# Non-tuberculous mycobacterial (NTM) infections – and their relevance to general respiratory practice

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## Background and prevalence

Non-tuberculous mycobacteria (NTM) are a group of bacteria that are capable of causing opportunistic lung infections and the development of NTM pulmonary disease (NTM-PD). They are distinct from Mycobacterium tuberculosis (TB) and Mycobacterium leprae and are found in the natural environment and water supplies such as taps and shower heads. Nearly 200 different species of NTM have been identified; Mycobacterium avium complex (MAC) is the commonest to cause infections in the UK. NTM can be inhaled into the lungs via aerosols and pulmonary disease accounts for the majority of infections caused by NTM. For healthy people they rarely cause a problem; however, in immunocompromised patients or those with underlying lung disease they can lead to serious lung infections.[1,2] The overall prevalence of NTM is around 7 cases per 100,000 population; in patients with chronic lung disease the prevalence is 16.5 times higher.[3]

It is agreed that the prevalence globally and in the UK is rising significantly over time in respiratory patients.[4-7] Indeed a recent systematic review and meta-analysis suggests that 10% of people with non-CF bronchiectasis have NTM infections.[8] At the current time NTM is not a notifiable disease like TB which has perhaps hindered more accurate prevalence rates in the UK.[1]

## Which of my patients are at increased risk?

NTM-PD is worth considering in people who are immunocompromised (linked to medical conditions or their treatment) and in people with pre-existing chronic lung disease such as COPD, bronchiectasis and cystic fibrosis.[9] Indeed, current national guidance suggest that people with cystic fibrosis[10] and those with clinically active bronchiectasis[11] should be screened for NTM on an annual basis with use of three early morning sputum specimens for Acid Alcohol Fast Bacilli (AAFB) culture.

In some patients the NTM can be the primary insult with the infection causing lung damage and bronchiectasis without any prior history of pre-existing lung disease.[12,13]

## How does it affect the lungs?

NTM-PD has two main patterns of pulmonary disease. The first is a nodular bronchiectatic form with features of “tree-in-bud” nodularity and bronchiectasis on a CT scan. The second pattern produces more extensive lung damage with fibrocavitary disease; this typically occurs in the upper lobes and can often mimic TB.[14] The nodular bronchiectatic form is associated with a certain body type, particularly tall, lean, and post-menopausal women.[15] Fibrocavitary disease is more commonly seen in men, smokers, and those with underlying structural lung disease, in particular COPD.[14]

### How might I identify this as a more general clinician?

The symptoms of NTM-PD are often non-specific. It is something that should be considered if our patient is not responding to treatment as we would expect. In general, this is often increasing breathlessness or cough and sputum, recurrent ongoing infections and evidence of overall deterioration (functional ability, weight loss, sweats etc.).

### What else might we want to think about?

In this group of patients, the differential diagnosis can be quite wide both in terms of infection and other co-morbidities. In patients with symptoms suggestive of ongoing infection then other persistent pathogens have to be considered, these include Aspergillus fumigatus, Pseudomonas aeruginosa, Staphylococcus aureus and Haemophilus influenzae. TB may be considered if sweats, fevers, and weight loss, particularly in a patient born in a high TB prevalence area. Many patients have a heavy smoking history; lung cancer and cardiac failure can also present with many of the symptoms of NTM pulmonary disease. Fortunately, many of the investigations are common to diagnose all of these conditions.

### Investigations

Once the symptoms are identified as being suspicious for NTM-PD then both sputum and radiology investigations are required to make the diagnosis. Often the diagnosis can be suspected on a chest x-ray (sometimes performed for other reasons) or CT scan. Plain chest x-rays are not usually diagnostic as many of the changes are non-specific; however, they can pick up cavities in patients with fibrocavitary pattern disease.

Standard sputum cultures will not normally identify NTM, but they will identify other bacteria that can present in a similar fashion. For NTM, three morning sputum samples for AAFB are required to try to identify the organism. If an AAFB sample is found to be positive on either microscopy or culture, then further specialist assessment is recommended and usually your local respiratory consultant physician will be able to investigate or forward to a colleague with a more specialist interest in this area. In the UK, the initial laboratory report usually states 'Mycobacterium culture positive'. This could represent either TB or NTM infection. Physicians have to make a judgement as to whether this could be TB based on clinical and radiological features whilst waiting for full differentiation by the reference laboratories. It is important to identify the NTM species as some are highly pathogenic whilst others are more likely to represent an incidental finding.

### Diagnosis

The diagnosis can be complex as other causes have to be excluded and it is important to establish that the NTM present is causing disease rather than just an incidental finding. If only a single sputum culture is positive for NTM then repeat sampling is usually required.

Guidelines require three components to be present in order to make a diagnosis of NTM-PD. These are (1) two or more positive sputum cultures (or a single positive bronchoscopy washing), (2) radiology showing changes consistent with NTM-PD, and (3) symptoms that are in keeping with NTM-PD.

### Treatment

The treatment for NTM-PD involves multiple antibiotics given over an extended period of time, often 18 months or more in duration. The treatment burden, together with drug toxicities, often means that the decision to treat is not always straightforward. Patients are often monitored in clinic until the risk-benefit assessment is favourable towards treatment; however, over half of patients will show radiological progression if they are not treated.[16] The decision to treat involves MDT discussions involving a wide range of specialities. When on treatment the sputum is monitored every 1-2 months to ensure a response to treatment, if NTM cultures remain positive after 6 months then a diagnosis of refractory disease is made, and treatment regimens need to be reconsidered.

Other aspects to consider include chest physiotherapy, encouragement of regular activity / exercise, maintain adequate nutrition, and optimise any underlying lung diseases. There is now a NTM charity that supports patient education (https://www.ntmaction.com).

### Prognosis

NTM pulmonary disease can be progressive and often fatal if left untreated. A recent meta-analysis in patients with MAC pulmonary disease found an overall five-year mortality to be 27%.[17] Patients with fibrocavitary disease are at higher risk of mortality than those with nodular bronchiectatic disease[18] and survival time may also differ according to the NTM species.[19]

Even after successful treatment the recurrence of NTM-PD is as high as 50% and should be considered if symptoms developed in a patient with a history of NTM-PD.[20] In most patients this is reinfection with a new organism, but relapse of an existing infection may occur in patients with fibrocavitary pattern disease.

## Conclusions

Non-tuberculous mycobacterium though a rare problem in primary care is a not inconsiderable cause of morbidity and mortality in high-risk patients. It is worth considering in the clinical work up of people who have progressive respiratory symptoms despite treatment with an established diagnosis – and in people who are immunocompromised. NTM is an important part of the differential diagnosis in non-resolving symptoms in people with respiratory symptoms, is complex to diagnose and treat which would be in a specialist environment.

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