Chapter 8

Nontuberculous mycobacterial infections

C.L. Daley

Summary

Nontuberculous mycobacteria (NTM) represent a large group of bacteria that have been isolated from environmental sources. When NTM are inhaled by a susceptible individual, infection can occur and lead to progressive lung disease. Epidemiological studies have described increases in the prevalence of NTM disease in multiple areas worldwide. Risk factors for disease include chronic lung diseases, such as bronchiectasis and chronic obstructive pulmonary disease, as well as various forms of immune deficiency. Patients typically present with either fibrocavitary or nodular bronchiectatic disease. Isolation of NTM from respiratory specimens does not always indicate disease so clinicians must evaluate clinical, radiographic and microbiologic information in order to diagnosis NTM-related lung disease. The American Thoracic Society has developed diagnostic criteria that can aid clinicians but the criteria cannot account for all clinical scenarios or for all NTM species given the large spectrum of pathogenicity encountered. Treatment usually consists of at least two antibiotics but the exact regimen will vary depending on the species and there is some variation in recommendations.

Keywords: Bronchiectasis, mycobacteria, Mycobacterium avium complex, nontuberculous mycobacterial infections

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Nontuberculous mycobacteria (NTM) comprise ~140 species, many of which have been reported to cause disease in humans. Based on their rate of growth in subculture, NTM have traditionally been divided into slowly and rapidly growing species (table 1) [1–3]. Also referred to as environmental mycobacteria, NTM have been isolated from natural and drinking water supplies, as well as soil [4–7]. The presumed source of infection is exposure to these environmental reservoirs because human-to-human transmission has not been documented. When inhaled by susceptible individuals, such as those with chronic obstructive lung disease or bronchiectasis, infection with NTM can lead to a chronic, progressive and sometimes fatal lung disease.
Despite their frequent isolation in the environment and human specimens, NTM were not widely recognised as a cause of human disease until the late 1950s. Since that time, the number of new species of NTM has grown dramatically [3] and the rate of disease related to NTM has also increased, overtaking the rate of tuberculosis (TB) in some areas [8]. Diagnosis and treatment of NTM lung disease remains challenging for clinicians and depending on the extent of disease and species involved, a cure may be difficult to achieve. When considering treatment, clinicians must weight the potential benefits of therapy against the cost and potential side-effects of current regimens.

### Epidemiology

#### Incidence and prevalence

The epidemiology of NTM disease has been difficult to determine because reporting is not mandatory in most countries and differentiation between infection and disease is often difficult. Although the incidence and prevalence of NTM infections have varied significantly across studies, recent studies have reported high rates of NTM pulmonary disease, particularly in older populations [9–12]. Among 933 patients with at least 1 NTM isolate in Oregon (USA), 527 (56%) met the American Thoracic Society (ATS) microbiological definition for disease giving an annualised prevalence of 5.6 cases per 100,000 for pulmonary disease [9]. The prevalence was significantly higher in females (6.4 cases per 100,000) than males (4.7 cases per 100,000) and was highest in persons aged ≥50 years (15.5 cases per 100,000). In another report from Oregon, the overall 2-year prevalence of NTM pulmonary disease was 8.6 cases per 100,000 and increased to 20.4 cases per 100,000 in those aged ≥50 years [10]. The annualised prevalence of NTM lung disease within four integrated healthcare delivery systems in the USA ranged from 1.4 to 6.6 per 100,000 [11]. Among persons aged ≥60 years, annual prevalence was 26.7 per 100,000.

Studies from Canada [8], Australia [12], Taiwan [13], the Netherlands [14] and the USA [11, 15] have reported increases in the incidence or prevalence of NTM. MARRAS et al. [8] reported an increase in the number of pulmonary NTM isolates in Ontario (Canada) from 9.1 per 100,000 in 1997 to 14.1 per 100,000 in 2003. Difficulty in eradicating NTM infections resulted in a prevalence higher than that of tuberculosis [16]. More recently, two studies from the USA reported increases in NTM pulmonary disease [11, 15]. In a study examining the prevalence of NTM lung disease in four integrated healthcare delivery systems, there was a 2.6% and 2.9% increase per year in females and males, respectively [11]. Pulmonary NTM hospitalisations increased significantly among both males and females between 1998 and 2005 in a study involving 11 states in the USA [15]. Annual prevalence increased among males and females in Florida (3.2% and 6.5%, respectively) and among females in New York (4.6% per year) with no significant changes in California.

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**Table 1. Examples of slowly growing and rapidly growing nontuberculous mycobacteria that have been reported to cause lung disease**

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<thead>
<tr>
<th>Slowly growing mycobacteria</th>
<th>Rapidly growing mycobacteria</th>
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<td>Mycobacterium arupense</td>
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<td>Mycobacterium intracellulare</td>
<td>Mycobacterium xenopi</td>
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<td>Mycobacterium kansasii</td>
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<td>Mycobacterium septicum</td>
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<td>Mycobacterium snaegmatis</td>
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<td>Mycobacterium thermoresistible</td>
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Earlier descriptions of pulmonary NTM disease described a male predilection for disease. However, in three recent studies from the USA, a higher proportion of disease was observed in females than males [9–11]. Over an 8-year period from 1998 to 2005, the overall prevalence rate of hospitalisations for NTM pulmonary disease in the USA was highest in females aged ≥70 years (9.4 per 100,000) compared with similarly age matched males (7.6 per 100,000) [11].

The reasons for the increase in incidence and prevalence have not been explained although increased awareness of the disease and improved diagnostic techniques could be factors. A true increase in incidence could be related to changes in the host such as an aging population, an increased prevalence of chronic lung disease or an increase in the number of immunocompromised individuals. The observation of a decreased incidence of pulmonary TB and an increased incidence of pulmonary NTM [8] could be explained by cross-immunity between mycobacterial species. Finally, an increase in the prevalence or virulence of organisms in the environment or changes in human behaviour that would lead to increased exposure to organisms could be contributors. In support of the latter, the frequency of skin reactivity to purified protein derivative-B, which used antigens from *Mycobacterium intracellulare*, increased from 11.2% in 1971–1972 to 16.6% in 1999–2000 [17].

**Risk factors for NTM infection and disease**

Studies utilising delayed type hypersensitivity reaction to subcutaneously injected mycobacterial antigens have estimated that 11–33.5% of the population in the USA has been exposed to NTM [18–21]. A prospective study using skin testing data from Palm Beach, Florida reported that 32.9% of 447 participants in a population-based random household survey had a positive reaction to *Mycobacterium avium* sensitin [21]. Predictors of a positive reaction included Black race, birth outside the USA and >6 years cumulative exposure to soil. Using data from the National Health and Nutrition Examination Survey (NHANES), investigators reported similar findings with regards to sensitisation to *M. intracellulare* [17]. Male sex, non-Hispanic Black race and birth outside the USA were each independently associated with sensitisation. These two studies are interesting in that skin test reactivity to either *M. avium* or *M. intracellulare* antigens was associated with factors probably associated with soil exposure. However, at least in the USA, disease seems to be more common in older Caucasian females. Thus, the risk factors for exposure and infection may be different from those associated with disease.

Historically male sex has been considered a risk factor for NTM lung disease and males continue to make up the majority of patients in some areas [14]. However, studies from the USA and South Korea have noted a female predominance. In Oregon, as noted previously, the rate of NTM pulmonary diseases was higher in females than males and females made up 60% of cases. Why the shift to a female predominance remains unclear. However, there is likely a genetic link because many females who develop bronchiectasis and NTM infection share a similar body type characterised by tall slender status with a higher frequency of pectus excavatum, kyphoscoliosis and mitral valve prolapse than females who do not have NTM infection [22–24]. This condition was first described by Prince et al. [25] in 1989 and later referred to as the “Lady Windermere Syndrome” after the character in Oscar Wilde’s play Lady Windermere’s Fan, the reference referring to fastidious behaviour in the character [26]. Recently, investigators reported that female patients with pulmonary NTM disease were taller, thinner and weighed less than matched control subjects [22]. To date, extensive evaluation of the immune system of these patients has been unrevealing but mutations in the cystic fibrosis transmembrane conductance regulator gene are common [22, 27].

Most NTM are significantly less pathogenic than *Mycobacterium tuberculosis* and probably require some degree of host impairment to result in disease. Impairment can be caused by immune defects or chronic lung disease of which the latter appears to be most common. NTM disease has been described in association with cystic fibrosis (CF), chronic obstructive pulmonary disease including α1-antitrypsin deficiency, cavitary lung disease, pneumoconiosis, bronchiectasis, prior TB,
pulmonary alveolar proteinosis and chronic lung injury due to aspiration from gastro-oesophageal disorders [28–34]. Bronchiectasis is an almost universal finding in females with NTM infection and it is seen in many males with NTM infection. However, NTM infections have been reported to occur in only 1–2% of bronchiectasis patients in two small series from the UK [35, 36]. In contrast, studies have documented a high prevalence of NTM from sputum cultures in patients with CF, with estimates ranging from 3% to 19.5% [37, 38].

Pulmonary disease due to NTM has been described in several other immunocompromised patient populations including transplant recipients [39–42], individuals taking tumour necrosis factor-α inhibitors [43–45], and patients with mutations in interferon (IFN)-γ receptor 1, IFN-γ receptor 2, interleukin (IL)-12 p40 and the IL-12 receptor [46, 47]. Most of these patients present with disseminated disease. Scientists have hypothesised that in slender, older females, decreased leptin, increased adiponectin and/or decreased oestrogens may account for the increased susceptibility to NTM infections [48]. Additionally, anomalies of fibrillin that lead to the expression of the immunosuppressive cytokine transforming growth factor-β may further increase susceptibility to NTM lung disease [48].

**Diagnosis and management**

Chronic pulmonary disease is the most common clinical presentation of NTM disease. In order to diagnose pulmonary NTM infection clinicians must weigh clinical, bacteriologic and radiographic information. Diagnostic criteria have been developed to aid the clinician in the diagnostic evaluation of persons suspected of having pulmonary NTM disease (table 2) [3, 49]. Although the diagnostic criteria provide a useful approach for the evaluation of patients with suspected NTM disease, the approach has yet to be validated and it is impossible for a single set of diagnostic criteria to be appropriate for all patients and species of NTM.

Unlike with TB, a single positive sputum culture for NTM is not diagnostic of pulmonary disease. However, when two or more sputum cultures are positive the diagnosis of disease is more likely. For example, 98% of patients with two or more positive sputum cultures for *M. avium* complex (MAC) had evidence of progressive disease in a study from Japan [50]. Whether this microbiologic criterion holds true for other NTM species is not known but given the wide range of pathogenicity among the various NTM species it is unlikely. Patients who are suspected of having NTM lung disease but do not meet the diagnostic criteria should be followed clinically until the diagnosis is either firmly established or excluded.

**Laboratory diagnosis**

Ultimately, the diagnosis of NTM disease is based on isolation of these organisms from clinical specimens. Both solid and broth media should be used for detection of mycobacteria and a semi-quantitative reporting of colony counts is recommended [3]. Most NTM grow within 2–3 weeks

<table>
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<tr>
<th>Respiratory specimen</th>
<th>ATS recommendations</th>
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<tr>
<td>Sputum specimen</td>
<td>At least two separate positive cultures</td>
<td>Positive cultures from specimens obtained at least 7 days apart</td>
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<tr>
<td>Bronchial wash/lavage</td>
<td>One positive culture Compatible histopathology (granulomatous inflammation) and a positive biopsy culture and/or a positive sputum or bronchial wash/lavage culture</td>
<td>Not described</td>
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<td>Tissue biopsy</td>
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on subculture and rapidly growing mycobacteria usually grow within 7 days of subculture. Identification of specific species can be based on phenotypic, chemotaxonomic and molecular methods [3]. However, none of these procedures are sufficient to differentiate all NTM.

The clinical usefulness of drug susceptibility testing in the management of patients with NTM disease remains controversial because in vitro results do not correlate well with clinical outcomes for some mycobacterial species. Unfortunately, there is no single susceptibility method that is recommended for all species of slowly growing mycobacteria. For MAC, a broth-based culture method with both microdilution and macrodilution methods are considered acceptable [3]. Initial isolates, as well as those from patients who fail or relapse, should be tested to clarithromycin. Isolates of *Mycobacterium kansasii* should be tested to rifampin as resistance to rifampin is associated with treatment failure/relapse [3]. Broth microdilution minimum inhibitory concentration (MIC) determination for susceptibility testing is recommended for rapidly growing mycobacteria.

As noted previously, skin test reactions to mycobacterial antigens are common in people living in endemic areas and, thus, are unable to distinguish NTM infection from disease. Tests that could distinguish infection from disease would be very helpful for clinicians. Measurement of anti-A60 immunoglobulin (Ig)G was reported to have a sensitivity of 87% and specificity of 97% for detection of *Mycobacterium abscessus* disease in patients with CF [51]. In Japan, Kitada et al. [52] evaluated the performance of an assay that detects serum IgA antibody to glycopeptidolipid core antigen for the diagnosis of MAC lung disease. The sensitivity and specificity of the assay for detecting MAC lung disease were 84% and 100%, respectively. Antibody levels were higher in patients with nodular bronchiectatic disease compared with fibrocavitary disease and levels correlated with extent of disease by chest computed tomography (CT) scans. In a follow-up study of patients who underwent bronchoscopy, the sensitivity, specificity, positive predictive and negative predictive values were 78.6%, 96.4%, 95.7% and 81.8%, respectively [53]. The sensitivity and specificity of the test for MAC pulmonary disease in patients with rheumatoid arthritis was 43% and 100%, respectively [54]. Although these serologic assays are not widely available, they may eventually find their way into diagnostic algorithms.

**Slowly growing mycobacteria**

The slowly growing mycobacteria include organisms with wide ranging pathogenicity such as *M. kansasii* and *Mycobacterium szulgai*, which are probably second only to *M. tuberculosis* in terms of disease producing capability and *Mycobacterium gordonae* and *Mycobacterium terrae*, which rarely cause lung disease (table 1). MAC is typically the most common NTM to cause pulmonary disease but the frequency of *M. avium* versus *M. intracellulare* has varied between studies. Recommendations for treatment vary between guidelines as highlighted in table 3 [3, 49, 55].

**Mycobacterium avium complex**

MAC includes the NTM species *M. avium*, of which there are several subspecies, *M. intracellulare*, and some that are as yet poorly described species. The traditionally recognised presentation of MAC lung disease has been as apical fibrocavitary lung disease similar to TB, usually in older males who have a history of cigarette smoking and alcohol abuse (fig. 1). MAC lung disease also presents with nodular and interstitial nodular infiltrates frequently involving the right middle lobe or lingula, predominantly in post-menopausal, nonsmoking Caucasian females. This form of disease, termed nodular/bronchiectatic disease, tends to have a much slower progression than cavitary disease. Nodular/bronchiectatic MAC lung disease is radiographically characterised by chest high-resolution CT (HRCT) findings that include multiple small centrilobular pulmonary nodules and bronchiectasis (fig. 2).

Treatment of MAC pulmonary disease involves a two to three drug regimen, which includes ethambutol, a rifamycin (rifampicin or rifabutin) and a macrolide (clarithromycin or azithromycin).
Unfortunately, treatment outcomes have varied significantly between studies [3, 56]. In a randomised controlled clinical trial conducted by the British Thoracic Society (BTS) comparing clarithromycin versus ciprofloxacin in combination with rifampicin and ethambutol for treatment of pulmonary MAC, the clarithromycin-containing arm was associated with a higher all-cause mortality (48% versus 30%) but lower rates of failure and relapse (13% versus 23%) compared with the ciprofloxacin-containing arm [55]. In a previous BTS study, rifampicin and ethambutol were associated with a failure and relapse rate of 41% compared to 16% in the comparator arm, which contained isoniazid. Because the macrolides are the only antimicrobial agents for which there is a correlation between *in vitro* susceptibility and clinical response and the high rate of poor outcomes reported with rifampicin and ethambutol, the ATS recommends inclusion of a macrolide in all patients. [57–62]. Therapy three times a week is recommended for patients with non-cavitary disease [3]: this recommendation is based on a study that demonstrated poor bacteriological responses in patients who were treated three times a week and had evidence of cavitary disease [63]. Intermittent therapy with ethambutol may be associated with a lower rate of optic neuritis [64].

In patients with extensive radiographic disease, cavitary disease, macrolide resistance disease or treatment failure, an injectable aminoglycoside (amikacin or streptomycin) should be considered. A randomised trial from Japan reported that patients who received streptomycin three times a week for the initial 3 months of therapy along with three other drugs had a faster sputum conversion rate compared with those that were in the placebo arm [65]. However, long-term relapse rates were not different between arms.

Macrolide-resistant MAC lung disease is associated with a poor prognosis [66]. The two major risk factors for macrolide-resistant MAC disease are macrolide monotherapy or treatment with macrolide and inadequate companion medications. The
treatment strategy associated with the most success for macrolide-resistant MAC lung disease includes the use of a multidrug regimen including a parenteral aminoglycoside (streptomycin or amikacin) and surgical resection (debulking) [66]. Clofazimine, in combination with ethambutol and a macrolide, has been used successfully to treat pulmonary MAC infections and, thus, may be a possible alternative drug for macrolide-resistant disease [67].

**Mycobacterium kansasii**

*M. kansasii* is one of the most common causes of NTM lung disease in the USA, as well as some parts of Europe and Asia. While most patients with *M. kansasii* lung disease have upper lobe fibro-cavitary abnormalities similar to TB (fig. 3), essentially any pattern of radiographic abnormality can occur, particularly in HIV-infected patients [68].

According to the ATS, the recommended regimen for treating *M. kansasii* pulmonary disease includes daily rifampicin (600 mg·day$^{-1}$), isoniazid (300 mg·day$^{-1}$) and ethambutol (15 mg·kg$^{-1}$·day$^{-1}$), all administered for 12 months beyond the date of culture conversion [3]. However, the BTS recommends rifampicin and ethambutol therapy for a total of 9 months [49]. Substitution of clarithromycin for isoniazid has been associated with good short-term treatment results with daily [69] and intermittent therapy [70].

Patients whose *M. kansasii* isolates have become resistant to rifampicin as a result of previous therapy have been treated successfully with a regimen that consists of high-dose daily isoniazid (900 mg), high-dose ethambutol (25 mg·kg$^{-1}$·day$^{-1}$) and sulfamethoxazole (1.0 g three times per day) combined with several months of streptomycin or amikacin [71]. The excellent *in vitro* activity of clarithromycin and moxifloxacin against *M. kansasii* suggests that multidrug regimens containing these agents are likely to be even more effective for treatment of a patient with rifampicin-resistant *M. kansasii* disease.
**Mycobacterium malmoense**

*Mycobacterium malmoense* is considered the second most serious pathogen after MAC in northern Europe, although the clinical relevance of *M. malmoense* isolates has varied between studies. For example, in the Netherlands [72, 73], 70–80% of isolates are reported to be clinically relevant whereas in the USA, *M. malmoense* is seldom considered clinically significant. Patients with *M. malmoense* lung disease frequently have pre-existing obstructive lung disease and present with radiograph findings similar to other cavitary NTM lung disease pathogens.

In a recent report, clarithromycin, rifampicin and ethambutol were compared with a regimen consisting of ciprofloxacin, rifampicin and ethambutol [55]. Overall, a more favourable response to therapy was reported with the macrolide-containing regimen, although overall mortality was not different between the two regimens. Although the optimal management of *M. malmoense* has yet to be determined [55, 73, 74] a two to four drug regimen is recommended that would include, at a minimum, ethambutol and rifampicin [73].

**Mycobacterium xenopi**

*Mycobacterium xenopi* is a common cause of NTM lung disease in Canada, the UK, and some parts of Europe [75]. Radiographic findings with *M. xenopi* pulmonary disease are variable but most often include upper lobe cavitary changes compatible with TB. *M. xenopi* isolates were reported to have favourable *in vitro* MICs to isoniazid, rifampin and ethambutol in a study from the Netherlands [75]; however, studies have failed to find a correlation between *in vitro* drug susceptibility results and treatment outcomes [76].

To date, the optimal treatment regimen has not yet been determined. In a multicentre, randomised trial comparing a regimen of...
clarithromycin, rifampin and ethambutol with ciprofloxacin, rifampin and ethambutol [55], there was no difference in the treatment success, failure or relapse rates between groups. All-cause mortality was relatively high and somewhat higher in the ciprofloxacin arm, but death directly related to *M. xenopi* was low. Even with variable treatment regimens, antimicrobial treatment cured 58% of patients who met ATS criteria for *M. xenopi* lung disease in a retrospective study from the Netherlands [75]. Currently, the BTS recommends ethambutol and rifampicin for 24 months of therapy whereas the ATS recommends the addition of a macrolide and isoniazid and possibly an aminoglycoside depending on the severity of disease.

**Rapidly growing mycobacteria**

Because many rapidly growing mycobacteria are not pathogenic in humans it is important to identify organisms within this group to the species level since this could affect both treatment and prognosis (table 1).

**Mycobacterium abscessus** complex

*M. abscessus* is one of the most common NTM infections in the USA and accounts for 65–80% of lung infections due to rapidly growing mycobacteria [29, 77]. Recent studies have demonstrated that *M. abscessus* consists of three species, *M. abscessus* (*sensu stricto*) *Mycobacterium massiliense* and *Mycobacterium boletii* [78, 79]. In the USA, most patients with pulmonary disease due to *M. abscessus* complex are nonsmoking, Caucasian females with a median age of ~60 years [29, 80]. Similarly, in South Korea the median age of patients with pulmonary disease is 55 years and almost all of the patients are nonsmoking females [81]. However, in the Netherlands, over half of the patients are male many of whom have predisposing lung disease [82].

The chest radiograph usually shows multi-lobar, reticulonodular or mixed reticulonodular-alveolar opacities [29]. HRCT findings include the presence of cylindrical bronchiectasis with multiple small nodules, similar to MAC lung disease (fig. 4) [29, 83, 84]. Cavitation has been reported in 10–44% of patients [29, 80, 81].

Unfortunately, *M. abscessus* has demonstrated *in vitro* activity to only a few antimicrobial agents. The ATS recommends therapy with 2–4 months of intravenous antibiotics such as imipenem or cefoxitin plus amikacin given daily or three times per week [3]. Oral agents that have demonstrated *in vitro* activity should be included in the treatment regimen. Unfortunately, macrolides are the only oral agents typically active *in vitro* against *M. abscessus*. Studies have demonstrated the presence of an erythromycin ribosomal methylase gene, *erm*(41), in *M. abscessus*, which could result in the development of macrolide resistance and possibly affect treatment responses [77, 85]. Other drugs that sometimes demonstrate *in vitro* activity

![Figure 4. A 70-year-old nonsmoking female with several year history of cough, fatigue and weight loss. The patient had a history of severe gastro-oesophageal reflux and recurrent pneumonias. Her sputum cultures were consistently positive for *Mycobacterium abscessus*. Chest computed tomography slice showing diffuse bronchiectasis with scattered centrilobular and subcentimeter nodules. There is an area of airspace of opacity in the posterior left lower lobe.](image-url)
include linezolid and tigecycline, however, both drugs are associated with frequent adverse effects [86, 87].

Because of the high levels of in vitro resistance, cure is difficult to achieve in patients with lung disease due to M. abscessus. In South Korea, Jeon et al. [81] reported the outcomes of 65 patients with pulmonary disease who were treated with a standardised regimen. Patients were hospitalised and treated with intravenous cefoxitin and twice daily amikacin plus oral clarithromycin, ciprofloxacin and doxycycline. After 1 month the intravenous drugs were stopped and the oral medications continued for a total of 24 months and at least 12 months beyond the date of culture conversion [81]. 83% of the patients reported improvement in symptoms and 74% had radiographic improvement as documented by HRCT. Sputum conversion and maintenance of negative sputum cultures for >12 months was achieved in 38 (53%) patients. However, drug-related adverse events were common. Neutropenia and thrombocytopenia associated with cefoxitin developed in 33 (51%) and four (6%) patients, respectively. Drug-induced hepatoxicity occurred in 10 (15%) patients. Cefoxitin had to be stopped, and in some cases switched to imipenem, in the majority of patients.

In a recent report from Denver, CO, USA, the outcomes of 107 patients treated for pulmonary M. abscessus disease were reported [80]. Treatment regimens varied but followed current ATS recommendations. Cough, sputum production and fatigue remained stable, improved or resolved in 80%, 69% and 59% of patients, respectively. Treatment outcomes were disappointing: 20 (29%) out of 69 patients remained culture positive, 16 (23%) patients converted but relapsed, 33 (48%) patients converted to negative and did not relapse and 17 patients (16%) died during the study period.

As noted previously, speciation of the rapidly growing mycobacteria may be important because outcomes may vary based on the species of NTM. Koh et al. [77] reported significant differences in the clinical, radiographic and microbiologic outcomes in patients treated for M. abscessus versus M. massiliense. Sputum conversion and maintenance of negative cultures occurred in 88% of patients with M. massiliense compared with 25% of patients with M. abscessus, despite receiving a similar treatment regimen. When isolates of M. abscessus were incubated with clarithromycin, all became resistant within 7 days and the MIC continued to increase at day 14. In contrast, none of the M. massiliense isolates acquired resistance upon exposure to clarithromycin. The \textit{erm(41)} gene was present in all of the M. abscessus isolates but was partially deleted in the M. massiliense isolates.

A combination of surgical resection and chemotherapy may increase the chance of cure in patients who have focal lung disease and who can tolerate resection. Among 14 (22%) patients with pulmonary M. abscessus infection in South Korea who underwent surgical resection, negative sputum culture conversion was achieved within a median of 1.5 months and was maintained in 88% of those with pre-operative culture-positive sputum. Similarly, in a study from the USA, patients who had surgical resection plus medical therapy were more likely to convert their cultures to negative and not relapse compared with medical therapy alone (65% versus 39%; p=0.041) [80]. Moreover, significantly more patients who underwent surgery converted sputum cultures to negative and remained negative for at least 1 year when compared with those who received medical therapy alone (57% versus 28%; p=0.022).

\textit{Mycobacterium chelonae} and \textit{Mycobacterium fortuitum}

Although \textit{Mycobacterium chelonae} and \textit{Mycobacterium fortuitum} are less likely to cause lung disease than \textit{M. abscessus} the clinical and radiographic presentations are similar [29, 88]. Of 26 patients in South Korea who grew \textit{M. fortuitum} from two or more sputum specimens, 25 were not treated and none showed evidence of progressive disease over a median of 12.5 months of follow-up [88].

Isolates of \textit{M. chelonae} are usually susceptible to the macrolides, linezolid, tobramycin and imipenem and uniformly resistant to cefoxitin [89–91]. Other active drugs may include amikacin,
clofazimine, doxycycline and fluoroquinolones. The ATS recommends that treatment of *M. chelonae* infections should consist of at least two drugs to which *in vitro* drug susceptibility has been demonstrated. Unlike *M. abscessus* and *M. fortuitum*, *M. chelonae* does not appear to possess a copy of *erm*(41) [85].

In contrast to *M. abscessus* and *M. chelonae*, *M. fortuitum* demonstrates broader *in vitro* susceptibility to both oral and intravenous antimicrobial drugs including the newer macrolides, fluoroquinolones, tetracycline derivatives, sulfonamides and intravenous drugs imipenem and cefoxitin [3]. Although most isolates of *M. fortuitum* are susceptible *in vitro* to the macrolides, they should be used with caution because of the presence of *erm*(41) [92]. As with *M. chelonae*, *M. fortuitum* lung disease should be treated with at least two drugs to which *in vitro* susceptibility has been demonstrated [3].

### Surgical therapy for NTM lung disease

Patients who have failed a standard therapeutic regimen, particularly those who harbour resistant organisms, may benefit from surgical resection of the most affected areas. In 12 published series involving a total of 602 patients (range 8–236), the post-operative sputum culture conversion rate ranged from 82% to 100% with a mean conversion rate of 94% [93]. Long-term relapse was not reported in all studies but ranged from 0% to 13%.

The benefits must be weighed against the possible complications of surgery. In seven surgical series reported during the macrolide era, the rate of complications varied from 0% to 44% averaging approximately 25% [94–100]. In the largest study to date in Colorado (USA), MITCHELL *et al.* [99] reported the outcomes of 236 patients who underwent lung resection for NTM pulmonary disease over a 23-year period. Minor complications were reported in 18.5% of the patients with 31 (11.7%) suffering from serious complications. Bronchopleural fistula occurred in 11 (4.2%) cases. No operative mortality was reported in six case series and post-operative mortality ranged from 0% to 11%. In the study from Colorado, seven (2.6%) patients died as a result of the procedure; however, the mortality rate was only 0.6% for the last 162 patients that were operated on from 2001 to 2006. Many of these latter patients underwent video-assisted thoracoscopic surgery. Because case volume may be associated with outcomes, surgery should be performed by thoracic surgeons with extensive experience in performing this type of surgery [99].

### Conclusion

NTM represent a broad array of organisms with varying prevalence and pathogenicity. Pulmonary infections due to NTM appear to be increasing and the epidemiology is shifting toward a female predominance in some areas. Clinicians must consider clinical, radiographic and bacteriologic information when diagnosing NTM pulmonary infection. Although diagnostic criteria exist, these have yet to be prospectively validated. Consideration of the species of NTM is an increasingly important element of diagnosis and may impact the outcomes of therapy. Treatment regimens vary by NTM species as do treatment outcomes. Future areas of research should focus on the epidemiology of NTM infections, transmission of infection, risks for disease progression, development of new diagnostics and ultimately development of new drugs and treatment regimens. Until we have a better understanding of the transmission and pathogenesis of these difficult to treat infections, it will be difficult to formulate a rationale plan for prevention of infection.

### Statement of interest

None declared.
References


