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REVIEW ARTICLE

NONTUBERCULOUS MYCOBACTERIAL INFECTION: AN ACHILLES HEEL FOR CLINICIAN

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Abstract:
Nontuberculous mycobacterial (NTM) o Atypical mycobacterial (ATM) infection is becoming an upcoming challenge for the clinicians. Atypical Mycobacterial infections range from pulmonary to extra pulmonary including skin and soft-tissue infections, traumatic and surgical wound infections, catheter and implant-associated infections. They are commonly misdiagnosed as tuberculosis caused by M. tuberculosis *(MTB). Appropriate diagnostic methods and tools are essential in order to facilitate the differential diagnosis of Atypical Mycobacterium from MTB infections. We aimed to collect data available on Atypical Mycobacterium for diagnosis and appropriate treatment and to create awareness among the physician to combat with challenges.*

Keywords: *Nontuberculous Mycobacterial Infection, Achilles heel for Clinician*

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Introduction:

Nontuberculous mycobacteria (NTM) or Atypical mycobacteria (ATM) are a diverse group of more than 190 species. Among them a few are associated with human infection. They are pervasive environmental bacteria that include mycobacterial species other than *Mycobacterium tuberculosis complex* (MTBC) and *Mycobacterium leprae.*[1]

NTM are found in the environment globally, specifically in water and soil. NTM disease and its localization frequently interplay between organism pathogenicity and host susceptibility. The most commonly encountered atypical mycobacteria that cause the majority of infection in humans are the *Mycobacterium avium complex bacteria (MAC), Mycobacterium avium, and Mycobacterium intracellulare,* also referred to as *Mycobacterium avium-intracellulare (MAI), Mycobacterium kansasii, Mycobacterium marinum, Mycobacterium ulcerans, Mycobacterium abscessus complex bacteria (abscessus, massiliense, and bolletii), Mycobacterium chelonae,* and *Mycobacterium fortuitum.*[2]

Because of their morphological appearance as MTB in sputum smears and their similar clinical presentation, they often misdiagnosed. Due to this, they are also under-reported, misclassified and improperly treated. With these given challenges, NTM have gained more attention in recent years and understanding of their biology, epidemiology, diagnosis, and management of infections caused by them has undergone considerable research globally. However, in our country, NTM are still struggling to get their importance due to their misdiagnosis or incorrect diagnosis. In resource-constrained settings, NTM are rarely diagnosed or sometimes given appropriate attention only after obtaining a history of failed anti-TB treatments[9]

The search terms included "Pulmonary NTM," "Extra pulmonary NTM," and "Antimicrobial susceptibility of NTM" in PubMed. We initially collected abstracts of 78 articles according to the relevance of the topic. After evaluation, 24 papers have been selected finally to write this review article.

The purpose of the review is to elucidate their importance and to establish the need for research in future studies.

Epidemiology:

Estimates of the rate of pulmonary disease are between 5 to 10 per 100,000 per year. Various studies have estimated the rate of all causes of atypical mycobacterial infection in children to be between 0.6 to 3.3 per 100,000. Estimates of the rate of all causes of infection in adults are between 20 to 47 per 100,000.[5]

The reported incidence of NTM species in pulmonary and extra-pulmonary clinical samples from India range from 0.7% to 34%[6].

Pathophysiology:

Nontuberculous mycobacteria are usually taken up by macrophages, causing them to release IL-12 and

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TNF-alpha. IL-12 release activates the IL-12-interferon gamma pathway. The macrophages, neutrophils, and T-cells recruited to the site of infection and result in granuloma formation and creates fibrinous mass walling off the infection. This isolating it from the rest of the body.

Histopathology:

Nontuberculous mycobacterium has a hydrophobic mycolic acid layer in their cell wall. They are not typically seen using Gram staining due to this reason. The best method for detecting atypical mycobacteria is fluorochrome staining which is a type of acid-fast staining and here these bacteria will appear as yellow to orange bacilli. Rapidly growing mycobacteria are noted to be more sensitive to the decolorization process in acid-fast staining. Using more delicate methods for decolorization can increase the chance of visualizing these bacteria. Other less sensitive staining method can also be used include the Ziehl-Neelsen method and the Kinyoun stain[8].

Classification of Atypical Mycobacteria:

The microbiological classification of NTM depends on two main factors[8].

1. Rate of growth (rapid growing or slow growing) and
2. Pigment production.

Table-I

Lists some of the clinically important NTM organisms[8]

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

Clinical presentation:

Pulmonary NTM infections are often misdiagnosed as tuberculosis. In case of NTM, fever is less common and the chest X-ray images shows the nodular lesions and pulmonary infiltrations. Clinical presentation usually found more commonly in middle-aged males with the risk factors of long-term alcohol and tobacco abuse. In these patients, they tend to form large fibro-cavitary lesions in the apex of the lung. The MAC lung disease more commonly affects postmenopausal Caucasian women. In this case, the bacteria form small pulmonary nodules and cylindrical bronchiectasis with a concentration of nodules in the right middle lobe and lingula of the left upper lobe of the lung. *Mycobacterium kansasii* and *Mycobacterium abscessus* tends to form large fibro cavities in the apex of the lung.

Lymphadenitis: The progression of atypical mycobacterial lymphadenitis has four stages. The first stage describes a unilateral lymphadenopathy that progress slowly over several days to months. Stage one is unlikely to show systemic symptoms. Then it shows tenderness indicative of necrosis within the lymph node & in stage three shows erythematous discoloration of the overlying skin & stage four describes the breach of skin and formation of sinus tracts.

Skin and soft tissue disease:

Atypical Mycobacteria enter into the skin and soft tissue through trauma, surgical procedures, or via indwelling medical equipment. Skin and soft tissue infection can be caused by all species. The most common species are *Mycobacterium chelonae, abscessus, fortuitum, ulcerans, and marinum. Mycobacterium marinum* infection is also known as the fish tank granuloma. They usually cause soft tissue infection in fish tank workers/enthusiasts. It most commonly causes localized erythema and granuloma formation of the digits and it can progress to develop nodular lymphangitis of the hands and forearms. They can also affect tendons, joint spaces and cause osteomyelitis. Immunocompromised patients also recorded cases of disseminated infection. Another atypical Mycobacteria *"Mycobacterium ulcerans"* cause Buruli ulcer. They cause large areas of skin involvement, deep ulceration, and marked cosmetic disfigurement. They present as a small, painless nodule, which slowly begins to ulcerate. These ulcers are characterized by poorly defined and irregular borders and can cover extensive sections of the body. *Mycobacterium ulcerans* infections can also cause osteomyelitis in 15% cases. *Mycobacterium fortuitum* most commonly presents as a solitary subcutaneous nodule. They usually cause low morbidity and limited infection. *Mycobacterium abscessus* most commonly causes painful sinus tracts, and progress to ascending lymphadenitis. *Mycobacterium chelonae* also presents as disseminated painful cutaneous nodules.[10]

Diagnosis and Drug-susceptibility Testing:

According to 2017 BTS and 2020 ATS/ERS/ESCMID/IDSA Guidelines, NTM infections is considered positive when more than one expectorated sputum culture is positive and the same NTM species/subspecies must be isolated in more than two sputum cultures. In Broncho alveolar lavage (BAL), NTM can also be found. These are suitable when patients are unable to expectorate. In Trans-bronchial/ lung biopsy, mycobacterial histopathological features are usually present (defined as granulomatous inflammation or presence of acid fast bacilli) this must be combined with a positive culture result. Radiological criteria include nodular or cavitary opacities on a chest X-ray. Bronchiectasis with multiple small nodules on HRCT.

Prior to initiating treatment, it is also now recommended that baseline drug susceptibility testing must be done[11].

Clinical considerations and decision to treat:

The most recent guideline recommends that careful assessment of the patient's clinical status, radiological findings, pathogenicity of the organism, risks and benefits of therapy, the patient's wish and ability to receive treatment as well as the goals of therapy should be discussed with patients prior to initiating treatment'. Depending on the above factors a 'watchful waiting' during clinical review, sputum cultures/bronchoscopy and imaging may sometimes be preferred to treatment. Treatment plan must include follow-up[11].

Treatment:

Treatment of NTM lung required at least three drugs should be used in order to minimize drug resistance and all patients should receive a minimum of 12 months of treatment after sputum conversion. The new guidelines suggest using three times weekly rather than daily treatment in patients with mild/moderate non-cavitary, less progressive, susceptible disease, which has been shown to be better tolerated. Expert advice should be sought where possible to treat species and subspecies accordingly, reduce toxicity, improve adherence and reduce development of resistance. This is particularly true in cavitary, severe, resistant or treatment-refractory disease (those who remain culture positive after 6 months of guideline-based treatment). Table 2 summarizes management of the four main disease classes based on the 2020 ATS/ERS/ESCMID/ IDSA guidelines. The guidelines were established based on currently available evidence and expert opinion. More detail on individual drugs follows, drawing on recent publications where available[11].

Disease characteristics	Guideline-based treatment	Treatment duration
MAC		
Macrolide susceptible, non-cavitary, non-severe	Macrolide+ Ethambutol+ Rifamycin -Three times weekly	≥12 months after culture conversion
Macrolide susceptible, cavitary/ severe	Macrolide+ Ethambutol + Rifamycin + parenteral aminoglycoside Daily (except aminoglycoside may be given three times weekly)	
Refractory	Macrolide+ Ethambutol+ Rifamycin+ ALISDaily (except aminoglycoside maybe given three times weekly)	
Macrolides resistant	Clofazimine OR Moxifloxacin OR linezolid+ Ethambutol+ Rifamycin+ parenteral aminoglycoside Daily (except aminoglycoside may be given three times weekly)	
M. Kansasii		
Non cavitary	Macrolide or Isoniazid+ Ethambutol+ Rifamycin, Macrolide-containing regimen three times weekly or INH-containing regimen daily	≥12 months
Cavitary	Macrolide or Isoniazid+ Ethambutol+ Rifamycin Daily	
Severe	Macrolide or Isoniazid+ Ethambutol+ Rifamycin+ parenteral aminoglycosideDaily (except aminoglycoside maybe given three times weekly)	
Rifampicin resistance/ intolerant	Macrolide+ Ethambutol+ fluoroquinolone Daily	
M. Xenopi		
Non-cavitary	Macrolide OR fluoroquinolone+ Ethambutol+ RifamycinDaily	≥12 months after culture conversion
Cavitary/ severe	Macrolide OR fluoroquinolone+ Ethambutol+ Rifamycin+ parenteral aminoglycosideDaily (except aminoglycoside maybe given three times weekly)	
M. Abscessus		
No mutational/ inducible macrolide resistance	Intensive phase:One or two parenteral agents: Amikacin/ Imipenem or Cefoxitin/ Tigecycline+ two oral agents' Macrolide/Clofazimine/ linezolid.Continuation phase:Two oral/ inhaled agents: Macrolide/ Clofazimine / linezolid/ inhaled amikacin Daily (except aminoglycoside maybe given three times weekly)	2 to 3-month intensive phase then continuation totaling ≥12 months
Macrolide resistant	Intensive phaseTwo or three parenteral agents: Amikacin/ Imipenem or Cefoxitin/ tigecycline+ two or three oral agents: Macrolide/ Clofazimine/ linezolidContinuation phase Two or three oral agents: Macrolide/ Clofazimine/ linezolid/ inhaled Amikacin.	

Treatment of lymphadenitis:

Treatment based on a two-drug regimen of one macrolide combined with rifampin or ethambutol. Antibiotics are dosed daily and taken until the resolution of symptoms.

Surgical resection of infected lymph nodes and tissue is typically used in combination with antibiotic therapy with significantly increased cure rates.

Duration of treatment: In case of Mild infections duration are usually 2-4 months of treatment, while severe ones can require 6 months or even longer. But Specific type of atypical mycobacteria have varying levels of resistance to antibiotics and duration of treatment according to the resistance pattern.

Response to therapy: Regular monitoring is crucial to assess progress and adjust the treatment plan if needed.

Skin and soft tissue infection:

Skin and soft tissue infections are treated with combination antibiotic therapy with a variety of options available, including macrolides, doxycycline, fluoroquinolones, trimethoprim/sulfamethoxazole, cephalosporins, or linezolid.

Empiric therapies are adjusted once susceptibility testing yields results; however, combination antibiotic therapy is continued due to inducible antibiotic resistance.

Surgical debridement is required for infections that are extensive and associated with necrosis.

Duration of treatment: In case of Mild infections duration are usually 2-4 months of treatment, while severe ones can require 6 months or even longer. But Specific type of atypical mycobacteria have varying levels of resistance to antibiotics and duration of treatment according to the resistance pattern. In case of musculoskeletal infections treatment are usually continued for 6-12 months. Immunocompromised individuals also need longer treatment durations.

Response to therapy: Regular monitoring is crucial to assess progress and adjust the treatment plan if needed[13].

Conclusion:

Due to rising incidence of NTM in recent years, there is a need for extensive research. A differential diagnostic test is required to discriminate the contaminants and pathogenic NTM for treatment options and in case of mixed infection to distinguish TB. Now a days, A well-formulated guideline is burning need for our country.

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