# Non-tuberculous mycobacterial pulmonary disease: a clinical update

Non-tuberculous mycobacteria infection is an emerging health problem with increasing global incidence and prevalence (Haworth et al, 2017). Non-tuberculous mycobacteria are all mycobacterium species other than those causing tuberculosis (*Mycobacterium tuberculosis* complex) and leprosy (*M. leprae* and *M. lepromatosis*) and are most commonly categorized microbiologically based on their growth rate – either slow-growing or rapid-growing species (pulmonary disease-causing species are summarized in *Table 1*). They are commonly found in soil, water and animals, so were called 'environmental mycobacteria' (Falkinham, 2009). While they are less virulent than *M. tuberculosis* they can cause human pulmonary disease in the presence of pre-existing lung disease or immunodeficiency (Field et al, 2004; Griffith et al, 2007). This article discusses the epidemiology and clinical syndromes of non-tuberculous mycobacteria infection in humans with a focus on pulmonary disease, and reviews current treatment guidelines.

## Epidemiology

Non-tuberculous mycobacteria species vary considerably between and within countries, with most studies reporting a rising incidence over the last 40 years (Hoefsloot et al, 2013; Haworth et al, 2017). *M. avium* complex (MAC), encompassing several species including *M. avium*, *M. intracellulare* and *M. chimaera*, is the most common non-tuberculous mycobacteria causing human disease in resource-rich nations, followed by *M. kansasii*. *M. abscessus* is especially prevalent in patients with cystic fibrosis (Griffith et al, 2007). Reports from the USA estimated that 94% of reported non-tuberculous mycobacteria cases were pulmonary in origin. However, as non-tuberculous mycobacteria were previously thought to be non-communicable, so not considered reportable, accurate estimation of prevalence has been difficult (Griffith et al, 2007). In the UK, the incidence of pulmonary non-tuberculous mycobacteria-positive cultures has increased from 4/100 000 to 6.1/100 000 between 2007 and 2012 (Shah et al, 2016). While this may reflect improved awareness and more efficient detection methods, several studies have reported a genuine increase in incidence (Khan et al, 2007; Marras et al, 2013).

**Table 1. Non-tuberculous mycobacteria species commonly causing lung infection in humans**

| Species | Slow *vs* rapid-growing | Pathogenicity |
|---|---|---|
| *M. malmoense* | Slow | ↑ |
| *M. kansasii* | Slow | |
| *M. abscessus* | Rapid | |
| *M. xenopi* | Slow | |
| *M. avium* complex (*M. avium*, *M. intracellulare* and *M. chimaera*) | Slow | |
| *M. chelonae* | Rapid | |

*From Falkinham (2009); Hoefsloot et al (2013)*

### Risk factors

While the lungs are the most common site of infection, non-tuberculous mycobacteria can colonize and infect other organ systems including lymph nodes, skin, sinuses, the CNS, musculoskeletal joints and urinary tract (Haworth et al, 2017). The main host-derived risk factor for pulmonary non-tuberculous mycobacteria infection is pre-existing lung disease. Conditions such as chronic obstructive pulmonary disease, asthma, cystic fibrosis and non-cystic fibrosis bronchiectasis, and primary ciliary dyskinesia all predispose individuals to infection. Other factors such as immunodeficiency (inherited or acquired), malnutrition, low vitamin D, gastro-oesophageal reflux disease or medications (immunosuppression or prolonged antibiotic use) all increase non-tuberculous mycobacteria infection rates (Haworth et al, 2017).

### Transmission

Person-to-person transmission of non-tuberculous mycobacteria was considered highly unlikely, owing to several studies showing solely environmental sources of infection, even in co-habited cystic fibrosis patients (Feizabadi et al, 1996; Klausen et al, 1997; Olivier et al, 2003). However, genome sequencing and epidemiological studies demonstrated person-to-person transmission of *M. abscessus* in cystic fibrosis cohorts. Despite this, direct transmission is still considered rare and has not been proven in patients who do not have cystic fibrosis. However, the discovery of direct person-to-person transmission in patients with cystic fibrosis prompted new national infection control policies (Bryant et al, 2013, 2016). It has also become apparent that patients undergoing cardiopulmonary bypass during cardiac surgery are at risk of developing non-tuberculous mycobacteria infections. Patients infected with *M. chimaera* have been identified in Europe (Sax et al, 2015) and the USA (Tan et al, 2016) and infections have been linked to contaminated water reservoirs in heater-cooler units used to warm or cool blood passing through bypass circuits (Götting et al, 2016; Sommerstein et al, 2017).

## Clinical syndromes of non-tuberculous mycobacteria infection

In broad terms, non-tuberculous mycobacteria can cause four distinct clinical presentations (Griffith, 2017):

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- Pulmonary disease, particularly in the elderly caused by MAC and *M. kansasii*, which is generally progressive
- Superficial lymphadenitis (particularly cervical) in children caused by MAC, *M. scrofulaceum*, *M. malmoense* and *M. haemophilum*
- Skin and soft tissue infection
- Disseminated disease in the severely immunocompromised.

Non-tuberculous mycobacteria can often transiently colonize the airways without causing overt infection, making decisions to treat complex. In other cases, infection can lead to progressive lung damage, termed 'non-tuberculous mycobacteria pulmonary disease'. Symptoms can be highly variable and include cough, fatigue, dyspnoea, malaise and occasional haemoptysis with fever and weight loss (although admittedly less common than in pulmonary tuberculosis).

Patients commonly present with recurrent chest infections that do not respond to conventional antibiotics. Examination can be normal or typical of any underlying lung condition which may increase the risk of non-tuberculous mycobacteria pulmonary disease. Parenchymal scarring from previous tuberculosis infection can increase the risk of non-tuberculous mycobacteria pulmonary disease which can pose a diagnostic challenge as tuberculosis reactivation must be considered and excluded in all cases of suspected non-tuberculous mycobacteria pulmonary disease (Griffith et al, 2007; Marras et al, 2013; Griffith, 2017; Haworth et al, 2017).

Two major pulmonary clinical presentations have been described, sometimes classified as either 'nodular bronchiectatic' or 'fibrocavitatory' (*Table 2*). The former is more commonly encountered by physicians, although the reason for this is unknown.

Uncommon presentations include solitary nodules resembling lung cancer and 'hot tub lung'. The latter presents similarly to hypersensitivity pneumonitis with fever, dyspnoea and gradual onset of cough (Fjällbrant et al, 2013). It is a diffuse granulomatous lung disease caused by inhaling water aerosol containing non-tuberculous mycobacteria antigens leading to a hypersensitivity reaction, and responds to avoidance of the offending agent (Griffith, 2017).

## Diagnosis

Diagnosis of non-tuberculous mycobacteria pulmonary disease is challenging as identification may represent colonisation rather than infection and non-tuberculous mycobacteria are ubiquitous in the environment, including in drinking water (Griffith et al, 2007; Haworth et al, 2017). As a result of toxic and prolonged treatment regimens, prompt, accurate diagnosis is essential. To meet the American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) 2007 criteria for non-tuberculous mycobacteria pulmonary disease, in the absence of other potential causes of pulmonary disease, a patient must have clinical symptoms with compatible radiology and two or more positive sputum samples with the same non-tuberculous mycobacteria species or one positive bronchial wash/lavage or compatible histopathology (*Table 3*) (Griffith et al, 2007; Haworth et al, 2017).

The ATS/IDSA 2007 criteria, while based on a relatively small amount of evidence, have been widely adopted and provide practical guidelines to identify patients most at need of assessment and treatment, while also identifying those in whom treatment will have minimal benefit or indeed harm (e.g. asymptomatic or one-off culture-positive patients). However, these criteria have not been validated in patients and treatment regimens may be ineffective in some cases.

Non-tuberculous mycobacteria pulmonary disease may present similarly to active *M. tuberculosis*; both can produce constitutional symptoms, haemoptysis as well as cavitatory pulmonary infiltrates on imaging and evidence of granuloma formation. *M. tuberculosis* should be excluded and other mimics such as sarcoidosis and fungal infection considered (Stout et al, 2016). Furthermore, as for *M. tuberculosis*, all patients being investigated for non-tuberculous mycobacteria pulmonary disease, especially those with disseminated disease, should be tested for immunodeficiency including HIV screening (Lake et al, 2016).

The British Thoracic Society guidelines (Haworth et al, 2017) proposed an algorithm for investigating suspected individuals with non-tuberculous mycobacteria pulmonary

**Table 2. Two major clinical presentations of non-tuberculous mycobacteria pulmonary disease**

| | Fibrocavitatory | Nodular bronchiectatic |
|---|---|---|
| History of lung disease | Almost always | Rarely – although evidence of interstitial patterns on radiography |
| History of smoking | Yes | No |
| Demographic | White, middle-aged or elderly men | Women over 50 years of age |
| Symptoms | Cough, weight loss; less severe symptoms than pulmonary tuberculosis | Persistent cough with purulent sputum in the absence of fever or weight loss |
| Radiology | Extensive lung destruction with large cavities on chest X-ray (*Figure 1*) | Associated with nodules and bronchiectatic changes (*Figure 2*) |
| Organisms responsible | *Mycobacterium avium* complex | *Mycobacterium avium* complex |
| Treatment | Treat early | Specific treatment less frequently used |

*From Griffith et al (2007); Griffith (2017); Haworth et al (2017)*

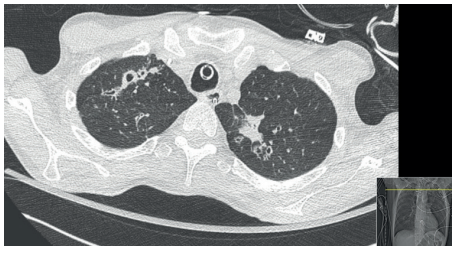

**Figure 1. Computed tomography image of fibrocavitatory disease exhibiting extensive lung destruction with large cavities.**

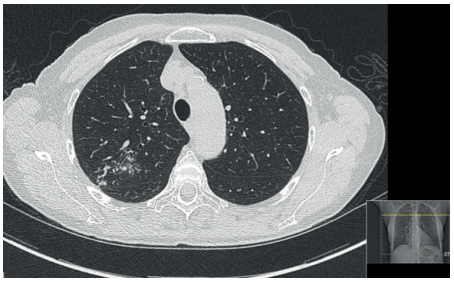

**Figure 2. Computed tomography image of nodular bronchiectatic disease exhibiting nodules and dilated bronchioles.**

disease (*Figure 1*). A minimum of two sputum samples on separate days should be sent for mycobacterial culture and if consistently negative, computed tomography-directed bronchial washings should be considered. Both a chest X-ray and a computed tomography scan should be performed in suspected individuals (Haworth et al, 2017).

Sputum, induced sputum, bronchial washings and bronchoalveolar lavage or transbronchial biopsy samples can be used to aid diagnosis, with appropriate infection prevention and control. Consider stopping antibiotics in patients undergoing diagnostic evaluation for 2 weeks before collecting samples. If there is a high clinical suspicion but negative cultures, consider discussion with a mycobacterial reference laboratory for further investigations (Haworth et al, 2017).

**Table 3. Criteria for diagnosing non-tuberculous mycobacterial lung disease**

| | |
|---|---|
| Clinical | Pulmonary symptoms, nodular or cavitatory opacities on chest radiograph or high resolution computed tomography showing multifocal bronchiectasis with multiple small nodules and |
| | Exclusion of other diagnoses |
| Microbiology | Positive culture results from at least two separate sputum samples or |
| | Positive culture results from at least one bronchial wash/lavage or |
| | Transbronchial or lung biopsy with mycobacterial histopathological features (acid-fast bacilli or granulomatous inflammation) and positive culture for non-tuberculous mycobacteria or biopsy showing mycobacterial histopathological features and one or more sputum or bronchial washings that are culture positive for non-tuberculous mycobacteria |

*Modified from Haworth et al (2017)*

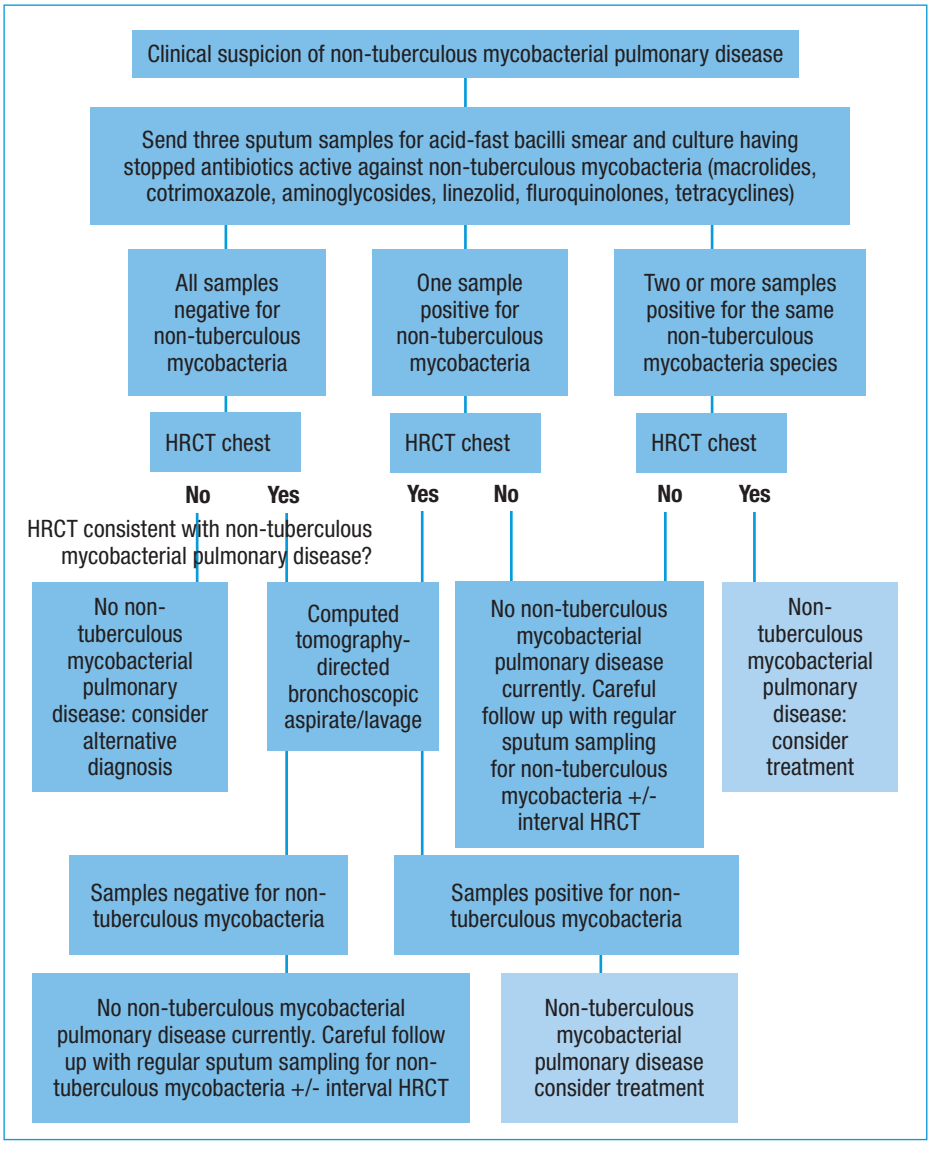


**Figure 1. A suggested algorithm for the investigation of individuals with clinical suspicion of non-tuberculous mycobacterial pulmonary disease. HRCT = high-resolution computed tomography. From Haworth et al (2017).**

## Laboratory findings

The gold standard for laboratory diagnosis of non-tuberculous mycobacteria pulmonary disease is culture which is also required for drug susceptibility testing and genotypic identification (Griffith et al, 2007; Kikuchi et al, 2014; Stout et al, 2016; Haworth et al, 2017). Non-tuberculous mycobacteria identification is clinically important as the treatment regimen, prognosis and length of treatment differ depending on the species. Gene sequencing is the most accurate method of identifying non-tuberculous mycobacteria species. Matrix-associated laser desorption/ionization time-of-flight mass spectrometry has been increasingly used to identify bacterial and fungal infections, and may be a potential tool for the identification for non-tuberculous mycobacteria species because of its accuracy, speed and cost-effectiveness, although it requires larger amounts of organism than sequencing (Kikuchi et al, 2014).

Drug susceptibility testing is essential to guide optimal treatment regimens. However, in non-tuberculous mycobacteria pulmonary disease, in-vitro and in-vivo drug susceptibility testing do not necessarily correlate. The most clinically relevant example is in MAC non-tuberculous mycobacteria pulmonary disease where evidence only supports a correlation between in vitro and in vivo drug susceptibility testing with macrolides and amikacin (Griffith et al, 2007; Aksamit et al, 2014; Haworth et al, 2017). Certain rapidly growing non-tuberculous mycobacteria, e.g. *M. abscessus*, inhibit macrolide antimicrobial agents through the presence of an inducible erythromycin-resistance methylase (erm) gene. Hence, an isolate of *M. abscessus* or *M. fortuitum* may be susceptible to macrolides in vitro but will not respond to these in vivo.

## Treatment

The treatment for non-tuberculous mycobacteria pulmonary disease is challenging; multiple antimicrobials are used depending on non-tuberculous mycobacteria speciation, toxicity, antimicrobial synergy, and resistance profile, severity of disease and length of treatment (Griffith et al, 2007; Ryu et al, 2016; Haworth et al, 2017). Length of treatment for non-tuberculous mycobacteria pulmonary disease often far exceeds that of standard *M. tuberculosis*, posing further difficulties with side effects and patient adherence.

Non-tuberculous mycobacteria pulmonary disease as a diagnosis does not obligate the initiation of treatment, and watchful waiting in patients with stable radiographic disease and unimpaired host immunity is often appropriate. Patients with fibro-cavitatory disease, which has a higher mortality rate, require prompt treatment in contrast to nodular bronchiectatic disease which often progresses slowly and occurs in the absence of significant comorbidity.

Molecular analysis can aid the decision process as certain mycobacterial genotypes are predictive of treatment response and disease progression (Kikuchi et al, 2014; Stout et al, 2016). It is essential that the management of such complex infections is undertaken in association with respiratory, infectious disease and microbiology physicians with experience of managing non-tuberculous mycobacteria pulmonary disease. The three most clinically relevant forms of non-tuberculous mycobacteria pulmonary disease are now discussed:

### *Mycobacterium avium* complex lung disease

As macrolide resistance predicts worse clinical outcomes, requiring augmented treatment, MAC non-tuberculous mycobacteria pulmonary disease which is clarithromycin sensitive is split into severe and non-severe infection as classified in *Table 4* (Griffith, 2017; Haworth et al, 2017).

Macrolide drugs are the cornerstone of MAC pulmonary disease treatment and intermittent treatment has a better tolerability profile in observational studies (Kikuchi et al, 2014; Stout et al, 2016; Haworth et al, 2017). Treatment outcomes of MAC pulmonary disease are poor with the overall success rate at 40–60% and recurrence after completion of antibiotic treatment (predominantly as a result of reinfection) at 30–50% (Wallace et al, 2014). Outcomes are slightly better in non-cavitatory nodular bronchiectatic disease as are re-infection rates. However, resistant and severe MAC pulmonary disease have poorer outcomes and cessation of treatment as a result of adverse drug effects (10–30%) contributes to this (Aksamit et al, 2014; Kikuchi et al, 2014; Wallace et al, 2014; Ryu et al, 2016; Stout et al, 2016; Haworth et al, 2017).

**Table 4. Classification and treatment of *Mycobacterium avium* complex non-tuberculous mycobacteria pulmonary disease**

| | *Mycobacterium avium* complex pulmonary disease | |
|---|---|---|
| | **Non-severe** | **Severe** |
| Acid-fast bacilli smear | Negative | Positive |
| Radiology | No lung cavitation or severe infection | Lung cavitation or severe infection |
| Symptoms | Mild–moderate symptoms | Moderate–severe symptoms |
| Evidence of systemic illness | No | Yes |
| Antibiotic regimen | Rifampicin 600 mg 3x/week and ethambutol 25 mg/kg 3x/week and azithromycin 500 mg 3x/week or clarithromycin 1 g in two divided sources 3/x week | Rifampicin 600 mg daily and ethambutol 15 mg/kg daily and azithromycin 250 mg daily or clarithromycin 500 mg twice daily and consider intravenous or nebulised amikacin |
| Duration of treatment | Treatment should continue for a minimum of 12 months after culture conversion | Treatment should continue for a minimum of 12 months after culture conversion |

*From Griffith (2017); Haworth et al (2017)*

### *Mycobacterium kansasii* lung disease

There is a paucity of randomized control trials involving *M. kansasii* non-tuberculous mycobacteria pulmonary disease, but observational studies have identified that rifampicin-based antibiotic regimens are associated with more rapid culture conversion and lower relapse rates (Kikuchi et al, 2014; Wallace et al, 2014; Haworth et al, 2017). In contrast to MAC pulmonary disease, *M. kansasii* pulmonary disease shows excellent treatment outcomes with antibiotic treatment which should continue for at least 12 months after negative culture conversion (Stout et al, 2016; Haworth et al, 2017).

### *Mycobacterium abscessus* lung disease

*M. abscessus* pulmonary disease is often indolent yet progressive, resulting in impaired quality of life. However, it can also be fulminant resulting in acute respiratory failure, particularly in patients with cystic fibrosis. *M. abscessus* is the only non-tuberculous mycobacteria to show clear human–human transmission, complicating the population where it predominates. Notoriously difficult to treat as a result of multiple inducible resistant genes which behave differently in vivo to in vitro, subspecies differentiation is increasingly important as treatment outcomes for *M. abscessus* pulmonary disease differ based on taxonomy (Lee et al, 2015). Specific antibiotic choice is dictated by sensitivities (specifically clarithromycin sensitivities) and current guidelines advise an initial antibiotic induction phase with intravenous and oral antibiotics (combination of intravenous amikacin, tigecycline and imipenem and oral clarithromycin), followed by a continuation phase consisting of inhaled and/or oral antibiotics (nebulised amikacin and oral clarithromycin)(Lee et al, 2015; Haworth et al, 2017).

### Adjuvant therapies

Antibiotic therapy may be unsatisfactory, hence adjuvant surgical resection could be considered in patients with localized disease with few comorbidities. Sputum conversion rates are >90% but risks include bronchopleural fistula (Stout et al, 2016; Haworth et al, 2017). Immunotherapy such as interferon gamma is not recommended as adjuvant therapy except if there is a clear immunodeficiency affecting interferon gamma signalling (Haworth et al, 2017).

## KEY POINTS

- Non-tuberculous mycobacteria infection is an emerging health problem with increasing global incidence and prevalence. Pulmonary involvement is the commonest presentation.
- *Mycobacterium avium* complex is the most common non-tuberculous mycobacteria causing human disease.
- The main host-derived risk factor for pulmonary non-tuberculous mycobacteria infection is pre-existing lung disease.
- Non-tuberculous mycobacteria mainly cause four distinct clinical presentations: pulmonary disease, superficial lymphadenitis, skin and soft tissue infection, or disseminated disease.
- Non-tuberculous mycobacteria can transiently colonize the airways without causing overt infection, making decisions to treat complex, while in other cases infection causes progressive lung damage.
- Symptoms can be highly variable and for diagnosis a patient must have clinical symptoms with compatible radiology and two or more positive sputum samples with the same species or one positive bronchial wash/lavage or compatible histopathology.
- The gold standard for laboratory diagnosis is culture, which is also required for drug susceptibility testing and genotypic identification.
- Treatment of non-tuberculous mycobacteria pulmonary disease is challenging and can have variable outcomes.

## Conclusions

Pulmonary diseases caused by non-tuberculous mycobacteria are complex and challenging infections with less than optimal outcomes, recurrence after completion of treatment regimens and difficult tolerability profiles of current antibiotic regimens. A lack of up-to-date randomized controlled trial data and difficulties in confirming pathogenicity further compound an already poor evidence base. Furthermore, increasing antibiotic resistance to commonly used drugs such as macrolides complicates the management of non-tuberculous mycobacteria pulmonary disease. Survival of patients with non-tuberculous mycobacteria pulmonary disease is primarily determined by underlying comorbidities, hence studies need to assess the impact of non-tuberculous mycobacteria disease on patients and their quality of life (Stout et al, 2016; Haworth et al, 2017). Clinical trials amalgamating both patient impact and optimal regimens would be ideal for the management of non-tuberculous mycobacteria pulmonary disease. **BJHM**

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*Conflict of interest: none.*

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