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The Other Nontuberculous Mycobacteria

Clinical Aspects of Lung Disease Caused by Less Common Slowly Growing Nontuberculous Mycobacteria Species

Marie Yan, MD; Sarah K. Brode, MD, MPH; and Theodore K. Marras, MD

Slowly growing nontuberculous mycobacteria (NTM) comprise a diverse group of environmental organisms, many of which are important human pathogens. The most common and well-known member of this group is *Mycobacterium avium*, the leading cause of nontuberculous mycobacterial pulmonary disease (NTM-PD) globally. This review focuses on the less common, but notable, species of slowly growing NTM with respect to lung disease. To prepare this article, literature searches were performed using each species name as the key word. Society guidelines were consulted, and relevant articles also were identified through the reference lists of key articles. The specific organisms highlighted include *Mycobacterium kansasii*, *Mycobacterium xenopi*, *Mycobacterium malmoense*, *Mycobacterium simiae,* and *Mycobacterium szulgai.* Although these organisms are closely related, they have distinct epidemiologic features and behavior as pathogens. Therefore, the diagnosis and management of NTM-PD require a nuanced approach that takes into consideration the unique characteristics of each species. There is limited evidence to inform the optimal treatment of NTM-PD. Antimicrobial therapy is often challenging because of the presence of drug resistance and few antibiotic options. Regimen selection should generally be guided by drug susceptibility testing, although the correlation between clinical outcomes and in vitro susceptibility thresholds has not been defined for most species.

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Nontuberculous mycobacteria (NTM) comprise a diverse group of organisms, with varying characteristics with respect to their impact on human health. NTM can be classified broadly into two categories based on their growth rate: (1) rapidly growing mycobacteria, such as *Mycobacterium abscessus*, that can form colonies on subculture within 7 days, and (2) slowly growing mycobacteria, such as *Mycobacterium avium* complex (MAC), that require more than 7 days to form colonies.[1]

This review focuses on several notable members of the slowly growing group, namely *Mycobacterium kansasii*, *Mycobacterium xenopi*, *Mycobacterium malmoense*, *Mycobacterium simiae,* and *Mycobacterium szulgai*. Discussions are centered around the epidemiologic features, clinical presentation, diagnosis, and treatment of nontuberculous mycobacterial pulmonary disease (NTM-PD) in immunocompetent patients. Despite being one of the most commonly isolated species in many regions, *Mycobacterium gordonae* has

ABBREVIATIONS: DST = drug susceptibility testing; MAC = *Mycobacterium avium* complex; MIC = minimum inhibitory concentration; NTM = nontuberculous mycobacteria; NTM-PD = nontuberculous mycobacterial pulmonary disease; PD = pulmonary disease; RCT = randomized controlled trial

AFFILIATIONS: From the Department of Medicine (M. Y., S. K. B., and T. K. M.), University of Toronto, the Division of Respirology (S. K. B. and T. K. M.), University Health Network, the Division of Respiratory Medicine (S. K. B.), West Park Healthcare Centre, Toronto, ON, and the Clinician Investigator Program (M. Y.), University of British Columbia, Vancouver, BC, Canada.

CORRESPONDENCE TO: Theodore K. Marras, MD; email: ted.marras@uhn.ca

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been relegated to e-Table 1 because it is an exceedingly rare cause of NTM-PD.

Although traditionally classified within the same genus, different NTM species exhibit significant heterogeneity in their epidemiologic characteristics and behavior as pathogens, which adds complexity to the recognition, diagnosis, and management of NTM-PD. The decision to initiate antimycobacterial therapy is nuanced, and clinicians should consider patient- as well as disease-related factors in their approach (Fig 1). The suggested antimicrobial regimens for each species are outlined in Table 1.[2,3] Drug doses and common toxicities are presented in Table 2.[2,4,5] e-table 1 contains clinical and treatment details regarding some additional less common or less relevant slowly growing species that may cause lung disease. The Runyon system, which classifies NTM based on growth rate and colony pigmentation, can be found in e-Table 2; it was used widely before the advent of molecular technology and, to some extent, may continue to help direct species identification.

M kansasii

M kansasii was one of the first NTM to be recognized as a human respiratory pathogen.[2] Globally, it is the sixth most commonly isolated species of NTM. It is frequently encountered in certain regions, especially in parts of Europe, South America, and Australia.[6,7] Infection is likely acquired from tap water, as this organism has been isolated mainly from municipal water supplies, rather than other environmental sources.[8,9]

Phylogenetic analyses have revealed that *M kansasii* is one of the most closely related species to the *Mycobacterium tuberculosis* complex.[10] Accordingly, the presentation of *M kansasii* pulmonary disease (PD) can be virtually indistinguishable from tuberculosis (TB).[11] Fibrocavitary disease—particularly in the upper lobes reminiscent of reactivation TB—is common, ranging from 44% to > 90% of patients in older studies.[12,13] A smaller proportion of patients present with the nodular bronchiectatic pattern. Pre-existing lung disease, including COPD, prior TB, bronchiectasis, and

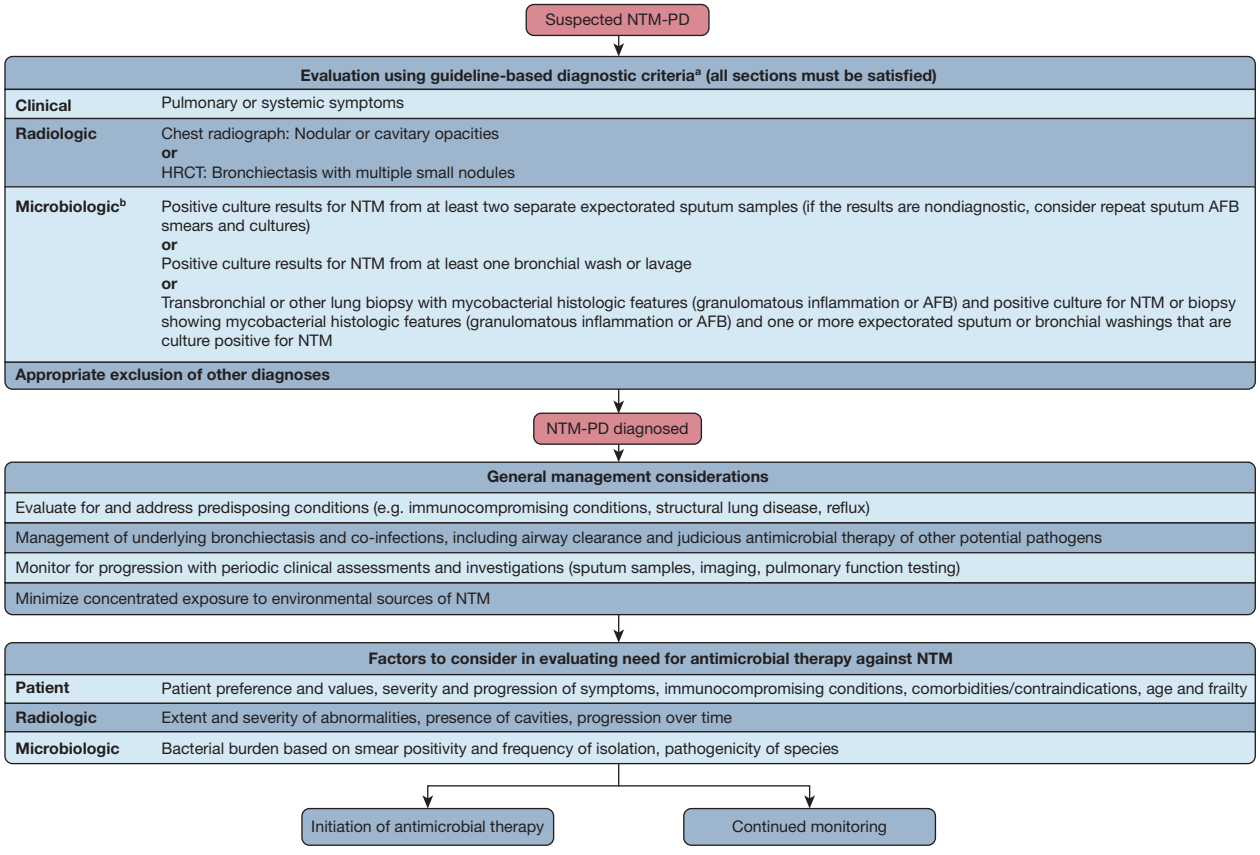

Figure 1 – *Overview of nontuberculous mycobacterial pulmonary disease diagnosis and management.* [a]*Diagnostic criteria outlined in the 2020 multisociety clinical practice guidelines.*[2] [b]*When two positive culture results are obtained, the isolates should be the same species (or subspecies in the case of* Mycobacterium abscessus*) to meet disease criteria. AFB = acid-fast bacilli; HRCT = high-resolution CT; NTM = nontuberculous mycobacteria; NTM-PD = nontuberculous mycobacterial pulmonary disease.*

TABLE 1] Summary of Nontuberculous Mycobacterial Pulmonary Disease Diagnosis and Treatment Considerations by Species[2,3]

Species	Diagnostic Considerations[a]	Antibiotic Regimen[b]	Minimum Duration	Comments
M kansasii	Considered to have high pathogenicity; therefore, a single positive culture finding may warrant treatment in the appropriate clinical and radiologic context	Rifampin-susceptible: **Rifampin** (rifabutin) **Ethambutol** **Azithromycin** (clarithromycin) or **isoniazid**	12 mo	Similar to TB in many aspects; generally good outcomes with treatment, rarely is adjunctive surgery considered
		Rifampin-resistant: Fluoroquinolone plus at least two other drugs guided by drug susceptibility testing		
M xenopi	Consider possibility of environmental contamination or pseudo-outbreaks	**Rifampin** (rifabutin) **Ethambutol** **Azithromycin** (clarithromycin), **moxifloxacin**, or both Consider amikacin IV for severe or cavitary disease[c]	12 mo beyond culture conversion	Highest all-cause mortality rate among NTM; consider adjunctive surgery in carefully selected patients
M malmoense	High proportion of isolates reported to be clinically relevant in Europe, but pathogenicity may vary depending on geographic region	At least three of: **Rifampin** (rifabutin) **Ethambutol** **Azithromycin** (clarithromycin) Moxifloxacin Clofazimine Consider amikacin IV for severe or cavitary disease[c]	12 mo beyond culture conversion	Consider adjunctive surgery in carefully selected patients
M simiae	Respiratory isolates usually are not indicative of disease; maintain high diagnostic threshold and consider other potential explanations for presentation	At least three of: Azithromycin (clarithromycin) Moxifloxacin Clofazimine Trimethoprim plus sulfamethoxazole Consider amikacin IV for severe or cavitary disease[c]	12 mo beyond culture conversion	Consider adjunctive surgery in carefully selected patients
M szulgai	Rarely encountered, accounts for < 1% of NTM-PD	At least three of: **Rifampin** (rifabutin) **Ethambutol** **Azithromycin** (clarithromycin) Moxifloxacin Clofazimine Amikacin IV[c]	12 mo if using preferred regimen, otherwise 12 mo beyond culture conversion	Generally favorable outcomes; insufficient evidence to recommend adjunctive surgery

NTM = nontuberculous mycobacteria; NTM-PD = nontuberculous mycobacteria pulmonary disease.

[a]American Thoracic Society/Infectious Diseases Society of America criteria should be applied in the diagnosis of NTM-PD for all species, with additional considerations as noted.

[b]Regimen selection for *M xenopi*, *M malmoense*, *M simiae*, and *M szulgai* should be guided by drug susceptibility testing; however, the correlation between in vitro testing and clinical response is uncertain; preferred options appear in boldface and alternate within-class agents appear in parentheses.

[c]Administer amikacin IV for at least several months or longer if tolerated and improvement is ongoing; nebulized formulation can be used as step-down therapy for remainder of treatment.

TABLE 2] Drug Dosing in Nontuberculous Mycobacterial Pulmonary Disease and Notable Adverse Effects[2]

Drug	Daily Dosing	Thrice Weekly Dosing	Notable Adverse Effects[a]	Comments
Oral				
Azithromycin	250-500 mg once per day	500 mg once per day	Tinnitus/hearing loss, hepatotoxicity, prolonged QTc	
Clarithromycin[b]	500 mg twice per day	500 mg twice per day	Tinnitus/hearing loss, hepatotoxicity, prolonged QTc	
Clofazimine[c]	100-200 mg once per day	N/A	Hyperpigmentation and dry skin, hepatotoxicity, prolonged QTc, enteropathy	Hyperpigmentation is common and can be mitigated by dose reduction; other toxicities are more likely to require dose interruption, but according to clinical judgment, reintroduction at a lower dose may be tolerated
Ethambutol[b]	15 mg/kg once per day	25 mg/kg once per day	Ocular toxicity, neuropathy	Refer to ophthalmology for monitoring with long-term use
Isoniazid[c]	5 mg/kg up to 300 mg once per day	N/A	Hepatotoxicity, peripheral neuropathy	Use with vitamin B6 (pyridoxine)
Moxifloxacin	400 mg once per day	N/A	Prolonged QTc, hepatotoxicity, tendinopathy	
Rifampin[c]	10 mg/kg (450 or 600 mg) once per day	600 mg once per day	Hepatotoxicity, cytopenias, hypersensitivity, orange discoloration of secretions	Beware of extensive drug-drug interactions
Rifabutin[b,c]	150-300 mg once per day[d]	300 mg once per day	Hepatotoxicity, cytopenias, hypersensitivity, orange discoloration of secretions, uveitis	Fewer drug-drug interactions compared with rifampin, but more difficult to tolerate
Trimethoprim plus sulfamethoxazole[b,c]	800 mg/160-mg tablet twice per day	N/A	Cytopenias, hypersensitivity, photosensitivity, hyperkalemia	
Parenteral				
Amikacin (IV)[b]	10-15 mg/kg once per day[e] with drug level monitoring	15-25 mg/kg once per day[e] with drug level monitoring	Vestibular toxicity, ototoxicity, nephrotoxicity, electrolyte disturbances	Drug level monitoring: trough < 5 mg/L; peak with daily dosing 35-45 μg/mL; peak with intermittent dosing 65-80 μg/mL[f]
Amikacin (inhaled, nonliposome)	250-500 mg once per day	N/A[g]	Dysphonia, dyspnea, cough, vestibular toxicity, ototoxicity, nephrotoxicity	Risks of systemic side effects are significantly lower compared with IV administration

N/A = not applicable; QTc = corrected QT interval.
[a]Gastrointestinal side effects may occur with all oral drugs listed.
[b]Renal adjustment required.
[c]Caution with hepatic impairment.
[d]Dose rifabutin at 150 mg once per day if used with clarithromycin.
[e]Permanent ototoxicity has been described in approximately one-third of patients receiving these doses for 15 weeks; limiting cumulative dose is important in avoiding significant ototoxicity, and clinicians should consider lower dose ranges, intermittent dosing, or both when more prolonged therapy is used.[4]
[f]The target peak levels were described previously using multiple serum samples with back extrapolation to a calculated peak and should be considered accordingly.[4]
[g]One group had defined 500 mg thrice weekly as an appropriate dosing regimen because of a relatively high frequency of toxicities associated with 500 mg daily.[5]

pneumoconioses are notable risk factors.[11,14] Disseminated disease is rare in the absence of an immunocompromising condition.[15]

Diagnosis of *M kansasii* PD follows the criteria outlined by the recent multisociety NTM guidelines.[2] Of note, the microbiologic definition of the criteria contains an exception specific to *M kansasii*, such that a single positive sputum culture may be sufficient for diagnosis in the proper context, as opposed to at least two positive sputum cultures for other species. This is because *M kansasii* is regarded as highly pathogenic relative to other NTM, perhaps reflecting its phylogenetic proximity to *M Tuberculosis*.[9] Previous studies have shown that *M kansasii* has a particularly high ratio of disease to isolation among NTM.[12,16,17] Therefore, the finding of even a single positive culture should be considered carefully and a lower diagnostic threshold may be applied in the proper context. However, this perception has been contested by several studies that followed individuals who initially produced only a single positive sputum culture for *M kansasii*, without finding a high rate of subsequent disease.[13,18,19]

Our understanding of *M kansasii* is expected to be refined by recent genomic advances. Although previously classified as a species with at least six subtypes with varying prevalence and clinical relevance, genome-wide studies have shown that these subtypes are designated more accurately as closely related species, together forming the *M kansasii* complex.[20] Former subtype I is by far the dominant clinical isolate worldwide and retains the designation of *M kansasii*, whereas the remaining subtypes have been renamed as newly derived species. Former subtype II (now *Mycobacterium persicum*) has been associated with disease in the setting of immunodeficiency, and the others are seldom seen in clinical samples (perhaps a sign that they are mostly nonpathogenic, although there is no corresponding difference in known virulence genes).[21] Moving forward, as this change is adapted by laboratories and as isolates are identified with increased precision, future research may provide more clarity in our understanding of *M kansasii* disease.

Before treatment, drug susceptibility testing (DST) is recommended for *M kansasii*, the key drugs being rifampin and clarithromycin. Susceptibility to rifampin is defined as a minimum inhibitory concentration (MIC) of < 2 μg/mL, and this threshold has been correlated with clinical outcomes.[2] Although clarithromycin-containing treatment has proven effective in patients with clarithromycin-susceptible strains—defined as an MIC of < 32 μg/mL—this threshold does not seem to be validated, insofar as associations between treatment outcomes and MICs have not been studied.[21] Rifampin resistance typically arises from prior therapy and reported rates are generally low, with most series describing rates of $< 5\%$, and lower still for clarithromycin resistance (1%).[22-24] The interpretation of MICs for other routinely used drugs such as isoniazid or ethambutol is unclear. Depending on the cutoff used, rates of resistance may exceed 70%, although this is not necessarily predictive of clinical response.[23]

Treatment of *M kansasii* also has parallels to TB in that rifampin forms the backbone of therapy in rifampin-susceptible strains. Current guidelines recommend treatment with rifampin, ethambutol, and either a macrolide or isoniazid (Table 1).[2] The importance of rifampin is illustrated by numerous observational studies showing higher sputum conversion rates after incorporation of rifampin into the regimen.[14] The relative efficacy of isoniazid vs macrolides as a companion drug has not been compared directly in a controlled setting, but both have been shown to lead to good outcomes.[11,14,21,25] The advantage of macrolides as a companion drug is that they can be administered thrice weekly instead of daily, which may be tolerated better. Intermittent treatment is not recommended for isoniazid-based therapy because of a lack of data. Although some studies have shown favorable outcomes for thrice weekly treatment even in cavitary *M kansasii* disease, daily treatment is still preferred in this setting.[21] Given the excellent response to oral regimens, adjunctive therapy with parenteral treatment (eg, amikacin) or surgery is rarely necessary.[2]

For rifampin-resistant strains or intolerance to first-line therapy, selection of a second-line regimen should be guided by DST, with the caveats that clinical data are lacking and in vitro sensitivities do not necessarily correlate with clinical response for most drugs. Fluoroquinolones are recommended and macrolides should also be considered, as both classes have shown good in vitro activity against *M kansasii*.[2,22-24,26] Other drugs that have been used as part of successful regimens in the treatment of rifampin-resistant disease include sulfamethoxazole, streptomycin, and amikacin.[8] Additional antimycobacterial drugs like clofazimine, linezolid, and newer agents including delamanid and

bedaquiline have also demonstrated low MICs, but it remains to be seen whether this will translate into clinical outcomes.[26-28]

In terms of treatment duration, several studies using 12 months of therapy have found high success rates and low rates of relapse.[14] One study using a shorter duration of 9 months with a 2-drug regimen resulted in a slightly higher relapse rate of 10%.[29] In all studies, sputum conversion rates were approaching 100%, typically achieved within 4 months.[14] Therefore, current data support a minimum treatment duration of 12 months after initiation, without the need to account for time to culture conversion, in contrast with usual convention for NTM.[2] The lack of timely sputum culture conversion (ie, within 4 months) should trigger a careful reassessment and expert consultation. Considering the near-universal sputum conversion and low relapse rates, treatment outcomes associated with *M kansasii* are highly favorable relative to other NTM species.[30]

M xenopi

The geographic distribution of *M xenopi* is highly variable. Worldwide, it has been reported as the third most encountered NTM species, but this is primarily driven by high isolation rates in parts of Canada and Europe.[3] In Hungary, it supersedes MAC as the most common NTM, comprising nearly half of all isolates. It is frequently found in potable water supplies and has been linked to nosocomial infections and pseudo-outbreaks resulting from contaminated medical devices.[31,32]

Recent studies estimate that 28% to 38% of *M xenopi* pulmonary isolates reflect true disease.[16,33-35] Most patients are men, typically with COPD or prior TB.[36,37] On imaging, a higher proportion of patients demonstrate fibrocavitary disease in contrast to MAC lung disease, where most show the nodular-bronchiectatic pattern.[38-40] Additionally, a sizeable minority demonstrate a pattern distinct from the two major types, consisting of random nodules or consolidation.[38] Extrapulmonary disease is uncommon and usually involves osteoarticular infections, sometimes from nosocomial contamination of hardware.[41]

M xenopi is associated with the highest mortality among NTM isolates, with all-cause 5-year mortality estimates of between 43% and 69%.[42-44] In a population-based study from Ontario, Canada, deaths associated with several different NTM species were compared and only *M xenopi* was found to have a significantly higher all-cause mortality compared with MAC as the reference (adjusted hazard ratio, 1.22; 95% CI, 1.13-1.31; $P < .0001$).[44] Data are conflicting regarding the reason for the observed mortality, with one study reporting that > 60% of deaths resulted from the infection itself; however, others attribute only a small proportion of deaths to *M xenopi*, suggesting that the high mortality may reflect the significant burden of comorbid conditions in these patients.[37,40,42]

The role of DST for *M xenopi* is not well defined, as there is insufficient evidence to guide meaningful interpretation of MICs. In vitro testing has suggested high rates of resistance to ethambutol (24%-70%) and isoniazid (75%-94%) and susceptibility to rifamycins, clarithromycin, ciprofloxacin, clofazimine, and amikacin in most strains.[24,37,42] However, the correlation between in vitro susceptibility and clinical response is not known.[42,45] Accordingly, the recent multisociety guidelines could not provide an evidence-based recommendation concerning the utility of DST for *M xenopi*.[2]

The optimal antimicrobial regimen for *M xenopi* PD is unclear. Two systematic reviews examining the treatment of *M xenopi* found mainly retrospective studies with considerable heterogeneity, which proved challenging for meaningful analysis.[30,36] A prior randomized controlled trial (RCT) evaluated rifampin and ethambutol plus either clarithromycin or ciprofloxacin in 34 patients and found similar outcomes.[46] This is complemented by preliminary results from an RCT comparing either clarithromycin or moxifloxacin in addition to rifampin and ethambutol, which showed essentially identical rates of 6-month culture conversion: 30 of 39 patients (76.9%) with clarithromycin and 25 of 33 patients (75.8%) with moxifloxacin.[47] In a preclinical study involving *M xenopi*-infected mice, clarithromycin and moxifloxacin again showed similar activity when combined with rifampin and ethambutol, while the addition of amikacin provided further benefit.[48] Data describing the combined use of clarithromycin and moxifloxacin are lacking. Isoniazid also has been used in the past, but the results have been lackluster.[36,45]

The 2020 guidelines support the use of rifampin and ethambutol in combination with either a macrolide, moxifloxacin, or both (minimum of three drugs) (Table 1).[2] Factors influencing drug choice include side-effects profile, patient comorbidities, and possibly MICs

(bearing in mind the limitations of interpretation). Considering the high mortality risk, daily treatment is favored over intermittent therapy; for cavitary or severe disease, the addition of parenteral amikacin is recommended based on evidence of benefit in murine models.[2] Nebulized amikacin has been suggested in cases where parenteral administration is unfeasible or contraindicated.[49] Amikacin liposome inhalation suspension has demonstrated efficacy in refractory MAC disease and shows promise in its application to other NTM diseases, but data are still lacking in this setting.[2,50] There is limited evidence to inform duration of treatment, and so the recommendation remains at 12 months after sputum conversion.

In our experience, adjunctive surgery is safe and effective for select patients with localized residual disease despite otherwise intensive therapy.[51] Judicious patient selection is critical, since those with poorly controlled infection, multifocal lung destruction, and extensive underlying lung disease are at significant risk for postoperative morbidity and mortality.

M malmoense

M malmoense is named after the city of Malmö, Sweden, where it was first described in 1977.[52] This species has been isolated from natural waters and soil in Europe, Japan, and Africa, but environmental sources are not well defined.[8,52] Clinical cases are concentrated heavily in Europe, particularly Northern Europe, with few cases reported elsewhere, suggesting that there may be regional differences in pathogenicity.[3] European studies have consistently found high proportions of patients meeting disease criteria, ranging from 70% to 88%.[52] In contrast, an older study from the United States reported that only 10% of isolates were clinically relevant.

MD malmoense usually leads to pulmonary involvement, which may mimic TB on presentation. The typical patient is an older man with COPD or prior TB.[52] On imaging, cavitating lesions are common, seen in 74% to 88% of cases.[53,54] Extrapulmonary cases frequently manifest as cervical lymphadenitis (particularly in children) and tenosynovitis in immunocompetent individuals.[52,53,55] Disseminated disease has also been described in immunocompromised patients.

Results of in vitro DST for *M malmoense* have been inconsistent between studies, possibly related to small sample sizes, laboratory techniques, or regional differences. Depending on the study, varying resistance rates have been reported for rifampin (0%-68%), rifabutin (0%-38%), ethambutol (4%-57%), amikacin (10%-79%), clofazimine (0%-57%), and ciprofloxacin (41%-88%). Most strains exhibited susceptibility to clarithromycin and resistance to isoniazid.[24,53,54,56-58] However, as with many NTM species, there seems to be poor correlation between in vitro testing and clinical response.[45,54]

Two RCTs were previously conducted concerning the treatment of *M malmoense*. In the first trial involving 106 patients, a two-drug regimen with rifampin and ethambutol was compared with a three-drug regimen with rifampin, ethambutol, and isoniazid. After 2 years of treatment, no differences were found in unfavorable outcomes (ie, treatment failure, relapse, or death) between the groups.[45] The second RCT included 167 patients with *M malmoense* (along with others with MAC and *M xenopi*) and compared clarithromycin vs ciprofloxacin in combination with rifampin and ethambutol for 2 years. Although no differences were found in the rate of unfavorable outcomes, a significantly higher proportion of patients in the clarithromycin group was classified as "completing treatment as allocated, alive and cured at 5 years" (38% vs 20%).[46] This seemed to be driven by the higher rate of protocol deviations in the ciprofloxacin group (43% vs 24%). There were also more side effects associated with ciprofloxacin.

Consensus recommendations concerning the management of *M malmoense* and other less common pulmonary NTM were recently published. The suggested regimen includes at least three drugs, typically a macrolide, rifampin, and ethambutol, in accordance with the evidence presented earlier (Table 1).[3] DST can be used to guide the selection of antibiotics, although it should be noted again that interpretation is nebulous because clinically relevant cutoffs have not been established. Moxifloxacin and clofazimine are viable alternatives in case of intolerance or resistance. Parenteral amikacin is suggested in the setting of cavitary or severe disease. Nebulized amikacin likely can be used as well based on its efficacy and clinical experience in other NTM species.[49] Adjunctive surgery has been described to be effective in case reports and may be an option in carefully selected patients.[59]

M simiae

The species name "simiae" refers to the fact that *M simiae* was first isolated from a colony of rhesus monkeys in 1965.[60,61] Since then, this organism has been

found in various environmental sources, including potable water supplies, and was later recognized as a potential human pathogen. Geographically, *M simiae* has been reported worldwide, but seems to favor arid regions such as the Middle East and Southwestern United States.[60]

Isolation of *M simiae* from clinical specimens does not usually indicate disease. Because of its presence in potable water systems, *M simiae* is a frequent contaminant and has been implicated in various pseudo-outbreaks.[61-63] Most reports estimate that only up to 22% of respiratory isolates are clinically relevant; however, one recent study from Lebanon—in an institution where *M simiae* had been the most prevalent NTM species—reported that 47% of patients met criteria for NTM-PD.[61,64-66] Overall, it seems that a relatively high diagnostic threshold should be applied when evaluating patients for *M simiae* PD, with diligent assessment to rule out other causes and consideration for regional prevalence.

When *M simiae* does cause disease, pulmonary involvement is the most common manifestation. Affected individuals typically have underlying lung conditions such as COPD or prior TB.[61,65] Chest imaging predominantly shows nodules and infiltrates, whereas a smaller proportion of patients develop cavitary lesions.[65,66] Disseminated infection seems to occur almost exclusively in the setting of significant immunocompromise.[60] Isolated extrapulmonary infections, such as cervical lymphadenitis, are rare but have been described in immunocompetent hosts.[8]

Treatment of *M simiae* infection is particularly challenging because of extensive in vitro drug resistance. This underscores the importance of discerning contamination or colonization vs disease and thus avoiding unnecessary treatment; even in those who meet the diagnostic criteria for NTM-PD, antibiotic therapy is not always warranted.[2,3] According to in vitro studies, there is near universal resistance to rifamycins, ethambutol, and isoniazid. Susceptibility data to other drugs are much more unpredictable, with large variations in resistance rates for clarithromycin (0%-84%), amikacin (4%-100%), moxifloxacin (8%-70%), ciprofloxacin (13%-100%), and clofazimine (0%-55%), depending on the region.[24,58,61,65-67] Data regarding trimethoprim plus sulfamethoxazole are limited, but two studies reported resistance rates in clinical strains of 81% and 100% (16 of 19 overall).[66,67]

Evidence in the existing literature is insufficient to determine the best treatment for *M simiae*. Case series describe varying success with marked heterogeneity among the regimens used.[61,65,66] In the absence of compelling evidence to suggest otherwise, construction of a suitable regimen should consider DST results, with the caveat that the correlation between in vitro testing and clinical outcome is unclear. Regimens should comprise at least three drugs (Table 1). Potential oral options include azithromycin or clarithromycin, moxifloxacin, clofazimine, and trimethoprim plus sulfamethoxazole (the latter recommended based on reports of clinical success, despite high rates of resistance). Parenteral amikacin should be considered in cases of severe or cavitary disease or when oral options are limited.[3] Based on expert opinion, the recommended treatment duration is at least 12 months after culture conversion. Surgical resection has been used successfully as adjunctive therapy and should be considered in patients who are appropriate candidates.[65]

M szulgai

Compared with the species described above, *M szulgai* is an uncommon cause of NTM disease. Over a 13-year period in Ontario, Canada, among 9,658 patients who fulfilled microbiologic criteria for NTM-PD, only 10 patients (0.1%) had *M szulgai* infection (T. K. Marras and F. B. Jamieson, unpublished data, 2015). Similarly low prevalence rates are also seen in Asia and the United States.[68,69] *M szulgai* does not seem to be encountered frequently in the environment. Previously identified environmental sources are primarily aquatic and include a swimming pool as well as a municipal water system.[70,71] There are also several reports of patients who presumably acquired the infection while caring for aquatic animals.[72,73] Cases of *M szulgai* have been reported across the globe and there does not seem to be any geographic predilection.

Lung disease secondary to *M szulgai* may resemble TB. Patients typically are older men with a history of smoking, and cavitary disease is not uncommon.[69,74] Previous studies estimate that 43% to 73% of respiratory isolates reflect true disease.[69,74] Extrapulmonary infections usually involve skin, soft tissue, or bone and manifest as cutaneous lesions, tenosynovitis, osteomyelitis, and so forth.[73,74] Disseminated disease is rare and usually only occurs in the presence of immunocompromise.[75]

M szulgai is generally susceptible to most antituberculous agents in vitro (apart from isoniazid).[24,75] However, clinically meaningful MIC thresholds remain undefined. Based on very low-level evidence from previous case reports and case series, consensus recommendations advise the use of at least three drugs in the treatment regimen, selected according to DST results.[3] A preferred regimen consists of rifampin, ethambutol, and azithromycin, for which cure was reported in 100% of patients (5/5) with guideline-defined disease and treatment durations of ≤ 12 months (Table 1).[75] Alternative options include clofazimine, fluoroquinolones, and amikacin; however, the duration of treatment should be extended to 12 months beyond sputum conversion if second-line drugs are used.[3] Although rifampin, ethambutol, and isoniazid were observed to be effective in 100% of patients (8/8) in one study, isoniazid-containing regimens are not favored because of high MICs.[69] Evidence is insufficient to recommend adjuvant surgery.

Conclusions

Significant heterogeneity exists among NTM species with respect to their geographic distribution, pathogenicity, and disease characteristics. This underscores the importance of accurately identifying the species at hand and a nuanced approach in the evaluation and management of NTM disease. Although the same criteria are applied in the diagnosis of NTM-PD, clinicians should calibrate their diagnostic threshold based on the pathogenicity of each species. The optimal approach to treatment has not been established due to a limited evidence base. Antimicrobial therapy can be challenging because of the presence of drug resistance and few antibiotic options. Whenever possible, regimen selection should be guided, but not dictated, by DST, recognizing that the correlation between in vitro activity and clinical response is uncertain.

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