Clinical Infectious Diseases

STATE-OF-THE-ART REVIEW

Nontuberculous Mycobacterial Pulmonary Disease: Patients, Principles, and Prospects

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Nontuberculous mycobacterial pulmonary disease (NTM-PD) is increasing in incidence globally and challenging to manage. The 2020 multisociety treatment guideline and the 2022 consensus recommendations provide comprehensive evidence-based guides to manage pulmonary diseases caused by the most common NTM. However, with >190 different NTM species that may require different multidrug regimens for treatment, the breadth and complexity of NTM-PD remain daunting for both patients and clinicians. In this narrative review, we aim to distill this broad, complex field into principles applicable to most NTM species and highlight important nuances, specifically elaborating on the presentation, diagnosis, principles of patient-centered care, principles of pathogen-directed therapy, and prospects of NTM-PD.

Keywords. mycobacteria; mycobacterium; mycobacteroides; bronchiectasis; cystic fibrosis.

Nontuberculous mycobacteria (NTM) are mycobacteria separate from the *Mycobacterium tuberculosis* complex (MTBC) and *Mycobacterium leprae* complex, comprising >190 species with varying virulence that can cause pulmonary and extrapulmonary diseases [1–4]. They inhabit soil, plumbing, dust, and natural and municipal water [5]. Inhalation of mycobacteria-laden soil, water, and dust aerosols is the primary route of pulmonary infection [5]. NTM pulmonary disease (NTM-PD) is increasing globally, with *Mycobacterium avium* complex (MAC) and *Mycobacterium abscessus* as the most common causative mycobacteria [6]. In the United States (US), rates are highest in Hawaii, Arizona, Florida, and other southeastern states [7]. Hot and humid states have larger water surface areas, higher evapotranspiration, and higher vapor pressure, factors that contribute to higher environmental aerosolization of NTM [8].

NTM are aerobic, nonmotile, gram-positive bacilli with a thick, lipid-dense cell envelope that includes a cell wall containing various glycolipids, lipoproteins, and mycolic acids (Figure 1) [9]. They are classified as either slowly growing mycobacteria (SGM) such as MAC, which require >7 days for visible growth on subculture, or rapidly growing mycobacteria (RGM) such as *M. abscessus*, which require <7 days [9, 10]. Their cell wall confers them with acid-fast staining, hydrophobicity, and an intrinsic barrier to many antimicrobials [9]. The hydrophobicity allows them to dwell on water surface microlayers and be easily aerosolized [5]. NTM can also form biofilms inside pulmonary alveolar walls, enhancing their survival against host immunity and antimicrobials [9]. Unlike MTBC, NTM have glycopeptidolipids (GPLs) in their cell wall, the content of which they can alter to switch between rough and smooth morphotypes, affecting their virulence and treatment response [9].

In susceptible hosts, mycobacteria induce a granulomatous inflammation that damages the airways and lung parenchyma [11–13]. Alveolar macrophages and dendritic cells phagocytose the mycobacteria, producing cytokines, notably interleukin 12, interferon-γ, and tumor necrosis factor (TNF), in an attempt to kill the pathogens intracellularly; however, mycobacteria can evade this process [11, 14]. They stimulate granuloma formation throughout the infected airways, leading to bronchiectasis, bronchiolitis, and nodules [11–13]. The mechanism by which NTM-PD cavities form is not precisely known but may include evolution from a cystic bronchiectatic airway or necrosis of a parenchymal lesion with drainage into the airways [12].

PRESENTATION AND DIAGNOSIS

Symptoms and Physical Signs

Patients with NTM-PD typically manifest chronic respiratory signs and symptoms such as dry or productive cough, dyspnea,

Received 04 April 2024; editorial decision 27 June 2024; published online 28 August 2024

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Clinical Infectious Diseases® 2024;79(4):e27–47

https://doi.org/10.1093/cid/ciae421

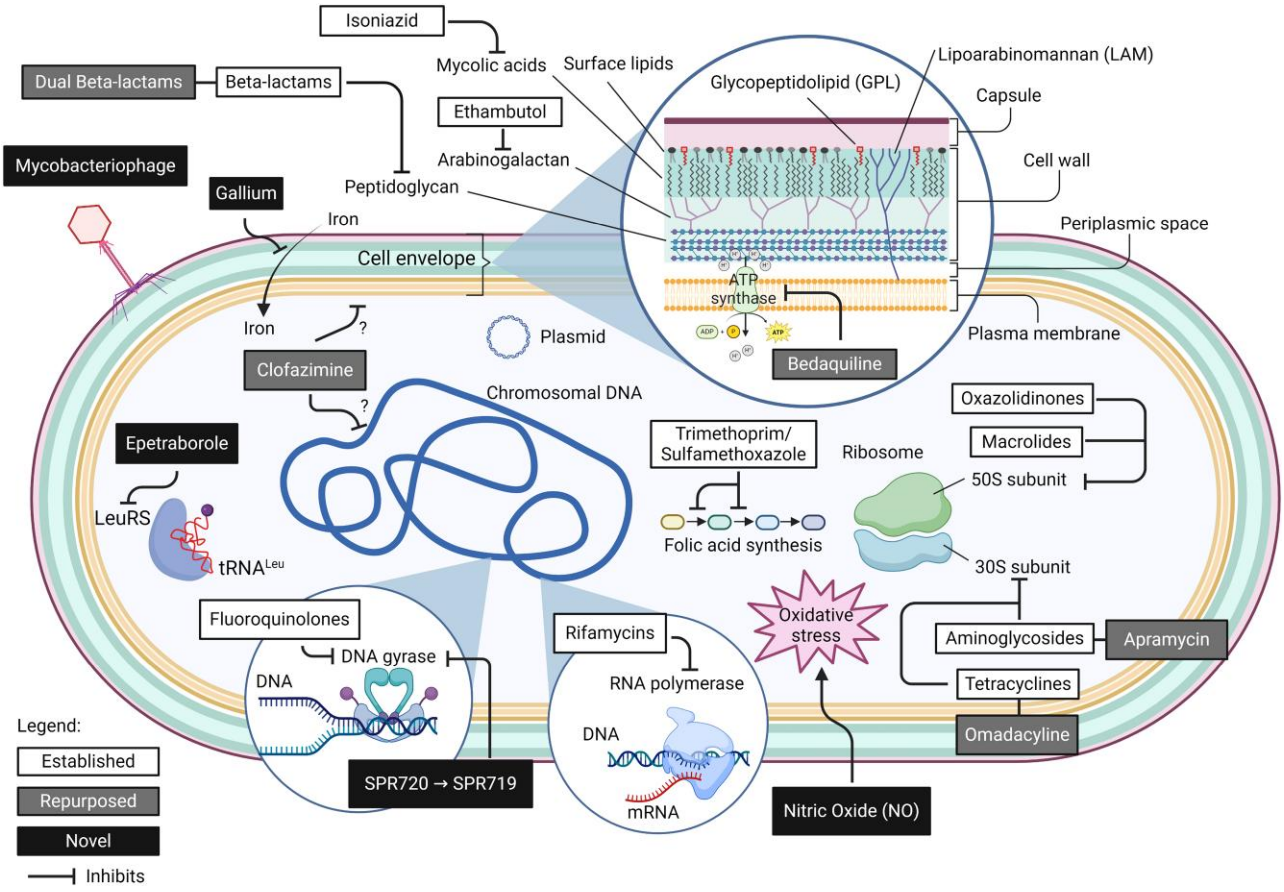

Figure 1. An illustration of the cellular biology of a nontuberculous mycobacterium and the sites of action for established, repurposed, and novel pathogen-directed therapeutics.

and, less commonly, hemoptysis due to bronchiectasis and inflammatory bronchiolitis. Constitutional symptoms such as fatigue, anorexia, and weight loss are also common. The presence of low body mass index (BMI) is common and can portend poorer microbiologic and clinical outcome. Other examination findings are nonspecific or reflect underlying comorbidities [3].

Radiologic Findings

On imaging, NTM-PD typically manifests as bronchiolitis—centrilobular nodules or tree-in-bud opacities—larger nodules, and bronchiectasis with or without cavitation, best detected on a high-resolution chest computed tomography scan (CT) [1, 13]. Other radiologic manifestations include consolidation, fibrocalcification, or, uncommonly, pleural effusion [3]. Radiologic classification distinguishes between nodular bronchiectatic and cavitary types, including subtypes of nodular bronchiectatic cavitary or fibrocavitary, to reflect disease severity (Figure 2) [1, 15]. Pulmonary disease due to *Mycobacterium kansasii* can mimic post–primary tuberculosis (TB) radiologically with upper lobe cavitary disease, likely because it is the NTM that is most closely related phylogenetically to MTBC (Figure 3) [3]. However, radiologic patterns alone are not specific enough to reliably distinguish NTM-PD from other pulmonary conditions or predict the causative NTM species without microbiological confirmation.

Laboratory Diagnosis and Antimicrobial Susceptibility Testing

Microbiological identification to the species/subspecies level is critical for accurate diagnosis, treatment, prognostication, and outbreak investigations [1]. The common yet imprecise identification of "*Mycobacterium avium* complex" encompasses multiple species/subspecies with varying virulence [16], limiting the ability to identify the specific pathogen leading to an outbreak or disease in a patient. Organism identification can be performed using various platforms. Matrix-assisted laser desorption/ionization–time of flight mass spectrometry is an accessible platform for many laboratories and can identify dozens of mycobacterial species. However, this methodology does not yet have the ability to differentiate very closely related organisms, such as species/subspecies of MAC and *M. abscessus*. Molecular assays, such as line probe assays or sequencing, can determine (*i*) the species/subspecies; (*ii*) mutations in the *rrs* and *rrl* genes, which confer constitutive

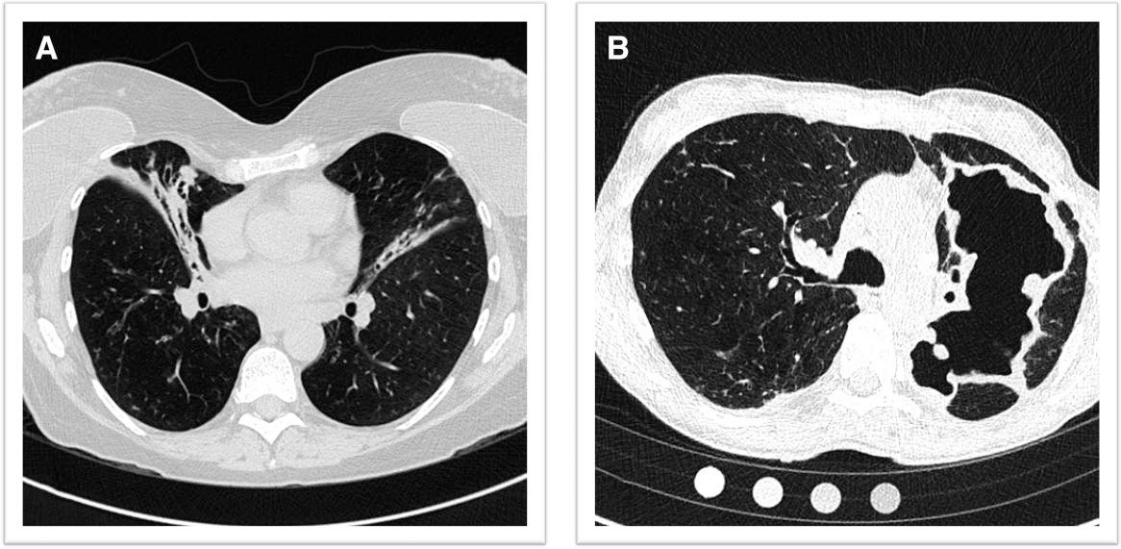

Figure 2. Axial chest computed tomography scans of 2 patients with *Mycobacterium avium* complex pulmonary diseases. *A*, A woman with a tall-slender build, pectus excavatum, and nodular bronchiectatic disease in the right middle lobe and lingula. *B*, A patient with fibrocavitary disease.

aminoglycoside and macrolide resistance, respectively; and (*iii*) *erm* sequevars predicting inducible macrolide resistance [10]. Such genotypic analyses correlate with phenotypic antimicrobial susceptibility testing (AST) >90% of the time and provide results in days [17–19].

Phenotypic AST by broth microdilution remains the most common method to determine antimicrobial selection [20]. Clarithromycin is the in vitro class representative of macrolides for NTM because of azithromycin's poor solubility [20]. While minimum inhibitory concentrations (MICs) are read at 3–5 days, an additional 14-day incubation should also be performed for clarithromycin against all RGM to determine the presence of inducible macrolide resistance [1, 20]. Certain RGM species/subspecies have erythromycin ribosomal methylases, encoded by *erm* genes, which are expressed after exposure to macrolides, resulting in induced macrolide resistance (Table 1) [21, 23–26]. While only certain RGM are confirmed to have *erm* genes to date, the varying frequencies of inducible resistance among species/subspecies and the novel discovery of *erm*(55) in *Mycobacterium chelonae* [25] suggest that all RGM should undergo 14-day incubation to avoid missing unexpected inducible macrolide resistance.

Other useful laboratory data include acid-fast bacilli (AFB) smear grade and time to culture positivity, which correlate directly and inversely, respectively, with bacterial burden and worse prognosis [10]. Colony morphology for *M. abscessus* is also important: the rough morphotype, with less GPL, is more virulent but more susceptible to mycobacteriophage therapy—a novel treatment using viruses that kill mycobacteria—than the smooth morphotype [27, 28]. Mycobacterial cultures are normally incubated at 35°C–37°C. For suspected fastidious NTM or respiratory samples that are acid-fast positive but fail to grow, clinicians should request different incubation temperatures (42°C–45°C for *Mycobacterium xenopi* and 28°C–30°C for *Mycobacterium haemophilum*), prolonged incubation times (8–12 weeks for *Mycobacterium genavense*), and nutrient supplementation to culture medium (sheep blood and charcoal for *M. genavense* and iron for *M. haemophilum*) [10, 20].

Making the Diagnosis

Diagnosing NTM-PD requires compatible symptoms, compatible radiologic abnormalities, reproducible microbiological detection of the same NTM species/subspecies, and exclusion of other diagnoses (Figure 4) [1]. Repeated detection of the same species/subspecies from multiple samples is necessary because NTM are environmental organisms [1, 4]. Compatible clinical manifestations in an at-risk patient should prompt clinicians to collect at least 3 sputa on separate days—ideally at least a week apart—and a chest CT. Chest CTs are preferred over chest radiographs for their sensitivity to assess pulmonary comorbidities, disease progression, treatment response, and surgical candidacy [1]. In challenging scenarios, such as when a patient is culture-positive for NTM but exhibits minimal symptoms or radiologic abnormalities, clinicians should critically appraise the patient data. They should weigh the NTM virulence in context with host vulnerability [4, 16], collect additional cultures, deliberate on alternative diagnoses, and assess disease progression over time.

PRINCIPLES OF PATIENT-CENTERED CARE

Goals, Expectations, and the Treatment Decision

Osler's aphorism "the good physician treats the disease; the great physician treats the patient" must resonate in the care of

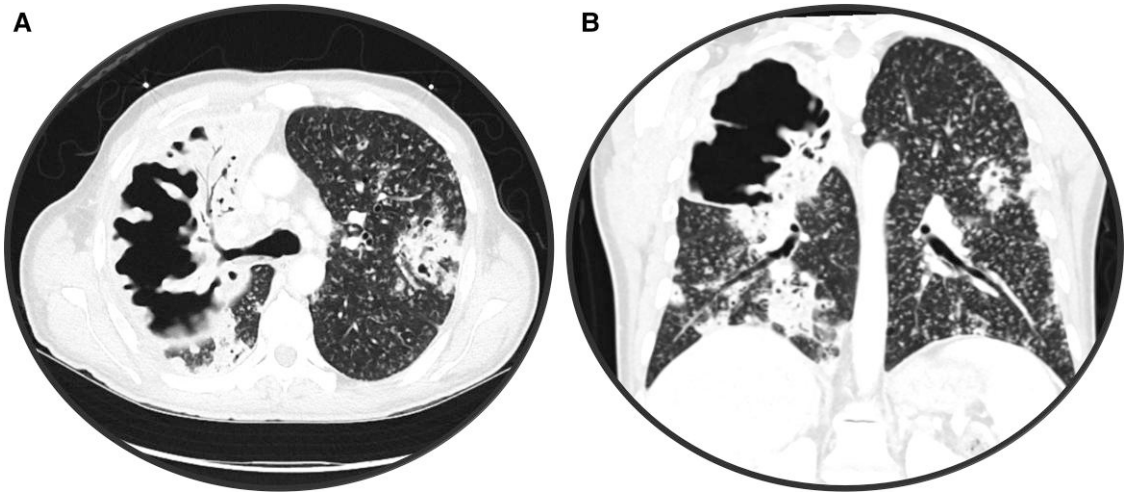

Figure 3. A chest computed tomography scan of a middle-aged man with a 30-pack-year tobacco smoking history and uncontrolled type 2 diabetes who presented with chronic cough, dyspnea, fatigue, weight loss, and night sweats. He had emigrated from Mexico years ago, where he had worked in a glass bottle factory. Since his arrival, he had been working in a granite factory. He was presumed to have cavitary pulmonary tuberculosis and was prescribed empiric antituberculous therapy after collection of sputum cultures. However, his cultures grew *Mycobacterium kansasii*, and he was clinically diagnosed with silicosis. Despite receiving an optimal *M. kansasii* antimicrobial regimen for 2 months, he worsened and had transitioned to hospice care by the time this manuscript was written. This patient's story illustrates *M. kansasii*'s mimicry of *Mycobacterium tuberculosis*, host risk factors' influence on disease susceptibility and severity, and palliative care's role in untreatable disease. *A,* An axial section view. *B,* A coronal section view.

patients with NTM-PD. After diagnosis, evaluation of disease severity and prognostication are essential to guide discussions on goals of care (Figure 4). Goals include attempting to cure, halting disease progression, alleviating symptoms, and preserving quality of life. In MAC-PD, disease progresses in 50%–60% of patients without antimicrobial treatment [29] and antimicrobial treatment success ranges from 52% to 65% [30], but progression and success depend on a patient's comorbidities and the NTM's virulence [4, 31–33]. It is important for patients to realize that disease progression and treatment success can be uncertain, antimicrobial treatment requires a minimum 12-month-long multidrug regimen with potential for adverse effects, and recurrences may occur [1]. Regardless of whether antimicrobial therapy is initiated, a multidisciplinary team should provide the following comprehensive care for nearly every patient: treat underlying comorbidities, optimize nutrition, and prescribe airway clearance therapy (ACT) in those with bronchiectasis (Figure 5, step I). In mild NTM-PD, it is reasonable to first prescribe the aforementioned measures and treat other antimicrobial-responsive clinically significant co-pathogens—such as *Pseudomonas*—and then reevaluate the patient periodically before initiating NTM-directed antimicrobials.

Although the 2020 guideline recommends generally starting antimicrobials over observation, it stresses the importance of an accurate diagnosis and personalization (Figure 4) [1]. Antimicrobial treatment is favored in those with severe disease or increased likelihood of progression or mortality, which are associated with cavitary or extensive radiologic disease, AFB smear positivity, older age, low BMI (<18.5 kg/m^2), multiple comorbidities, elevated inflammatory markers, and low albumin [29, 34]. The rate of radiologic change over time should heavily influence treatment decisions. Although a long antimicrobial treatment course with adverse effects and uncertainties can cause patients consternation, they may feel motivated when they know that they are at the center of a thoughtful, multidisciplinary care plan that aims to achieve their goals and responds to their concerns. Table 2 illustrates common patient-centered talking points to facilitate shared decision-making.

Host Risk Factors and Management of Underlying Comorbidities

Despite ubiquitous environmental exposure, NTM-PD is relatively uncommon, implying that it is driven heavily by host vulnerability [33]. NTM-PD commonly arises in individuals with underlying pulmonary comorbidities with compromised mucociliary clearance, chiefly bronchiectasis (Figure 6). These risk factors or comorbidities can either be inherited, acquired, or a mosaic of both. Inheritable disorders include α-1-antitrypsin (AAT) deficiency, common variable immunodeficiency (CVID), cystic fibrosis (CF), primary ciliary dyskinesia, and pulmonary alveolar proteinosis [31–33]. AAT deficiency causes both emphysema and bronchiectasis [31]. CVID is an inheritable condition that causes recurrent respiratory infections, which can then cause bronchiectasis [35]. CF is the classic cause of inheritable bronchiectasis due to dysfunctional CF transmembrane conductance regulator (CFTR) protein channels for chloride, promoting tenacious secretions [36]. Common acquired risk factors include tobacco smoke–associated

Table 1. Rapidly Growing Mycobacteria With Known Erythromycin Ribosomal Methylase (*erm*) Genes and Proportion of Strains With Inducible Macrolide Resistance

Genus	Species/Subspecies	*erm* Gene	Proportion of Strains With Inducible Macrolide Resistance
M. abscessus [18, 21, 22]	*M. abscessus* subsp. *abscessus*	*erm*(41); a small proportion has a T28C mutation, rendering it nonfunctional	70%–92%
	M. abscessus subsp. *bolletii*	*erm*(41)	100%
	M. abscessus subsp. *massiliense*	*erm*(41); truncated, rendering it nonfunctional	0%
M. fortuitum complex [23, 24]	*M. fortuitum*	*erm*(39)	84%
	M. peregrinum		31%
	M. porcinum		90%
	M. septicum		86%
	M. boenickei		Unknown
	M. houstonense		Unknown
	M. senegalense[a]	*erm*(39); nonfunctional	0%
Other [24–26]	*M. goodie, M. smegmatis*	*erm*(38)	Unknown
	M. chelonae, M. iranicum[b], *M. obuense*[b]	*erm*(55) (plasmid)	Rare
	M. chelonae	*erm*(55) (chromosomal) *erm*(55) (transposon)	Rare
	M. mageritense, M. wolinskyi	*erm*(40)	Unknown

[a]Previously known as *M. conceptionense*.

[b]Determined by in silico analysis.

emphysema, bronchiectasis from prior TB, pneumoconiosis (Figure 3), interstitial lung diseases, and chronic aspiration [31–33]. Inhaled corticosteroids or systemic immunosuppressants, particularly TNF antagonists, are iatrogenic risk factors [31–33]. Aging is associated with NTM-PD, likely due to multiple factors including repeated NTM exposure, accumulation of comorbidities, and declining immunity [33, 37].

An emerging paradigm recognizes that multiple partial defects and combinations of risk factors contribute to host susceptibility to NTM-PD. Whole-exome sequencing of patients with NTM-PD indicated that possessing variants of several genes in the immune, connective tissue, ciliary, and CFTR categories may additively increase vulnerability to NTM-PD [38]. Certain women predisposed to NTM-PD lack any singular risk factor but exhibit a tall-slender build and bronchiectasis of the right middle lobe, lingula, or right upper lobe, a condition historically called "Lady Windermere syndrome" and presumed to have a genetic basis, noting that up to 37% of these women have a single CFTR mutation in one series [39]. Such individuals often have other shared traits of scoliosis, pectus excavatum, and mitral valve prolapse [39, 40].

Appropriate treatment of NTM-PD requires treatment of its underlying comorbidities (Figure 5, step I). Management of bronchiectasis consists of implementing ACT, treating and preventing exacerbations, and addressing any underlying etiology [41, 42]. In this regard, CFTR modulators have revolutionized CF care in the past decade and have been shown to reduce incident NTM culture positivity [43] and improve NTM eradication [44], serving as a vanguard for host-directed therapies for NTM-PD. Table 3 summarizes the management of the most common underlying comorbidities.

Nutrition

Low body fat and malnutrition, distinct but inextricably tied, both heighten the risk for NTM-PD, which further perpetuates cachexia and nutrient malabsorption [45]. Low body fat is associated with low leptin, a hormone that enhances the immune response and therefore increases the host vulnerability [33, 39, 40]. Patients with a BMI <18.5 kg/m^2 face a greater likelihood of disease progression and mortality [34, 49]. Malnutrition impairs both adaptive and innate immune responses and further exacerbates this vulnerability [45]. Fat-free mass depletion, a metric of malnutrition irrespective of body fat, is associated with increased morbidity and mortality in chronic pulmonary diseases [46]. Vitamin deficiencies, particularly vitamin D, are linked to a higher risk of NTM-PD [31, 33]. Although no trials have studied nutritional interventions in NTM-PD, high-protein and high-calorie diet interventions were associated with better outcomes in TB [47, 48]. A 2023 randomized trial in India found a 40% reduction in TB incidence in contacts receiving nutritional intervention versus a control group [48]. Thus, it is prudent to aim for weight restoration in underweight NTM-PD patients with guidance from a nutritionist (Figure 5, step I) [34, 49].

Airway Clearance Therapy

ACT encompasses breathing and coughing techniques, oscillatory positive expiratory pressure devices, oscillatory percussive vests, and mucoactive agents, such as 3% or 7% hypertonic saline, that facilitate clearance of airway secretions [41, 42]. In patients with bronchiectasis, ACT was found to increase sputum volume, reduce cough, reduce airway obstruction, reduce inflammatory cells in sputum, and improve exercise capacity

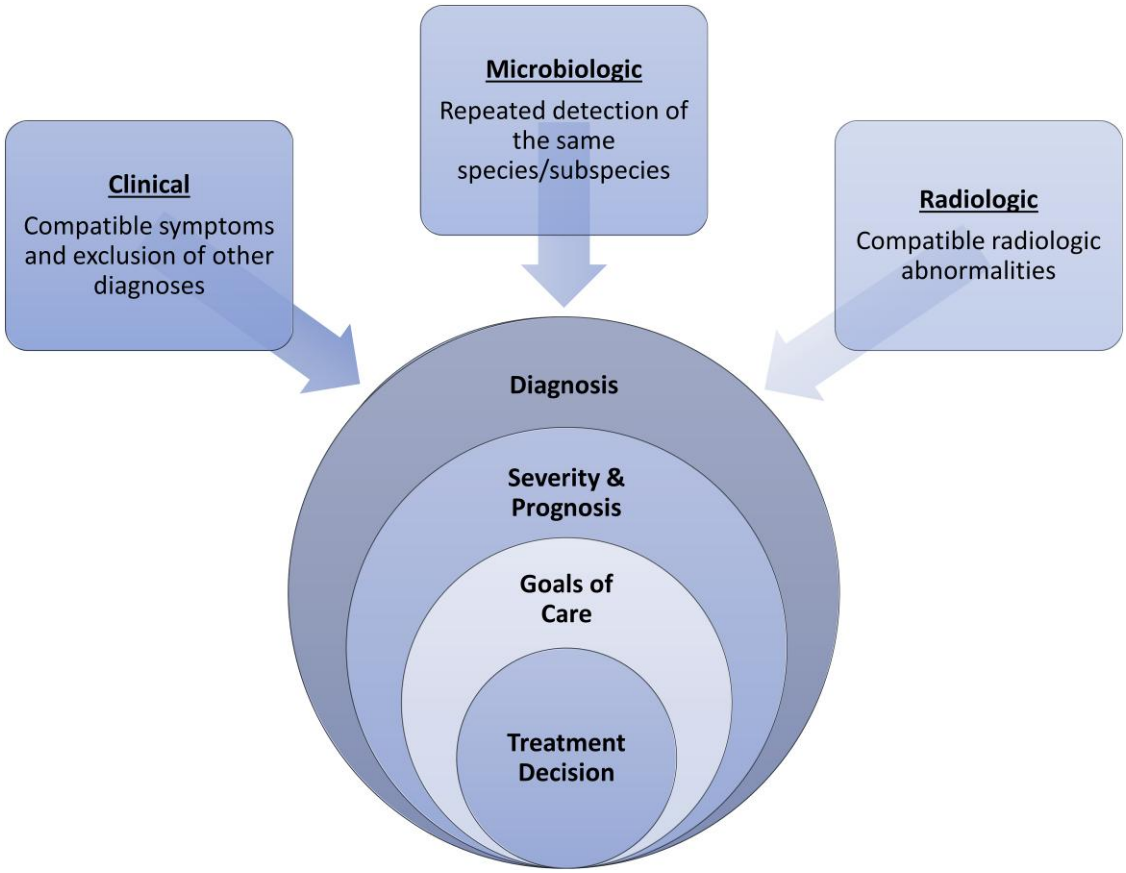

Figure 4. A conceptualization of the evaluation process for a patient with nontuberculous mycobacterial pulmonary disease. The diagnosis requires meeting all 3 major criterial categories: clinical, radiologic, and microbiologic [1]. Following the diagnosis is a stepwise assessment of the disease severity and patient prognosis, goals of care, and finally, treatment. Clinical, radiologic, and microbiologic characteristics also inform severity and prognosis and thus influence goals of care and the treatment decision.

[41]. Furthermore, ACT has a favorable benefit-to-risk profile and is endorsed by patients and experts [50]. Hence, ACT should be prescribed for patients with NTM-PD with concomitant bronchiectasis, with type and intensity of therapy individualized and instructed by a respiratory therapist or other expert in ACT (Figure 5, step I) [31, 41].

PRINCIPLES OF PATHOGEN-DIRECTED THERAPY

The 2020 guideline [1] and 2022 consensus recommendations [2] for NTM-PD provide comprehensive guidance for antimicrobial regimens for the 11 most common NTM. To complement them, this section distills their recommendations into a treatment framework that can apply to most NTM, including rarer species lacking data-driven guidance. This framework underscores the significance of macrolides, ethambutol for SGM, aminoglycosides, and surgery (Figure 5).

Constructing the First-line Antimicrobial Regimen

The regimen generally pivots around the macrolide and aminoglycoside as they are 2 of the most potent antimicrobial classes against NTM susceptible to them, with aminoglycosides often reserved for severe or treatment-limited disease [1, 2]. For this review, "severe" refers to either (*i*) extensive radiologic involvement or (*ii*) cavitation, and "treatment-limited" refers to either (*i*) important antimicrobial loss due resistance or intolerability or (*ii*) treatment-refractory NTM-PD. The guideline supports AST specifically for macrolides and aminoglycosides against MAC and *M. abscessus* and rifampin against *M. kansasii* due to evidence linking in vitro susceptibility to treatment outcomes [1]. In other instances, MICs fail to correlate with clinical outcomes for ethambutol against MAC and likely most SGM, rifampin against specifically MAC or *M. xenopi*, and isoniazid against *M. kansasii* [1].

For the remaining antimicrobials and NTM, their in vitro–in vivo correlations are understudied. In these scenarios, while not guideline-recommended, we think it is reasonable to use AST, in combination with tolerability and accessibility, to guide antimicrobial selection as in vitro potency is the best available data point for potential clinical efficacy. Clinical and Laboratory Standards Institute (CLSI) MIC breakpoints should be used when available [51]. As a caveat, for RGM isolates that

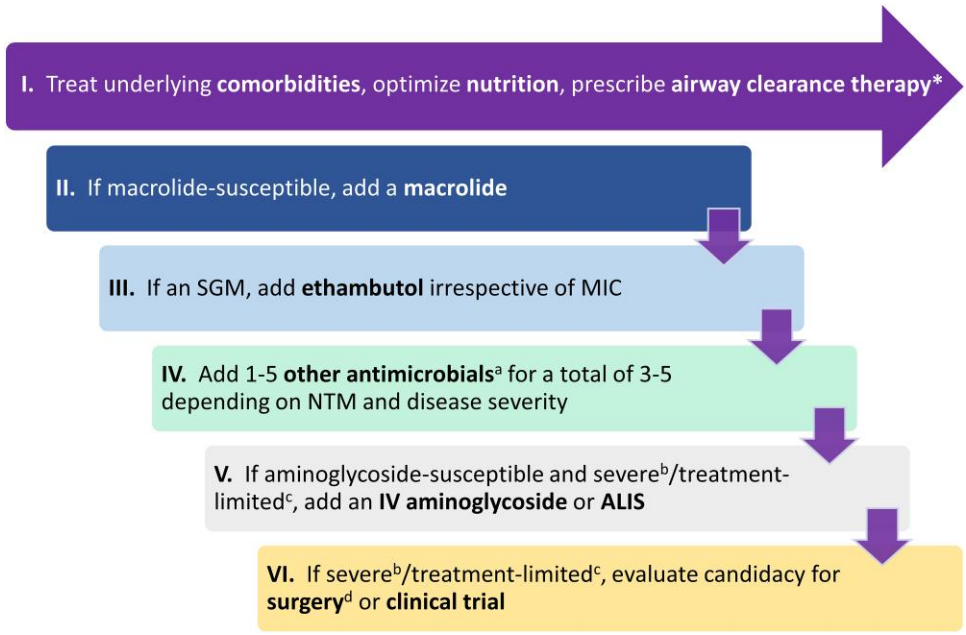

Figure 5. A treatment framework that can apply to pulmonary disease caused by most nontuberculous mycobacteria (NTM). As caveats and nuances exist, the framework illustrated should only supplement, not supplant, patient-specific clinical judgment, expert guidance, and the guideline and consensus recommendations [1, 2]. Antimicrobial loss means that an antimicrobial cannot be used because of resistance from the pathogen or intolerability from the patient. *Airway clearance therapy should only be prescribed to patients with concomitant bronchiectasis. [a]Selection based on guideline or consensus recommendations, antimicrobial susceptibility testing, patient tolerability, drug accessibility, and expert opinion. [b]"Severe" includes either extensive radiologic abnormalities or cavitation. [c]"Treatment-limited" includes either macrolide loss, ethambutol loss for antimicrobial susceptibility testing, loss of the most potent antimicrobial for that NTM, or treatment-refractory. [d]Surgery is indicated if disease is focal and severe/treatment-limited. Abbreviations: ALIS, amikacin liposome inhalation suspension; IV, intravenous; MIC, minimal inhibitory concentration; NTM, nontuberculous mycobacteria; SGM, slowly growing mycobacteria.

are resistant to imipenem (MIC ≥32 μg/mL), we still recommend using it due to the recognition of imipenem's instability in testing solutions and observed positive clinical outcomes from our collective experience [51]. For antimicrobial and NTM combinations without CLSI breakpoints, tolerability and accessibility should be the primary determinants for selection, followed by an appreciation that MIC values are generally inversely correlated with potency. A trial of 3–6 months to assess clinical response and tolerability is often the best approach, with patient-specific guidance and second opinions from NTM experts highly encouraged.

The first priority in antimicrobial treatment is to prescribe a macrolide if the isolate is macrolide-susceptible (Figure 5, step II). The importance of this determination is evinced by the fact that the sputum conversion rate drops from 70%–95% in macrolide-susceptible to 5%–36% in macrolide-resistant MAC-PD [1, 52–54]. This difference in treatment outcomes is echoed in *M. abscessus* disease. Most strains of *M. abscessus* subsp. *abscessus* (70%–92%) and *M. abscessus* subsp. *bolletii* (100%) have a functional *erm*(41) gene conferring inducible macrolide resistance (Table 1) [1, 18, 22]. In contrast, *M. abscessus* subsp. *massiliense* has a truncated *erm*(41) gene and is associated with a 72%–88% culture conversion rate compared to 25%–35% for *M. abscessus* subsp. *abscessus* [22, 55]. Within *M. abscessus* subsp. *abscessus* for which a T28C mutation in *erm*(41) renders the gene nonfunctional, studies show that the C28 sequevar had a 86%–93% culture conversion rate versus the T28 sequevar's 38% [56, 57].

This macrolide-first approach applies to most other NTM with some caveats [1, 2]. *M. kansasii* treatment is rifampin-oriented, traditionally combined with isoniazid and ethambutol, but we suggest macrolides over isoniazid based on in vitro data [1, 3]. While there are no direct comparative trials, observational studies show 80%–100% cure rates with both macrolide-containing and isoniazid-containing regimens [1]. For *M. xenopi*, a macrolide-based regimen remains applicable, but the macrolide can be substituted with a fluoroquinolone [1]. While clarithromycin is the AST representative, azithromycin is generally preferred for more convenient dosing, better tolerability, and fewer drug–drug interaction [58]. The macrolide should be dosed daily in severe disease but can be dosed 3 times weekly in mild MAC-PD. The latter dosing scheme has not been studied for other NTM and should be extrapolated with caution [1, 2].

If the pathogen is an SGM, ethambutol should be added irrespective of its MIC (Figure 5, step III). Ethambutol's raison d'être is to prevent acquired macrolide resistance in MAC-PD [1, 52, 59]; substituting ethambutol with a fluoroquinolone

Table 2. Common Talking Points With Patients With Nontuberculous Mycobacterial Pulmonary Disease

Common Question	Suggested Answer
Why and how did the patient get NTM-PD?	NTM are common environmental organisms, but only a few people develop the disease. The reason is that affected individuals possess underlying comorbidities that make them more vulnerable to an NTM lung infection, particularly structural lung diseases such as bronchiectasis.
What environmental avoidance should the patient pursue?	Although there are limited data to support the benefits of environmental avoidance, it is prudent to abstain from high-risk behaviors, including use of hot tubs, indoor pools, and charcoal-based water filters. Wearing a face mask while gardening may help.
What proportion of patients with NTM-PD require treatment?	Nearly all patients should receive non-antimicrobial care, which includes treatment for their underlying lung diseases, nutrition optimization, and airway clearance therapy if they have concomitant bronchiectasis. More than half of patients with mild MAC-PD progress and require antimicrobials, with progression occurring over months to years. However, this proportion varies with other NTM, disease severity, and patient risk factors. Patients with only nodular bronchiectatic disease will progress more slowly than those with cavitary disease, with cavitation alone being a strong factor to start antimicrobial therapy.
Why should the patient begin antimicrobial treatment?	It depends on the patient's goals of care. Antimicrobial therapy has the potential to cure the disease, improve symptoms, prevent further lung damage, and improve survival. If the disease progresses, the patient will sustain more irreversible lung damage.
Can the patient pick and choose which antimicrobials to take, how many, and when to stop any of them?	If patients do start antimicrobials, they should adhere to guideline/consensus-based regimens [1, 2] aided by susceptibility testing to ensure the best outcome. NTM are hardy pathogens, and hence, they require multiple antimicrobials for a long duration to treat. Taking a suboptimal regimen increases the risk for both treatment failure and development of antimicrobial resistance. Clinicians must balance involving patients in decision-making with guiding them toward the most effective antimicrobials. Clinicians should clearly explain the necessity of adhering to the prescribed treatment and address any issues of intolerability to ensure patient adherence.
Is the antimicrobial treatment worse than the disease?	In most cases, the answer is no. While antimicrobial adverse effects frequently occur, most patients can tolerate them and see symptoms improve. Factors that can enhance successful outcome include appropriate antimicrobial choices, vigilant monitoring for adverse effects, and adjustment of the regimen as needed.
What is the treatment success rate for NTM-PD?	In MAC-PD, it ranges from 52% to 65%. However, this rate varies with other NTM, disease severity, and patient risk factors.
What is the recurrence rate for NTM-PD?	In MAC-PD, it ranges from 25% to 50%, with most recurrences caused by reinfection rather than relapse of the prior infection. However, this rate varies with other NTM, disease severity, and patient risk factors.

Abbreviations: MAC, *Mycobacterium avium* complex; NTM, nontuberculous mycobacteria(l); PD, pulmonary disease.

was associated with worse outcomes [60, 61]. Even absent a macrolide, ethambutol demonstrated direct antimycobacterial effects and still improved outcomes in macrolide-resistant MAC-PD [62]. While its macrolide-protective effect has not been studied in other SGM, we still recommend ethambutol because of the grave consequence of macrolide loss along with supportive outcomes data against other SGM [1, 2]. As with the macrolide, ethambutol can be dosed either daily or 3 times weekly based on MAC-PD recommendations [1].

At least 2 effective antimicrobials are needed to avoid selecting for resistant strains, with the guideline and consensus generally recommending 3–5 antimicrobials depending on the NTM and disease severity [1, 2]. For example, the guideline recommends a 3-drug regimen for MAC-PD and a *minimum* 3-drug regimen for *M. abscessus* pulmonary disease [1]. However, it is worth noting that a 2-drug regimen is conceivable for mild disease with *M. chelonae* and *Mycobacterium fortuitum* [2], and a phase 2/3 clinical trial is currently evaluating a 2-drug regimen for mild nodular bronchiectatic MAC-PD (NCT03672630). Therefore, 1 or more additional antimicrobials are needed to complete the regimen (Figure 5, step IV). These additional antimicrobials vary with NTM and should be chosen based on the guidelines, AST, patient tolerability, drug accessibility, and expert opinions [1, 2].

For SGM, especially MAC and *M. kansasii*, the third antimicrobial is usually a rifamycin [1, 2]. While both rifampin and rifabutin appear to have similar efficacy [1, 3], rifampin is generally favored for its better tolerability; additionally, clarithromycin, if coadministered, increases rifabutin concentration and toxicity risk [3, 58]. In certain patients, rifabutin may be chosen over rifampin, if tolerated, for its different drug–drug interaction profile, theoretical ability to prevent macrolide resistance [63], or generally lower MIC values [19]. If rifamycins cannot be used, clofazimine, a lipophilic phenazine dye with potent in vitro activity against mycobacteria, can be a suitable third antimicrobial [1, 2, 64]. Other potential antimicrobials are oxazolidinones and possibly fluoroquinolones depending on the NTM and AST [1, 2].

For RGM, the regimen is typically divided into an initial phase and a continuation phase. After choosing the macrolide if susceptible, the remaining antimicrobial choices are determined by AST, patient tolerability, drug accessibility, and expert opinions [1, 2]. The intensive initial phase should include 3–4 antimicrobials, 1–2 of which should be intravenous (IV), such as imipenem or cefoxitin—the former we prefer for better tolerability—an aminoglycoside, or a newer-generation cycline for 4–16 weeks, accompanied by 1–2 oral antimicrobials, such as clofazimine, an oxazolidinone, bedaquiline, or for *M. fortuitum*, a fluoroquinolone, trimethoprim-sulfamethoxazole, or doxycycline. The continuation phase then transitions to just 2–3 oral antimicrobials [1, 2]. Table 4 summarizes established NTM antimicrobials and their dosing schemes.

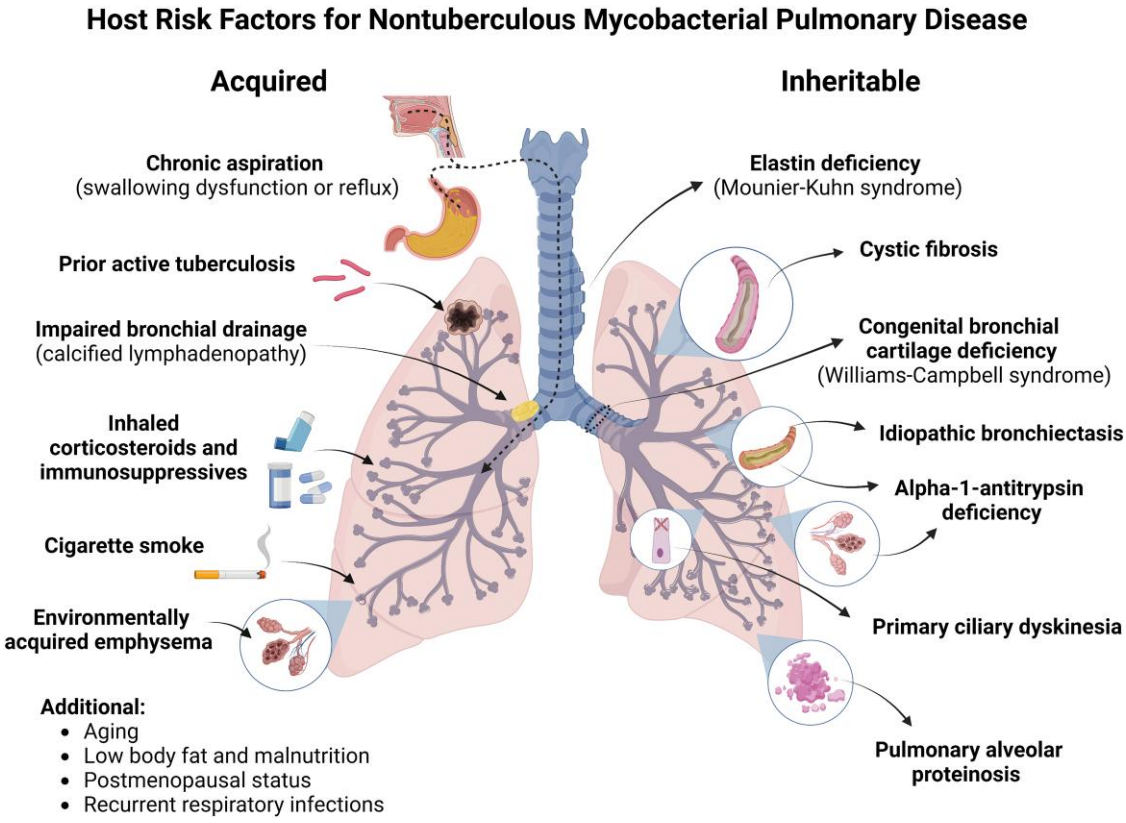

Figure 6. An illustration of common host risk factors or underlying comorbidities for nontuberculous mycobacterial pulmonary disease.

Management for Severe or Treatment-Limited Disease

Aminoglycosides have potent activity but carry the risk of ototoxicity and nephrotoxicity; thus, they are recommended in severe or treatment-limited diseases where their benefits outweigh risks (Figure 5, step V) [1, 3]. Except for *M. kansasii*, for which an oral regimen is usually sufficient even in severe disease, an IV aminoglycoside for the first 8–12 weeks of treatment is recommended for most severe NTM-PD [1, 2]. In RGM disease, especially with *M. abscessus*, an IV aminoglycoside is often used in the initial phase even for moderate, noncavitary disease. For *M. chelonae*, IV tobramycin is preferred given its MIC is lower than amikacin's. The IV aminoglycoside should be dosed 3 times weekly to minimize toxicity [1, 2]. For IV amikacin, we suggest targeting an undetectable minimum concentration (trough) and a maximum concentration (peak) that is up to 3 times the amikacin MIC of the isolate, a practice extrapolated from a hollow fiber study on amikacin against *M. abscessus* [67], but no higher than 80 μg/mL as suggested by the guideline [1].

Management of treatment-limited NTM-PD is based on MAC-PD. While most antimicrobial losses can be substituted, macrolide loss in most NTM disease and ethambutol loss in most SGM disease are the most consequential. Patients who are intolerant to one macrolide should trial the other. An IV aminoglycoside is recommended in macrolide-resistant MAC-PD [1], a practice often applied to other macrolide-resistant NTM. An additional 1–2 antimicrobials should be considered to further compensate for the macrolide loss. *Mycobacterium kansasii* and *M. xenopi* diseases are exceptions to this strategy, as the macrolide can be substituted by isoniazid for *M. kansasii* or a fluoroquinolone for *M. xenopi* [1]. For patients with SGM disease who have developed ethambutol toxicity, finding a suitable substitute is problematic because no other antimicrobial has been proven as effective as ethambutol at preventing macrolide resistance based on MAC-PD studies [3]. Thus, a deliberate evaluation of suspected ethambutol toxicity is paramount. Its only potential substitute appears to be an aminoglycoside based on a small mouse study suggesting that amikacin may prevent macrolide resistance in MAC [68].

Under the treatment-limited disease umbrella is treatment-refractory disease, defined as failure to convert sputum cultures to negative after 6 months of guideline-based treatment for MAC-PD [1, 69]. Failure to culture convert at 6 months of treatment predicts failure at 12 months [70]. In such cases, the first step is to address patient adherence, repeat AST, and perform therapeutic drug monitoring (TDM) (Table 4) [1].

The guideline recommends adding amikacin liposome inhalation suspension (ALIS) for patients with treatment-refractory MAC-PD based on 2 randomized clinical trials showing

Table 3. Management of Common Host Risk Factors or Underlying Comorbidities Associated With Nontuberculous Mycobacterial Pulmonary Disease

Risk Factor or Comorbidity	Diagnostics	Therapeutics
Bronchiectasis[a]	• Chest CT	• Airway clearance therapy • Prevention or treatment of associated bacterial or fungal infections • Bronchodilator therapies • Pulmonary rehabilitation
Underlying conditions causing bronchiectasis and their additional specific management		
Allergic bronchopulmonary aspergillosis	• Testing for predisposing conditions (asthma, cystic fibrosis) • Aspergillus serologies and precipitins • Total IgE • Eosinophil count • Skin testing for molds	• Systemic corticosteroids • Antifungals • Anti-IgE, anti-IL-4, or anti-IL-5 antibody therapies
α-1 antitrypsin deficiency	• AAT genotype and level • Isoelectric focusing • Liver ultrasound	• AAT augmentation therapy
Common variable immunodeficiency	• Immunoglobulin levels • Pre- and postvaccination responses	• Immune globulin replacement therapy (IV or subcutaneous) • Treatment and prophylaxis of infections
Congenital bronchial cartilage deficiency (Williams-Campbell syndrome)	• Chest CT	• None for the condition specifically
Cystic fibrosis	• Sweat chloride • Nasal potential difference • Measures of pancreatic exocrine function • Chest and sinus CT • Genetic testing	• CFTR modulator therapies • Dornase alfa (inhaled) • Treatment of bronchiectasis exacerbations and sinusitis • Pancreatic enzyme replacement
Dysphagia-associated aspiration	• Direct observation of swallowing • Modified or tailored barium swallow (videofluoroscopic swallowing study) • Fiber-optic endoscopic evaluation of swallowing	• Speech/swallow therapy through speech language pathology services • Dietary modifications
Gastroesophageal reflux disease–associated aspiration	• Esophagram • Esophagogastroduodenoscopy • 24-hour pH impedance probe • Wireless ambulatory pH monitoring (eg, Bravo capsule) • Esophageal manometry • Functional lumen imaging probe	• Weight loss • Behavioral changes, including head of bed elevation and dietary mitigation measures • Acid suppression • Drugs modulating esophageal contractility and lower esophageal sphincter tone • Less invasive or surgical interventions (eg, magnetic ring or fundoplication)
Hyperimmunoglobulin E syndrome (Job syndrome)	• Physical examination (eg, facies) • Increased IgE • Eosinophilia prior to infection • Genetic testing for STAT3 mutation	• Treatment of skin, respiratory, and sinus infections • Skin care • Management of pathologic bone fractures • Lung surgery for pneumatoceles
Inflammatory bowel disease	• Endoscopic procedures • Bowel biopsy	• Corticosteroids • Disease-specific immunomodulatory medications • Surgery
Primary ciliary dyskinesia	• Nasal nitric oxide • Ciliary biopsy of sinuses or bronchi with transmission electron microscopy or high-speed videomicroscopy analysis • Cell culture • Genetic testing	• Treatment of respiratory, sinus, and ear infections • Infertility management (eg, in vitro fertilization)
Rheumatoid arthritis	• Rheumatoid factor and anti-cyclic citrullinated peptide antibodies • Physical exam and imaging of joints	• Anti-inflammatory agents • Disease-specific immunomodulatory medications • Analgesics • Surgery
Sjögren disease	• Laboratory studies, including autoimmune serologies (antinuclear antibodies, anti-SS-A and anti-SS-B, anti-double-stranded DNA), serum β-2-microglobulin, rheumatoid factor, and hypergammaglobulinemia) • Salivary gland imaging • Sialometry • Labial salivary gland biopsy • Ophthalmalogic evaluation (including Schirmer testing)	• Treatments for dry eyes • Treatments for dry mouth • Disease-specific immunomodulatory medications

Table 3. Continued

Risk Factor or Comorbidity	Diagnostics	Therapeutics
Tracheobronchomegaly (Mounier-Kuhn syndrome)	• Chest imaging including dynamic expiratory imaging • Bronchoscopy • Evidence of extrapulmonary elastolysis	• Stenting for severe disease
Other risk factors or conditions		
COPD or emphysema	• Pulmonary function testing • Chest imaging	• Inhaled long- and short-acting β-2-agonists • Muscarinic antagonists • Inhaled corticosteroids • Treatment of exacerbations • Phosphodiesterase-4 inhibition • Supplemental oxygen • Pulmonary rehabilitation • Lung volume reduction surgery
Environmental exposures, including tobacco smoke, air pollutants, and occupational inorganic dusts	• History	• Avoidance of environmental exposures
Immunosuppressive medications, including inhaled corticosteroids, systemic corticosteroids, or TNF antagonists	• History and medication reconciliation	• Stopping, reducing, or substituting these medications as tolerated while maintaining control of underlying disease • Communication with specialists prescribing these medications
Interstitial lung diseases	• Chest imaging including high-resolution chest CT • Pulmonary function testing • Lung biopsy • Serologic studies (for rheumatologic causes) • Hypersensitivity pneumonitis antibodies	• Cessation of causative exposures • Treatment of infectious exacerbations • Systemic corticosteroids • Tyrosine kinase inhibitors • Disease-specific immunomodulatory medications • Supplemental oxygen • Pulmonary rehabilitation • Lung transplantation
Low body fat and malnutrition	• Weight • Body mass index • Fat-free mass index • Albumin and prealbumin • 25-hydroxyvitamin D	• Nutritionist consultation • High-calorie, high-protein oral supplementation • Appetite stimulants • Assisted feeding
Pulmonary alveolar proteinosis	• Chest imaging • Bronchoscopy • Anti-GM-CSF antibody testing • Genetic testing • Surgical lung biopsy	• Whole lung lavage • Recombinant GM-CSF • Therapies for refractory disease including rituximab, plasma exchange, or lung transplantation

Table synthesized from expert opinions and references [31, 33, 35, 42, 43, 45–48].

[a]Management of bronchiectasis (not otherwise specified) applies to all conditions causing bronchiectasis.

Abbreviations: AAT, α-1 antitrypsin; COPD, chronic obstructive pulmonary disease; CT, computed tomography scan; CFTR, cystic fibrosis transmembrane conductance regulator; GM-CSF, granulocyte macrophage colony-stimulating factor; IgE, immunoglobulin E; IL, interleukin; IV, intravenous; TNF, tumor necrosis factor.

significantly improved culture conversion over guideline-based antimicrobials alone [1, 69, 71], a practice that we often apply to other NTM. ALIS penetrates biofilms, enhances drug uptake by macrophages, and reduces systemic amikacin exposure [69]. Although ALIS is currently approved by the US Food and Drug Administration only for treatment-refractory MAC-PD, we sometimes prescribe it as an alternative to an IV aminoglycoside in severe or treatment-limited diseases to reduce systemic amikacin toxicity (Figure 5, step V). A 2023 prospective study found that 50% of patients with treatment-limited *M. abscessus* pulmonary disease treated with ALIS achieved culture conversion [72]. Currently, 2 clinical trials are evaluating ALIS in treatment-naive MAC-PD (NCT04677543 and NCT04677569). If neither ALIS nor IV administration of an aminoglycoside is tolerated or feasible, nebulization of parenteral amikacin for inhalation can be an alternative [73].

Other approaches to improve culture conversion in treatment-refractory disease include intensifying 3 times weekly dosing to daily dosing, which improves culture conversion by 30% in MAC-PD [74]. The addition of an IV aminoglycoside (if ALIS cannot be used) [1], clofazimine, or bedaquiline—a diarylquinoline that inhibits ATP synthase—can be considered, with adding either of the latter 2 shown to improve culture conversion for treatment-refractory MAC and *M. abscessus* diseases [75, 76]. Last but far from least, surgery should be highly considered [1].

Surgery

Early identification of appropriate patients for adjunctive surgical resection can significantly alter their disease outcomes. Surgery, often minimally invasive, is recommended for patients with focal disease that is either (*i*) severe, (*ii*) treatment-limited,

or (*iii*) predicted to be treatment-limited (Figure 5, step VI) [1, 77]. A multidisciplinary team including a thoracic surgeon with expertise in NTM lung resection should evaluate surgical candidacy, and patients must be on an optimized antimicrobial regimen presurgery, usually including an IV aminoglycoside for 6–8 weeks [77]. A 2023 systematic review on NTM surgical resections showed a 93% postoperative sputum conversion rate, 9% recurrence, 17% complications, and 0% in-hospital mortality among 1071 patients [78]. The University of Colorado School of Medicine, an experienced institution, reported a 7% complication rate, 3% conversion to open thoracotomy, and a median 3-day hospitalization for minimally invasive right middle lobe and lingula resections for NTM-PD [79].

Monitoring Response to Therapy and Adverse Effects

Antimicrobial therapy of NTM-PD requires at least 12 additional months of treatment following initial, sustained sputum culture conversion to negative except for uncomplicated *M. kansasii* or *Mycobacterium szulgai* disease, for which a total of 12 months is sufficient [1, 2]. TDM is recommended for patients with suspected malabsorption, abnormal drug metabolism, drug interactions, risk for toxicities, or risk for failure [1, 80]. In particular, TDM appears more influential in severe disease where it can favorably affect clinical outcome [81]. Regular follow-up visits, every 1–3 months, are recommended to assess treatment response and adverse effects, which often occur within the first 120 days [58]. Sputum specimens should be collected every 1–2 months to confirm culture conversion, and low-dose chest CTs done every 6–12 months, ideally marking major treatment changes or disease milestones [1]. Posttreatment surveillance should be individualized and symptom-driven, with a minimum of yearly assessments for stable patients.

Management of antimicrobial adverse effects is a difficult but prominent responsibility of NTM-PD care. The most important principle is to sustain the tolerability to the most important antimicrobial classes as long as possible, which primarily includes macrolides for macrolide-susceptible NTM, ethambutol for SGM, rifamycins for *M. kansasii*, and aminoglycosides for severe or treatment-limited disease. Their adverse effects typically need to be severe and verified to warrant full discontinuation. For mild intolerances, such as nausea or a mild rash, symptom-directed medications should be employed, such as the use of antiemetics and antihistamines. Taking antimicrobials at bedtime appears to alleviate many mild gastrointestinal intolerances and fatigue. As alluded to previously, swapping between azithromycin and clarithromycin can alleviate mild adverse effects, including gastrointestinal intolerances, mild-moderate hypersensitivity reactions, and ototoxicity, which is reversible unlike that of aminoglycosides. QTc prolongation can be reversed by optimization of electrolytes and minimization of other unnecessary QTc-prolonging medications. Ethambutol should be held immediately for worsening vision but only permanently discontinued if optic neuritis is confirmed by an ophthalmological exam. For *M. kansasii* disease, rifampin and rifabutin can be interchanged for a trial of better tolerability. Prevention of aminoglycoside toxicities requires vigilance with renal function, audiograms, and TDM; cessation is warranted for either nephrotoxicity or ototoxicity. For ALIS, common adverse effects include dysphonia and hoarseness, which often resolve on their own after a one-week holiday, and bronchospasm, which can be mitigated with pretreatment with albuterol. Gastrointestinal intolerances can occur when the drug is accidentally ingested during inhalation and therefore can be prevented or rectified with proper instructions on technique to avoid swallowing the drug. Table 4 describes the suggested management for notable adverse effects of the most common NTM antimicrobials.

Palliative Approach

A palliative approach is recommended for patients with NTM-PD for whom treatment is predicted to impact little on their prognosis or likelihood of cure but may not necessarily need to transition to full palliative or end-of-life care. This approach primarily aims to (*i*) alleviate symptoms and (*ii*) slow the progression of NTM disease to preserve quality of life. Identifying these patients early in their care facilitates timely discussions about the goals, expectations, and antimicrobial utility. These patients often have untreatable, end-stage comorbidities, such as underlying emphysema, or have severe or treatment-limited NTM-PD for which viable treatment options have been exhausted. A time-limited trial of antimicrobials of 3–6 months can be used to assess tolerability and palliative (symptom-relieving or disease-slowing) benefits from the antimicrobials [82]. In patients for whom the antimicrobial regimen is intolerable, all the antimicrobials in that regimen should be avoided or stopped—partial therapy is discouraged as it will select for antimicrobial resistance. However, if the regimen is tolerable and provides palliation, then it can be continued as long as the patient desires. When patients have transitioned to full palliative or end-of-life care, such as the patient described in Figure 3, antimicrobials should be avoided or stopped, and consultation with a palliative care specialist is advised. Non-antimicrobial care, such as ACT in those with bronchiectasis, can be continued as long as it provides symptomatic relief [41].

PROSPECTS

Unfortunately, the current therapeutic landscape for NTM-PD is suboptimal, causing many patients to suffer from refractory or recurrent disease despite adhering to the best current therapies available. More research is needed, particularly on new

Table 4. Summary of Antimicrobial Dosing, Target Therapeutic Drug Monitoring Values, Adverse Effects, Drug Interactions, and Respective Management

Antimicrobial	Dosing	Therapeutic Drug Monitoring Targets	Adverse Effects and Drug Interactions	Suggested Monitoring and Management
Macrolides				
Azithromycin, PO/IV	250–500 mg PO/IV once daily. 500 mg/day PO/IV, 3 times weekly. No dose adjustments needed for renal or hepatic impairment.	C_{max}: 0.2–0.7 μg/mL	Gastrointestinal intolerance (diarrhea, nausea, and abdominal pain), hearing loss (reversible), tinnitus, QTc prolongation, hypersensitivity[a], transient transaminitis, hepatotoxicity (rare). Does not inhibit CYP3A.	Clinical evaluation. LFTs every 1–2 mo. Audiogram and ECG at baseline and repeat as clinically indicated. For hearing loss, tinnitus, or hepatotoxicity, discontinue. We recommend changing to clarithromycin for ototoxicity, gastrointestinal intolerances, and mild-moderate hypersensitivity. For QTc >500 ms, hold and optimize QTc (replete potassium and magnesium, stop or dose reduce other QTc-prolonging agents if possible), then repeat ECG and if QTc has normalized, can rechallenge.
Clarithromycin, PO	500 mg PO twice daily. 500 mg PO twice daily, 3 times weekly. Reduce dose by 50% if CrCl <30 mL/min (500 mg once daily). No dose adjustment needed for hepatic impairment.	C_{max}: 2–7 μg/mL	Gastrointestinal intolerance (diarrhea, nausea, and abdominal pain), hearing loss (reversible), tinnitus, prolonged QTc, hypersensitivity[a], transient transaminitis, hepatotoxicity (rare). Inhibits CYP3A leading to many drug–drug interactions; always review prior to prescribing. Notably increases rifabutin concentrations.	Clinical evaluation. LFTs every 1–2 mo. Audiogram and ECG at baseline and repeat as clinically indicated. For hearing loss, tinnitus, or hepatotoxicity, discontinue. We recommend changing to azithromycin for ototoxicity, gastrointestinal intolerances, and mild-moderate hypersensitivity. For QTc >500 ms, hold and optimize QTc (replete potassium and magnesium, stop or dose reduce other QTc-prolonging agents if possible), then repeat ECG and if QTc has normalized, can rechallenge.
Aminoglycosides				
Amikacin, IV	10–15 mg/kg IV once daily. 10–25 mg/kg IV 3 times weekly. Decrease dose or increase dosing interval for renal impairment. No dose adjustment needed for hepatic impairment.	C_{max}: 35–45 μg/mL; can be as high as 65–80 μg/mL when dosed 3 times weekly. Consider targeting up to 3× the MIC but 80 μg/mL maximum. C_{min}: <5 μg/mL	Hearing loss, vestibular dysfunction, nephrotoxicity, electrolyte disturbances (hypokalemia, hypomagnesemia).	Clinical evaluation. Cr and electrolytes every 1–2 wk. Audiograms every 1–2 mo. For abnormal Cr or electrolytes, hold treatment. For renal failure, discontinue. For ototoxicity, discontinue.
Amikacin liposome inhalation suspension, oral inhalation	590 mg/8.4 mL oral inhalation once daily. No dose adjustments needed for renal or hepatic impairment.		Hoarseness, dysphonia, cough, bronchospasm, hemoptysis, dyspnea, hearing loss, tinnitus, fatigue, headache, nausea, diarrhea, pneumonitis (rare). Gastrointestinal intolerance is suggestive of inappropriate ingestion of drug.	Clinical evaluation. Baseline spirometry and repeat with symptoms of bronchospasm. Chest CT for worsening dyspnea. To prevent bronchospasm, premedicate with albuterol. For hoarseness or dysphonia, can rechallenge after approximately 1-wk holiday. For gastrointestinal intolerance, instruct on proper technique to avoid ingestion of drug. Avoid rechallenging for pneumonitis, hemoptysis, or hearing loss.
Amikacin (nebulized parenteral formulation), oral inhalation	250–500 mg oral inhalation once daily. Diluted in 3 mL of normal saline. No dose adjustments needed for renal or hepatic impairment.		Oral cavity discomfort, hoarseness, dysphonia, hemoptysis, oral candidiasis, hearing loss, tinnitus, vertigo, digestive issues, epistaxis.	Clinical evaluation. Baseline spirometry and repeat with symptoms of bronchospasm. Chest CT for worsening dyspnea. For oral cavity discomfort, hoarseness, or dysphonia: can rechallenge after approximately 1-wk holiday. Avoid rechallenging for pneumonitis, hemoptysis, or hearing loss.

Table 4. Continued

Antimicrobial	Dosing	Therapeutic Drug Monitoring Targets	Adverse Effects and Drug Interactions	Suggested Monitoring and Management
Streptomycin, IV	10–15 mg/kg IV once daily. 10–25 mg/kg/day IV, 3 times weekly. Decrease dose or increase dosing interval for renal impairment. No dose adjustment needed for hepatic impairment.	C_{max}: for the 15 mg/kg dose, 35–45 μg/mL C_{min}: <5 μg/mL	Hearing loss, vestibular dysfunction, nephrotoxicity, electrolyte disturbances (hypokalemia, hypomagnesemia)	Clinical evaluation. Cr and electrolytes every 1–2 wk. Audiograms every 1–2 mo. For abnormal Cr or electrolytes, hold treatment. For renal failure, discontinue. For ototoxicity, discontinue treatment.
Tobramycin, IV	5–7 mg/kg IV once daily. 4.5–7 mg/kg/day IV, 3 times weekly. Decrease dose or increase dosing interval for renal impairment. No dose adjustment needed for hepatic impairment.		Hearing loss, vestibular dysfunction, nephrotoxicity, electrolyte disturbances (hypokalemia, hypomagnesemia).	Clinical evaluation. Cr and electrolytes every 1–2 wk. Audiograms every 1–2 mo. For abnormal Cr or electrolytes, hold treatment. For renal failure, discontinue. For ototoxicity, discontinue treatment.
Rifamycins				
Rifampin, PO/IV	10 mg/kg (450 or 600 mg) PO/IV once daily. 600 mg/day PO/IV, 3 times weekly. No dose adjustment needed for renal impairment. No dose adjustment recommended in hepatic impairment but use with caution.	C_{max}: 8–24 μg/mL	Orange discoloration of urine and body fluids, leukopenia, thrombocytopenia, rash, hepatoxicity, arthralgias, flu-like illness, fatigue, hemolytic anemia, renal failure (rare). Induces multiple CYP enzymes leading to many drug–drug interactions; always review prior to prescribing. Rifamycins' effects on metabolizing enzymes can take a few weeks to wash out. Notably reduces macrolide concentrations.	Clinical evaluation. LFTs and CBC every 1–2 mo. For mild rash, can continue with treatment with an oral antihistamine or a topical corticosteroid. For hepatitis (LFTs >3× ULN with symptoms or 5× ULN without symptoms), severe pancytopenia, renal failure, or hemolytic anemia, then discontinue.
Rifabutin, PO	5 mg/kg (150 or 300 mg) PO once daily. 300 mg/day PO, 3 times weekly. Use 150 mg PO once daily when coadministered with clarithromycin. No dose adjustment needed in renal impairment, but use with caution in patients with CrCl <30 mL/min. No dose adjustment recommended in hepatic impairment but use with caution.	C_{max}: 0.45–0.90 μg/mL	Orange discoloration of urine and body fluids, leukopenia, thrombocytopenia, rash, hepatoxicity, arthralgias, flu-like illness, fatigue, hemolytic anemia, renal failure (rare), uveitis (rare). Induces CYP2C9 and CYP3A4 leading to many drug–drug interactions; always review prior to prescribing. Rifabutin's effects on metabolizing enzymes are generally less severe than those of rifampin. Rifamycins' effects on metabolizing enzymes can take a few weeks to wash out. Notably reduces macrolide concentrations.	Clinical evaluation. LFTs and CBC every 1–2 mo. For mild rash, can continue with treatment with an oral antihistamine or a topical corticosteroid. For hepatitis (LFTs >3× ULN with symptoms or 5× ULN without symptoms), severe pancytopenia, renal failure, hemolytic anemia, or uveitis, then discontinue.
Fluoroquinolones				
Ciprofloxacin, PO/IV	500–750 mg PO twice daily. Dosing with IV formulation is case-dependent. Reduce dose or increase dosing interval for renal impairment. No dose adjustment needed for hepatic impairment.	C_{max}: 4–6 μg/mL	QTc prolongation, hepatitis, nausea, vomiting, tendonitis, tendon rupture, aortic dissection (rare and controversial). Avoid coadministration of divalent cations (magnesium, calcium), milk products, within 2 h.	Clinical evaluation. ECG at baseline, at 1–2 wk if giving with a second QTc-prolonging agent, and then every 1–2 mo. Cr and LFTs every 1–2 mo. For QTc >500 ms, hold and optimize QTc (replete potassium and magnesium, stop or dose reduce other QTc-prolonging agents if possible), then repeat ECG and if QTc has normalized, can rechallenge. For hepatitis, tendon rupture, aortic dissection, discontinue.
Levofloxacin, PO/IV	750–1000 mg PO/IV once daily. Increase dosing interval for renal impairment. No dose adjustment needed for hepatic impairment.	C_{max}: 8–12 μg/mL	QTc prolongation, hepatitis, nausea, vomiting, tendonitis, tendon rupture, aortic dissection (rare and controversial). Avoid coadministration of divalent cations (magnesium, calcium), milk products, within 2 h.	Clinical evaluation. ECG at baseline, at 1–2 wk if giving with a second QTc-prolonging agent, and then every 1–2 mo. Cr and LFTs every 1–2 mo. For QTc >500 ms, hold and optimize QTc (replete potassium and magnesium, stop or dose reduce other QTc-prolonging agents if possible), then repeat ECG and if QTc has normalized, can rechallenge. For hepatitis, tendon rupture, aortic dissection, discontinue.

Table 4. Continued

Antimicrobial	Dosing	Therapeutic Drug Monitoring Targets	Adverse Effects and Drug Interactions	Suggested Monitoring and Management
Moxifloxacin, PO/IV	400 mg PO/IV once daily. No dose adjustment needed for renal impairment. No dose adjustment recommended in hepatic impairment, but use with caution.	C_{max}: 3–5 μg/mL	QTc prolongation, hepatitis, nausea, vomiting, tendonitis, tendon rupture, aortic dissection (rare and controversial). Avoid coadministration of divalent cations (magnesium, calcium), milk products, within 2 h.	Clinical evaluation. ECG at baseline, at 1–2 wk if giving with a second QTc-prolonging agent, and then every 1–2 mo. Cr and LFTs every 1–2 mo. For QTc >500 ms, hold and optimize QTc (replete potassium and magnesium, stop or dose reduce other QTc-prolonging agents if possible), then repeat ECG and if QTc has normalized, can rechallenge. For hepatitis, tendon rupture, aortic dissection, discontinue.
Oxazolidinones				
Linezolid, PO/IV	600 mg PO/IV once daily. No dose adjustments needed for renal or hepatic impairment.	C_{max}: 12–26 μg/mL C_{min}: <2 μg/mL	Myelosuppression (thrombocytopenia is most common), peripheral neuropathy (dose-dependent risk), optic neuropathy, rash, lactic acidosis, uncontrolled hypertension. Rare risk of serotonin syndrome if given with other serotonin agonists; always review prior to prescribing.	Clinical evaluation. CBC every 1–2 mo. For peripheral neuropathy, hold for a holiday, and then rechallenge at a lower dose or an increased dosing interval. For blurred vision or change in color vision, discontinue. For any severe adverse effects, discontinue.
Tedizolid, PO/IV	200 mg PO/IV once daily. No dose adjustments needed for renal or hepatic impairment.		Myelosuppression (thrombocytopenia is most common), peripheral neuropathy, optic neuropathy, rash, lactic acidosis. Rare risk of serotonin syndrome if coadministered with other serotonin agonists; always review prior to prescribing.	Clinical evaluation. CBC every 1–2 mo. For peripheral neuropathy, hold for a holiday, and then rechallenge at a lower dose or an increased dosing interval. For blurred vision or change in color vision, discontinue. For any severe adverse effects, discontinue.
Cyclines				
Doxycycline, PO/IV	100 mg PO/IV twice daily. No dose adjustments needed for renal or hepatic impairment.		Photosensitivity, nausea and vomiting, pill esophagitis, dizziness, hepatitis (rare).	Clinical evaluation. LFTs every 1–2 mo. For any severe adverse effects, discontinue. Counsel patients to avoid prolonged sun exposure and use strong sunscreens to mitigate photosensitivity.
Eravacycline, IV	1.5 mg/kg once daily. Can increase to 1.5 mg/kg twice daily when coadministered with CYP3A4 inducers. No dose adjustments needed for renal impairment. Reduce to 1 mg/kg once daily for severe hepatic impairment.		Nausea and vomiting, cytopenias (rare), hepatitis (rare), acute pancreatitis (rare). Concentrations are decreased by CYP3A4 inducers; always review prior to prescribing.	Clinical evaluation. LFTs, CBC, amylase, and lipase every 1–2 wk. For any severe adverse effects, discontinue.
Omadacycline, PO/IV	300 mg PO once daily (no loading dose needed). 100 mg IV once daily (no loading dose needed). No dose adjustments needed for renal or hepatic impairment.		Nausea and vomiting, cytopenias (rare), hepatitis (rare), acute pancreatitis (rare).	Clinical evaluation. LFTs, CBC, amylase, and lipase every 1–2 mo. For any severe adverse effects, discontinue.
Tigecycline, IV	25–50 mg IV once or twice daily. No dose adjustment needed in renal impairment. No dose adjustment recommended in hepatic impairment, but use with caution.	C_{max}: 1 μg/mL	Nausea and vomiting, cytopenias (rare), hepatitis (rare), acute pancreatitis (rare).	Clinical evaluation. LFTs, CBC, amylase, and lipase every 1–2 wk. For any severe adverse effects, discontinue.

Table 4. Continued

Antimicrobial	Dosing	Therapeutic Drug Monitoring Targets	Adverse Effects and Drug Interactions	Suggested Monitoring and Management
Other				
Bedaquiline, PO	400 mg PO once daily for the first 14 d, followed by 200 mg/day PO, 3 times weekly. No dose adjustments needed for renal or hepatic impairment.		QTc prolongation, hepatitis, elevated amylase, nausea, loss of appetite, rash, headaches, joint pain.	Clinical evaluation. ECG at baseline, 2, 12, and 24 wk of treatment. LFTs every 1–2 mo. For QTc >500 ms, hold and optimize QTc (replete potassium and magnesium, stop or reduce other QTc-prolonging agent), then repeat ECG and if QTc has normalized, can rechallenge. For hepatitis, discontinue.
Cefoxitin, IV	2–4 g IV 2–3 times daily (maximum daily dose is 12 g/d). Reduce dose or increase dosing interval for renal impairment. No dose adjustment needed for hepatic impairment.		Diarrhea (including risk for *Clostridioides difficile* colitis), nausea and vomiting, hepatitis, cytopenias, rash, hypersensitivity[a], increased risk of seizures in patients with seizure disorders.	Clinical evaluation. Cr, LFTs, and CBC every 1–2 wk. For any severe adverse effects, discontinue.
Ceftaroline[b], IV	600 mg IV twice daily. Reduce dose for renal impairment. No dose adjustment needed for hepatic impairment.		Diarrhea (including risk for *Clostridioides difficile* colitis), nausea and vomiting, hepatitis, cytopenias, rash, hypersensitivity[a], increased risk of seizures in patients with seizure disorders.	Clinical evaluation. Cr, LFTs, and CBC every 1–2 wk. For any severe adverse effects, discontinue.
Clofazimine, PO	100–200 mg PO once daily. No dose adjustment needed for renal impairment. No dose adjustment recommended for hepatic impairment, but use with caution.	C_{max}: 0.5–2.0 μg/mL	Hyperpigmentation, gastrointestinal issues, photosensitivity, QTc prolongation, ichthyosis, dry skin, pruritus, rash, retinopathy, gastrointestinal bleeding (rare), bowel obstruction (rare).	Clinical evaluation. ECG at baseline, at 1–2 wk if giving with a second QTc-prolonging agent, and then every 6 mo. For QTc >500 ms, hold and optimize QTc (replete potassium and magnesium, stop or reduce other QTc-prolonging agents), then repeat ECG and if QTc has normalized, can rechallenge. For hepatitis, discontinue. Counsel patients to avoid prolonged sun exposure and use strong sunscreens to mitigate hyperpigmentation.
Ethambutol, PO	15 mg/kg (lean body weight) PO once daily. 25 mg/kg (lean body weight)/day PO, 3 times weekly. Preferably round down to accommodate tablet dose-size. Decrease dose to 15 mg/kg (lean body weight)/day PO, 3 times weekly for renal impairment (CrCl <30 mL/min). No dose adjustment needed for hepatic impairment.	C_{max}: 2–6 μg/mL	Optic neuritis (rare), peripheral neuropathy (rare).	Visual acuity and color vision screening (Ishihara test) every month. For peripheral neuropathy, hold for a holiday, then rechallenge at a lower dose or an increased dosing interval. For blurred vision or change in color vision, hold and request an ophthalmological exam—if optic neuritis is confirmed or deemed likely, discontinue; if vision changes are caused by an alternative diagnosis, can rechallenge with closer vision monitoring.
Imipenem-cilastatin, IV	500–1000 mg IV 2–3 times daily. Reduce dose or increase dosing interval for renal impairment. No dose adjustment needed for hepatic impairment.	C_{max}: 35–60 μg/mL	Diarrhea (including risk for *Clostridioides difficile* colitis), nausea and vomiting, hepatitis, cytopenias, rash, hypersensitivity[a], increased risk of seizures in patients with seizure disorders. Reduces valproic acid concentrations.	Clinical evaluation. Cr, LFTs, and CBC every 1–2 wk. For any severe adverse effects, discontinue.
Isoniazid, PO/IV/IM	5 mg/kg or 300 mg PO/IV/IM once daily. No dose adjustment needed for renal impairment. No dose adjustment recommended in hepatic impairment, but use with caution.	C_{max}: 3–6 μg/mL	Hepatitis, peripheral neuropathy, arthralgias, central nervous system abnormalities ("brain fog"), arthralgias, diarrhea, drug-induced lupus (rare).	Clinical evaluation. LFTs every 1–2 mo. Give with vitamin B6 (pyridoxine) 25–50 mg PO once daily to prevent peripheral neuropathy. For hepatitis (LFTs >3× ULN with symptoms or 5× ULN without symptoms) or peripheral neuropathy, discontinue.

Table 4. Continued

Antimicrobial	Dosing	Therapeutic Drug Monitoring Targets	Adverse Effects and Drug Interactions	Suggested Monitoring and Management
TMP-SMX, PO/IV	800 mg/160 mg twice daily. 15–20 mg/kg/d of trimethoprim divided every 6–8 h. Reduce dose by 50% if CrCl is 15–30 mL/min. No dose adjustment recommended in hepatic impairment, but use with caution.		Gastrointestinal intolerance (diarrhea, nausea, and abdominal pain), cytopenias, hypersensitivity[a], hyperkalemia, acute kidney injury, interstitial nephritis, rash, drug fever, Stevens-Johnson syndrome, toxic epidermal necrolysis, hepatitis.	Clinical evaluation. Cr, electrolytes, LFTs, and CBC every 1 mo. For any severe adverse effects, discontinue.

Table synthesized from expert opinions and references [1, 2, 65].

Abbreviations: CBC, complete blood count; C_{max}, peak or maximum serum concentration (measured usually at 2 hours or 6 hours postdose, but varies by drug); C_{min}, trough or minimum serum concentration (measured usually immediately before administration of the next dose); Cr, creatinine; CrCl, creatinine clearance; CT, computed tomography scan; ECG, electrocardiogram; IM, intramuscular; IV, intravenous; LFTs, liver function tests; MIC, minimum inhibitory concentration; PO, by mouth; TMP-SMX, trimethoprim-sulfamethoxazole; ULN, upper limit of normal.

[a]Hypersensitivity reactions range from mild rash and urticaria to severe conditions like anaphylaxis.

[b]Ceftaroline has shown in vitro synergy with imipenem-cilastatin against *Mycobacterium abscessus* but should not be used alone [66].

effective therapies and understanding refractory disease and recurrences, 46%–74% of which are caused by reinfections as opposed to relapses from old infections [15, 83]. Thankfully, new pathogen-directed and host-directed treatments are under investigation, creating more clinical trial opportunities for patients (Figure 5, step VI). Furthermore, emerging research on the microbiome, health disparities, and climate change in relation to NTM are likely to generate novel advancements in prevention and treatment.

Repurposed and Novel Pathogen-Directed Therapies

Several repurposed and novel compounds are in preclinical and clinical development including phase 1 through phase 3 clinical trials (Figure 1). Apramycin, a veterinary aminoglycoside showing potent in vitro bactericidal activity against *M. abscessus*, is being explored for human therapeutic use [84]. Omadacycline, an oral and IV aminomethylcycline, has shown activity against *M. abscessus* in various models and reasonable tolerability in observational studies [85, 86]. It is currently being investigated in a phase 2 clinical trial for *M. abscessus* pulmonary disease (NCT04922554). In vitro studies have demonstrated that dual β-lactam combinations, such as imipenem with ceftaroline against *M. abscessus*, and cefuroxime with amoxicillin against MAC, exert synergistic effects by redundantly binding mycobacterial transpeptidases [66, 87]. Epetraborole is a novel boron-containing, orally available, inhibitor of bacterial leucyl-tRNA synthetase with excellent in vitro, hollow fiber, and in vivo activity against both SGM and RGM [88, 89]. SPR720 is a novel aminobenzimidazole, gyrase B inhibitor that is converted to the active moiety SPR719, with activity against SGM in vitro and in hollow fiber and mouse models [90] and is currently being evaluated in a clinical trial (NCT05496374). Non-antimicrobial agents such as mycobacteriophages and inhaled gallium are in the early stages of clinical development. Therapy with mycobacteriophages, viruses that infect mycobacteria, was associated with favorable clinical or microbiologic responses in 11 of 20 patients with treatment-limited NTM-PD [27]. Gallium, a novel compound targeting mycobacterial iron metabolism, has shown in vitro efficacy against MAC and *M. abscessus* [91] and is under investigation in a phase 1 trial for patients with CF and NTM-PD (NCT04294043).

Host-Directed Therapies and the Microbiome

New developments are addressing the host and microbiome. Brensocatib, a dipeptidyl peptidase 1 inhibitor that inhibits neutrophil serine protease activity, was found to reduce exacerbations and neutrophil elastase concentrations in sputa of patients with non-CF bronchiectasis [92]. Glutathione, a tripeptide that reduces inflammation [33], is being evaluated in a Phase 2 clinical trial, pending analysis (NCT05495243). Inhaled granulocyte-macrophage colony-stimulating factor,

which enhances macrophage activity, was shown to increase the sputum culture conversion rate compared to a historical control group in treatment-refractory MAC-PD in a small open-label pilot study [93]. Other agents, like metformin, statins, and resveratrol, have been shown to enhance host immunity against MTBC and are hypothesized to be applicable to NTM [14, 33]. Both respiratory and gut microbiomes affect susceptibility to NTM-PD, with arginine-induced gut microbiome changes shown to enhance pulmonary immune defense against NTM [94, 95].

Health Disparities and Climate Change

Since the diagnosis of NTM-PD and determination of any underlying host risk factors often require specialized testing, it is likely that NTM-PD is underdiagnosed in patients who experience socioeconomic disadvantage. Wisconsin residents living in neighborhoods with higher scores of social disadvantage had higher incidence of NTM isolation, irrespective of race or ethnicity [96]. Individuals living in areas with higher disadvantage scores were shown to live in areas with environmental factors that predispose them to NTM-PD, such as vanadium and molybdenum in water sources [97] or higher benzo[a]pyrene pollution in the air [98]. Other population-based studies in Wisconsin and Hawaii have shown that the incidence of NTM isolation from respiratory samples was substantially higher among people who identify as Black or Asian [96, 99]. Future research should include socially disadvantaged individuals who may be at risk for NTM-PD due to underlying comorbid conditions as study participants. This will allow better characterization of the epidemiology of NTM-PD and identify gaps in care.

Climate change is expected to impact NTM-PD given that NTM are soil and water inhabitants [100, 101]. NTM infection incidence correlated with increased rainfall and peak temperature events in Australia [101]. Climate change has increased the frequency and severity of natural disasters, which create large aerosolization events while increasing host vulnerability to NTM-PD through stress-induced immunosuppression, malnutrition, and loss of access to care [100]. Unsurprisingly, some of the states with the highest rates of NTM-PD in the US are those most afflicted by natural disasters [7, 100]. Thus, future research should also investigate the change in NTM-PD incidence and species distribution in relation to climate change–associated environmental factors and natural disasters, potentially leading to better understanding and strategies to prevent NTM infections and reinfections in vulnerable patients.

CONCLUSIONS

NTM-PD is a growing worldwide health threat. Its management is challenging and complex but has foundational principles. Optimal care starts with an accurate diagnosis of both the presence of NTM-PD and the culprit NTM species/subspecies, assessment of severity and prognosis, and understanding patient goals of care. Treatment of underlying comorbidities, optimization of nutrition, and implementation of ACT are the cornerstones of comprehensive therapy. Antimicrobial treatment generally entails a 3-drug minimum, macrolide-based regimen, accompanied by ethambutol for SGM, and intensified by an aminoglycoside for severe or treatment-limited disease. Surgical lung resection, enrollment in clinical trials, or a palliative approach should be considered for specific patients. Despite many uncertainties, patients appreciate and benefit from judicious care that centers on their goals and avoids unnecessary treatment. New pathogen- and host-directed therapeutics and research on how the microbiome, health disparities, and climate change affect NTM-PD are on the horizon.

Notes

Author contributions. All authors contributed to the manuscript. M.-V. H. N. organized the manuscript, performed the literature search and writing for some sections of the manuscript, integrated all sections from all authors, and reviewed and edited the whole manuscript. M. K. H. performed the literature search and writing for some sections of the manuscript, and reviewed and edited the whole manuscript. S. H. K. performed the literature search and writing for some sections of the manuscript, and reviewed and edited the whole manuscript. V. C. N. d. M. designed and produced the figures, performed writing for some sections of the manuscript, and reviewed and edited the whole manuscript. J. J. E. performed the literature search and writing for some sections of the manuscript, and reviewed and edited the whole manuscript. J. D. M. performed the literature search and writing for some sections of the manuscript, and reviewed and edited the whole manuscript. R. K. performed the literature search and writing for some sections of the manuscript, and reviewed and edited the whole manuscript. D. E. G. performed the literature search and writing for some sections of the manuscript, and reviewed and edited the whole manuscript. E. D. C. performed the literature search and writing for some sections of the manuscript, and reviewed and edited the whole manuscript. C. L. D. co-organized the manuscript, performed the literature search and writing for some sections of the manuscript, and reviewed and edited the whole manuscript.

Acknowledgments. Alyssa Y. Castillo (Division of Infectious Diseases, Department of Medicine, University of Colorado, Aurora) shared the patient case described in Figure 3. Thomas J. Gintee (Department of Pharmacy Services, University of California, Davis Health, Sacramento) reviewed and suggested edits for Table 4. Tilman L. Koelsch (Department of Radiology, National Jewish Health, Denver, Colorado) provided the high-resolution radiology images. Perplexity AI assisted with spelling and grammatical editing. Figures 1 and 6 were created with BioRender.com under a paid subscription.

Financial support. M.-V. H. N. is supported by the National Jewish Health Lowerre Mycobacterial Research Fellowship.

Potential conflicts of interest. S. H. K. reports consulting with AN2 Therapeutics, Insmed, and Paratek Pharmaceuticals; investigator work with Insmed; and speaker work with AN2 Therapeutics, Insmed, and Paratek Pharmaceuticals. J. D. M. reports consulting with Intuitive Surgical. D. E. G. reports advisory board work with Insmed and consulting with AN2 Therapeutics, Insmed, and Paratek Pharmaceuticals. C. L. D. reports grant support from AN2 Therapeutics, Bugworks, Insmed, Juvabis, and Paratek Pharmaceuticals; advisory board work with AN2 Therapeutics, AstraZeneca, Cepheid, Hyfe, Insmed, MannKind, Matinas Biopharma, NobHill, Spero Therapeutics, and Zambon; consulting with

Genentech and Pfizer; and data monitoring committee work with Otsuka Pharmaceutical and the Gates Foundation. All other authors report no potential conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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