Approach to the diagnosis and treatment of non-tuberculous mycobacterial disease

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Keywords: Non-tuberculous mycobacteria Mycobacterium avium Mycobacterium abscessus

ARTICLE INFO

Abstract

Non-tuberculous mycobacteria (NTM) is a collective name given to a group of more than 190 species of Mycobacterium other than Mycobacterium tuberculosis and Mycobacterium leprae [1]. These organisms are ubiquitous in the environment, in particular in soil and water sources, and are increasingly recognized as a cause of human disease. Non-tuberculous mycobacteria cause infection not only in immunocompromised populations, but also in otherwise healthy individuals. A substantial number of challenges are associated with the diagnosis and management of NTM infections.

The clinical presentation for most NTM infections is non-specific, often resulting in delayed diagnosis. Once NTM is suspected, growing NTM from biological specimens for identification can be difficult secondary to variable growth time and requirements. Furthermore, the actual identification of the organism often requires molecular methods that may not be widely available. Identification of NTM from biological specimens is not equivalent to a diagnosis of NTM infection; the ubiquitous presence of NTM in the environment creates the dilemma of distinguishing between colonization and true infection.

The treatment of NTM infections can also be challenging. Antimicrobial-susceptibility testing (AST) is not available for all NTM species and drugs of interest. Where it is available, it is not always reliable and the clinical applicability is uncertain. Optimal dosing of recognized anti-mycobacterial drugs is unknown, and guidelines for the optimal number of drugs and treatment duration are largely opinion-based. Furthermore, current guidelines for NTM infections lump NTM into a small number of categories. Thus differences among NTM species factors such as virulence, relevant host factors, resistance profile, and response to treatment are inadequately addressed. Herein, we review different NTM syndromes, appropriate diagnostic tests, and treatment regimens.

1. Introduction

Non-tuberculous mycobacteria (NTM) is a collective name given to a group of more than 190 species of Mycobacterium other than Mycobacterium tuberculosis and Mycobacterium leprae [1]. These organisms are ubiquitous in the environment, in particular in soil and water sources, and are increasingly recognized as a cause of human disease. Non-tuberculous mycobacteria cause infection not only in immunocompromised populations, but also in otherwise healthy individuals. A substantial number of challenges are associated with the diagnosis and management of NTM infections.

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Abbreviations: ADR, adverse drug reactions; AFB, acid fast bacilli; AST, antimicrobial-susceptibility testing; ATS, American Thoracic Society; BCG, Bacille Calmette-Guerin; CLSI, Clinical and Laboratory Standards Institute; COPD, chronic obstructive pulmonary disease; ECG, electrocardiogram; EMB, ethambutol; Erm, erythromycin ribosomal methylase; FDA, Food and Drug Administration; HIV, human immunodeficiency virus; HRCT, high resolution computed tomography; IDSA, Infectious Disease Society of America; INF-γ, interferon- γ; INH, isoniazid; MAC, Mycobacterium avium complex; MIC, minimum inhibitory concentrations; MALDI-TOF, matrix-assisted laser desorption ionization time-of-flight mass spectrometry; MGIT, mycobacteria growth indicator tube; NTM, non-tuberculous mycobacteria; PCR, polymerase chain reaction; PFT, pulmonary function test; TB, tuberculosis; TDM, therapeutic drug monitoring.

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https://doi.org/10.1016/j.jctube.2021.100244

Available online 8 May 2021

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2. When should one suspect NTM infections?

The clinical manifestations of NTM infections are typically non-specific. In general, NTM infection is suspected in an individual with persistent symptoms (for example fever, respiratory symptoms, skin lesions) that do not respond to traditional anti-bacterial therapy. Alternatively, an understanding of common NTM infection syndromes and the context-clinical scenario in which they occur, can heighten the suspicion for the presence of an NTM infection. Pulmonary NTM infection continues to be the most common clinical presentation [2], but there are several other distinct clinical syndromes described with NTM. These are classified by organ system of involvement and summarized in Table 1. Additionally, several NTM species have unique clinical syndromes associated with them. These should be considered in appropriate clinical scenarios and are summarized in Table 2.

3. Diagnosing non-tuberculous mycobacteria infections

There are no pathognomonic tests for diagnosis of NTM infections. Diagnosis requires correlation of the clinical syndrome with radiographic findings, and ultimately microbiologic confirmation of the etiologic agent. Specimen collection and testing may need to be repeated on several occasions to confirm or exclude a diagnosis of NTM infection. In view of the complexities involved, tests should be interpreted in consultation with specialists experienced in management of NTM infections, especially if the microbiologic results are not congruent with the clinical picture.

3.1. Microbiologic diagnosis

NTM are ubiquitous in the environment and are commonly found in soil and water, including municipal and household water supply systems. Therefore, caution must be exercised to avoid environmental contamination of biologic specimens to prevent false positive results. Specimens can be obtained from nearly any tissue or organ suspected to be infected.

The guidelines provided by American Thoracic Society (ATS) and Infectious Disease Society of America (IDSA) for diagnosis of pulmonary NTM infection require positive sputum culture results on at least two separate occasions [3,4]. Alternatively, a single positive culture from a lower respiratory specimen such as bronchial lavage or washing is considered adequate for diagnosis. If clinical suspicion for pulmonary NTM infection is high and initial tests remain non-diagnostic, then additional sputum cultures should be obtained [3,4]. Induction of sputum or bronchoscopy may be necessary in patients unable to expectorate sputum. The optimal interval between sample collections is unknown. Separating specimen collection by at least a week may be a reasonable timeframe to consider as the interval between sample collections, such that transient environmental contamination does not confuse the diagnosis [5]. Lung biopsy is rarely described as necessary for diagnosis, but may provide additional information beyond positive stains and cultures, demonstrating histopathology findings of mycobacterial infections, such as granuloma formation.

In non-pulmonary disease, source of culture is determined by site of involvement. For example, lymphadenitis may require excisional biopsy or fine needle aspiration for microscopy and mycobacterial culture. When NTM disease is disseminated, mycobacterial blood cultures may prove diagnostic. In the presence of cytopenias, bone marrow or liver biopsy may be useful for diagnosis [6]. It is important to note that skin infections are best evaluated with biopsy rather than superficial swabs since swabs may represent environmental exposure rather than infection [6].

When clinical suspicion exists, the requisite biologic samples should be obtained and sent to the microbiology laboratory, with notification of the suspicion for NTM infection, so that the laboratory personnel process these specimens appropriately. Different staining and culture techniques may be required to maximize yield. If NTM species with special culture requirements are suspected, such as growth at lower temperatures for some species, these specimens should be obtained from nearly any tissue or organ suspected to be infected.

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| Clinical Syndrome | Most Common Species | Other Species | Risk Factors/ Associations |
|-------------------|---------------------|---------------|--------------------------|
| Pulmonary44, [110] | MAC                 | M. abscessus  | α1-Antitrypsin deficiency |
|                   | M. kansasii         | M. fortuitum  | Ciliary dyskinesia        |
|                   |                     | M. szulgai    | Cystic fibrosis           |
|                   |                     | M. xenopi     | GERD                     |
|                   |                     | M. celatum    | Bronchiectasis            |
|                   |                     | M. asiaticum  | Pulmonary histoplasmosis  |
|                   |                     | M. shinoides  | Low BMI with scoliosis, pectus excavatum, mitral valve prolapse |
|                   |                     | M. malmoense (Scandinavian Peninsula; Northern Europe) | Smoking or heavy alcohol use (M. malmoense) |
|                   |                     |               | Lymphopenia               |
|                   | MAC                 | M. malmoense  | Children; 1–5 yrs         |
|                   | M. scrofulaceum     |               | Men with lung cancer      |
| Cervical Lymphadenitis3, [4,111] | MAC | M. malmoense |                               |
| Skin, soft tissue infection | M. ulcerans       | M. szulgai    | Bathing in water from bore holes insect bites |
|                   | M. kansasii         | MAC           | Possible association with pedicures |
|                   | M. marinum*         | M. terrae     | “Exposure to fish tanks or other contaminated marine water sources |
|                   | MAC                 | M. szulgai    |                               |
|                   | M. abscessus        | M. malmoense  |                               |
|                   | M. xenopi           |               |                               |
| Bone disease [112,113] | M. kansasii     | MAC           | May occur via direct trauma or haematogenous seeding |
|                   | M. fortuitum        | M. xenopi     |                               |
|                   |                     | M. chelonae   |                               |
|                   |                     | M. abscessus  |                               |
| Disseminated disease [114,115] | MAC | M. kansasii | Severe Immunosuppression: |
| FISIO              |                     | M. abscessus  | HIV infection/AIDS (CD4 count <50 cells) |
| BSI                |                     | M. chelonae   | SOT or stem cell transplant |
| Abscesses          |                     | M. haemophilum M. scrofulaceum | long-term, high dose steroids |
| Peritonitis        |                     | M. malmoense  |                               |

Abbreviations: BMI - Body Mass Index, BSI – Blood Stream Infection, FUO – Fever of Unknown Origin, HIV – Human Immunodeficiency Virus, MAC – Mycobacterium Avium Complex, SOT – Solid Organ Transplant.
improve the microbiologic yield [3,4]. Decontamination with contamination or bacterial overgrowth. When processing these speci-

### Abbreviations:
- Reduced with formalin.

Commonly used stains for detection of acid fast bacilli.

| Stain | Specimen type | Appearance | Other Findings | Mycobacteria |
|-------|---------------|------------|----------------|--------------|
| Ziehl-Neelsen [121] | Any clinical specimen | Bright red with blue background | Weakly acid fast organisms, do not appear bright red | M. fortuitum, M. chelonae, M. abscessus |
| Modified Kinyoun [121] | Cytospin or solid culture media | Bright red | | |
| Rapid Modified Auramine O Fluorescent [122] | Any clinical specimen | Yellow to orange or bright green with dark background | Some rapid growing mycobacteria may not fluoresce well | MAC |
| Fite [123] | Preferred for tissue specimens | Pink with blue background | | Preferred stain for M. leprae |
| Gomori-methenamine Silver Stain [124] | AFB in tissue specimens | Brown to black | | M. kanslii, MAC |
| Periodic Acid Schiff Stain [124] | AFB in tissue specimens | Pink | | M. chelonae, M. abscessus, M. kanslii, MAC from skin |

*Reduced with formalin.

Abbreviations: AFB – Acid Fast Bacilli, MAC – Mycobacterium Avium Complex.
organisms. Several organisms need special culture conditions to improve yield. Time to growth is usually earlier in liquid media than solid media.

NTM are commonly classified into rapid and slow growers based on time to growth of mature colonies on solid culture media [12]. Rapid growing NTM grow in less than seven days; slow growing NTM take more than seven days to grow. The characteristics of rapid (RGM) and slow-growing NTM species are summarized in Table 4.

Slow growing mycobacteria colonies are typically first seen at 2 weeks and mature colonies are expected at 3 weeks on solid media such as L-J agar [13] and the Middlebrook agars [12]. In contrast, the rapid growing mycobacteria colonies are typically seen by 4 days. Middlebrook 7H10 is a non-selective medium that can be utilized for quantitative reporting and to differentiate chromogenic from non-chromogenic mycobacteria (Table 5) [14]. MGIT is a liquid broth medium that allows automated detection of mycobacterial growth based on emission of fluorescence (MGIT 960 instrument; BD) [15,16]. The sensitivity and specificity for detection of NTM for this system is 98.8% and 100%, respectively [17].

### Table 4

Classification of non-tuberculous mycobacteria based on time to growth.

| Classification | Time to Growth | Major Groups | Common Species | Growth Requirements | Common Clinical Syndromes |
|----------------|----------------|--------------|----------------|---------------------|---------------------------|
| Rapidly Growing | <7 days | *M. fortuitum* [125] | *M. fortuitum* | 35°–37 °C | SSTI, Skeletal infection |
|                |       | *M. peregrinum* | *M. peregrinum* | 35°–37 °C | Skeletal infection |
|                |       | *M. senegalense* | *M. senegalense* | 35°–37 °C | Skeletal infection |
|                |       | *M. setense* | *M. setense* | 35°–37 °C | Skeletal infection |
|                |       | *M. porcinum* | *M. porcinum* | 35°–37 °C | Skeletal infection |
|                |       | *M. haustorium* | *M. haustorium* | 35°–37 °C | Skeletal infection |
|                |       | *M. boenickei* | *M. boenickei* | 35°–37 °C | Skeletal infection |
|                |       | *M. brisbanense* | *M. brisbanense* | 35°–37 °C | Skeletal infection |
|                |       | *M. neworleansense* | *M. neworleansense* | 35°–37 °C | Skeletal infection |
|                |       | *M. chelonae* | *M. chelonae* | 35°–37 °C | Skeletal infection |
|                |       | *M. salmoniphilum* | *M. salmoniphilum* | 35°–37 °C | Skeletal infection |
|                |       | Subspecies of *M. abscessus*: | *M. abscessus*: | 35°–37 °C | Skeletal infection |
|                |       | *M. bolleti* | *M. bolleti* | 35°–37 °C | Skeletal infection |
|                |       | *M. massiliense* | *M. massiliense* | 35°–37 °C | Skeletal infection |
|                |       | *M. abscessus* | *M. abscessus* | 35°–37 °C | Skeletal infection |
|                |       | *M. mucogenicum* [127] | *M. mucogenicum* | 35°–37 °C | Bacteremia in ICH |
|                |       | *M. aubagnense* | *M. aubagnense* | 35°–37 °C | Bacteremia in ICH |
|                |       | *M. phocaicum* | *M. phocaicum* | 35°–37 °C | Bacteremia in ICH |
|                |       | Late pigmenting RGM | *M. chelonae* | 35°–37 °C | Pneumonia |
|                |       | *M. abscessus* | *M. abscessus* | 35°–37 °C | Pneumonia |
|                |       | Subspecies of *M. abscessus*: | *M. abscessus*: | 35°–37 °C | Pneumonia |
|                |       | *M. bolleti* | *M. bolleti* | 35°–37 °C | Pneumonia |
|                |       | *M. massiliense* | *M. massiliense* | 35°–37 °C | Pneumonia |
|                |       | *M. abscessus* | *M. abscessus* | 35°–37 °C | Pneumonia |
| Slow Growing | >7 days | MAC | *M. intracellulare* | 35°–37 °C | Pulmonary disease, Lymphadenitis, Disseminated infection, Hypersensitivity pneumonitis |
| Non-pigmenting RGM |       | *M. mageritense* | *M. mageritense* | 35°–37 °C | SSTI, CIED Infection |
|                |       | *M. wolinskyi* | *M. wolinskyi* | 35°–37 °C | CIED Infection |
|                |       | *M. xenopi* | *M. xenopi* | 42°–45 °C | Pulmonary disease, Disseminated infection, Skeletal infection |
|                |       | *M. kansasii* | *M. kansasii* | 35°–37 °C | Disseminated infection, Cervical lymphadenopathy, Skeletal infections |
|                |       | *M. simiae* | *M. simiae* | 35°–37 °C | Disseminated infection, Pulmonary disease, Prosthetic valve endocarditis |
|                |       | *M. lentiflavum* | *M. lentiflavum* | 35°–37 °C | Disseminated infection, Prosthetic valve endocarditis, SSTI |
|                |       | *M. terrae/nonchromogenicum* | *M. terrae/nonchromogenicum* | 35°–37 °C | Disseminated infection, Pulmonary disease, Prosthetic valve endocarditis |
|                |       | *M. arupense* | *M. arupense* | 35°–37 °C | SSTI, Lymphadenitis |
|                |       | *M. kumamotoense* | *M. kumamotoense* | 35°–37 °C | SSTI, Lymphadenitis |
|                |       | *M. heraklionense* | *M. heraklionense* | 35°–37 °C | SSTI, Lymphadenitis |
|                |       | *M. longobardum* | *M. longobardum* | 35°–37 °C | SSTI, Lymphadenitis |
|                |       | *M. haemophilum* | *M. haemophilum* | 28°–30 °C requires hemin or iron | SSTI, Lymphadenitis |
|                |       | *M. genavense* | *M. genavense* | 28°–30 °C requires hemin or iron | SSTI, Lymphadenitis |
|                |       | *M. xenopi* | *M. xenopi* | 42°–45 °C | SSTI, Lymphadenitis |
|                |       | *M. ulcerans* | *M. ulcerans* | 28°–30 °C | SSTI, Lymphadenitis, “Buruli ulcer” |
|                |       | *M. marinum* | *M. marinum* | 28°–30 °C | SSTI, Lymphadenitis, “Fish tank Granuloma” |
|                |       | *M. gordonae* | *M. gordonae* | 35°–37 °C | SSTI, Lymphadenitis |

Abbreviations: BSI – Blood Stream Infection, CIED – Cardiovascular Implantable Electronic Device, ICH – Immunocompromised Host, MAC – Mycobacterium Avium Complex, RGM – Rapid Growing Mycobacteria, SSTI – Skin and Soft Tissue Infection.
Identification of NTM species is essential in the evaluation of a patient with NTM disease. Species identification allows for assessment of clinical significance, prognosis, and expected antimicrobial resistance. Unlike M. tuberculosis, no widely adopted techniques for species identification directly from clinical specimens exist. Therefore, culture remains the first step in identification. Once an organism has been isolated in culture, a number of diagnostic modalities can be employed to identify the organism to species level. Matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) is very effective at identifying most NTM. It is usually cheaper and simpler than commercial nucleic acid amplification assays or whole genome sequencing. However, it requires pure isolates and may not be able to differentiate between closely related mycobacteria such as M. chimaera and M. intracellulare. It is also limited by the breadth of the spectra library available to the instrument [18].

Molecular diagnostics has revolutionized the practice of species identification, but can be applied only after identification of growth on culture media [6]. A variety of Food and Drug Administration (FDA)-approved DNA probes for species specific RNA is available. If MALDI-TOF and species-specific probes are unable to identify an organism, sequencing of the 16s RNA may be useful. Two regions of the 16s RNA can be helpful in identifying NTM species. Several commercially available systems that offer out-of-the box sequencing are available. However, several species may not be differentiated as there is not enough genomic divergence to allow for accurate diagnosis beyond species complex level. Similar to MALDI-TOF, test characteristics depend on the library of available sequences [19].

Identifying organisms directly from clinical specimen is an area of ongoing research. Polymerase chain reaction (PCR)-based assays of respiratory samples for rapid identification of NTM species are currently in development. Assays used to diagnose TB such as Xpert MTB/RIF Ultra and TrueNAT (MoBio) may have some cross reactivity with NTM species, but they are not a primary means for diagnosis of NTM disease [20]. Line probe assays do have the ability to identify some species of NTM and test for aminoglycoside and macrolide resistance, but they are not widely available. MALDI-TOF may also be effective at identifying NTM species directly from clinical specimens [18]. However, these techniques are at present experimental, but hold the promise for a more rapid identification of NTM infections in the future.

Histology. In the majority of patients, diagnosis of pulmonary NTM disease can be made without a tissue sample. When other microbiological criteria are met, biopsies are not required [3,4,21]. In contrast to this, the diagnosis of extra-pulmonary NTM infections typically requires obtaining a tissue sample. The histologic hallmark of mycobacterial disease is necrotizing or non-necrotizing granulomatous inflammation with the presence of an NTM organism. A single tissue sample with these features is sufficient to establish NTM disease [22]. In immunocompetent patients, NTM histologic findings can mirror that of tuberculosis [23]. Granulomatous inflammation alone is not specific for NTM. Lung biopsy may be culture negative due to the small tissue sample, and an NTM diagnosis can still be made with evidence of granulomatous inflammation and one or more cultures with NTM growth [3,4,24].

| Colony Count | Interpretation |
|--------------|----------------|
| None         | Negative       |
| <50          | Actual count   |
| 50–100       | +              |
| 100–200      | ++             |
| 200–500 (Almost confluent growth) | +++ |
| >500 (Confluent growth) | ++++ |

Appearance of Colonies

| White, Cream, Buff | Non-chromogenic |
| Lemon, Yellow, Orange, Red | Chromogenic |

4. Radiographic diagnosis of NTM infections

No radiographic pattern is pathognomonic for pulmonary NTM disease. Two radiographic patterns are commonly encountered in pulmonary NTM disease: fibro-cavitary disease and nodular bronchiectasis. A combination of these two radiographic patterns or a ‘mixed’ pattern may also be seen.

Fibro-cavitary NTM pulmonary disease: Fibro-cavitary disease usually occurs in middle age or older men with underlying structural lung disease such as COPD or pneumoconiosis. Fibro-cavitary disease can be identified on chest X-ray and is difficult to distinguish from tuberculosis (TB) and endemic fungal infections with X-ray alone (Fig. 1). This presentation is characterized by upper lobe predominant, thin or thick walled cavities with surrounding pleural thickening [30]. Whereas TB usually has calcified lymphadenopathy and associated parenchymal infiltrates, NTM is not typically associated with these findings [30]. Nonetheless radiographic findings alone should not be used to discern between TB and NTM infections. Pulmonary malignancies (particularly squamous cell carcinoma), fungal infections and pulmonary vasculitides...
Nodular bronchiectatic NTM pulmonary disease: Nodular bronchiectasis usually manifests in elderly, thin women and is associated with pectus excavatum, scoliosis, and mitral valve prolapse [31]. Nodular bronchiectasis may be visualized as 'tram tracking' with micro nodularity on chest roentgenogram but is best observed on high resolution computed tomography of the chest (HRCT). On HRCT, this appears as cylindrical bronchiectasis with branching centrilobular nodules (i.e. "tree-in-bud") (Fig. 2) [32]. These changes are usually bilateral but preferentially involve the lingula and right middle lobe. Overall these radiographic findings are non-specific and can be seen in aspiration and other bacterial infections. When the cause of tree-in-bud opacities can be determined, less than half are attributed to NTM infection [33].

Hypersensitivity pneumonitis: Hypersensitivity pneumonitis secondary to inhalation of MAC is another variation of NTM associated lung disease that is worth mentioning. This entity is better known as "hot tub" lung disease [34] and is presumed to be secondary to a hypersensitivity reaction to aerosolized MAC rather than true infection since clinical symptoms and radiographic changes improve with antigen avoidance and/or glucocorticoids [35]. However, NTM infection and hypersensitivity features can coexist [35,36]. HRCT findings are consistent with acute hypersensitivity pneumonitis: upper lobe predominant, bilateral ground glass opacities with air trapping on expiration and centrilobular nodularity.

Extra-pulmonary NTM disease: Radiographic features of extra-pulmonary NTM infection are non-specific and variable, depending on the site of infection. For skin and soft tissue NTM infections, radiographic imaging studies are not routinely required for diagnosis. However, imaging studies such as sonography, CT, and MR can be useful to localize an abscess or determine if infection extends into deeper soft tissues or adjacent bone, in particular in situations where the response to treatment is sub-optimal. Radiographic features of NTM lymphadenitis include decreased echogenicity on ultrasound, corresponding to intranodal liquefactive/cystic necrosis, as well as an enlarged nodal mass with central necrosis on CT or MRI [37,38]. Common radiographic features of NTM osteomyelitis include permeative osteolysis, bone sequestration, and periostitis. Articular NTM infections manifest radiographic findings ranging from regional osteopenia to marginal and subchondral osseous erosions [39].

5. Checking interleukin-2 and interferon gamma pathways

Certain patients are more susceptible to NTM disease than others. This is illustrated in other mycobacterial diseases by the large number of patients with positive tuberculin skin testing who never progress to active disease, and the small number of patients who receive bacille Calmette-Guerin (BCG) vaccination and develop disseminated BCG-osis [42]. Protection from mycobacterial infection is provided by the type I cytokine pathway; investigations have shown that defects in the genes encoding IL-12, IL-23, and interferon-γ (INF-γ) receptors lead to reduced immunity to mycobacteria [43]. Patients with these primary immunodeficiencies are said to have ‘Mendelian susceptibility to mycobacterial disease’.

While not addressed in the 2020 or prior ATS/IDSA guidelines [4,44], it is reasonable to assess patients for primary defects in cell mediated immunity who present with disseminated NTM infection without known secondary cause, especially if family members are also ill. This information informs prognosis and may affect treatment decisions [45]. These patients are also susceptible to other infections including cytomegalovirus, human herpes virus-8, herpes simplex virus, Listeria, and Histoplasma infections [46].

6. Distinguishing infection from colonization

Non-tuberculous mycobacteria are ubiquitous in the environment; isolation of NTM species from non-sterile samples does not equate to infection. Most NTM isolated from a respiratory source may not meet currently established criteria for NTM infection [47]. The respiratory tract can be colonized with NTM, especially if underlying structural airway and/or lung disease are present. MAC is the most commonly
described NTM airway “colonizer” [48], but it is unclear if this is true colonization or low grade infection. Colonization without infection is an unproven concept in pulmonary NTM disease; however, this does not imply that all patients with NTM respiratory isolates require antimicrobial treatment. The current criteria for NTM pulmonary infections were established by a joint guideline from ATS and IDSA in 2007 but were more recently updated in 2020 [3,4]. These guidelines by necessity focus on the most commonly encountered and best described NTM species—MAC, M. kansasii, and M. abscessus. Presumably these guidelines apply to other less common and lesser-known NTM species, but data and experience with these NTM species are limited. The diagnosis of pulmonary NTM disease requires clinical, radiographic, and microbiologic correlation. These criteria are of equal importance, and all must be met to diagnose pulmonary NTM disease [3].

7. Clinical manifestations of NTM infections

Pulmonary disease is the most common manifestation of NTM infections [48], but NTM can also cause localized infection of the skin, bones and soft tissues; disseminated infections in patients with severely compromised immune systems can also occur. The current ATS/IDSA guidelines review these alternate manifestations but do not specifically address the diagnosis and treatment of extra-pulmonary NTM [3,44]. Common NTM infection syndromes are summarized in Table 1.

The clinical manifestations of NTM infections are variable and non-specific. Most patients with pulmonary NTM disease will have chronic or recurring cough with or without sputum production [49]. This may be accompanied by constitutional symptoms (e.g. fever, fatigue, weight loss, and night sweats), chest pain, or shortness of breath. These latter symptoms may only be present with advanced disease. Because many patients with pulmonary NTM disease have underlying lung disease such as bronchiectasis or chronic obstructive pulmonary disease (COPD), it can be very challenging to determine if NTM infection is the cause of the presenting symptoms.

Patients with skin, soft tissue, and musculoskeletal NTM infections may present with skin nodules, ulcers, wound drainage or abscesses in addition to the constitutional symptoms noted above. Musculoskeletal NTM infections may present with joint pain, stiffness, and swelling as well as muscle wasting and draining sinuses. Mycobacterial lymphadenitis presents typically with enlarged lymph nodes, often times non-tender. Disseminated NTM infection may present with scattered skin lesions. In patients with advanced HIV infection, disseminated MAC infection presents as a systemic febrile illness with abdominal pain and diarrhea.

Physical findings reflect the system or organs affected but are variable and nonspecific. For example, features of skin and soft-tissue NTM include or pain, erythema, warmth, local pain, swelling, ulcers, and abscesses. It should be noted that cosmetic surgeries are common precipitant for NTM skin and soft tissue infections. A firm, painless mass with overlying skin changes is a common physical examination finding in NTM lymphadenitis. Hepatosplenomegaly is a common physical examination finding in disseminated MAC disease.

8. Antimicrobial treatment of non-tuberculous mycobacterial infections

As described in the preceding sections, the treatment of NTM infections is complex and limited by several issues, including the need for multidrug regimens, prolonged treatment durations, and the use of drugs that are often associated with adverse reactions and not well-tolerated. Co-morbidities that are often present in patients with NTM infections add another layer of complexity to the management. The optimal drug doses, drug combinations, and treatment durations have not been reliably established for most, if not all, NTM infections. It

Table 6

| Isolate(s) | Drugs |
|-----------|-------|
| **Slow Growing NTM** | |
| MAC | Human: AMK [129] AZ [130] CFZ [131] CLR [132] BDQ [133] EMB [130] Rif [130] RFB [130] SM [134] LZD [135] MOX [136] Micro: CTZ/AV [137] ETO [138] TIG [139] TZD [140] |
| M. kansasii | Human: CLR [141] EMB [142] INH [142] LFX [143] Rif [142] RFB [144] SM [142] Micro: AMK [145] AZ [146] BDQ [146] CFZ [146] GIP [145] DLM [146] LFX [146] LZD [146] MOX [146] SMX [145] TIG [146] TZD [140] |
| M. marinum | Human: AMK [147] CLR [148] DOX [148] EMB [149] MIN [146] Rif [149] RFB [150] SMX/TMP [151] Micro: CPX [152] IMI [152] INH [152] LFX [152] LZD [152] MOX [152] TIG [152] TZD [140] |
| M. leprae | Human: CFZ [154] CLR [155] DOX [156] MIN [154] MOX [154] OFX [154] RIF [158] micro: LFX [159] |
| **Rapid Growing NTM** | |
| MABC | Human: AMK [160] AZ [160] BDQ [161] CFZ [160] CFZ [161] CLA [160] CLA [162] DOX [162] DOX [163] EMB [161] LFX [120] LFX [162] LFX [164] Micro: EMA [165] OMA [165] LZX [166] TZD [140] |
| M. chelonae | Human: AMK [167] AZ [168] CFZ [169] CLR [170] CFZ [170] DOX [172] IMI [173] LFX [174] LFX [175] LFX [176] TIG [164] TOB [177] Micro: MIN [179] OMA [178] TIG [140] |
| MFCa | Human: AZ [179] AMK [180] CLR [181] DOX [182] IMI [173] LFX [183] MIN [184] OX [180] SMX/TFM [185] Micro: CPX [186] MOX [187] LZX [166] OMA [178] TIG [188] TOB [189] TZD [140] |
| MSAa | Human: AMK [190] CFX [190] DOX [190] IMI [190] SMX/TFM [190] TOB [190] |
| M. immunogenum | Human: AMK [193] CLR [194] Micro: AMK [195] CLR [195] LZX [140] TIG [188] TZD [140] |
| M. mucogenicum | Human: AMK [196] AZ [196] CFZ [196] LFX [197] MFX [198] Micro: AMK [127] AMX/CLV [197] CFX [199] CPX [199] DOX [199] IMI [199] LZX [198] MIN [199] SMX/TFM [199] |

**Abbreviations:** AMK — amikacin, AMX/CLV — amoxicillin/clavulanate, AZ — azithromycin, BDQ — bedaquiline, CFX — cefoxitin, CFZ — clofazamine, CLR — clarithromycin, CPX — ciprofloxacin, CTZ/AV — ceftazidime/avibactam, DAP — dapson, DOX — doxycycline, DLM — delaminid, EMB — ethambutol, ERA-eravacycline, ETO — ethionamide, IMP — imipenem, INH — isoniazid, LFX — levofloxacin, LZX — linezolid, MIN — minocycline, MFX — moxifloxacin, OFX — ofloxacin, OMA-omadacycline, RFB — rifabutin, RIF — rifampin, SM — streptomycin, SMX — sulfamethoxazole, TIG — tigecycline, TOB — tobramycin, TMP — trimethoprim, TZD — tedizolid.

aM. fortuitum, M. abscessus subspecies abscessus, and M. abscessus subspecies bolletii, and M. smegmatis have the erm gene for inducible macrolide resistance which should be tested for if considering macrolide [290].

bM. wolinii isolates intrinsically resistant to tobramycin [191].
Table 7
Typical drug dosing for NTM disease.

| Drug               | Standard dose                                                                 | Renal adjustment                      |
|--------------------|-------------------------------------------------------------------------------|----------------------------------------|
| Amikacin           | 15 mg/kg³ IV daily                                                            | Est crcl < 30 ml/min:12-15 mg/kg³ three times weekly |
| Azithromycin       | 250 mg once daily                                                             | No adjustment                          |
| Bedaquiline Fumarate| Week 1–2: 400 mg once daily with food                                          | No adjustment                          |
|                    | Week 3–24: 200 mg three times weekly with food                                 |                                        |
| Cefoxitin          | 200 mg/kg/day IV in 3 divided doses² (maximum 12 g/24 h)                      | Est crcl 30–49 ml/min: 1–2 g 8–12 h    |
|                    |                                                                               | Est crcl 10–29 ml/min: 1–2 g q12-24 h  |
|                    |                                                                               | Est crcl < 10 ml/min: 1–2 g q24–48 h   |
|                    |                                                                               | Est crcl 10–49 ml/min: 250–500 mg twice daily                                   |
|                    |                                                                               | Est crcl < 10 ml/min: 250–500 mg daily                                         |
| Ciprofloxacin      | 500–750 mg twice daily                                                        | Est crcl < 30 ml/min: 500 mg once daily                                         |
|                    |                                                                               | -OR-                                   |
|                    |                                                                               | 250 mg twice daily                    |
| Clarithromycin     | 500 mg twice daily or 1000 mg once daily (extended release)                   | Est crcl < 30 ml/min: 500 mg once daily                                         |
|                    |                                                                               | -OR-                                   |
|                    |                                                                               | 500 mg twice daily                    |
| Clavulanic         | 100 mg daily                                                                  | No adjustment                          |
| Delaminid          | 100 mg twice daily                                                            | Est crcl < 30 ml/min: Not recommended                                         |
| Doxycycline        | 100 mg twice daily                                                            | No adjustment                          |
| Ethambutol         | 15–20 mg/kg (maximum 1600 mg) daily                                            | Est crcl < 30 ml/min: 20–25 mg/kg three times weekly                           |
| Ethionamide³       | 15–20 mg/kg/day (max 1000 mg) daily in divided doses                          | No adjustment                          |
| I/C                | Imipenem 1000 mg/Glistatin 1000 mg given intravenously twice daily             | Est crcl 20–40 ml/min: 750 mg –750 mg (I/C) every 12 h.                       |
|                    |                                                                               | Est crcl < 20 ml/min: 500 mg –500 mg (I/C) every 12 h.                       |
| Isoniazid²         | 5 mg/kg (max 300 mg) daily                                                   | No adjustment                          |
| Levofloxacin       | 750 mg daily                                                                  | Est crcl 20–49 ml/min: 500–750 mg every 48 h                                   |
| Linezolid³         | 600 mg daily                                                                  | Est crcl < 20 ml/min: 250–500 mg every 48 h                                   |
| Minocycline        | 200 mg once, then 100 mg twice daily                                          | No adjustment                          |
| Moxifloxacin       | 400 mg daily                                                                  | Est crcl < 10 ml/min: Standard dose: -OR-                                    |
|                    |                                                                               | 200 mg once, then 100 mg once daily                                           |
| Rifabutin          | 5 mg/kg (max 300 mg) daily                                                   | No adjustment                          |
| Rifampin           | 10 mg/kg (max 600 mg) daily                                                   | Est crcl < 30 ml/min: Consider standard dose: -OR-                            |
| Streptomycin       | 15 mg/kg² daily                                                               | No dose adjustment                    |
| SMX/TMP            | SMX/TMP 800 mg/160 mg twice daily                                             | Est crcl < 30 ml/min: 12-15 mg/kg³ 3 times weekly                             |
| Tedizolid          | 200 mg once daily                                                            | Est crcl 15–20 ml/min: SMX/TMP 800 mg/160 mg once daily                       |
| Tigecycline        | 100 mg IV once, then 50 mg twice daily                                        | No adjustment                          |

Abbreviations: Est crcl – Estimate creatinine clearance, I/C – Imipenem/ Glistatin, IV – intravenous, kg – Kilogram, mg – Milligram, SMX/TMP – Sulfamethoxazole/Trimethoprim.

1Use an adjusted body weight (IBW + 0.4(ABW – IBW) for empiric dosing in the setting of obesity and follow serum levels.

2Some providers use reduced dose or schedule to optimize long-term tolerability.

3Consider Vitamin B6 25–50 mg daily to decrease risk of toxicity.

4Renally-cleared metabolite accumulation can occur. Monitor closely for toxicity.

5Rifabutin: May consider decreasing to 50% of standard dose and monitoring serum drug levels to avoid toxicity. Standard dosing appropriate for patients on dialysis.

6The optimal management of NTM infections requires a well-coordinated multidisciplinary approach, involving infectious diseases physicians, pulmonologists, pharmacists, microbiologists, radiologists, nurses, respiratory therapists, and dietitians.

7The antimicrobial drugs currently used for treating NTM infections were not specifically developed for that purpose. Their utility in treating NTM infections was derived from demonstration of activity in-vitro or in animal models, drug susceptibility testing, and observations from clinical practice. Antimicrobials that have demonstrated activity against NTM species and/or infections in vitro are highlighted in Table 6.

8Treatment of NTM infections, even treatment of limited skin or soft tissue infection, typically requires the use of at least 2 drugs in

should be noted that several new medications used for the treatment of multi-drug resistant TB such as, bedaquiline, pretomanid and delamanid have in-vitro activity against NTM species but in vivo data is lacking at this time [50,51]. Consensus guidelines for the management of NTM infections exist. However, they are based on limited data and expert opinion rather than evidence from adequately powered controlled trials with sufficiently long follow-up period. This notwithstanding, the following general considerations can be noted.

- In general, anti-mycobacterial treatment should be offered only when the clinical, radiographic, and microbiologic criteria for the diagnosis of NTM infections are met.
Empiric therapy:

Treatment of NTM is often provided in 2 phases: An initial phase with Ethambutol 1200 mg (3 tablets) once daily DAY 4 DAY 5 DAY 6

- Rifampin 300 mg (1 capsule) once daily
- Ethambutol 1200 mg (3 tablets) once daily

After 7-14 days, the maintenance phase is started with fewer drugs, and when possible, an all oral drug regimen. The duration of the initial phase of therapy is variable, often in the range of 1–3 months. This recommended duration is not evidence based; in clinical practice, it is often shortened because of intolerance or treatment-emergent drug adverse events.

Empiric therapy:

Species level identification is necessary to determine the most appropriate treatment regimen. For most NTM infections, susceptibility-based treatment is preferred over empiric therapy. Notwithstanding the poor in vitro susceptibility correlation with clinical outcomes, baseline susceptibility testing, to guide but not to dictate treatment, is recommended for NTM isolates from patients believed to have definite disease. However in disseminated or severe infections, waiting for the full microbiologic results prior to initiation of anti-mycobacterial therapy may endanger patients’ lives. In such cases, empiric therapy based on the prevailing understanding of the usual antimicrobial susceptibility profile of the putative causative organism is recommended. For example, for infections by slow-growing NTM, a regimen consisting of an oral macrolide, rifamycin, ethambutol, and amikacin may be considered as empiric therapy; whereas, a regimen comprising of amikacin, imipenem, and a macrolide may serve as appropriate empiric therapy for infections presumed to be caused by rapid-growing NTMs. Empiric therapy should be tailored once the pathogen has been fully identified and AST results are available.

- For some patient populations, initiating a full dose multi-drug regimen all at once may be intolerable. In such cases, clinicians may wish to consider initiating therapy sequentially, adding a drug every few days until the desired multidrug regimen is achieved. Sequential drug addition with dose titration during therapy initiation (Table 8) often facilitates tolerance of a difficult drug regimen. This approach affords minimal risk of drug resistance due to the slow replication of NTM compared to other bacterial species. This approach can be used for both pulmonary and non-pulmonary NTM infections. Moreover given the slow replication of NTM species in general and prolonged duration of therapy, this approach can also be used to improve tolerance even in severe infections.

- The optimal duration of treatment for individual NTM species and infections is not known. In general, treatment is prolonged, ranging from 3 to 4 months for limited skin and soft tissue infections to 12 months and longer for severe lung and disseminated infections. Factors that guide the decision to discontinue antimicrobials include clinical, microbiologic, and radiologic response to treatment, as well as the tolerability of the treatment regimen. For example, drug therapy for pulmonary NTM disease should generally continue for 12 months after confirmed culture conversion.

- Chronic suppressive therapy: For some NTM infections, no antimicrobial regimen has been shown to effect long-term microbiologic or clinical cure. In situations where curative treatment is not possible, the goal of therapy shifts from definitive eradication of infection to minimization of symptoms. For example, if source control is not possible (e.g. infected retained prosthetic material, severe structural lung abnormalities) then chronic suppressive therapy may be warranted. Non-pharmacologic adjunctive interventions (discussed below) such as aggressive pulmonary hygiene should be optimized in these patients.

9. Monitoring for clinical response to treatment

Clinical, radiographic, and microbiologic assessments are typically
### Table 9: Adverse drug reactions of NTM therapy and monitoring guidance [201,202].

| Drug                  | Adverse drug reactions                                      | Laboratory/ Clinical monitoring                                      |
|-----------------------|-------------------------------------------------------------|---------------------------------------------------------------------|
| Amikacin (parenteral) | Kidney toxicity, electrolyte abnormalities                   | Clinical: consider audiometry, balance assessments                   |
|                       | (K, Mg, Ca), vestibular, toxicity, hearing loss             | Laboratory: BMP w/Scr, BUN, K (2x/weekly), TDM for durations >1 week |
| Amikacin (inhaled)    | Sore mouth/throat, bronchospasm, cough, wheezing/SOB, dysphonia | Clinical: pre-/post administration respiratory status               |
| Amoxicillin-Clavulanate| Rare: abdominal discomfort, diarrhea, nausea, vomiting     | Laboratory: SCR (monthly), serum trough level                        |
|                       | Rare: hyper-sensitivity, rash                               | (to confirm lack of systemic accumulation) after 1 week of therapy   |
| Azithromycin          | GI (abdominal pain, nausea, vomiting, diarrhea, dyspepsia), headache, visual disturbance | Clinical: GI effects                                                  |
|                       | Rare: hearing loss, QT prolongation                          | Laboratory: CBC w/differential, ALT and SCR (1 month, 3 months, then annually) |
| Bedaquiline           | Nausea, arthralgia, headache, chest pain,                   | Clinical: ECG (baseline, 2 weeks, 12 weeks, and 24 weeks)           |
| Emafutate             | QT prolongation, hepatotoxicity                             | Laboratory: serum Ca, Mag, and K (baseline); liver function tests: AST, ALT, bilirubins, alk phos (baseline, then monthly) |
| Cefoxitin             | Injection site reactions, hypotension, transaminisit,      | Clinical: rash and hypersensitivity symptoms                         |
|                       | leukopenia, thrombocytopenia                                 | Laboratory: CBC w/differential, ALT, and BMP w/Scr, BUN, K (weekly) |
| Ciprofloxacin         | GI (abdominal pain, nausea, vomiting, diarrhea, dyspepsia), hypoglycemia, CNS effects (agitation, nervousness, disorientation, memory impairment), rash | Clinical: consider ECG, signs of hypoglycemia/ CNS effects           |
|                       | Rare: peripheral neuropathy, tendon rupture, QT prolongation| Laboratory: CBC w/differential, ALT, and SCR (1 month, 3 months, then annually) |
| Clarithromycin        | GI (taste disturbance, abdominal pain, nausea, vomiting, diarrhea, dyspepsia) | Clinical: consider audiometry, GI effects, consider EGG^†             |
| Clofazimine           | Orange/red discoloration of body fluids/feaces, skin manifestations (hyperpigmentation ichthyosis, xeroderma pruritus, phototoxicity, rash), GI disturbance (nausea, vomiting, diarrhea, anorexia, abdominal pain) | Laboratory: CBC w/differential, ALT, and SCR (1 month, 3 months, then annually) |
| Doxycycline           | GI effects (nausea, vomiting, diarrhea, dyspepsia), photosensitivity, rash | Clinical: ECG (baseline, 2 weeks, 12 weeks, and 24 weeks)           |
| Eihambutol            | optic neuritis, GI effects (nausea/vomiting)                | GI adverse effects, psychological disturbances (depression/ anxiety) related to skin effects |
|                       | Rare: peripheral neuropathy                                 | Laboratory: liver function tests: AST, ALT, bilirubins, alk phos (baseline, then monthly) |
| Ethionamide           | GI (nausea, vomiting, anorexia, taste disturbance, diarrhea, endocrine (gynecomastia, hair loss, acne, impotence, menstrual irregularity, reversible hypothyroidism), hepatotoxicity, neurotoxicity (peripheral neuropathy, optic neuritis, depression, and psychosis) | Clinical: monthly visual acuity assessment and red-green color-discrimination assessment (fihihara), fundoscopic exam (baseline and every 3 months) |
| Imipenem/Clarithromycin| GI effects (nausea, vomiting, diarrhea), rash              | Laboratory: SCR (baseline and monthly)                              |
| Isoniazid             | Peripher neuropathy, asymptomatic transaminisit elevations, hepatitis | Clinical: signs of hepatitis-toxicity (nausea, abdominal pain, jaundice) and neuropathy |
| Levofloxacin          | GI (nausea, diarrhea) hypoglycemia, CNS effects (dizziness, agitation, nervousness, disorientation, memory impairment, insomnia) | Laboratory: LFTs: AST/ALT, alk phos, bilirubins (baseline and monthly), TSH (baseline and every 3 months) |
| Linezolid             | GI effects (nausea, vomiting, diarrhea), headache, hematologic myelosuppression (thrombocytopenia, leukopenia, anemia) | Clinical: signs of hepatoxicity (nausea, abdominal pain, jaundice) and neuropathy |
| Minocycline           | GI effects (nausea, vomiting, diarrhea), skin effects (rash, photosensitivity, skin pigmentation), dizziness, headache | Laboratory: BMP w/Scr, BUN, K (2x/weekly), TDM for durations >1 week |
| Moxifloxacin          | GI (nausea, diarrhea) hypoglycemia, CNS effects (dizziness, agitation, nervousness, disorientation, memory impairment, insomnia) | Clinical: Consider EGG, signs of hypoglycemia/CNS effects           |
|                       | Rare: peripheral neuropathy, tendon rupture, QT prolongation| Laboratory: CBC w/differential, ALT, and SCR (1 month, 3 months, then annually) |
| Rifabutin             | Discoloration (orange/red) of body fluids, cutaneous effects (pruritus, rash), GI effects (nausea, vomiting), hepatitis, anterior uveitis, hematologic toxicity (leukopenia, neutropenia), arthralgias/myalgias | Clinical: GI effects, cutaneous effects |
| Rifampin              | Discoloration (orange/red) of body fluids, cutaneous effects (pruritus, rash), GI effects (nausea, vomiting), hepatitis, hematologic toxicity (leukopenia, hemolytic anemia) | Laboratory: CBC w/differential, ALT, and SCR (1 month then every 3 months) |
| Streptomycin          | Kidney toxicity, electrolyte abnormalities (K, Mg, Ca), vestibular, toxicity, hearing loss | Clinical: Monitor DDI, GI/ cutaneous effects |
| Tigecycline           | GI effects (nausea, vomiting, diarrhea, anorexia, dyspepsia), dizziness, rash | Laboratory: CBC w/differential, ALT, and SCR (1 month then every 3 months) |

(continued on next page)
used to determine if a patient is responding to therapy.

Clinical symptoms should be assessed at each clinical encounter. Improvement in symptoms can be a key indicator of response to treatment, but clinical symptoms do not always correlate with changes in radiographic or microbiologic status. Furthermore, complete resolution of symptoms at the end of treatment is not universal given the multifaceted nature of NTM disease and comorbid illness that can contribute to symptomatology. Oftentimes clinical monitoring is dictated by the need to assess for the presence of drug toxicities in order to determine if drug and dose changes are necessary.

For pulmonary NTM infections, serial sputum cultures serve as a marker for treatment response. Current guidelines recommend monitoring sputum cultures every 1–2 months; confirmed sputum culture conversion (subsequent negative cultures one month apart) provides a basis for microbiologic cure and is a key factor in determining treatment duration. In situations where spontaneous expectorated sputum specimens cannot be collected, induced sputum should be obtained; obtaining deep respiratory samples via bronchoscopy for the purpose of monitoring response to therapy is not usually required.

For extra-pulmonary NTM infections, treatment response monitoring based on serial collection of microbiologic data is less well prescribed and is usually performed at the discretion of clinicians based on clinical progress.

Radiographic imaging studies are also surrogates for treatment response. Imaging is often performed during therapy and at the end of a planned treatment period to confirm treatment response. The optimal intervals for imaging performance are not well established.

### 10. Safety monitoring during anti-mycobacterial therapy

Adverse drug reactions (ADRs) are very common during the treatment of NTM infections and are associated with treatment interruption or early treatment cessation [27,52,53]. Not surprisingly, some evidence exists that ADRs also impact treatment outcome [54]. Therefore, educating patients about the likely ADRs that they may encounter with the drug-regimen that they have been prescribed, and monitoring them for treatment-emergent ADRs is a key component of the management of the treatment of NTM infections. This monitoring is conducted in a variety of ways; there is no evidence basis for the optimal frequency of monitoring of patients with NTM for adverse drug reactions. At a minimum, active assessment for the development of ADRs, through questions or physical examination, should be part of each clinical encounter. A high potential for drug interactions exists with many of the antimicrobials used to treat NTM infections; therefore, a close review of the medication list is warranted at every clinical encounter.

Safety monitoring for antimicrobial toxicity will vary based on multiple factors: co-morbid medical conditions, baseline functional status, liver function, kidney function, drug-drug interactions, concomitant medications with additive toxicity profile, intravenous versus oral therapy, drug dose, and the availability of laboratory resources. Nonetheless, it is important for clinicians to anticipate potential adverse reactions. Table 9 highlights the more notable adverse effects, while providing guidance on clinical and laboratory monitoring for extended therapy. These recommendations are meant to provide general guidance. More detailed monitoring may be warranted based on patient age, comorbidities, concurrent drugs, overlapping drug toxicities, and availability of healthcare resources.

Therapeutic drug monitoring (TDM) is the clinical practice of measuring drug concentrations in serum during a treatment course to ensure that target drug concentrations are achieved. The routine use of TDM other than to manage aminoglycoside therapy for NTM infections is not common. However, TDM of other drugs should be considered in situations where there are concerns for inappropriate drug exposure. Low therapeutic exposure could lead to treatment failure and/or resistance development while high exposure can lead to exposure dependent toxicity and intolerability of the drug program. Common reasons to consider TDM would include: sub-optimal treatment response, drug-drug interactions, exposure dependent toxicity development, renal/hepatic compromise, or malabsorption [4,27].

We recommend 2 h and 6-h serum drug levels following the end of infusion for amikacin, streptomycin, and tobramycin to calculate a back-extrapolated Cmax. We recommend the following targets: goal amikacin Cmax of 20–45 mcg/ml for 15 mg/kg once daily dosing [27]. A Cmax of 65–80 mcg/ml may also be considered for a 25 mg/kg dose given three times weekly [55]. We recommend a goal tobramycin (for *M. chelonae*) Cmax of 20–30 mcg/ml on 7 kg/day daily dosing. If Cmax levels are not feasible, consideration may be given to a single serum level taken 1 h following the end of infusion for amikacin or streptomycin targeting a serum range of 25–35 mcg/ml. For tobramycin, a single serum level taken 6–14 h following the start of infusion can be used, applying the Hartford nomogram [56]. After attainment of appropriate goal targets with stable renal function, we recommend weekly trough monitoring with a goal of ‘undetectable’ to ensure no drug accumulation.

### 11. Adjunctive therapies for NTM infections

**Reduction of immunosuppression.** Immunosuppressive therapies, such as oral and inhaled corticosteroids and TNF-alpha inhibitors, increase the risk for NTM disease. Prednisone equivalent doses of greater than 15 mg per day or inhaled fluticasone doses more than 800 mg per day are associated with a higher risk of NTM disease [57]. For patients taking TNF-alpha inhibitors, a United States’ study showed a 5–10 fold higher rate of NTM pulmonary disease as compared to the general population and rheumatoid arthritis patients on other therapies [58]. Infliximab showed the highest rates of NTM lung disease. However, Etanercept therapy was associated with more serious infections, including fatal MAC lung disease, fatal pulmonary *M. abscessus* infection, *M. chelonae* endophthalmitis, and *M. xenopi* spinal osteomyelitis [59].

Unlike with *M. tuberculosis*, routine screening for NTM disease prior to the initiation of TNF-alpha inhibitors is not recommended. However, certain patients, such as those with refractory, chronic cough may
benefit from CT imaging and sputum testing for NTM disease prior to the start of immunosuppressive therapy [57]. When NTM disease is diagnosed, decreasing or discontinuing immunosuppressive medications can be beneficial. For patients that need to continue on immunosuppressive medications, non-biologic agents such as methotrexate and low risks therapies such as abatacept should be considered [57].

Surgical resection. For extra-pulmonary NTM infections, such as skin/soft tissue, musculoskeletal, and lymphadenitis, surgical interventions such as debridement, excision, and drainage of abscesses are often a necessary and important component of the management of these infections [60–65].

The situation is vastly different when it comes to pulmonary NTM infections. Here, surgical resection plays a role only in select situations and in facilities where a surgical and multidisciplinary team experienced in managing such interventions is available. Typical indications for surgical therapy include failure of medical therapy and alleviation of life-threatening symptoms such as hemoptysis. In areas of extensive lung damage, antimicrobial penetration is low leading to treatment failure [3,4]. In a trial of 371 patients with mostly cavitary NTM disease, only 36% of patients achieved a cure after 24 months of multi-drug therapy [66]. In such cases, de-bulking surgery may slow disease progression as an adjunct to medical therapy. Drug therapy and medical interventions should precede surgery and continue afterward. Nutrition status should also be optimized prior to surgery. Studies reporting outcomes of surgical therapy in pulmonary NTM infections are mostly observational, heterogeneous in their patient and mycobacterial characteristics, and suffer from inherent selection bias. That notwithstanding, most reports indicate that adjunct surgical therapy can lead to improved patient outcomes with a low rate of complications [67–71].

Interferon-γ. INF-γ, a cytokine produced by CD4 lymphocytes, has been administered exogenously for the treatment of a variety of syndromes ranging from chronic granulomatous disease to hematologic malignancies [72,73]. INF-γ plays a critical role in host defenses against mycobacteria through the activation of macrophages [74,75]. The identification of low INF-γ production in certain individuals susceptible to NTM disease led to exploration of exogenous administration of various formulations of INF-γ for NTM treatment [76–78]. A randomized, double blind, placebo-controlled study performed in Cuba assessed 32 patients assigned to either placebo or recombinant, intramuscular INF-γ once daily for a month then three times per week up to 6 months as adjuvant to traditional antimicrobials. At the final evaluation, 72% of patients in the treatment group and 36% in the placebo group were deemed complete responders [78]. In contrast, a brief report from 2001 describes no sustained benefit of subcutaneous INF-γ therapy and an inability of INF-γ to improve the production of Th1 cytokines [79]. Flu-like symptoms including fevers, chills, and malaise are common with INF-γ [80]. Treatment with INF-γ may be a consideration in the treatment of select non-HIV patients with progressive, refractory NTM disease associated with a demonstrated INF-γ deficiency.

Rituximab. A specific syndrome of lymphadenitis associated with disseminated, rapid-growing NTM organisms has been identified in persons of Asian descent without HIV infection [81,82]. Co-infection with endemic fungi, herpes viruses, salmonella as well as reactive skin diseases is common [81,82]. High titers of antibodies neutralizing interferon-γ are seen resulting in increased susceptibility to these infections; thus, immune modulating therapies have been employed as adjunctive therapy to augment the body’s natural defenses [83–89]. Rituximab is a chimeric anti-CD20 monoclonal antibody that rapidly depletes circulating and tissue B-cells which has been used in the treatment of several autoantibody diseases including pemphigus vulgaris, pulmonary alveolar proteinosis, myasthenia gravis and red cell aplasia [90–95]. Rituximab was employed to halt progressive NTM disease by neutralizing anti-interferon-γ antibodies in a small number of cases in Asian patients without HIV infection. In both reports, patient’s anti-interferon-γ levels were shown to be elevated at baseline. Subsequent to rituximab treatment, autoantibody titer was reduced and IFN-γ signaling was improved. In conjunction with laboratory marker improvement, all patients showed clinical improvement and none experienced significant adverse effect from rituximab [96,97]. Rituximab dosing was based on lymphoma regimens at 375 mg/m² given every 7 for at least 4 doses [90]. In one of the case reports, methylprednisolone was also given at 100 mg daily [96]. There is a small body of evidence that rituximab may serve as an important adjunctive to antimycobacterials for immune restoration purposes in patients with progressive, severe anti-interferon-γ associated NTM disease.

Non-pharmacological interventions. Beyond antimicrobial therapy, non-pharmacological interventions can contribute to the alleviation of symptoms and improvement in the quality of life of patients with NTM infections, and as such should be a component of the overall management of NTM infections [98]. These interventions include tobacco cessation (where applicable), pulmonary rehabilitation/pulmonary hygiene, exercise programs, and nutritional support.

Pulmonary hygiene. Many patients with NTM pulmonary disease also have bronchiectasis and signs of airway mucous plugging. In patients with concomitant bronchiectasis, bronchial hygiene regimens with active airway clearance interventions can be used as adjunctive therapy to theoretically facilitate clearance of NTM and prevent superimposed bacterial infections [4,98]. Retrospective data suggests that pulmonary hygiene alone with active surveillance may be appropriate in patients with mild nodular bronchiectatic MAC pulmonary disease. Active airway clearance interventions have not been prospectively studied in NTM patients with bronchiectasis, but potential benefits are suspected based on expert opinion [99]. These regimens can include mucous clearance devices, such as flutter valves and chest vest, and inhaled medications such as, hypertonic saline nebulizations. An individualized approach and careful introduction of these treatments by a respiratory therapist or experienced nurse are recommended since these can cause bronchospasm and/or airflow irritation. Short acting bronchodilators should precede administration of nebulized hypertonic saline in patients with airway hyper-reactivity.

Exercise training. The evidence supporting the benefit of exercise in the management of NTM infections is largely an extrapolation of studies conducted in patients with bronchiectasis, a common comorbidity in patients with NTM lung disease. These studies were of variable duration (3–8 weeks) and of variable design (inpatient or outpatient; with or without supervision; with or without respiratory physiotherapy). Overall, these programs resulted in improvements in exercise capacity and health-related quality of life, as well as decreases in the frequency of acute exacerbations [100–103].

Nutrition. The linkage between infection and nutrition is not new. Poor nutrition can predispose to infection, infection in turn can contribute to malnutrition [104]. Weight loss is a common symptom in patients with NTM infections and may be further exacerbated by decreased appetite, nausea, early satiety, related to the treatment of the NTM infection itself [105,106]. Poor nutritional status has been associated with poor outcomes in MAC lung disease [107,108]. Vitamin A deficiency was strongly associated with the prevalence and risk for NTM pulmonary disease [109]. Dietitians and nutritionists are important members of the NTM management team. Nutrition assistance can ensure adequate protein and caloric intake, while providing guidance regarding other nutritional supplements, vitamins, micronutrients, and antioxidants.

12. Summary
Non-tuberculous mycobacterial infections are an increasingly important contributor to human disease, causing a wide range of infection from localized soft-tissue infiltration to disseminated life-threatening conditions. Having a ubiquitous presence in nature can make it challenging to discern NTM biological sample contamination from a true NTM infection. The clinical and radiographic features are non-specific; microbiologic diagnosis is cumbersome and insufficiently
informative. Treatment is complex, requiring multi-drug regimens with substantial associated toxicity, administered for a prolonged period. Defining treatment milestones is difficult; clinical outcomes are often disappointing.

Given these considerable challenges, a thorough systematic approach to the diagnosis and treatment of NTM infections should be adopted to maximize the likelihood of positive treatment outcomes. Early diagnosis is key and requires a high index of suspicion and an understanding of the clinical scenarios suggestive of the presence of NTM infection. Identification of the causative organism to the species level should be performed; antimicrobial susceptibility should be tested on all isolates where suspicion of a true NTM infection exists. Treatment should be directed by AST results, in compliance with prevailing guidelines, and with careful attention paid to patient education and proactive monitoring for treatment responses as well as treatment-emergent adverse drug reactions. Antimicrobial therapy should be complemented by adjunct therapies such as pulmonary hygiene measures, nutritional support, and exercise training programs to improve clinical outcomes and quality of life.

Ethical statement

This paper has been written, revised, and reviewed by all co-authors.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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