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REVIEW

Contemporary Pharmacotherapies for Nontuberculosis Mycobacterial Infections: A Narrative Review

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ABSTRACT

Nontuberculous mycobacteria (NTM) are a group of atypical bacteria that may cause a spectrum of clinical manifestations, including pulmonary, musculoskeletal, skin and soft tissue, and cardiac infections. Antimycobacterial medication regimens for NTM infections require multiple agents with prolonged treatment courses and are often associated with poor tolerance in patients and suboptimal clinical outcomes. This review summarizes NTM pharmacotherapy, including treatment concepts, preferred medication regimens according to NTM species and site of infection, and emerging treatment methods for difficult-to-treat species.

Keywords: Antimycobacterials; β-lactam/β-lactamase inhibitors; Clofazimine; *Mycobacterium abscessus*; *Mycobacterium avium* complex; Mycobacterial infections; Nontuberculous; Nontuberculous mycobacteria; Omadacycline; Tedizolid

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Key Summary Points

Mycobacterial infections constitute a substantial worldwide problem because of their ubiquitous nature, inherent drug resistance, and increasing incidence.

Designing safe and effective nontuberculous mycobacterial infection treatments is challenging because of variability in treatment regimens for different mycobacterial species, infection sites, and disease severity, in addition to medication adverse effects, the prolonged duration of therapy, and common patient comorbid conditions.

Nontuberculous mycobacterial treatment regimen framework designs generally include the use of at least two drugs, which may include an intensive stage followed by a maintenance stage, and drug choices are often informed by microbiologic data.

Emerging treatments include tetracycline derivatives, oxazolidinones, combination β-lactams, β-lactamase inhibitors, and phage therapy.

INTRODUCTION

As a human pathogen, *Mycobacterium tuberculosis* (which causes tuberculosis) is familiar to clinicians, but infections caused by nontuberculous mycobacteria (NTM) may be less well known. NTM most commonly cause pulmonary infections, especially among patients with structural airway disease (e.g., cystic fibrosis and bronchiectasis), but can also cause lymphadenitis, skin and soft tissue infection (SSTI), cardiac infection, bone and joint infections, and disseminated disease [1, 2].

Mycobacteria are aerobic organisms known for their acid-fastness and thick, lipid-rich cell walls [3]. Cell wall impermeability, along with biofilm formation, contributes to the antimicrobial, high-temperature, and disinfectant resistance of mycobacteria [4]. NTM are ubiquitous in the environment and commonly found in water and soil reservoirs. Inhalation and ingestion are the purported leading routes of transmission, and direct person-to-person transmission is rare, unlike that of *M. tuberculosis*. NTM commonly colonize hot tubs, peat-based potting soils, hemodialysis clinics, fish tanks, and domestic water systems, and have been linked to nosocomial outbreaks [5, 6].

More than 190 NTM species and subspecies have been identified to date, many of which were recently discovered because of advances in culture techniques and molecular diagnostics [7, 8]. Classically, NTM have been divided into rapid ($\leq$ 7 days for mature colony formation in solid media) and slow (> 7 days for colonization) growers. Of the NTM species known to cause human disease, notable rapid growers include *Mycobacterium abscessus* complex (Mabs, comprising *M. abscessus* subsp. *abscessus*, *M. abscessus* subsp. *bolletii*, and *M. abscessus* subsp. *massiliense*), *Mycobacterium fortuitum*, and *Mycobacterium chelonae*. Slow growers known to cause human disease include *Mycobacterium avium* complex (MAC, comprising *Mycobacterium avium*, *Mycobacterium intracellulare*, and *Mycobacterium chimaera*), *Mycobacterium kansasii*, and *Mycobacterium xenopi*. Among both rapid and slow growers, MAC is the most common cause of NTM pulmonary disease in the US, followed by *M. kansasii* and Mabs [8].

NTM infections appear to be increasing worldwide, with an estimated incidence of 4.1–14.1 cases per 100,000 patient-years [9, 10]. Proposed reasons for this increase include higher air pollution levels, a population increasing in age and comorbid conditions, use of immunosuppressive therapies, and chronic use of inhaled corticosteroids [9, 10]. However, improved diagnostics may also contribute to the apparent increase in NTM infections [6, 11]. Diagnosis of NTM infections is based on a combination of clinical, microbiologic, and radiographic criteria that often involve infectious diseases and/or pulmonary specialists. NTM diagnostic criteria and the decision to initiate treatment are described in detail

elsewhere and are considered outside the scope of this pharmacotherapy review [8, 12].

Mycobacterial infections pose a substantial problem because of their widespread prevalence worldwide and their increasing incidence [13]. Treatment of these infections is challenged by the need for multiple antimicrobial agents, varying resistance patterns among mycobacterial species, and long duration of therapy. Here, we review current and emerging approaches to pharmacologic management of NTM infections.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

CURRENT TREATMENTS

Treatment Concepts

Antimycobacterials are often used in combination with bronchial hygiene/clearance regimens and/or surgical resection to decrease bacterial burden [8]. However, designing safe and effective pharmacotherapy for NTM disease is complex, in part because of treatment regimen variability based on different NTM species, infection sites, and disease severities. Patient-specific factors can increase this complexity, including advanced patient age, body weight extremes, and comorbid conditions. NTM treatment commonly requires the administration of multiple drugs for long durations, accompanied by clinical and laboratory monitoring. In addition to the lack of association between in vitro and in vivo activity for most antimicrobials, systematic controlled trials of first-line treatment regimens, including preferred drug choice, dose, and duration, for various NTM species and diseases are also sparse [12].

Despite these challenges, a general framework for NTM treatment can be useful after reaching a definitive diagnosis and should contain the following elements:

1. At least 2 drugs with likely or confirmed activity against the isolated NTM species should be used. Combination therapy prevents emergent resistance, and certain drug pairings can be synergistic. Disease severity and infection location guide the number of drugs initially used. Up to 4 drugs are commonly used for severe disease, such as fibrocavitary and pulmonary MAC infection, whereas 2 drugs may be used for uncomplicated NTM SSTI.
2. For infections caused by certain species, such as Mabs, treatment may occur in 2 stages: an initial, intensive phase lasting approximately 1–3 months, followed by a prolonged maintenance phase. The initial phase typically contains more drugs and intravenous (IV) administration when indicated. The maintenance phase ideally involves only orally administered drugs and may include as few as 2 drugs. Total treatment duration is guided by clinical response and patient tolerability. Treatment duration is best defined for pulmonary NTM infection as continuing for 12 months after sputum culture conversion to negative [8].
3. *Mycobacterium* species identification and susceptibility testing guide drug choice. Data showing an association between in vivo clinical outcomes and in vitro susceptibility test results are lacking for most NTM infections, although amikacin and clarithromycin are notable exceptions for MAC and Mabs infections, as well as rifampin for *M. kansasii* infection. Nevertheless, performing susceptibility testing is generally recommended. Empiric treatment based on usual susceptibility patterns is often initiated for severe and/or disseminated disease while awaiting further microbiologic test results. Macrolides, except when resistance is evident, are a backbone of most NTM treatment regimens [12].

Patients should be counseled about the NTM disease process, goals of therapy, chances of treatment success, medication administration and adverse effects, and laboratory monitoring requirements before committing to NTM therapy. A multidisciplinary team supporting the patient is key to success and may include infectious diseases and pulmonary physicians, advanced practitioners, pharmacists, surgeons,

respiratory therapists, nurses, dieticians, microbiologists, and radiologists.

Common Pharmacotherapeutics for MAC

Because MAC infections are overwhelmingly the most common NTM infection type, MAC is the most extensively studied NTM species. Many studies have aimed to determine optimal MAC treatment, and uniform treatment regimens are supported by high-level evidence from randomized, controlled trials. In contrast, treatment recommendations for other species are less extensively investigated. Therefore, the following discussion focuses on MAC treatment recommendations. Other species and active antimicrobial agents are summarized in Table 1.

Guidelines for pulmonary MAC recommend a three-drug regimen consisting of a macrolide (azithromycin or clarithromycin), ethambutol, and a rifamycin (rifampin or rifabutin) [8]. Macrolides are generally regarded as the cornerstone of MAC treatment, and clinical outcomes do not differ between azithromycin and clarithromycin treatment [8]. Azithromycin may be favored more than clarithromycin because azithromycin is associated with fewer drug–drug interactions, better patient tolerance, and a lower pill burden [8].

Hallmark adverse effects of macrolides include gastrointestinal and taste disturbances, QTc prolongation, other cardiac disturbances, and auditory toxicities [8]. Because ethambutol helps prevent the development of macrolide resistance in MAC infections, it is the preferred second agent. Notable adverse effects of ethambutol include ocular toxicity and peripheral neuropathy [8]. The addition of a rifamycin to macrolide/ethambutol combination treatment may provide further protection against macrolide resistance [8]. Rifampin causes many drug–drug interactions by inducing several cytochrome P450 enzymes, most notably CYP3A4, and UDP-galactose transporter. Rifampin also causes red–orange discoloration of bodily secretions (e.g., urine, saliva, perspiration, and tears), hepatotoxicity, and cytopenia [8].

The aminoglycoside amikacin has considerable activity against most NTM species, including MAC. IV amikacin is a potential fourth drug in macrolide-nonsusceptible and cavitary MAC disease, although some experts may recommend an inhaled route for noncavitary disease [8, 14]. Inhaled or IV amikacin are both options for refractory pulmonary disease [8]. Both formulations are associated with a risk of kidney, vestibular, and auditory toxicity, although these risks are considerably lower with inhalation [8, 14]. Medications with activity against MAC and other NTM species are listed in Table 1.

THERAPEUTIC DRUG MONITORING

Therapeutic drug monitoring (TDM) is standard for patients receiving IV amikacin because of its drug toxicity risks. An extrapolated peak of 35–45 mcg/mL and trough of less than 5 mcg/mL are targeted with daily administration of IV amikacin (15–20 mg/kg ideal body weight) [8]. Amikacin peaks can be extrapolated with 2- and 6-h postinfusion concentrations to avoid sampling before reaching serum–tissue drug equilibrium. If two serum concentrations are not readily available, an approximate peak can be measured 1 h after the end of infusion, with a peak goal of 25–35 mcg/mL. A 3timesaweek IV amikacin dose of 25 mg/kg, with a peak goal of 65–80 mcg/mL and undetectable trough, is an alternative dosing strategy for pulmonary NTM infection [8, 20].

Serum TDM of oral NTM agents is not well established but is considered in certain circumstances, such as concern for adequate drug absorption (e.g., a history of Roux-en-Y procedure, graft-versus-host disease of the gut, and severe gastrointestinal disease such as Crohn's disease), pharmacokinetic drug interactions, kidney or liver dysfunction, or a lack of clinical/microbiologic response to therapy. Measuring serum drug levels at two time points, typically at 2–3 h after drug administration and again at 6 h after administration, is generally used with oral TDM to assess for potential delayed drug absorption [15]. Table 2 includes the target C_{max} concentrations (i.e., peak blood/serum drug

Table 1 Classification of NTM species and pharmacotherapeutics with in vitro microbiologic activity [8, 12, 15–19]

Classification and major groups	Pharmacotherapeutics	
	Preferred agents[a]	Alternative agents
Slow-growing NTM (colonization > 7 days)		
M. avium complex[b]	AMK, AZM, EMB, RFB, RIF	BDQ, CLO, CLR, CZA, ETO, LZD, MXF, SXT, TGC, TZD
M. kansasii	AZM, CIP, EMB, INH, LVX, MXF, RFB, RIF	AMK, BDQ, CLO, CLR, LZD, SXT, TGC, TZD
M. marinum	AZM, EMB, RFB, RIF	AMK, CIP, CLR, DOX, INH, IPM, LVX, LZD, MIN, MXF, SXT, TZD
M. scrofulaceum	AZM, CIP, CLR, LVX, MXF	EMB, LZD, MIN, RFB, RIF
M. haemophilum	AZM, CIP, CLR, RFB, RIF	AMK, CLO, DOX, SXT
M. terrae complex[c]	AZM, CLR, EMB, RIF	AMK, CIP, ETO, LVX, LZD, MXF, SXT
M. xenopi	AZM, CLR, EMB, RFB, RIF	AMK, INH, LVX, MXF
M. ulcerans	AMK, AZM, EMB, RFB, RIF	CLR, MXF, SXT, TET
M. malmoense	AZM, EMB, LVX, MXF, RFB, RIF	CLR, INH
M. celatum	AZM, EMB, LVX, MXF, RFB	AMK, CLR, INH, PZA
M. genavense	AZM, RFB, RIF	AMK, CLO, CLR, EMB, LVX, MXF
M. simiae complex[d]	CLR, EMB, MXF, RFB, RIF, SXT	AMK, CLO, LZD
M. szulgai	AZM, EMB, RIF	AMK, CLR, INH, LVX, MXF, PZA
M. gordonae	AZM, CLR, EMB, RIF	INH, LVX, LZD, MXF, RFB, SXT
Rapid-growing NTM (colonization ≤ 7 days)		
M. fortuitum complex[e]	AMK, CIP, DOX, IPM, LVX, MIN, MXF, SXT	FOX, LZD, OMC, TGC, TOB
M. chelonae	AZM, IPM, LZD, TOB	CIP, CLO, CLR, DOX, LVX, MIN, MXF, OMC, SXT, TGC
M. abscessus complex[f]	AMK, AZM, FOX, IPM	BDQ, CIP, CLO, CLR, ERV, IMR, LVX, LZD, MXF, OMC, TGC, TZD
M. smegmatis group[g]	AMK, CIP, DOX, MXF, SXT	AZM, CLO, CLR, EMB, FOX, IPM
M. immunogenum	AMK, AZM, TGC	CLR, IPM, LZD, TZD

Table 1 continued

Classification and major groups	Pharmacotherapeutics	
	Preferred agents[a]	Alternative agents
M. mucogenicum	AMK, AZM, CIP, FOX, IPM, LVX, MXF, SXT	AMX, CLR, DOX, LZD, MIN

AMK amikacin, *AMX* amoxicillin, *AZM* azithromycin, *BDQ* bedaquiline, *CIP* ciprofloxacin, *CLO* clofazimine, *CLR* clarithromycin, *CZA* ceftazidime/avibactam, *DOX* doxycycline, *EMB* ethambutol, *ERV* eravacycline, *ETO* ethionamide, *FOX* cefoxitin, *IMR* imipenem/relebactam, *INH* isoniazid, *IPM* imipenem, *LVX* levofloxacin, *LZD* linezolid, *MIN* minocycline, *MXF* moxifloxacin, *NTM* nontuberculous mycobacterial, *OMC* omadacycline, *PZA* pyrazinamide, *RFB* rifabutin, *RIF* rifampin, *SXT* sulfamethoxazole/trimethoprim, *TET* tetracycline, *TGC* tigecycline, *TOB* tobramycin, *TZD* tedizolid

[a]Complete regimen is typically composed of 2–4 agents according to infection site and disease severity. Drug selection is based on clinical evidence for effectiveness, safety, ease of administration, and medication tolerability

[b]*M. avium* complex comprises *M. avium, M. intracellulare*, and *M.* subsp. *chimaera*

[c]*M. terrae* complex comprises *M. terrae*, *M. triviale*, *M. nonchromogenicum*, and *M. hiberniae*

[d]*M. simiae* complex comprises *M. simiae*, *M. sherisii*, *M. lentiflavum*, *M. triplex*, *M. heidelbergense*, and *M. simiae* subsp. *palustre*

[e]*M. fortuitum* complex comprises *M. fortuitum*, *M. neworleansense*, *M. peregrinum*, *M. boenickei*, *M. alvei*, *M. porcinum*, *M. conceptionense*, *M. farcinogenes*, *M. senegalense*, and *M. mageritense*

[f]*M. abscessus* complex comprises *M. abscessus* subsp. *abscessus* (sensu stricto), *M. abscessus* subsp. *massiliense*, and *M. abscessus* subsp. *bolletii*

[g]*M. smegmatis* group comprises *M. smegmatis*, *M. wolinskyi*, and *M. goodii*

concentrations) for TDM during NTM infection treatment.

ALTERNATIVE NTM PHARMACOTHERAPY AGENTS

Treating mycobacterial infections is challenging because of the complexity of the disease and therapeutics used. NTM harbor intrinsic resistance and also quickly acquire resistance, which renders many antimicrobial classes ineffective. Medication tolerability issues with traditional NTM pharmacotherapeutics can arise, especially because long-term treatment courses are generally required. Relatively established alternative NTM agents with distinct pharmacologic considerations are summarized in Table 3. Studies of select alternative pharmacotherapy agents are reviewed in Table 2.

Bedaquiline

Bedaquiline is a diarylquinoline antibiotic that inhibits the proton pump of mycobacterial ATP synthase, which is conserved across mycobacterial species [33]. Bedaquiline is used to treat pulmonary multidrug-resistant tuberculosis [34] and has a dose-dependent bacteriostatic effect against MAC and Mabs in vitro and synergism with clofazimine [35]. Bedaquiline was added as off-label salvage therapy for 10 patients with treatment-refractory MAC or Mabs lung infections. Despite a modest microbiologic and clinical response, no cures were reported [23]. Bedaquiline is administered as a daily 400mg dose for 2 weeks, followed by 200 mg administered 3 times per week (with food) and taken in combination with other drugs for at least 6 months [34].

Bedaquiline is metabolized via CYP3A4, and potential drug interactions should be assessed, particularly with CYP3A4 inducers. Substantially decreased serum concentrations of bedaquiline occur with coadministration of rifamycins [36], which limits the usefulness of bedaquiline for MAC treatment. Extreme caution must be used when substituting a rifamycin with moxifloxacin because both medications can prolong the QTc interval,

Table 2 Common pharmacotherapeutics used to treat NTM infections [8, 12, 15, 16, 19–22]

Pharmacotherapeutics	Standard NTM dosing	Typical C_{max}, mcg/mL[a]	Adverse drug events	Therapeutic drug monitoring	Comments
Amikacin (IV)	15 mg/kg (daily 5 times/wk) or 25 mg/kg (daily 3 times/wk)	35–45 (1 time/d) 65–80 (3 times/wk)	Ototoxicity, nephrotoxicity	BMP, audiography, peak and trough concentrations	
Amikacin (inhaled liposomal)	590 mg (every 24 h)	N/A	Sore throat, bronchospasm, dysphonia, tinnitus	Respiratory status, SCr, serum level if indicated, audiography	
Amoxicillin/clavulanate (oral)	875 mg/125 mg (every 12 h)	N/A	GI symptoms, rash, hepatotoxicity	CBC, ALT, SCr	
Azithromycin (oral/IV)	250–500 mg (every 24 h) or 500 mg (3 times/wk)	0.2–0.7	GI symptoms, prolonged QT, hearing loss	ECG, LFT, audiography	
Bedaquiline (oral)	400 mg (every 24 h for 2 wk, then 200 mg 3 times/wk thereafter)	1.0–2.5	GI symptoms, prolonged QT, hepatotoxicity, arthralgia	ECG, CMP, CBC	Limited distribution through 1 specialty pharmacy in the US; must be shipped to a health care facility and cannot be sent directly to patient home
Cefoxitin (IV)	2–4 g (every 8–12 h)	N/A	Hepatotoxicity, myelosuppression, rash	CBC, LFT, SCr	
Ceftazidime/avibactam (IV)	Not established	N/A	Hepatotoxicity, myelosuppression, rash	CBC, LFT, SCr	
Ciprofloxacin (oral/IV)	500–750 mg (every 12 h)	4–6	GI symptoms, prolonged QT, tendinitis, AAA	ECG, SCr	

Table 2 continued

Pharmacotherapeutics	Standard NTM dosing	Typical C_{max}, mcg/mL[a]	Adverse drug events	Therapeutic drug monitoring	Comments
Clarithromycin (oral)	500 mg (every 12 h) or 500 mg (every 12 h on 3 d/wk)	2–7	GI symptoms, prolonged QT, hearing loss	ECG, LFT, audiogram	CYP3A4 inhibitor
Clofazimine (oral)	50–100 mg (every 24 h)	0.5–2.0	Body fluid discoloration, skin changes, GI symptoms, prolonged QT, hepatotoxicity	ECG, LFT	Obtain through IND or expanded access MPP
Doxycycline (oral/IV)	100 mg (every 12 h)	N/A	GI symptoms, photosensitivity, esophageal ulceration		
Ethambutol (oral)	15–20 mg/kg (every 24 h), maximum 1600 mg	2–6	Optic neuritis, peripheral neuropathy	Eye examination, Ishihara test	
Ethionamide (oral)	15–20 mg/kg (every 24 h), maximum 1000 mg	2–5	Optic neuritis, peripheral neuropathy, hepatotoxicity	Eye examination, LFT	
Imipenem-cilastatin (IV)	1000 mg (every 12 h)	N/A	Hepatotoxicity, myelosuppression, seizure	CBC, LFT, SCr	
Imipenem-cilastatin/relebactam (IV)	Not established	N/A	Hepatotoxicity, myelosuppression, seizure	CBC, LFT, SCr	
Isoniazid (oral/IM)	5 mg/kg (every 24 h), maximum 300 mg	3–6	Peripheral neuropathy, hepatotoxicity	LFT	Administer with pyridoxine 50–100 mg daily

Table 2 continued

Pharmacotherapeutics	Standard NTM dosing	Typical C_{max}, mcg/mL[a]	Adverse drug events	Therapeutic drug monitoring	Comments
Levofloxacin (oral/IV)	500–750 mg (every 24 h)	8–13	GI symptoms, prolonged QT, tendinitis, AAA	ECG, SCr	
Linezolid (oral/IV)	300–600 mg (every 24 h)	12–26	GI symptoms, myelosuppression, neuropathy	CBC	
Minocycline (oral/IV)	100 mg (every 12 h)	N/A	GI symptoms, photosensitivity, esophageal ulceration, dizziness		
Moxifloxacin (oral/IV)	400 mg (every 24 h)	3–5	GI symptoms, prolonged QT, tendinitis, AAA	ECG	
Omadacycline (oral/IV)	300 mg (every 24 h)	N/A	GI symptoms, hepatotoxicity	LFT	
Pyrazinamide (oral)	25–40 mg/kg (every 24 h), maximum 2000 mg	20–60	GI symptoms, arthralgia, myalgia, hepatotoxicity	CBC, SCr, LFT	
Rifabutin (oral)	5 mg/kg (every 24 h), maximum 300 mg	0.45–0.90	Discoloration of body fluids, GI symptoms, uveitis, myelosuppression, arthralgia	CBC, LFT	CYP3A4 inducer
Rifampin (oral/IV)	10 mg/kg (every 24 h), maximum 600 mg	8–24	Discoloration of body fluids, GI symptoms, myelosuppression, arthralgia, hepatotoxicity	CBC, LFT	Multiple CYP inducer
Sulfamethoxazole/trimethoprim (oral/IV)	800 mg/160 mg (every 12 h)	N/A	GI symptoms, rash, nephrotoxicity, myelosuppression	CBC, BMP, LFT	

Table 2 continued

Pharmacotherapeutics	Standard NTM dosing	Typical C_{max}, mcg/mL[a]	Adverse drug events	Therapeutic drug monitoring	Comments
Tigecycline (IV)	50 mg (every 12–24 h)	N/A	GI symptoms, hepatotoxicity	LFT	
Tedizolid (oral/IV)	200 mg (every 24 h)	2–3	GI symptoms, myelosuppression, neuropathy	CBC	
Tobramycin (IV)	5–7 mg/kg (every 24 h)	20–30 (1 time/d)	Ototoxicity, vestibulotoxicity, nephrotoxicity	BMP, audiogram, peak and trough drug levels	

AAA abdominal aortic aneurysm, *ALT* alanine aminotransferase, *BMP* basic metabolic panel, *CBC* complete blood cell count, *CMP* comprehensive metabolic panel, *CYP* cytochrome P450, *ECG* electrocardiography, *GI* gastrointestinal, *IM* intramuscular, *IND* investigational new drug, *IV* intravenous, *LFT* liver function testing, *MPP* multipatient protocol, *N/A* not applicable, *NTM* nontuberculous mycobacterial, *SCr* serum creatinine

[a] C_{max} is defined as the peak drug concentration in sampled blood or plasma

which increases risk of ventricular arrhythmia [37]. Electrocardiographic monitoring of patients treated with bedaquiline is recommended. Adverse effects include hepatotoxicity, peripheral neuropathy, otovestibular toxicity, anemia, thrombocytopenia, neutropenia, and kidney impairment [37, 38]. A clinical trial comparing bedaquiline with a rifamycin in a treatment regimen for pulmonary MAC infection is ongoing and has an estimated completion date in late 2024 (clinicaltrials.gov, NCT04630145).

Clofazimine

Clofazimine is an antimicrobial phenazine dye that inhibits bacterial proliferation by binding to DNA. It also acts on the bacterial cell wall to generate toxic lysophospholipids [39]. It has in vitro bacteriostatic activity against MAC and Mabs and synergism with amikacin and/or clarithromycin [40]. Substituting rifampin with clofazimine in ethambutol/clarithromycin-containing regimens enhanced bacterial clearance in a murine model of pulmonary MAC infection, and this substitution led to equivalent patient outcomes in retrospective analyses [24, 41]. Addition of clofazimine and/or aerosolized amikacin to drug regimens for macrolide-resistant pulmonary MAC infection is recommended, although prospective studies have not been performed [14]. In a murine model of pulmonary Mabs infection, administration of clofazimine increased bacterial clearance, which was enhanced by the addition of bedaquiline [42]. Retrospective analyses of infection in humans show moderate effectiveness against Mabs when clofazimine is combined with other antibiotics [25].

Adverse effects of clofazimine include discoloration of the conjunctiva and skin (orange to brownish-black) that may not reverse for months to years after discontinuation. Crystallization of the drug in tissues such as the intestinal mucosa may cause abdominal pain with nausea and vomiting and can rarely lead to intestinal obstruction. Clofazimine may increase concentrations of CYP3A4/5 substrates. QTc prolongation is not a major risk but may be enhanced in combination with certain medications; thus, electrocardiographic monitoring

Table 3 Recent reports of NTM in vivo pharmacotherapy[a]

Pharmacotherapeutic/ citation	Study design and methods	Notable outcomes	Conclusion
BDQ			
Philley et al. [23], 2015	Case series of off-label use of BDQ for treatment failure in lung disease caused by MAC or Mabs in 10 adult patients treated with best-available concurrent NTM therapy Included patients needed access to BDQ and ≥ 12-mo treatment failure for MAC and ≥ 6 mo for Mabs Oral BDQ 400 mg 1 time/d for 2 wk then 200 mg 3 times/wk (600 mg/wk)	After 6 mo of therapy, microbiologic response rate was 60%, with 50% ≥ 1 negative culture result Common adverse effects were nausea (60%), arthralgias (40%), anorexia, subjective fever (30%) No abnormal ECG findings were observed	Potential clinical and microbiologic activity of BDQ for advanced MAC or Mabs lung disease Needs confirmation by larger studies
CLO			
Jarand et al. [24], 2016	Retrospective review of clinical and microbiologic outcomes for MAC-LD in those receiving CLO and/or RIF with macrolide and ethambutol Adult patients with MAC-LD who were treated and monitored for ≥ 6 mo after treatment were included (n = 170)	Majority (84%) were treated with CLO and (13%) with RIF Most patients (95%) had conversion from positive to negative sputum culture results in mean (SD) 4.5 (4.2) mo More patients treated with CLO had conversion to negative culture results vs. patients treated with RIF (100% vs. 71%, $P < 0.001$) Microbiologic relapse occurred in 52 of 107 patients (49%)	Initial outcomes and retreatment rates were at least as good in patients treated with CLO-containing regimens as in patients receiving RIF-containing regimens CLO should be considered as an alternative drug for MAC-LD

Table 3 continued

Pharmacotherapeutic/ citation	Study design and methods	Notable outcomes	Conclusion
Yang et al. [25], 2017	Evaluated clinical efficacy of CLO-containing regimen for Mabs-LD via retrospective review Patients with Mabs-LD who were treated with CLO-containing regimens for initial or refractory disease were included (n = 42)	Treatment response rate was 81% according to symptoms and 31% according to radiographic findings Sputum culture conversion was achieved in 10 (24%) patients after CLO-containing antibiotic treatment Substantial decreases in positive semiquantitative sputum culture results for acid-fast bacilli in both the initial and salvage groups during treatment	CLO-containing regimens may improve treatment outcomes in patients with Mabs-LD, and a prospective evaluation is warranted
Martiniano et al. [26], 2017	Observational cohort study assessed CLO in 112 pediatric and adult patients with and without CF and pulmonary or extrapulmonary Mabs, MAC, or various NTM infections as part of a multidrug regimen	Median (range) CLO duration was 383 (3–2419) days Sixteen patients (14%) stopped CLO because of ADRs after a median (95% CI) of 101 (63–119) days Half of patients with pulmonary disease had sputum culture conversion within 12 mo	CLO was safe, reasonably tolerated, and active for NTM infection in pediatric and adult patients with and without CF CLO should be considered as an alternative drug for NTM disease
LZD			
Parize et al. [27], 2016	Report the efficacy and tolerability of LZD with CLR for *M. chelonae* infection in patients who were immunocompromised	All patients had rapid clinical efficacy without relapse after a median follow-up duration of 2.25 y ADRs were frequent, including thrombocytopenia, myalgia, and mitochondrial toxicity All ADRs were reversible after discontinuing LZD	LZD/CLR combination was suggested as an initial therapy for *M. chelonae* skin infections in patients who are immunocompromised

Table 3 continued

Pharmacotherapeutic/ citation	Study design and methods	Notable outcomes	Conclusion
Winthrop et al. [28], 2015	Retrospective cohort study of LZD tolerability in 102 patients with NTM infections at 6 NTM treatment centers in North America	Median (range) LZD therapy duration after initial drug start was 21.4 (1–201) wk Most (79%) were administered 600 mg (1 time/d); 12%, 300 mg (1 time/d); 5%, 600 mg (2 times/d) ADRs occurred in 46 (45%) patients, including peripheral neuropathy (n = 24, 24%), GI intolerance (n = 9, 9%), anemia (n = 8, 8%), and thrombocytopenia (n = 6, 6%)	LZD can be used for long durations in multidrug NTM treatment ADRs necessitating drug discontinuation were common, occurring in > 40% of patients regardless of concomitant vitamin B6 use
OMC			
Pearson et al. [29], 2020	Case series of 4 patients treated with OMC with multidrug therapy for Mabs infection	NTM syndromes were cutaneous disease (n = 2), pulmonary disease (n = 1), osteomyelitis, and bacteremia (n = 1) Median (range) duration of OMC treatment was 166 (104–227) d Clinical cure was achieved in 3 of 4 patients, with 1 patient improving with ongoing treatment A patient discontinued OMC after 6 mo because of nausea	OMC is a novel oral option for the treatment of Mabs Further data are required to determine its definitive role
Morrisette et al. [30], 2021	Case series of 12 patients treated with OMC with multidrug therapy for Mabs infection	Majority were pulmonary infections (n = 7/12, 58%) Median (IQR) OMC treatment duration was 6.2 (4.2–11.0) mo Clinical success occurred in 9 of 12 (75%) patients. Three patients had a possible ADR	Prospective studies and larger postmarket reports are needed for OMC as NTM therapy

Table 3 continued

Pharmacotherapeutic/ citation	Study design and methods	Notable outcomes	Conclusion
Duah and Beshay [31], 2022	Case series of 3 patients administered OMC as part of a first-line treatment for Mabs pulmonary infection	All 3 patients had reported clinical improvement One patient had a possible ADR (nausea/vomiting)	Findings support future study of OMC as a potential oral first-line option for Mabs pulmonary disease
TDZ			
Poon et al. [32], 2021	Single-center retrospective cohort study of adult solid-organ transplant recipients receiving LZD or TDZ for NTM infection	During 7 wk, LZD and TZD did not differ for platelet counts, ANC, or hemoglobin, but ANC was significantly decreased for both LZD and TZD ($P = 0.04$) Approximately 20% of patients in each arm discontinued LZD or TZD because of an ADR Seven of 12 (58%) and 2 of 3 (67%) patients were cured or clinically cured	No significant safety benefit of TZD vs. LZD TZD and LZD had potential benefit for symptomatic and microbiologic improvement for NTM infections in solid-organ transplant recipients

ADR adverse drug reaction, *ANC* absolute neutrophil count, *BDQ* bedaquiline, *CF* cystic fibrosis, *CLO* clofazimine, *CLR* clarithromycin, *ECG* electrocardiograph, *GI* gastrointestinal, *LD* lung disease, *LZD* linezolid, *Mabs Mycobacterium abscessus*, *MAC Mycobacterium avium* complex, *NTM* nontuberculous mycobacteria, *OMC* omadacycline, *RIF* rifampin, *TZD* tedizolid

[a]All reports published in 2015 or later

is recommended [26]. Aluminum/magnesium antacids may interfere with clofazimine oral absorption. Clofazimine (50–100 mg) should be taken 2 times daily with a meal and separately from aluminum/magnesium-containing antacids.

Rifabutin

Rifabutin, similar to rifampin, is a semisynthetic rifamycin antibiotic that inhibits the bacterial DNA-dependent RNA polymerase, which inhibits transcription of bacterial RNA and leads to cell death. Rifabutin has in vitro activity against most NTM species and is recommended for pulmonary MAC, *M. kansasii*, and *Mycobacterium xenopi* infections [8]. In a preclinical murine model, daily rifabutin (10 mg/kg) for 10 days reduced Mabs concentration by 1 log, which is similar to that with clarithromycin [43]. Rifabutin is usually orally administered as a daily 150 to 300mg dose or 3 times a week at 300 mg, depending on indication and potential drug–drug interactions [8].

Rifabutin adverse effects include orange-brown discoloration of body fluids, rash, gastrointestinal symptoms (e.g., nausea and diarrhea), and neutropenia [44]. Rifabutin induces CYP3A4 activity and therefore reduces the concentrations of many drugs, although

typically to a lesser extent than does rifampin. However, rifabutin is also metabolized by CYP3A4 and thus has greater potential for bidirectional drug interactions than does rifampin [44].

Linezolid

Linezolid is an oxazolidinone antibiotic that binds to bacterial 23S ribosomal RNA of the 50S subunit to inhibit bacterial protein synthesis and has in vitro activity against most mycobacterial species [45–47]. Clinical outcomes data in humans are most readily available for Mabs and *M. chelonae* infections [27, 28, 48]. Linezolid is also considered an alternative treatment option for MAC [28]. Long-term tolerability is limited by hematologic and neurologic toxicities, including pancytopenias and peripheral and optic neuropathies. A daily 600mg dose of linezolid is often used for mycobacterial infections to improve long-term tolerability, although outcomes studies directly comparing 1- vs. 2-time daily dosing are not available [49]. Other methods to limit drug toxicities, including pyridoxine (vitamin B6) supplementation, were not beneficial [28].

Linezolid has reversible, weak inhibitory properties against monoamine oxidase, which led to labeling precautions for serotonin syndrome when it is combined with other serotonergic agents and for hypertensive crisis with tyramine-rich foods. Serotonin syndrome risk, although low overall, may increase with concomitant administration of serotonergic agents and according to their serotonergic potential [50–52].

EMERGING TREATMENTS

NTM treatment outcomes remain suboptimal with established regimens. This highlights the need for developing novel therapeutics and repurposing currently approved therapeutics for antimycobacterial management. Studies of such emerging treatments are reviewed in Table 2.

Tetracycline Derivatives

Tetracyclines reversibly bind to the bacterial 30S ribosomal subunit and inhibit protein synthesis. Tigecycline is a third-generation tetracycline approved for complicated skin and intra-abdominal infections. It also has been studied for its efficacy against NTM disease and is currently recommended as a preferred IV antimycobacterial agent for Mabs in multiple NTM treatment guidelines [8, 53–55]. However, tigecycline use is associated with dose-limiting nausea and vomiting and has a boxed warning for increased risk of death. This boxed warning resulted from outcomes in patients treated for bacterial bloodstream infections [56]. Tigecycline is available only as an IV formulation because of its poor oral absorption [57].

Omadacycline was recently approved for bacterial pneumonia and SSTI, and eravacycline was approved for complicated intra-abdominal infections. Both drugs are better tolerated than their predecessor tigecycline [58] and are attractive therapeutic options for NTM disease. Two in vitro studies reported eravacycline activity against NTM [59, 60], and several in vitro [60–64] and in vivo case reports/series described the use of omadacycline [29–31, 65] in combination therapy for Mabs infection. Omadacycline is under investigation in a phase 2 clinical trial for NTM infection treatment (clinicaltrials.gov, NCT04922554).

Omadacycline is the only novel tetracycline derivative available as an oral formulation. Administering food 2 h before oral omadacycline reduced omadacycline concentrations by 40–63% in clinical trials [66]. Therefore, fasting is recommended for oral omadacycline administration, with no food or drink, except water, consumed 4 h before or 2 h after administration. Absorption is further impaired by antacids containing polyvalent cations, such as calcium or aluminum. Dairy products, antacids, and multivitamins should not be consumed for at least 4 h after omadacycline administration. Although the approved dosing for oral omadacycline includes a loading dose, omitting the loading dose in NTM treatment may increase gastrointestinal tolerability [29]. Eravacycline is a CYP3A4 substrate that can interact with

CYP3A4 inducers such as rifampin. Because both omadacycline and eravacycline depress plasma prothrombin activity, concomitant anticoagulant treatment may require dose reduction.

Tedizolid

Tedizolid is a novel oxazolidinone antibiotic that inhibits bacterial protein synthesis in a similar mechanism to that of linezolid. In vitro activity of tedizolid is reported for many slow-growing and rapid-growing NTM species, including MAC, *M. kansasii*, Mabs, *M. chelonae*, *M. fortuitum*, *Mycobacterium marinum*, *Mycobacterium smegmatis* group, and *Mycobacterium immunogenum*. Minimum inhibitory concentrations (MICs) for tedizolid are generally comparable to or several dilutions lower than those of linezolid [67–71]. Clinical evidence for tedizolid use for NTM treatment is limited. Discrepant effectiveness and safety findings of tedizolid in comparison with linezolid are reported [32, 72, 73]. Two case reports describe successful tedizolid use for NTM infection in patients with previous linezolid-induced cytopenia [72, 73]. Tedizolid has greater antibacterial potency, better pharmacokinetic/pharmacodynamic profiles, and lower hematologic and neurologic toxicity than does linezolid [74, 75]. The relatively weak monoamine oxidase inhibition and poor central nervous system penetration of tedizolid may also lead to fewer drug interactions with serotonergic agents [76, 77]. The improved long-term safety, high bioavailability, and daily dosing regimen are favorable factors for tedizolid use in NTM therapy.

Combination β-Lactams

Dual β-lactam combination therapy is an evolving area of interest, in which two β-lactam agents are used to induce synergistic bactericidal activity. Such combinations are most extensively studied for Mabs infections, which often have limited treatment options and poorer clinical outcomes than infections with other NTM species, with culture conversion rates of 25–42% among macrolide-resistant isolates [16]. In vitro synergistic activity is reported for several combinations, including imipenem/ceftaroline, ceftazidime/ceftaroline, imipenem/cefoxitin, imipenem/cefdinir, and imipenem/doripenem [78–82]. Imipenem/ceftaroline synergism was also replicated in an in vivo mouse model of pulmonary Mabs infection [83].

Several possible mechanisms of synergy have been proposed. Both cefoxitin and imipenem are slowly hydrolyzed by the Mabs class A β-lactamase (Bla_{Mab}). In the absence of readily available inhibitors of Bla_{Mab}, dual β-lactam combination therapy may overwhelm Bla_{Mab} to allow more drug to reach the target binding site. Cephalosporins and carbapenems have different binding affinities to Mabs L,D-transpeptidase proteins LdtMab1–5 [84, 85]. These different affinities may provide greater saturation of molecular targets with both drugs than with either agent alone. This mechanism is analogous to ampicillin and third-generation cephalosporin synergy against *Enterococcus faecalis* infection [86]. Molecular simulation studies suggest that LdtMab2 undergoes ligand-induced conformational changes in which initial imipenem docking may alter or open additional binding sites for ceftaroline [85].

β-Lactamase Inhibitors

Although imipenem and cefoxitin are often recommended as first-line IV NTM therapy [8], the presence of Bla_{Mab} renders them inactive [87]. However, in vitro models suggest that novel β-lactamase inhibitors may block Bla_{Mab} and restore β-lactam activity. Relebactam and avibactam (diazabicyclooctane β-lactamase inhibitors) and vaborbactam (boronic acid β-lactamase inhibitor) have been studied in various combinations. Relebactam and vaborbactam (4 mcg/mL) reduce the MIC of *M abscessus* subsp. *abscessus* when combined with oral and IV carbapenems and cephalosporins [88]. Another in vitro study assessed different ratios of β-lactam to β-lactamase inhibitor for efficacy against *M abscessus* subsp. *abscessus*, *M abscessus* subsp. *bolletii*, and *M abscessus* subsp. *massiliense*. Although the currently available dose/

ratio of imipenem/relebactam was optimized, no combination of ceftazidime/avibactam was effective. However, triple-combination imipenem, relebactam, and meropenem resulted in the lowest MICs and minimum bactericidal concentrations for all three subspecies [89]. Other studies have shown that the addition of ampicillin to imipenem/relebactam, and to a lesser extent to ceftazidime/avibactam, can result in lower Mabs MICs [89, 90]. Currently, all three β-lactamase inhibitors are available only in coformulations with β-lactams: imipenem/cilastatin with relebactam, ceftazidime with avibactam, and meropenem with vaborbactam. To achieve potentially active combinations that include meropenem or ampicillin, the patient must also receive noncontributory β-lactams, such as ceftazidime.

Thus far, β-lactam and β-lactamase inhibitor combinations have been studied only in vitro, and the optimal combination, dose, and tolerability in humans are unknown. The risk of bone marrow suppression with long-term β-lactam use is a theoretical concern and may be exacerbated by overlapping drug toxicity profiles. Therefore, caution is needed when using these combinations in clinical practice.

Phage Therapy

Mycobacteriophages are viruses that infect mycobacterial hosts. Phage therapy uses bacteriophages to specifically target and lyse pathogenic bacteria [91] and is an emerging strategy to combat multidrug-resistant infections, including mycobacterial infections [92]. Successful phage therapy for nonmycobacterial infections has been described [93].

Dedrick et al. [91] reported a case of a 15-year-old patient with cystic fibrosis who had a disseminated Mabs infection after lung transplant and was successfully treated with phage therapy. A 2022 report describes the use of phage therapy in 20 patients with drug-resistant mycobacterial disease [94]. Therapy was administered by IV infusion, aerosolization, or both. No adverse reactions were reported, and favorable clinical or microbiological responses occurred in 11 patients. These data suggest that phage therapy is a strategy for NTM infections without other viable treatment options [94, 95]. Challenges for the broader use of this therapy include the limited availability of therapeutically useful bacteriophages, variability in bacteriophage susceptibility among clinical isolates, unclear dosing and route of administration, lack of understanding of the added benefit of cotreatment with antimicrobials or antiinflammatory agents, and the need to counter bacteriophage resistance. More research is needed to establish best practices for using this evolving technology.

EXPERIMENTAL AND PRECLINICAL THERAPIES

The repurposing of commercially available antibiotics with in vitro antimycobacterial activity has expanded the available therapeutic options. In addition, several antimycobacterial agents are currently undergoing first-in-human testing in phase I and II clinical trials [96]. Addition of inhaled nitric oxide or granulocyte–macrophage colony-stimulating factor has been used as adjunctive therapy for patients with pulmonary NTM infections [97, 98]. Nonpharmacologic interventions, such as host modulation with stem cells, photodynamic therapy, antibiofilm therapy, nanoparticles, vaccines, and antimicrobial peptides, are also currently in development [99].

CONCLUSION

NTM infections are increasingly common and pose a substantial problem worldwide. Strategies used to treat NTM infections include multidrug therapy, modification of existing antibiotic classes, and phage therapy. Although further evidence is needed to establish novel treatments as a standard of care, a multidisciplinary management approach can optimize treatment for the breadth of NTM infections.

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