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Nontuberculous mycobacterial disease in childhood – update on diagnostic approaches and treatment

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Summary Recent studies suggest that the incidence of nontuberculous mycobacterial infections in children may be increasing. Nontuberculous mycobacterial lymphadenitis, skin and soft tissue infection, and pulmonary disease each present unique challenges in relation to diagnosis and treatment. In this update, we critically review the recent literature on the epidemiology, clinical features, diagnostic approaches and treatment of nontuberculous mycobacterial disease in children. In addition, we outline key areas warranting further research.
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Epidemiology of nontuberculous mycobacterial infections

There are more than 170 recognised species of nontuberculous mycobacteria (NTM).[1] However, the majority of disease in humans is caused by fewer than 20 of these. Compared with tuberculosis (TB) the literature on NTM infections in humans is limited, with the majority of publications comprising case series and small retrospective studies.

Only a few studies have attempted to determine the incidence of NTM disease in children. A recent study from Australia estimated the incidence of NTM disease to be approximately 0.6 to 1.6 cases per 100,000 children per year.[2] Another nationwide study conducted in The Netherlands estimated the incidence to be 0.77 per 100,000 children per year; 80% of the cases captured by this study were children younger than 5 years of age.[3] A study in Canada estimated the incidence of NTM disease in Quebec to be approximately

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2.15 per 100,000 children.[4] A prospective, nationwide study in Germany reported a cumulative incidence of 3.3 cases per 100,000 children over a 2.5-year period.[5]

The majority of children with NTM lymphadenitis are previously healthy children without underlying immunodeficiency.[2,3] In contrast, the majority of children and adolescents with pulmonary NTM disease have underlying lung disease, such as cystic fibrosis, bronchopulmonary dysplasia or primary ciliary dyskinesia.[2,4,6] Disseminated NTM disease occurs almost exclusively in immunocompromised children. Therefore, disseminated disease warrants detailed immunological investigations, particularly to exclude HIV infection and defects in the interferon-γ/IL-12 pathway.[7,8]

Transmission of nontuberculous mycobacteria

NTM are ubiquitous in the environment, and can be found in soil, tap water, fresh water, brackish water, salt water, foodstuffs, and a variety of animals.[9] The mode of transmission depends on the type of the infection. Pulmonary infections are acquired by inhalation of aerosolised NTM. Skin and soft tissue infectious are generally caused by direct inoculation into the skin or subcutaneous tissue as a result of trauma. One classic example is 'fish tank granuloma', a skin infection caused by *Mycobacterium marinum*, which fish fanciers can acquire following often relatively minor injuries and exposure to contaminated fish tank water.[10,11] In contrast, the pathogenesis of NTM lymphadenitis is poorly understood, and it remains uncertain whether this infection originates from inhalation or from ingestion of NTM. In patients with immunocompromise and disseminated NTM infection, the primary source of infection often remains occult. In HIV patients, Mycobacterium avium-intracellulare complex (MAIC) infections predominate, which typically manifest as pulmonary disease or disseminated infection.[12,13]

A variety of NTM species have the ability to form biofilms on biologic and synthetic materials.[14–16] Biofilm formation is thought to be a key process in the pathogenesis of central venous catheter (CVC)-related NTM infections, commonly caused by *Mycobacterium fortuitum*.[17] Furthermore, NTM can cause peritonitis in patients undergoing peritoneal dialysis.[18,19] Biofilm formation on peritoneal catheters is the likely source of infection in that setting. Other probable biofilm-related NTM infections involving synthetic materials include chronic otitis media associated with tympanostomy tubes (*Mycobacterium abscessus* and MAIC) and implant infections (*M. fortuitum, M. abscessus, Mycobacterium mucogenicum*).[9]

It was previously thought that human-to-human transmission of NTM infections does not occur. However, a recent study in a cohort of cystic fibrosis patients, in whom all NTM isolates from respiratory samples were analysed by whole-genome sequencing, provides compelling data indicating that pulmonary NTM infections can in fact be transmitted between patients.[20] Whether this mode of transmission exclusively occurs in individuals with pre-existing lung pathology currently remains uncertain.

Seasonality of nontuberculous mycobacterial disease

The first study to identify that seasonal variation occurs in NTM disease was the aforementioned study from Australia.[2] Complex time-trend analyses identified annual incidence peaks in late winter and spring, and troughs in autumn. The underlying mechanism for this seasonal pattern remains uncertain, although seasonal variation in vitamin D levels, a micronutrient that plays an important role in human anti-mycobacterial immune responses,[21] has been postulated as a potential cause.[2]

This discovery is intriguing in light of previous studies that have reported seasonal variation in the incidence of TB disease, caused by *Mycobacterium tuberculosis*, in geographical regions with temperate climate.[22,23] Interestingly, in accordance with the observations made in the Australian study, the majority of those studies also found that the peaks of TB disease occurred in winter and spring, while the lowest incidence rates were observed in autumn.

Spectrum of nontuberculous mycobacterial disease in children

The majority of studies related to NTM disease have focused on one particular NTM species or one particular disease entity, while few have attempted to capture the entire spectrum of NTM disease in children. Existing data suggest that lymphadenitis is the most common form of NTM disease in children, followed by skin and soft tissue infections and pulmonary NTM disease. The Australian study, which captured 140 cases at a single tertiary centre over a 10-year period, included 107 cases (76%) with NTM lymphadenitis, 25 cases (18%) with skin and soft tissue infection and five cases (4%) with pulmonary NTM disease.[2] These data contrast with the results of another single-centre study from Texas that identified 75 paediatric cases with NTM disease over a 5-year period, which included 30 cases (40%) with NTM lymphadenitis, 17 cases (23%) with skin and soft tissue infection and 17 cases (23%) with pulmonary NTM disease.[24] This report also included a surprisingly large number of children with NTM bacteraemia (n=11; 15%), all of which were associated with CVCs or underlying immunodeficiency. In the aforementioned Dutch study, which was designed to include all manifestations of NTM disease, 56 (92%) of the total of 61 cases captured had NTM lymphadenitis.[3] In the German study, which also aimed to include all types of NTM disease in children, of the total study population of 102 patients, 99 (97%) had NTM lymphadenitis.[5] The Canadian study, which involved 10 paediatric tertiary referral centres, captured 45 patients with NTM disease, comprising 34 (76%) cases with lymphadenitis, four (9%) cases with skin and soft tissue infection and seven (16%) cases with pulmonary NTM disease.[4]

Lymphadenitis

Isolated lymphadenitis is the most common type of NTM disease in children, and therefore the following sections will focus on this infection. The great majority of patients with NTM lymphadenitis are younger than five years of age, contrasting with TB lymphadenitis, which most commonly affects teenagers and young adults.[2,3,5,25]

Causative organisms of lymphadenitis

MAIC has been the most common causative organism of NTM lymphadenitis in all of the larger clinical studies conducted

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