompt a clinician to suspect an underlying immunodeficiency. Single positive NTM cultures from nonsterile specimens, including those from gastric aspirates, endoscopy material and skin, must be interpreted with caution.

The diagnosis of NTM-associated lymphadenitis and skin or soft tissue infection involves obtaining adequate specimens for AFB stain, culture and histopathologic examination and this is best obtained via excision. Fine needle aspiration/biopsy of an involved node may yield histologic evidence of mycobacterial disease and a positive culture, but may result in fistula formation. Incision and drainage are discouraged because of poor wound healing and increased risk of a sinus tract developing. Infectious fluid from involved lymph nodes, draining wounds or soft tissue abscesses should be evaluated for cytopathologic changes and sent for AFB stain and culture. Respiratory samples from CF patients should include 3 early morning sputum specimens on subsequent days and should be collected at least 2 hours following ingestion of tap water (to reduce the risk of contamination).

Culture remains the gold standard for diagnosis. Specimens are cultured on both solid media (aerobic, anaerobic, Sabouraud agar, Löwenstein-Jensen slants or Middlebrook media) and in broth media. Sterile body fluids can be directly inoculated into BACTEC blood culture or Septi-Chek broths (Becton-Dickinson and Company). RGM may grow in 7 days; most slow growing NTM take 2–3 weeks, but some require up to 12 weeks of incubation. While most NTM species grow well at temperatures of 35–37°C, some require lower (*M. haemophilum, M. marinum*) or higher temperatures for growth; the laboratory should be alerted if these species are suspected. Molecular probes are available for rapid species identification of the more common NTM species (MAC, *M. kansasii* and *Mycobacterium gordonae*). Other species identification can be achieved rapidly with DNA sequence analysis, shown to have a sensitivity of 85–100% and specificity of 100%.

Drug susceptibility testing is recommended only for NTM for which clinical studies have shown a correlation between susceptibility profile and treatment outcomes. Clinical studies have failed to validate *in vitro* susceptibility testing for most slow-growing NTM species other than MAC and *M. kansasii.* For MAC, knowing the clarithromycin susceptibility is critical, as macrolides are the mainstay of successful treatment, and this is the only class of drugs for which the clinical response correlates with *in vitro* drug susceptibility results.[9] For *M. kansasii*, susceptibility testing is recommended for rifampin. For RGM, clinical trials have revealed that *in vitro* susceptibility results correlate to some degree with clinical outcomes. Testing for amikacin, cefoxitin, clarithromycin, ciprofloxacin, doxycycline, linezolid, sulfamethoxazole, and tobramycin is generally recommended.[10]

TST and IGRAs can aid in diagnosis of NTM infection. The purified protein derivative in the TST contains dozens of mycobacterial antigens that cross-react with many NTM species. Usually, TST reactions measure <10 mm of induration in cases with NTM infection, but can occasionally measure >15 mm, making it difficult to distinguish between NTM and *Mycobacterium tuberculosis* infection. IGRAs use only 2 or 3 antigens and are therefore more specific for *M. tuberculosis*, although there is cross-reaction with several NTM species (*M. kansasii, M. marinum*, *M. szulgai*). For children with a mycobacterial lymphadenitis, a "positive" TST with a negative interferon-gamma release assay result suggests that an NTM is likely the cause of the infection.

TREATMENT OF COMMON NTM INFECTIONS

A general approach to treatment of NTM infection is often a combination of medical and surgical therapy including removal of foreign bodies and infected tissue, followed

by antimycobacterial antibiotics. Determining the optimal therapy includes consideration of: the species causing the infection; the anatomic location of the infection; the results of drug susceptibility testing; the patient's immune status and the need for empiric treatment of *M. tuberculosis* until it is ruled out. For patients in whom *M. tuberculosis* or a slow-growing NTM—especially MAC—is suspected, an empiric regimen of isoniazid, rifampin, ethambutol and a macrolide can be used. Additionally, there is a group of NTM organisms in which clinical response to antituberculosis treatment regimens has been reported.

NTM Lymphadenitis

The optimal treatment of NTM lymphadenitis is uncertain due to the lack of randomized controlled trials. NTM lymphadenitis will resolve spontaneously but often takes 6–12 months and can leave significant scarring. The "gold standard" treatment of NTM lymphadenitis in children has been complete excision of the involved tissue. When achieved, this procedure is both diagnostic and curative. Benefits of complete surgical excision include: a greater chance of isolating the causative organism; higher cure rates; faster healing times; less need for repeat surgical interventions and improved esthetic results.[2,3,5] An alternative surgical procedure is curettage that is used for those patients with higher risk of facial nerve paralysis or extensive postsurgical scarring.[2,3] Several small studies have documented cure with medical management alone but have generally required prolonged antimicrobial regimens. Cross-comparison studies have revealed that surgical excision is superior to conservative antimicrobial management with cure rates of 81–95% and 66%, respectively; many of the patients treated with medical therapy experience drug-related side effects. However, in the 1 randomized controlled trials comparing surgical and medical management, 11% of those who had surgery developed facial palsy, although this was permanent in only a few cases.[5] Drug treatment is directed against MAC unless a different NTM species has been isolated. Therapy of 3–6 months with clarithromycin or azithromycin combined with ethambutol or rifampin may be beneficial for those patients with incomplete surgical excision due to having disease near the facial nerve or with recurrent disease.[3,5]

NTM Skin and Soft Tissue Infections

The management of skin and soft tissue RGM infections usually involves abscess drainage, surgical excision of involved tissue and foreign body removal along with targeted antimicrobial therapy with multiple agents for 4–6 months. Treatment regimens for RGM have included usually 2 of the following: amikacin, cefoxitin, clarithromycin/azithromycin, ciprofloxacin, doxycycline, linezolid, sulfamethoxazole and tobramycin. Although the existing data are very limited, for infections involving *M. marinum*, generally rifampin and ethambutol or monotherapy with doxycycline are given for 1–2 months following resolution of symptoms (generally 3–4 months). Other cases with small lesions have been treated with observation or surgical resection. *M. ulcerans* infections in the preulcerative phase are probably best treated with excision followed by primary closure or a trial of rifampin plus streptomycin for 4 weeks followed by rifampin plus clarithromycin for 4 weeks (based on 1 randomized controlled trials).[11] However, as the disease progresses, cure is difficult with antimicrobial therapy and fibrosis can be extensive.

NTM in CF Patients

Managing NTM infection in CF patients is a challenge, must be considered on a case-by-case basis and is not supported by published randomized trials. Microbiologic cure is generally not a realistic goal, and treatment regimens are often started to monitor for clinical improvement. Patients must be monitored closely for adverse events as the basis of treatment is really risk versus benefit. For MAC infections, treatment is often initiated with a macrolide, ethambutol and rifampin with or without the addition of an aminoglycoside. For *M. abscessus*, treatment is more complex and often unsuccessful, as this organism is multidrug resistant. Most experts use a combination of a macrolide, amikacin and cefoxitin or imipenem initially and follow clinical response. The duration of therapy is prolonged and dependent on the patient's clinical and radiologic response to treatment and ability to tolerate the drugs. Most patients receive therapy for months and serial sputum cultures are obtained; therapy may be interrupted once sputum cultures are negative and clinical improvement is achieved. Disease recurrence is not uncommon and treatment may be reinitiated in those who have recurrence of positive cultures, radiographic evidence of new disease and a recurrence of symptoms.[1]

REFERENCES

1. Griffith DE, Aksamit T, Brown-Elliott BA, et al.; ATS Mycobacterial Diseases Subcommittee; American Thoracic Society; Infectious Disease Society of America. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. *Am J Respir Crit Care Med*. 2007;175:367–416.
2. Lindeboom JA, Kuijper EJ, Bruijnesteijn van Coppenraet ES, et al. Surgical excision versus antibiotic treatment for nontuberculous mycobacterial cervicofacial lymphadenitis in children: a multicenter, randomized, controlled trial. *Clin Infect Dis*. 2007;44:1057–1064.
3. Lindeboom JA. Surgical treatment for nontuberculous mycobacterial (NTM) cervicofacial lymphadenitis in children. *J Oral Maxillofac Surg*. 2012;70:345–348.
4. Luong A, McClay JE, Jafri HS, et al. Antibiotic therapy for nontuberculous mycobacterial cervicofacial lymphadenitis. *Laryngoscope*. 2005;115:1746–1751.
5. Lindeboom JA, Lindeboom R, Bruijnesteijn van Coppenraet ES, et al. Esthetic outcome of surgical excision versus antibiotic therapy for nontuberculous mycobacterial cervicofacial lymphadenitis in children. *Pediatr Infect Dis J*. 2009;28:1028–1030.
6. Franklin DJ, Starke JR, Brady MT, et al. Chronic otitis media after tympanostomy tube placement caused by *Mycobacterium abscessus*: a new clinical entity? *Am J Otol*. 1994;15:313–320.
7. Olivier KN, Weber DJ, Wallace RJ Jr, et al; Nontuberculous Mycobacteria in Cystic Fibrosis Study Group. Nontuberculous mycobacteria. I: multicenter prevalence study in cystic fibrosis. *Am J Respir Crit Care Med*. 2003;167:828–834.
8. Olivier KN, Weber DJ, Lee JH, et al.; Nontuberculous Mycobacteria in Cystic Fibrosis Study Group. Nontuberculous mycobacteria. II: nested-cohort study of impact on cystic fibrosis lung disease. *Am J Respir Crit Care Med*. 2003;167:835–840.
9. Esther CR Jr, Esserman DA, Gilligan P, et al. Chronic *Mycobacterium abscessus* infection and lung function decline in cystic fibrosis. *J Cyst Fibros*. 2010;9:117–123.
10. National Committee for Clinical Laboratory Standards. Susceptibility testing of mycobacteria, nocardiae, and other aerobic actinomycetes. Approved Standard. Wayne, PA: NCCLS; 2003. Document No. M24-A.
11. Nienhuis WA, Stienstra Y, Thompson WA, et al. Antimicrobial treatment for early, limited *Mycobacterium ulcerans* infection: a randomised controlled trial. *Lancet*. 2010;375:664–672.