Guidelines on the diagnosis and treatment of pulmonary non-tuberculous mycobacteria infection

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Introduction

Non-tuberculous mycobacteria (NTM) is a group of environmental bacteria that does not usually cause disease in humans (Table 1). They are quite unlike Mycobacterium tuberculosis (TB) and Mycobacterium leprae (leprosy) which are well-described human pathogens.

They are found predominantly in water, food, soil and dust (1,2). They grow comfortably in any environment that kills competing organisms, thus allowing them easier access to nutrients (e.g. chlorinated water).

Non-tuberculous mycobacteria are opportunistic pathogens that require a breakdown in host defence before successfully infecting the host. Examples of this breakdown include damaged mucosal or skin barriers, underlying lung disease, or immunosuppression because of HIV, malignancy or drugs. These organisms usually cause skin infections, lymphadenitis, lung disease and disseminated disease in severely immunocompromised individuals.

While TB cases are decreasing in the developed world, NTM infection rates are increasing. A number of groups from around the world have demonstrated this fact in both immunocompromised and immunocompetent patients (3). These increased rates of detection are probably a result of increased awareness of these pathogens, increasingly advanced detection methods, and increased exposure to, for example, chlorinated water, through showering and washing. Diagnosis rates are higher than ever before and it may be that the new techniques employed to accurately identify NTM in culture will contribute to a further increase in diagnosis over the coming years.

Accurate diagnosis is important as the drug regimens used to treat these organisms can have significant and troublesome side effects. The American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) guidelines which were updated in 2007, highlight the importance of following microbiological and clinical criteria in making a diagnosis of NTM lung infection (4).

More common lung pathogens

Mycobacterium avium complex (MAC) is the most common cause of NTM lung disease (5). It can also cause lymphadenitis and disseminated disease in severely immunocompromised patients such as those suffering from AIDS. Symptoms include night sweats, fever, malaise, fatigue, cough, sputum...
Mycobacterium malmoense was first reported in four patients from Malmo in 1977 (11). Since then, cases which closely resemble tuberculosis have been reported throughout the world. M. malmoense can cause lung disease, soft tissue disease and lymphadenitis. Disseminated disease can occur in immunocompromised individuals. In a study performed by the British Thoracic Society, the mean age of patients was 58 years and the majority of cases had smear positive sputum with radiologic evidence of cavitation (12). M. malmoense can be confused with other slow growing non-pigmented mycobacterium species as its identification can be very difficult. Since the introduction of more sensitive laboratory techniques, M. malmoense has been increasingly detected in the absence of clinical disease. Pulmonary involvement because of M. malmoense is almost indistinguishable radiologically and clinically from tuberculosis (13).

Mycobacterium chelonei more commonly causes soft-tissue and skin infection rather than lung infection. It is extremely resistant to many antibiotics (14) and disinfectants including in some instances gluteraldehyde (used to clean bronchoscopes) and cases of bronchoscope contamination have been described which have led to many pseudoepidemics (15). It is usually found as a contaminant in sputum or bronchoalveolar lavage (BAL) however lung disease can occur, albeit in rare circumstances.

Mycobacterium abscessus is a rapidly growing mycobacterium that leads to fibronodular bronchiectasis although opacities and cavities can also be found on HRCT (16). It is very similar radiographically to MAC but clinically it does not disseminate in immunocompromised patients in the way MAC does. It is associated with cystic fibrosis (CF) where it was the second most common NTM infection found after MAC (17) and it has also been associated with chronic gastro-oesophageal reflux (18). M. abscessus is very resistant to most antibiotics and localised surgery is often required in patients with adequate lung function in order to truly cure them of the disease (19).

Mycobacterium fortuitum is another of the rapidly growing mycobacteria which is more associated with postsurgery wound infection. It may also cause lung disease clinically similar to that of M. abscessus, which may be slow burning and almost subclinical (20). This tends to occur in patients with chronic vomiting or gastro-oesophageal disease.

Mycobacterium gordonnae is frequently cultured from sputum but rarely causes pathogenic lung disease (21). It frequently contaminates tap water and like M. chelonei, has caused frequent pseudoepidemics in many parts of the world (22–24). As with M. chelonei, it can cause infection especially in immunosuppressed patients with underlying lung disease (21). It is the most frequently isolated NTM contaminant and has even been isolated from laboratory taps (25).

Mycobacterium kansasii is often isolated from tap water and has been found in increased prevalence in coal and gold mining areas (26,27). There are seven subtypes of M. kansasii but type 1 is the most common lung pathogen (28). It usually causes cavitating lung disease but fibrobronodular bronchiectasis has also been described. While its disease pattern can be similar to MAC (29), M. kansasii disease tends to occur more in patients with underlying emphysema giving rise to more cavities and often a tree in bud appearance (30).

Mycobacterium xenopi infection occurs most frequently in Europe and Canada. It can grow in tap water and on biofilms and occurs more commonly in individuals with underlying lung disease, especially chronic obstructive pulmonary disease (COPD), interstitial lung disease, TB and lung cancer. Infection occurs more commonly in men in the seventh decade. Upper lobe cavitation is the most common radiological finding. Clinical presentation is similar to other NTM infection but mortality is high because of other comorbidities.
The first described disease because of NTM was cavitary tuberculosis of the upper lobes similar to that seen in traditional TB patients (31). The typical patient was a male smoker and drinker who had underlying disease (32). It was quickly noted that there was no person-to-person spread (31). Symptoms of this NTM cavitary disease were very much like those of TB with fever, sweats, weight loss, productive cough and even haemoptysis.

Patients infected with MAC and \( M. kansasaii \) tended to demonstrate a reticulonodular appearance on HRCT rather than the traditional cavitational seen with TB (29,33). Prince et al. (6) looked at MAC lung disease in Philadelphia and demonstrated that fibronodular bronchiectasis was quite common and that this spectrum of disease could aggressively progress without any form of cavitation. Unlike the male smokers with underlying lung disease that suffered from cavitating disease these individuals tended to be elderly females who did not have a history of smoking or underlying lung disease. A productive cough is the most common symptom and constitutional symptoms are rare (6).

A condition very similar to hypersensitivity pneumonitis has been demonstrated in patients exposed to certain NTM. A number of cases have been published where individuals that were exposed to NTM in swimming pools and jacuzzis developed granulomatous lung disease that either resolved spontaneously or required antibiotics and steroids (10,34,35).

Non-tuberculous mycobacteria is also a common cause of immune reconstitution inflammatory syndrome (IRIS). HAART reduces HIV RNA levels with a resultant increase in CD4+ lymphocytes thus allowing individuals to mount a defensive inflammatory reaction towards any insults including infection. This inflammatory reaction may lead to clinical deterioration of the patient. MAC is the most common cause of NTM-related IRIS (46). In a study in Canada, 3.5% of HIV patients started on HAART experienced IRIS because of NTM (46). In a study in Canada, 3.5% of HIV patients started on HAART experienced IRIS because of NTM. IRIS is more common in patients on HAART who experience early opportunistic infection or rapid reduction in CD4+ counts (47).

Studies have revealed that NTM is prevalent in 4–20% of CF patients and that this prevalence increases with age (17,36,37). An American multicentre trial in CF patients revealed that MAC was cultured in 72% and \( M. abscessus \) was identified in 16% of NTM cultures (17).

Bronchiectasis may be a risk factor for, but also a sequel of, NTM infection. The NTM may be a coloniser, have a slow burning course in bronchiectatic patients or it may be aggressive, contributing to further bronchiectasis and cavitation. MAC and \( M. abscessus \) are well described as pathogens that induce bronchiectasis in susceptible individuals (38). Chest wall deformities such as pectus excavatum and scoliosis are associated with MAC disease (39).

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The role of underlying lung disease

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Non-tuberculous mycobacteria infection has also been described in patients who have undergone solid organ or stem-cell transplantation. In lung transplant patients, MAC infection is the most common NTM disease of the lung isolated, followed by *M. abscessus* (48). In one centre where heart–lung transplant occurs, 7% of the patients were infected with NTM (49). NTM infection is much less common in renal transplantation although dissemination is much more common than pulmonary disease. Queipo et al. (50) found five cases of NTM lung disease in 1261 renal transplant cases in Spain, all of which were due to *M. kansasii*. Renal transplants complicated by *M. chelonae* and *M. xenopi* lung infection (48, 50) have also been described. It is important to remember that treating these conditions can be difficult given the interactions between the immunosuppressive drugs and the antibiotics required.

### Guidelines on the diagnosis of pulmonary NTM

Clinical suspicion is the first step on the road to a diagnosis of NTM lung disease. Patients with underlying lung disease, immunosuppression or constitutional symptoms should trigger thoughts of this condition in the physician’s mind. Many samples are sent for sputum culture with a suspicion of TB only to reveal a diagnosis of NTM. The minimum evaluation of a patient suspected of NTM lung disease should include (i) chest radiograph or, in the absence of cavitation, chest HRCT scan; (ii) three or more sputum specimens for acid fast bacilli (AFB) analysis and (iii) exclusion of other disorders such as TB and lung malignancy (4). In most patients, a diagnosis can be made without bronchoscopy or lung biopsy (4).

In the laboratory floochorome staining is rapid and the preferred stain of choice for initial microbiological samples (51). Specimens are also treated with sodium hydroxide and *N*-acetylcysteine to prevent overgrowth of *Pseudomonas aeruginosa* that is frequently present in CF and bronchiectasis patients (52). The specimens are then cultured in both solid and liquid media. It can take approximately 3–6 weeks for slow growing mycobacteria to grow on solid media. However, this is shortened to 1–2 weeks in liquid media (4). TB is differentiated from NTM through its catalase, nitrate reductase and niacin production and nucleic acid amplification techniques are also now used to rapidly distinguish NTM from TB. Once growth is detected on solid media in sufficient quantity, it normally takes a further 3–6 weeks to identify the species (53). However, with the development of modern techniques such as high-performance liquid chromatography, restriction fragment length polymorphism analysis amplification techniques, DNA sequencing and the use of DNA probes, it is now possible to rapidly identify the NTM species.

Antibiotic susceptibility testing is routinely performed on clinically significant isolates and is extremely important in MAC and *Mycobacterium kansasii* disease where clarithromycin and rifampicin resistance are tested respectively. Drug resistance can mean treatment failure (54). Susceptibility studies may be extremely helpful if patients do not respond to empiric therapy or relapse. There is also evidence suggesting testing of combinations of drugs instead of single drugs *in vitro* may be more predictive of *in vivo* response.

Clinically, it is helpful to know those symptoms and signs that may differentiate NTM from TB. Fever, night sweats, weight loss and haemoptysis are all more common in TB infection but equally may occur in cases of NTM infection especially in advanced disease. A positive tuberculin skin test along with a history of exposure also points to a diagnosis of TB, although a previous Bacillus Calmette-Guerin (BCG) vaccination and NTM sensitisation may give a false-positive result. Interferon-γ release assays (IGRAs) can help distinguish tuberculosis infection from skin test sensitisation because of NTM by utilising antigens highly specific for *M. tuberculosis*. One recent study of an IGRA system has suggested that the IGRA may be useful in distinguishing active tuberculosis from NTM (55). Radiological evidence of upper lobe involvement with cavitation may also suggest TB but ultimately does not exclude NTM infection. NTM, like *M. tuberculosis*, are acid-fast and can be detected by conventional or floochorome microscopy. Wright et al. (56) analysed more than 6500 respiratory specimens and found that NTM was as likely as *M. tuberculosis* to yield positive floochorome staining of sputum or bronchial wash specimens, with a positivity rate of approximately 60% for NTM. In the past, it was long held that many isolates represented benign colonisation or contamination and as a result, difficulty arose in identifying NTM disease from patients with underlying lung disease that had colonised or had microbiologic sample contamination. Studies of imaging and histology along with the observation that high colony counts of NTM were frequently associated with clinical disease over time (57), have led to the development of diagnostic criteria, thus removing for the time being, any confusion surrounding diagnosis.

Lung infection because of NTM is almost impossible to distinguishable both radiologically and clinically from tuberculosis but findings such as existing pneumoconiosis, volume loss, larger cavities and air
fluid levels are seen more frequently on chest radiographs of patients with certain NTM than on those with *M. tuberculosis* (13). Koh et al. (58) found that patients with NTM were more likely to be older, non-smokers, have had previous TB treatment and have bilateral disease with middle or lower zone involvement in the absence of a pleural effusion, when compared with TB patients. Differentiation from TB is important as the treatment regimen for TB is less complicated with a straightforward duration of therapy. However, TB contacts must be tracked unlike NTM which is not transmissible. On the other hand, NTM treatment can last for years, with drug susceptibility problems, high rates of drug side effects, poor compliance and high relapse rates.

The ATS/IDSA guidelines of 2007 (4) have set down certain criteria for the diagnosis of NTM (Figure 1). The requirements for the diagnosis of pulmonary infection include clinical and microbiological criteria. Both are required for diagnosis.

Clinically, pulmonary symptoms, nodular or cavitary opacities on chest radiograph, or a HRCT scan that shows multifocal bronchiectasis with multiple small nodules along with appropriate exclusion of other diagnoses are required. Microbiologically, one of the following is required: (i) positive culture results from at least two separate expectorated sputum samples or (ii) positive culture result from at least one bronchial wash or lavage or (iii) transbronchial or other lung biopsy with mycobacterial histopathologic features (granulomatous inflammation or AFB) and positive culture for NTM, or biopsy showing mycobacterial histopathologic features (granulomatous inflammation or AFB) and one or more sputum or bronchial washings that are culture positive (4).

**Guidelines on the treatment of pulmonary NTM**

As *M. tuberculosis* is almost always in the differential diagnosis for patients with NTM lung disease, empiric therapy for TB (especially with positive AFB smears) may be necessary pending confirmation of the diagnosis of NTM lung disease. At this stage, the drug regimen may need to also be changed depending on the organism identified (Table 2). The treatment of NTM is not as similar to TB treatment as one might expect. NTM are well known for having *in vitro* susceptibility to certain antibiotics that do not always correlate with clinical improvement (59). The physician should be guided by, but in the case of unresponsive patients, not stringently adhere to, the *in vitro* susceptibility results. In general, it is widely accepted that some NTM are treated in a very straightforward manner yet others can be quite

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**Figure 1** Recommended American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) guidelines on the diagnosis of pulmonary non-tuberculous mycobacterial infection. Both clinical criteria in combination with one of the microbiological criteria are required for diagnosis.
problematic. Duration of treatment tends to continue until 12 months of negative sputum samples have been collected. Hypersensitivity lung disease due to NTM should be treated by avoiding the precipitant (60). Corticosteroids and a short course of antibiotic therapy have been recommended but consensus is not clear.

For the treatment of MAC lung disease, a regimen of clarithromycin 1000 mg or azithromycin 500 mg, rifampicin 600 mg and ethambutol 25 mg/kg three times per week is recommended for treatment in patients with nodular/bronchiectatic disease (4). In severe nodular/bronchiectatic disease or fibrocavitary MAC lung disease, a daily regimen of clarithromycin 500–1000 mg or azithromycin 250 mg, rifampicin 10 mg/kg (maximum 600 mg/day) or rifabutin 150–300 mg, and ethambutol 15 mg/kg is recommended. In addition, amikacin or streptomycin three times weekly early in therapy should be considered (4). Clarithromycin resistant MAC involves a more complex treatment regimen that requires consultation with a physician experienced in this disease. Treatment tends to include isoniazid, rifampin (possibly rifabutin), ethambutol, with amikacin/streptomycin for the first 3–6 months of therapy (4). Surgery may be beneficial in those patients that have localized disease that are poorly responding to drug therapy or who have clarithromycin resistance (61).

*Mycobacterium kansasii* treatment involves a recommended daily regimen of isoniazid 5 mg/kg/day, rifampicin 10 mg/kg/day (maximum 600 mg), ethambutol 15 mg/kg/day and pyridoxine 50 mg/day. (4). If rifampicin resistant, daily high dose isoniazid (900 mg), ethambutol (25 mg/kg), pyridoxine (50 mg) with sulphonmethoxazole 1 g three times a day combined with daily or five times per week streptomycin or amikacin for the initial 2–3 months, followed by amikacin or streptomycin intermittently for a total of 6 months is recommended (4).

*Mycobacterium abscessus* disease may benefit from periodic administration of a macrolide in combination with parenteral agents such as imipenem, amikacin and cefoxitin in order to control progression of the disease. The only curative therapy is surgery for focal disease combined with antibiotic therapy (4).

*Mycobacterium malmoense* lung infection may be difficult to treat. An optimal regimen is unknown but microbiologic improvement has been seen with combinations of rifampicin, isoniazid and ethambutol, plus or minus macrolides and quinolones, depending on antibiotic susceptibility (4).

The most effective therapy for *Mycobacterium gordonnae* pulmonary infection includes combinations of rifabutin, ethambutol, linezolid, fluoroquinolones and clarithromycin. Two agents are generally used and physicians should be guided by antibiotic susceptibility testing (4).

*Mycobacterium chelonae* infection has no recommended regimen but is susceptible to imipenem, clarithromycin, tobramycin, doxycycline, ciprofloxacin, amikacin and clofazimine. Two agents are generally required, one usually being clarithromycin. Physicians should be guided by susceptibility testing (4).

*Mycobacterium gordonnae* pulmonay infection includes combinations of rifabutin, ethambutol, linezolid, fluoroquinolones and clarithromycin. Two agents are generally used and physicians should be guided by antibiotic susceptibility testing (4). Two agents are usually required (4).

### Table 2 Recommended treatment regimens for the more common pulmonary non-tuberculous mycobacteria

<table>
<thead>
<tr>
<th>Species</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Mycobacterium malmoense</em></td>
<td>Rifampicin, isoniazid and ethambutol ± macrolide ± quinolone</td>
</tr>
<tr>
<td>MAC</td>
<td>Rifampicin, ethambutol and macrolide. Include aminoglycoside for cavitary disease. If macrolide-resistant use rifampicin, isoniazid, ethambutol and amikacin/streptomycin (first 3–6 months). Administer 3 times weekly for limited disease and daily for extensive disease</td>
</tr>
<tr>
<td><em>Mycobacterium xenopi</em></td>
<td>Clarithromycin, rifampicin, isoniazid, ethambutol ± streptomycin (first 3–6 months)</td>
</tr>
<tr>
<td><em>Mycobacterium kansasii</em></td>
<td>Rifampicin, isoniazid and ethambutol. If rifampicin resistant, use isoniazid, ethambutol, sulphonmethoxazole, ±amikacin/streptomycin (first 3–6 months)</td>
</tr>
<tr>
<td><em>Mycobacterium gordonnae</em></td>
<td>2 agents with <em>in vitro</em> susceptibility</td>
</tr>
<tr>
<td><em>Mycobacterium chelonae</em></td>
<td>Clarithromycin + additional agent (<em>in vitro</em> susceptibility)</td>
</tr>
<tr>
<td><em>Mycobacterium fortuitum</em></td>
<td>2 agents with <em>in vitro</em> susceptibility</td>
</tr>
<tr>
<td><em>Mycobacterium abscessus</em></td>
<td>Macrolide + 1–2 additional agents ± resection if limited disease</td>
</tr>
</tbody>
</table>

MAC, *Mycobacterium avium* complex.
**Mycobacterium xenopi** treatment involves a combination of clarithromycin, isoniazid, ethambutol streptomycin and rifampicin; however, *in vitro* susceptibility testing is not accurate. The optimal treatment of *M. xenopi* has not been established. Once therapy is initiated, sputum converts quickly but relapse rates are high (63).

*Mycobacterium gordonae* has very few antimicrobial susceptibility data available. However, consistent *in vitro* activity has been described with ethambutol, rifabutin, clarithromycin, linezolid and the fluoroquinolones (4).

**Discussion**

As the prevalence of NTM disease increases, it is important that patients are investigated and treated appropriately. Confusion may arise when NTM is isolated in sputum or BAL samples as physicians try to decide whether or not they are dealing with contamination or real infection. The clinician, therefore, should always know the context in which an NTM isolate was obtained in order to assess accurately the clinical significance of that isolate. Guidelines now exist to assist with the accurate investigation, diagnosis and treatment of these organisms (4,64). The ATS/IDSA guidelines 2007 which update the previous 1997 guidelines have relaxed the microbiological criteria for diagnosis (a single NTM culture from bronchial washing fluid, in a well-defined class of patients, or two positive sputum cultures now suffice to establish the diagnosis) whilst making the clinical criteria more specific (65). Despite the fact that better detection systems exist and newer, more active antimicrobials have been developed, treatment success with antimicrobial therapy can be elusive because of poor compliance with the long duration of required therapy combined with the troublesome side effects and drug interactions. Henry et al. (66) demonstrated the importance of adhering to the published guidelines for the treatment of NTM pulmonary disease where they highlighted marked contrast in outcomes between those patients who received appropriate treatment regimens and those who did not. He also demonstrated that almost all of the 49 subjects (in their study of non-HIV patients with clinically relevant pulmonary disease) had underlying lung disease. In particular, for example, in the case of *M. malmoense* infection, eight patients were predisposed with COPD, two patients with previous TB disease, one with bronchiectasis, one patient with CFA and one patient with lung cancer (66). Over all, 22 cases of MAC, 18 cases of *M. malmoense*, three of *M. kansasii*, three of *M. xenopi* and three cases of rapidly growing NTM were identified as lung pathogens (66). One thing is clear continued vigilance amongst at-risk populations plus strict adherence to published international treatment guidelines will improve outcomes in pulmonary NTM disease. Further research and randomised controlled trials are required to optimise future international guidelines.

**References**


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