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Atypical mycobacteria: an important differential for the general physician

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Background

Atypical mycobacteria, or more correctly non-tuberculous mycobacterial (NTM) species, are a ubiquitous group of environmental organisms that have potential to cause pathological presentations, varying from skin and superficial infections to deeper infections with or without systemic dissemination. Many NTM species are well-recognised pathogens, whereas others are newly emerging and their pathogenic potential is yet to be understood.

Some features of NTM pathologies are shared with diseases caused by the biologically related *M. tuberculosis*, but there are significant differences.

The microbiological classification of NTM depends on two main factors:[1] rate of growth (rapid growing or slow growing) and pigment production. Table 1 lists some of the clinically important NTM organisms.[2,3]

Importance

NTM are opportunists and have the potential to cause severe disease in immuno-compromised hosts. Their management can be challenging due to difficulties in culturing the bacteria and the complex combinations of antibiotics used in therapy.[4]

The wider use of immuno-suppressants means that more patients are becoming prone to these infections.[3,4] The capacity of NTM organisms to infect any system reflects their importance and relevance to all medical specialties and hence the need to consider NTM pathology as part of a wider differential.

NTM have a wide geographical distribution but the prevalence of NTM disease is difficult to determine because of the lack of routine reporting and notification.

Pathology

NTM organisms are common in the environment, particularly in water and soil, but systemic and severe infections are invariably limited to immuno-compromised hosts, suggesting that these organisms have low virulence. The onset of illness is typically insidious with an indolent course inevitably ending in a severe illness, with serious implications if not recognised and treated. The key objective of this article is to provide an overview of NTM infections and to emphasise their importance to general medicine (Table 2 and Box 1).[4]

Pulmonary symptoms are probably the most common presentation of NTM disease, usually in the context of underlying chronic pulmonary disease (such as cystic fibrosis [CF], bronchiectasis or chronic obstructive pulmonary disease [COPD]), although NTM organisms can still cause pulmonary symptoms in those with no pre-existing lung disease. The disease is usually caused by the *M. avium-intracellulare* complex (MAC), although other species of mycobacteria have been reported to cause pulmonary disease.[4]

Disease in the immuno-competent host is rare but sometimes presents as a typical febrile respiratory syndrome with fever, cough, dyspnea and night sweats. By contrast, in the immuno-compromised host, the presentation is rather non-specific and usually manifests as an unexplained fever and weight loss.

Diagnosis is usually challenging and can be laborious as it entails the elimination of a list of more common respiratory pathologies. The American Thoracic Society (ATS)/Infectious Disease Society of America (IDSA) guidelines suggest a triad of radiological, bacteriological and clinical criteria to establish the diagnosis (Table 3).[4]

Lymph node disease is more common in children than in adults and is often caused by MAC, although other NTM organisms are also known to cause it. The disease is usually localized, affecting the cervical lymph nodes, and has no systemic manifestations. It tends to follow a chronic course and can resolve with no specific intervention.

M. scrofulaceum is a well-known pathogen that causes the so-called 'scrofula', a granulomatous cervical adenitis usually seen in children; this organism can also cause pulmonary disease in adults. Mediastinal adenitis due to *M. kansasii* is well documented and can obviously mimic other clinical entities (infective and non-infective) making its diagnosis more challenging.[3,4,8,9]

Skin and soft-tissue infections caused by NTM typically present in the form of isolated or multiple nodules, commonly in a linear distribution following the local blood

Table 1. Classification of *Mycobacterium* species.

Rapid growing	Slow growing
M. abscessus	*M. avium-intracellulare complex*
M. chelonae	*M. hemophilum*
M. fortuitum	*M. kansasii*
	M. malmoense
	M. marinum
	M. scrofulaceum
	M. ulcerans
	M. xenopi

Table 2. Some important clinical syndromes and the organisms involved.

Clinical presentation	Organisms
Pulmonary	MAC, *M.* kansasii, *M. abscessus*
Skin/soft tissue	*M. marinum, M. ulcerans*
Lymph node	MAC, *M. scrofulaceum, M. chelonae, M. fortuitum*
Disseminated	MAC, *M. chelonae, M. fortuitum, M. kansasii*

MAC = *Myocbaterium avium-intracellulare* complex.

Box 1. Predisposing factors.

- Immune deficiency or suppression, including HIV
- Chronic illness: COPD, bronchiectasis, CF, diabetes, hematological malignancies
- Intravenous drug use
- Tattoos
- Extremes of age
- Occupational and lifestyle exposure (eg contact with aquatic organisms)

CF = cystic fibrosis; COPD = chronic obstructive pulmonary disease; HIV = human immunodeficiency virus.

or lymphatic vessels. The regional nodes are invariably involved. Other non-specific inflammatory changes and plaque forms are common. Underlying structures such as sinuses can also be infected.[4–6]

A very common soft-tissue presentation is the so-called 'fish tank granuloma', which is caused by *M. marinum*. As the name implies, this pathology is usually encountered in those exposed to aquatic environments and it usually affects the upper limbs.

In warmer and tropical environments, *M. ulcerans* results in 'Buruli ulcer', which, in contrast to marinum infection, is primarily a disease of the lower extremities.[7] The disease is characterized by the lack of an inflammatory response and can pass unnoticed for some time. Systemic involvement is unusual in these infections, but the late presentation and chronicity makes their management difficult and surgical intervention might be required to achieve cure.

Systemic or complicated cutaneous fungal infection can present in a similar fashion and should be included in the differential diagnosis of these lesions.

Disseminated disease can occur at the extreme end of the spectrum of NTM illness. From a prognostic point of view, such NTM disease indicates a debilitating underlying immune deficiency, which can make management difficult.[19] This presentation is commonly caused by MAC but other species, such as *M. kansasii* and *M. chelonae*, have been reported to cause similar illness.

Patients are typically human immunodeficiency virus (HIV) positive, with a CD4 count of less than 50, or bone marrow transplant patients and those established on immunosuppressive therapy.[4,10,11]

Diagnosis can be rather difficult and delayed, and a high index of suspicion should therefore be maintained. Positive culture from sterile sites is diagnostic, but more often than is usual, the diagnosis is made on the basis of a myriad of evidence sources (clinical, radiological, bacteriological or histopathological). Bone marrow biopsy is usually undertaken in the patient groups in which these pathologies are common and relevant culture and molecular studies of these specimens should always be performed.

Another important aspect relevant to this group of patients is the fact that, upon regaining immune function, they are prone to immune reconstitution syndrome. For example, this systemic inflammatory response against the infective aetiology (resulting, at times, in no cause being evident on microbiological cultures) often occurs when the CD4 count improves in patients who are established on highly active anti-retroviral therapy (HAART). Prompt recognition and appropriate management of NTM disease is therefore vital.

Table 3. Diagnostic features of NTM-related pulmonary disease.

Clinical	Pulmonary signs, exclusions of other pathologies (TB, malignancy)
Radiological	CXR with nodular or cavitatory lesions, HRCT with multifocal bronchiectasis and multiple small nodules
Bacteriological	At least two culture-positive sputum samples, at least one culture-positive bronchial washing or lavage, biopsy with consistent features (granulomas, positive AFB stain) and positive culture result (sputum, endobronchial or biopsy specimens); at least one of these bacteriological criteria must be met within 1 year

AFB = acid fast bacillus; CXR = chest X-ray; HRCT = high resolution computed tomography; TB = tuberculosis.

Gastrointestinal tract disease caused by MAC is well-described in the literature and can present as part of a disseminated illness. Common findings include hepatosplenomegaly, colonic ulcers, mesenteric involvement and abscess formation.[12]

Musculo-skeletal disease is not a common presentation for NTM, but all atypical mycobacteria have the potential to cause musculoskeletal infection and it is important to recognise this possibility if clinically plausible.[4,13,14]

Other disease – Fast-growing organisms such as *M. fortuitum* can cause nosocomial and catheter-related infection.[4]

No body part or system is spared by atypical mycobacteria and the literature is quite rich of case reports of various presentations including endocarditis, ophthalmologic, central nervous system (CNS) and ear, nose and throat (ENT) infections.

Diagnosis

It is important to understand that none of the clinical signs listed below is enough to make a diagnosis in isolation.[4]

Clinical suspicion

Clinical awareness is important in making a prompt diagnosis and offering timely treatment.

Bacteriology

These organisms can be grown from all types of clinical specimens, depending on the site, provided these are sent to the laboratory in an appropriate medium. Culture is important as it allows sensitivity studies and further studies to characterise the organisms. Nevertheless, the culture results need careful interpretation as a positive culture doesn't necessarily mean a clinical infection.

Microscopy using various stains is still practiced but doesn't help to differentiate these organisms.

Molecular studies based on the polymerase chain reaction (PCR) are increasingly used to identify NTM organisms.

Cross-contamination while handling specimens can result in diagnostic inaccuracy and is another reason to be extremely cautious when interpreting bacteriology results.

Radiology

X-ray findings are not usually specific enough to be helpful in making a diagnosis of NTM-related disease and CT is usually required to further examine the presence or absence of abnormalities caused by these organisms. Findings can mimic those of tuberculosis (TB) but common features include nodular opacities, cavities, brochiectasis and lymphadenopathy.

Histology

The presence of granulomas helps to support the diagnosis of NTM-related disease but as their formation is dependent on the host immune response, their absence or the finding of non-specific inflammatory changes doesn't rule out the possibility of NTM infection.

Key points

- Non-tuberculous mycobacteria (NTM) are similar to *Mycobacterium tuberculosis*, the causal agent of tuberculosis, but do not have the same clinical and infective ramifications
- NTM include a number of different organisms that are ubiquitous and are pathogenic in specific host-related circumstances
- NTM can cause both pulmonary and extrapulmonary disease
- Diagnosis of NTM-related disease can be difficult and can require molecular techniques
- Disease management, if required, is complex and requires a combination of anti-mycobacterial drugs for a prolonged period

KEYWORDS: Atypical mycobacteria, non-tuberculous mycobacteria, immuno-compromised host

Management

The management of NTM infections can be challenging due to several factors.[4] Firstly, it can be difficult to grow and identify the bacteria in order to make a bacteriological diagnosis. A second pathogen-related factor is that these organisms are more resistant than others to antimicrobials. Host-specific challenges to the management of NTM infections include underlying immune suppression, other co-morbidities, drug interactions and toxicities.

Management is typically multi-disciplinary and usually led by an infectious diseases physician or a microbiologist, but surgical interventions and the participation of other relevant specialties are invariably involved to achieve bacteriological cure and better outcome.

Medical management requires a prolonged course of multiple agents with macrolides, clarithromycin and azithromycin representing the back-bone of most regimens. Most drug treatments can be continued on an outpatient basis provided the patient is not critically ill.[16–18]

Other effective agents include (usually on the basis of sensitivity testing): common antimycobacterial agents, such as rifabutin, ethambutol and less commonly (due to resistance) isoniazid; an aminoglycoside, such as amikacin or streptomycin; fluoroquinolones, commonly in the form of moxifloxacin; and less commonly used agents such as cefoxitin and para-aminosalicylate.

Prognosis and follow up

Prognosis is good in most cases, with a greater chance of cure with close medical follow up and supervised therapy.

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