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Non-tuberculous mycobacterial pulmonary disease (NTM-PD): Epidemiology, diagnosis and multidisciplinary management

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ABSTRACT

Non-tuberculous mycobacteria (NTM) are ubiquitous environmental organisms that can cause significant disease in both immunocompromised and immunocompetent individuals. The incidence of NTM pulmonary disease (NTM-PD) is rising globally. Diagnostic challenges persist and treatment efficacy is variable. This article provides an overview of NTM-PD for clinicians. We discuss how common it is, who is at risk, how it is diagnosed and the multidisciplinary approach to its clinical management.

Background

Non-tuberculous mycobacteria (NTM), which comprise all mycobacterial species other than those that cause tuberculosis (TB) and leprosy, are ubiquitous in the environment and are found particularly in water or soil. To date, approximately 200 NTM species having been identified. In humans, they most commonly infect the lungs. This can lead to NTM pulmonary disease (NTM-PD) (Fig. 1).[1] NTM infection incidence is rising both in the UK and globally.[2,3] NTM-PD is particularly seen in patient populations with structural lung diseases or impaired immunity; but it can also occur in people with no apparent risk factors.[4] It remains an under-recognised condition that is difficult to diagnose and challenging to treat due to the toxicity of drug therapies that often have limited efficacy. It can be associated with poor treatment outcomes in an often-older population with comorbidities.

As many people at high risk of NTM-PD are often reviewed and managed on the acute medical take or in general medicine clinics, it is important for general physicians to know about this condition and its treatment. Here, we provide a multidisciplinary overview of managing and

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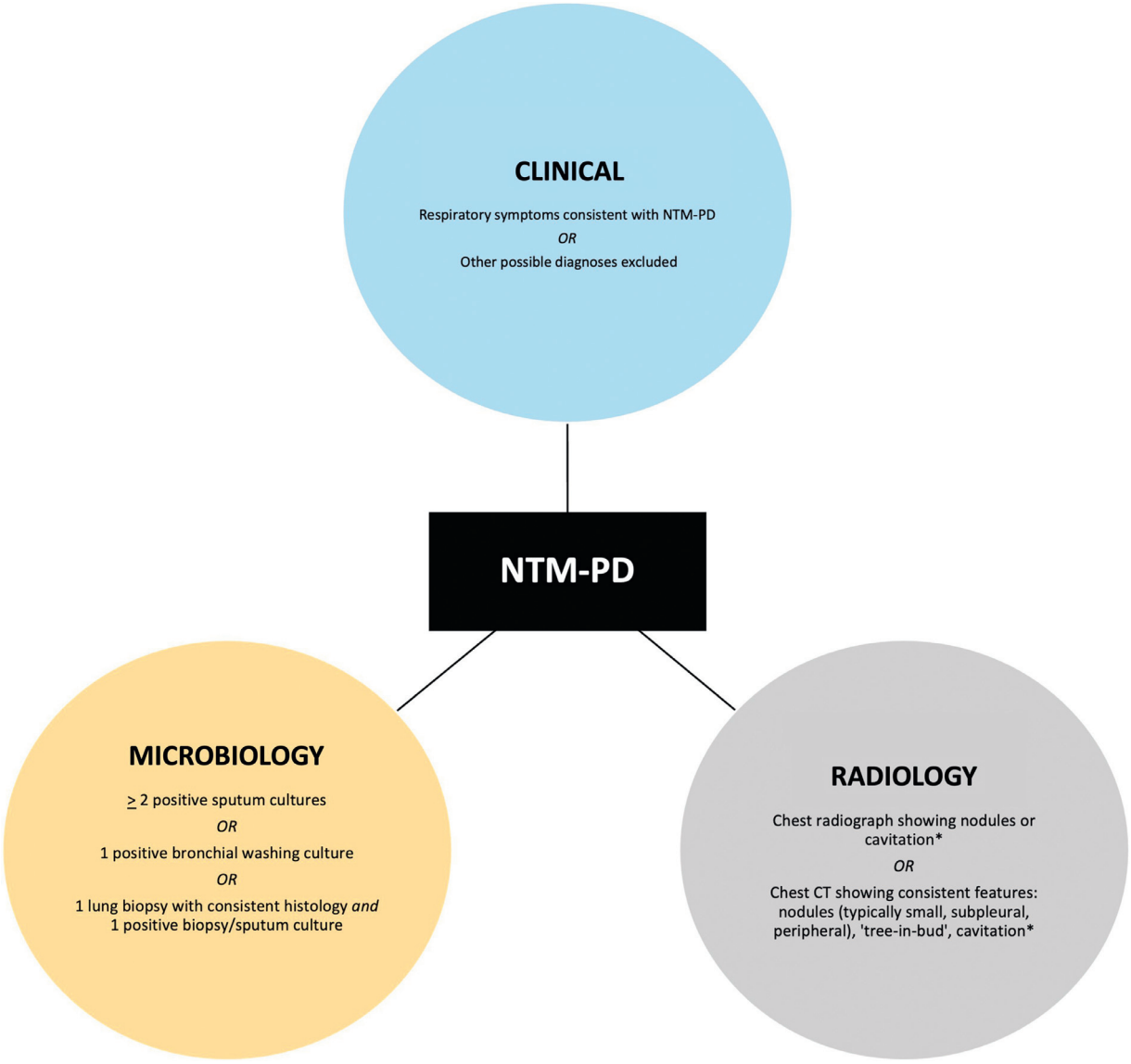

Fig 1. Diagnostic triad for NTM-PD.[1]
*Chest CT is preferrable to a chest pain radiograph; even on CT, there may be no specific radiological features for NTM-PD.

living with NTM-PD. Using comments from patients involved in the development of this article, we consider its epidemiology, predisposing risk factors, how it is diagnosed and important aspects of its clinical management.

Epidemiology and risk factors

NTM belonging to *Mycobacterium avium* complex (MAC), which comprises *M avium*, *M intracellulare* and *M chimaera*, are the most frequently isolated in the UK.[5] *M abscessus* is often seen in east Asia; in the UK, it is typically associated with significant immunocompromise or cystic fibrosis (CF).[5,6] Other common respiratory NTM species are *M kansasii*, *M malmoense* and *M xenopi*. NTM-PD is not a notifiable disease in the UK or in most jurisdictions and therefore understanding its epidemiology relies on local and regional surveillance mechanisms.[4] Between 2007 and 2012, the incidence of NTM culture positive isolates increased in England, Wales and Northern Ireland from 5.6/100,000 to 7.6/100,000; among those with pulmonary infections, incidence increased from 4.0/100,000 to 6.1/100,000.[2] In Scotland, NTM infection incidence rose from 3.4/100,000 to 6.5/100,000 between 2011 and 2019.[7] The 5-year all-cause mortality for MAC lung disease ranges between 10 and 48%.[8]

NTM are often isolated from soil and water, and exposure to water supplies contaminated with NTM has been associated with an increased risk of developing NTM disease. NTM have been isolated in taps, shower heads, swimming pools and hot tubs.[9] Epidemiological studies have shown that high levels of humidity are associated with increased pulmonary NTM infection.[10] While NTM infections are generally not considered to be transmissible between people, some *M abscessus* clones may be communicable between certain at-risk individuals via fomites or aerosols.[11] Studies on potential transmission mechanisms are ongoing.

Host risk factors that predispose to NTM-PD can be divided into underlying structural lung diseases (including certain genetic disorders), impaired immunity and other associated conditions. Some people with NTM-PD have one or more of a characteristic set of features including chest wall or spinal abnormalities, mitral valve prolapse and cystic fibrosis transmembrane conductance regulator protein dysfunction.[12] The most common comorbid risks are chronic obstructive pulmonary disease (COPD) and bronchiectasis. Hence there should be a low threshold to suspect NTM-PD in these patients (Table 1).[13]

Table 1
Host risk factors for NTM-PD.

Host risk factor	Examples
Structural lung disease	• Bronchiectasis • Chronic obstructive pulmonary disease (COPD) • Cystic fibrosis • Idiopathic pulmonary fibrosis • Primary ciliary dyskinesia • α1-antitrypsin deficiency • Williams-Campbell syndrome (airway cartilage deficiency) • Mounier-Kuhn syndrome (airway elastin deficiency) • Silicosis • Coal workers' pneumoconiosis
Impaired immunity	• Inherited: ○ Mendelian susceptibility to mycobacterial disease (mutations in interleukin-12/interferon-γ/STAT1 pathway)[a] ○ MonoMAC syndrome (mutations in GATA2)[a] • Acquired: ○ Immunosuppressive drugs, eg corticosteroids (particularly high dose), anti-tumour necrosis factor-α agents ○ Acquired immunodeficiency syndrome secondary to HIV infection ○ Solid tumours ○ Haematological malignancies ○ Haematopoietic stem cell transplantation ○ Solid organ transplantation
Other associated conditions	• Low body mass index • Gastro-oesophageal reflux disease • Rheumatoid arthritis

[a] Typically a risk factor for disseminated NTM infection.

Diagnosis

The diagnosis of NTM-PD is contingent on a triad of clinical, microbiological and radiological criteria being satisfied (Fig. 1).[1] This is important when differentiating between incidental airway presence of NTM and significant pulmonary disease.

Clinical features

'Many patients may be symptomatic for years before being tested for NTM.' (Patient expert)

The clinical presentation of NTM-PD is similar to that of several other respiratory conditions, including lung cancer and TB, as well as pre-existing lung disease. Symptoms may include a persistent cough, sputum production, haemoptysis, breathlessness, fever, night sweats, unintentional weight loss and significant fatigue.[1] It is important to look for clues such as a person reporting an increased frequency of lower respiratory tract infections despite antibiotics. This is most relevant in those with COPD or bronchiectasis where symptoms may be indistinguishable and the persistence or duration of symptoms becomes key.

Microbiology

Specific microbiological criteria must be met for NTM-PD to be diagnosed. Three separate sputum samples should be collected, ideally on different days and in the early morning if possible. Acquiring samples by bronchoscopy is in most settings more of an undertaking than using sputum to diagnose NTM-PD. It should be considered if sputum is either unavailable or negative (including induced sputum samples, where available) and there is a high level of clinical suspicion.[14] Microbiological confirmation is important because different underlying NTM species are associated with varying clinical courses and require appropriately tailored antibiotic regimens. Slow-growing NTM can take up to 6–8 weeks to culture and include MAC, *M kansasii*, *M malmoense* and *M xenopi*. Rapid-growing NTM usually culture within 7 days and include *M abscessus*, *M chelonae* and *M fortuitum*. Alongside culture-based techniques, speciation can be achieved using line probe assays, matrix-assisted laser desorption ionization–time-of-flight mass spectrometry or gene sequencing.[15–18]

Drug susceptibility testing (DST) is important when choosing antimicrobial therapy, though *in vitro* DST results are frequently inconsistent with *in vivo* effectiveness and discussion with an expert in NTM infection is advised.[19] As a minimum, MAC should be tested against clarithromycin (which will also give information on azithromycin sensitivities) and amikacin; *M abscessus* against clarithromycin, amikacin and cefoxitin; and *M kansasii* against rifampicin.[1]

Radiology

All patients in whom NTM-PD is suspected should have a baseline chest radiograph and preferably high-resolution chest CT imaging. There are two broad radiological patterns observed in NTM-PD: fibrocavitary disease, characterised by multiple, thin-walled cavities, usually in the upper lobes of the lungs (Fig. 2); and nodular bronchiectatic disease, with nodules, bronchiectasis and bronchial wall thickening (Fig. 3).[20] The latter is commonly seen in individuals with no known pre-existing lung disease, but can often be mixed with cavitating nodular change.[21]

Additional considerations

Specialist tests for immune deficiency should be considered in people with a history of recurrent pulmonary or extrapulmonary infections or in those with a known family history of immunodeficiency.[22] All patients with bronchiectasis should have immunoglobulins measured. Furthermore, there is a potential link between NTM-PD and *Aspergillus* pulmonary infections.[23,24] It is therefore prudent to consider checking sputum fungal cultures and fungal serology to exclude concomitant or sequential fungal pulmonary infections.[25]

Management

'People with NTM-PD should be encouraged to ask questions and seek clarification about all aspects of their diagnosis and treatment.' (Patient expert)

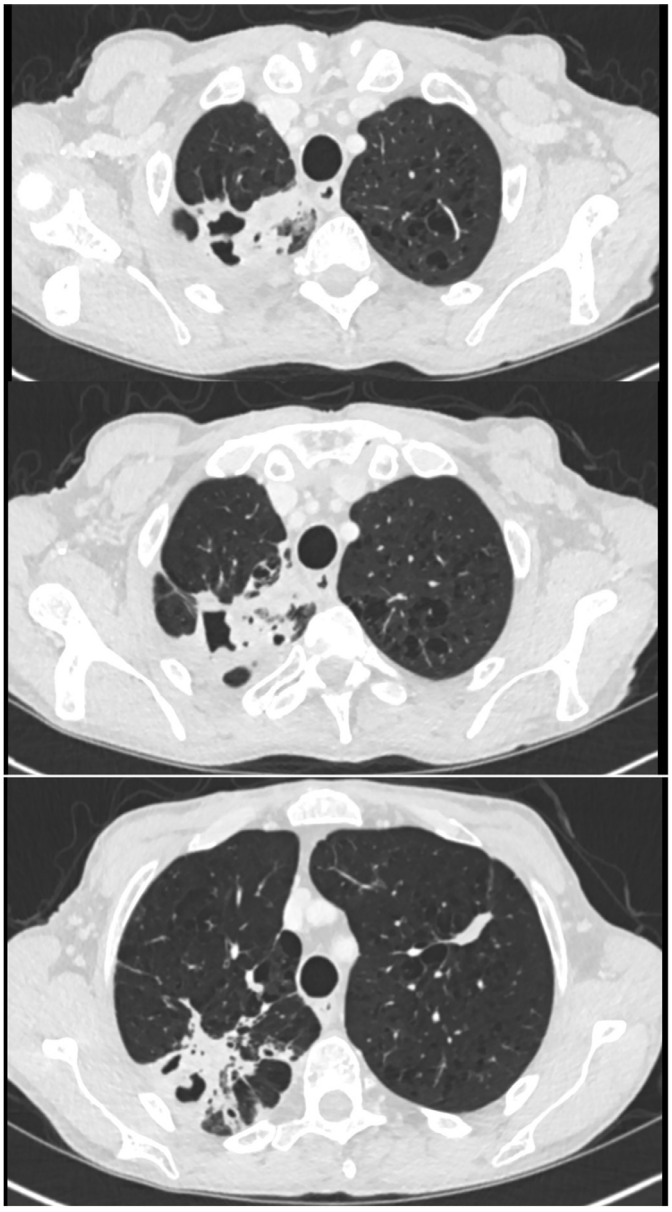

Fig 2. Serial cross-sectional chest CT images from an individual with cavitary NTM-PD secondary to *Mycobacterium avium* complex. Note the co-existent emphysema.

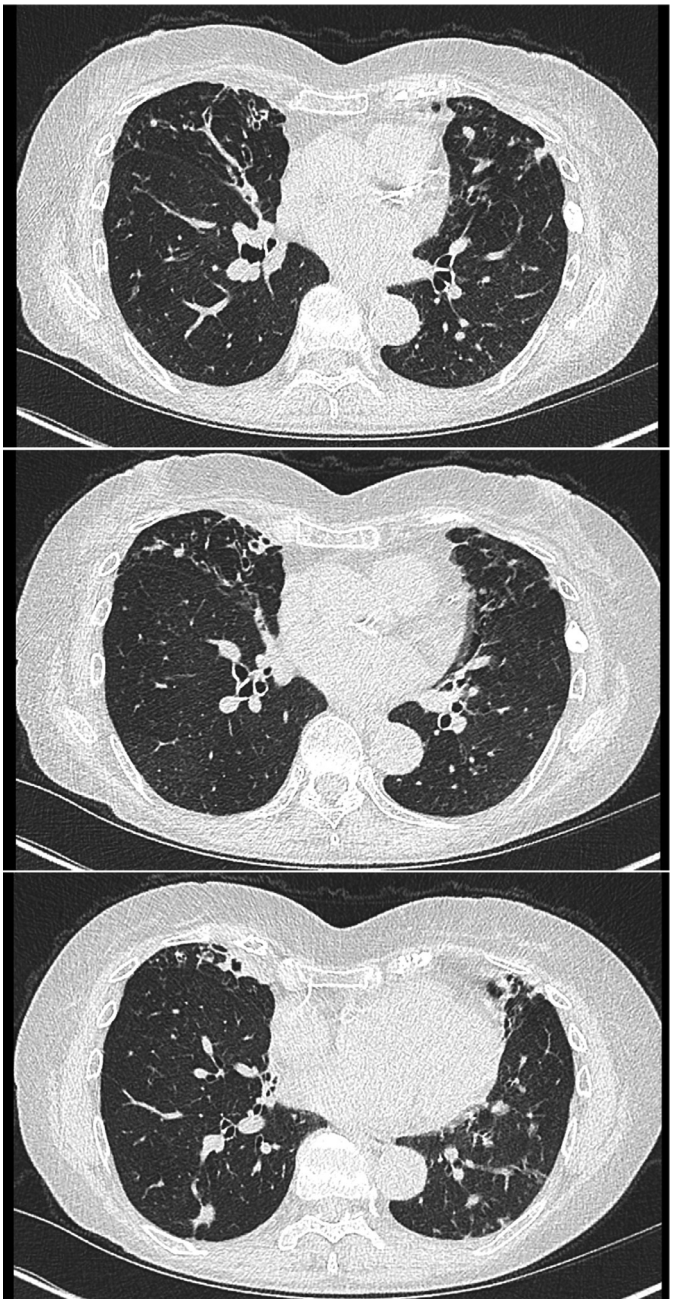

Fig 3. Serial cross-sectional chest CT images from an individual with nodular NTM-PD secondary to *Mycobacterium avium* complex. Note the associated middle lobe bronchiectasis.

The decision to start treatment should be based on national guidelines and involve a multidisciplinary team with experience of delivering high-quality, standardised care for NTM infection (Table 2).[26] The benefits, risks and potential outcomes of commencing treatment should be discussed with patients.

Pharmacological treatment

> *'Patients should be informed of the potential need for oral, nebulised or intravenous medications and understand that the efficacy of different regimens may vary. Treatment regimens should be commenced following clear and detailed discussions between patients and their clinical team.' (Patient expert)*

As current drug therapies are associated with significant tolerance and toxicity issues, the decision to commence treatment should consider the NTM species, severity of disease, risks of progression, comorbidities

Table 2
Possible multidisciplinary team members managing NTM-PD (listed in alphabetical order).

• Clinical immunologists
• Dietitians
• Microbiologists
• Nurses
• Pharmacists
• Physicians with expertise in NTM-PD
• Physiotherapists
• Psychologists
• Radiologists

Table 3
Treatment regimens for NTM-PD (adapted from British Thoracic Society NTM-PD guidelines from 2017).[1]

NTM species	Treatment regimen for associated pulmonary disease	Comments
Mycobacterium avium complex (MAC)	Rifampicin + Ethambutol + **Either** clarithromycin **or** azithromycin	• Non-severe disease: Three times per week regimen • Severe disease:[a] Daily regimen and consider adding in IV aminoglycoside • Macrolide-resistant MAC: Substitute the macrolide with either isoniazid (with pyridoxine) or moxifloxacin; and consider adding in IV amikacin
M kansasii	Rifampicin + Ethambutol + **Either** clarithromycin **or** azithromycin **or** isoniazid (with pyridoxine)	• Rifampicin-resistant *M kansasii:* three-drug regimen guided (but not dictated) by DST
M malmoense	Rifampicin + Ethambutol + **Either** clarithromycin **or** azithromycin	• Severe disease: consider adding in IV aminoglycoside
M xenopi	Rifampicin + Ethambutol + **Either** clarithromycin **or** azithromycin + **Either** moxifloxacin **or** isoniazid	• Severe disease: consider adding in IV aminoglycoside
M abscessus	**Initial phase** Amikacin (IV) + Tigecycline (IV) + Imipenem (IV)[b] + **Either** clarithromycin **or** azithromycin **Continuation phase** Amikacin (NEB) + **Either** clarithromycin **or** azithromycin + One to three of the following: clofazimine, linezolid, minocycline, moxifloxacin, co-trimoxazole	• New drug to consider: omadacycline • Constitutive macrolide resistance: adjusted regimen required

Route of drug administration is oral unless otherwise stated. DST = drug susceptibility testing. IV = intravenous. NEB = nebulised.
[a] Severe disease includes cavitary disease and/or smear positive sputum.
[b] Medication given if tolerated.

and patient choice.[1] The goals of treatment should be agreed at the outset.

Recommendations are available for treating the most common NTM species that cause NTM-PD: MAC, *M kansasii*, *M malmoense*, *M xenopi* and *M abscessus* (Table 3). Treatment is usually continued for at least 12 months after achieving culture conversion.[1,14] Nebulised liposomal amikacin has recently been approved in the UK as an add-on treatment for refractory MAC lung disease, which is where the patient remains culture positive despite treatment.[27] Although treatment response varies, overall about two-thirds of patients with MAC will have a sustained improvement following therapy. However, up to half may then relapse again (often with a different organism to the original infection). Treatment of *M abscessus* lung disease is particularly complex and practice is not standardised. Antibiotic choices are guided by DST, patient tolerance and MDT discussion. The optimised regimen has not yet been determined (Table 3).

The complex drug regimens pose a significant challenge for many patients due to overlapping toxicities (Table 4) and potential drug–drug interactions with their pre-existing medications. Pharmacists are well placed to advise patients how to take their treatment and the importance of good adherence to regimens, as well as identifying and managing any adverse effects. Monitoring for toxicity through blood tests, ECG and audiometry should be performed regularly according to national recommendations and the potential toxicity profiles of the prescribed drugs.[1,14] *TB drug monographs* is a helpful resource for clinicians in this regard.[28]

Clinical response to treatment should be assessed regularly by using sputum culture every four to 12 weeks until culture conversion and by evaluating symptoms, quality of life measures and radiological parameters. People who remain culture positive despite 6 months of NTM treatment are more likely to have poor outcomes and may require extended treatment. Surgical intervention may be warranted in specific clinical contexts, such as massive haemoptysis.

Respiratory physiotherapy

> *'Prompt review by respiratory physiotherapists is paramount.' (Patient expert)*

Respiratory physiotherapy is an integral part of the daily management of NTM-PD. Persistent detection of NTM in sputum is associated with worse outcomes[29] and physiotherapy interventions have been shown to mitigate this in people with bronchiectasis and CF.[30,31] The aims of physiotherapy are to maintain ventilation in all parts of the lungs; postpone progression of pulmonary disease; stimulate establishment and retention of normal physical capacity; and avoid pain and mus-

Table 4
Common side effects and adverse drug reactions during the treatment of NTM-PD.

Drug	Side effects and adverse drug reactions	Approach to symptoms and suggested management
Rifampicin	Orange-red discolouration of urine and other body secretions	• Occurs due to excretion of rifampicin in body fluids and is harmless • Patients should be advised on this effect to avoid undue alarm
Rifampicin Ethambutol Azithromycin Clarithromycin Tigecycline Clofazimine Co-trimoxazole Imipenem Linezolid Minocycline Moxifloxacin	Gastrointestinal (nausea, vomiting and diarrhoea)	• May be caused by many antibiotics used to treat NTM-PD • Symptoms are usually mild and settle with time • Anti-emetics or anti-diarrhoea medication may be required • Tigecycline and imipenem can cause severe nausea and vomiting (in some cases adversely affecting nutritional status); multiple anti-emetics may be required to support continued treatment
Isoniazid Linezolid	Peripheral neuropathy (PN)	• In view of the potential risk of isoniazid-induced PN, ensure patients are prescribed prophylactic pyridoxine 10 mg once daily (especially in those identified to be at high risk of PN, eg patients who are alcoholic, diabetic, malnourished, elderly or immunocompromised) • The dose of pyridoxine can be increased up to 50 mg three times daily in cases of severe PN • Other treatment of severe PN includes discontinuing the implicated antibiotic where possible; gabapentin/pregabalin or tricyclic antidepressants may be used to manage the neuropathy • Pyridoxine is unlikely to have a protective effect for linezolid-induced PN
Rifampicin	Flu-like symptoms	• Fever, shivering, headaches, dizziness or joint pain have been reported with rifampicin; these may be tolerated over time • In rare cases, this may be followed by thrombocytopenia, purpura, dyspnoea, asthma-like attacks, haemolytic anaemia, shock and acute renal failure; treatment may need to be discontinued
Ethambutol Linezolid	Optic neuritis	• Ethambutol- or linezolid-induced optic neuritis is rare, but may present late into treatment • Baseline visual acuity and colour assessment are important to track any changes during treatment. People with renal impairment may be at higher risk • Where optic neuritis is suspected, ethambutol / linezolid should be stopped and the patient referred to an ophthalmologist for urgent assessment
Moxifloxacin	Musculoskeletal	• Fluoroquinolones may cause tendonitis and tendon rupture (especially but not limited to the Achilles tendon) early or several months into treatment; fluoroquinolones should be discontinued at the first sign of tendonitis
Rifampicin Isoniazid Moxifloxacin Linezolid Tigecycline	Hepatotoxicity	• Hepatotoxicity is an adverse drug reaction of a number of antibiotics used to treat NTM-PD • If LFTs are significantly elevated (>5 times the ULN or 3–5 times ULN and symptomatic), the offending drug(s) should be suspended • Treatment may be cautiously reintroduced when LFTs normalise, but in some cases, a non-hepatotoxic drug regimen may be required
Amikacin	Nephrotoxicity	• The risk of nephrotoxicity increases with prolonged use and age; the risk is higher for intravenous compared to nebulised administration • The dose may be reduced in older adults and should be stopped if there is acute kidney injury
Amikacin Azithromycin	Ototoxicity	• Prior to commencing amikacin, consider genetic testing for mitochondrial mutations (particularly the m.1555A>G mutation); this test is increasingly available across the UK • Loss of hearing with amikacin is usually the first symptom and is detected by regular audiometric testing; treatment should be discontinued if there is 20 dB loss from baseline or a 10 dB loss between two tests • Vertigo, loss of balance and auditory disturbances (tinnitus) are also signs of ototoxicity • A three-times-weekly amikacin regimen may reduce ototoxicity but this regimen is not advised for *M abscessus* • Azithromycin may cause tinnitus and hearing loss; azithromycin ototoxicity is dose-dependent and may respond to dose reduction or may necessitate stopping the drug

(*continued on next page*)

Table 4 (*continued*)

Drug	Side effects and adverse drug reactions	Approach to symptoms and suggested management
Azithromycin Clarithromycin Moxifloxacin Clofazimine (possible)	Cardiovascular	• These drugs are known to prolong QTc interval • ECGs should be monitored at baseline and after treatment initiation • Consider serial ECGs in at-risk patients and aim to correct risk factors if possible eg low body weight, electrolyte imbalances, renal/liver impairment, multiple QTc prolonging medications
Rifampicin Macrolides Clofazimine Co-trimoxazole Minocycline Imipenem Tigecycline Moxifloxacin	Rash	• In many cases, drug-induced rashes are mild and self-limiting • Antihistamines may provide symptomatic relief; but in more severe cases, discontinuation of the likely causative antibiotic and treatment with corticosteroids may be required • Clofazimine, minocycline and moxifloxacin may rarely cause a photosensitivity rash; patients should be advised to avoid exposure to UV radiation and strong sunlight during treatment • Clofazimine can commonly cause dry skin and eyes; adequate hydration and a good moisturising regimen can be helpful, while moisturising eye drops/ointments can also relieve dry eyes
Clofazimine	Skin discolouration	• A pink to brownish-black skin discolouration (resembling sun-tanning) within 1–4 weeks occurs in most people; usually disappears 6–12 months after the end of treatment

PN = peripheral neuropathy; ULN = upper limit of normal

culoskeletal complications due to pulmonary or bone disease. The wider role of the physiotherapist in NTM-PD can minimise the consequences of repeated respiratory exacerbations by educating patients in airway clearance techniques and through the use of adjunctive and nebulised therapies.[30] Physiotherapists adapt and optimise treatment regimens for individual patients in line with their age and disease progression. They offer education and support for people living with NTM-PD enabling them to self-manage their respiratory symptoms.

Nutritional aspects

> *'Access to dietitians for advice about nutrition is important.' (Patient expert)*

Low body mass index (BMI) and malnutrition are recognised risk factors for the development and progression of NTM-PD.[32,33] Current research is notably lacking in identifying whether weight restoration can positively impact outcomes in this context. In the broader landscape of respiratory diseases, a low BMI is consistently correlated with reduced lung function and compromised immune responses.[34,35] In cases of frequent or severe respiratory infections, malnutrition tends to follow, leading to higher mortality rates, increased hospitalisation and reduced quality of life. Moreover, treatment modalities that produce gastrointestinal side effects can further exacerbate malnutrition through anorexia, weight loss or restrictive dietary patterns. In light of the paucity of specific research in this area, it is prudent to advocate for universal malnutrition assessment using the internationally recognised Malnutrition Universal Screening Tool (MUST).[36] Robust referral systems to dietitians should be established, mirroring practices in analogous respiratory conditions, until further research can inform more targeted support in this area.

Nursing considerations

> *'People living with NTM-PD should be directed towards support and resources, including NTM Patient Care UK (www.ntmpatientcare.uk).' (Patient expert)*

Most NTM services are in need of specific NTM specialist nurse provisions and rely on *ad hoc* support from TB, infectious disease and respiratory clinical nurse specialists.[37] Given the current absence of a standard of care model for NTM-PD patients, the role of nurse specialists has been articulated using the Royal College of Nursing case management tool for people with TB.[38] This defines the level of case management required and provides a standard care framework for every patient.[39] In light of the chronicity and complexity of NTM-PD, the relationship between the patient and their nurse specialist may be particularly important as nurses are typically the first point of contact and well-placed to provide long-term support, education and treatment supervision. Liaising with psychology services should be considered if appropriate.

Summary

NTM-PD is a complex lung condition. Recognition of the disease (and hence when it is diagnosed following symptom onset) can be considerably delayed. Even then, it may be difficult to treat. It should be considered in people with a relevant clinical history, especially in COPD or bronchiectasis. Improving the accuracy and timeliness of diagnosis while enhancing clinical outcomes in those living with NTM-PD are important clinical priorities. Achieving these will be contingent upon clinicians recognising those at risk, understanding the variable presentation of the disease and arranging timely investigations. Respiratory or infectious disease specialist input should be sought to discuss potential cases. Multidisciplinary management is essential to ensure that care remains holistic and patient-centred, particularly when long-term drug treatment is initiated.[26]

Key points

- Non-tuberculous mycobacterial pulmonary disease (NTM-PD) is becoming more common and may present with non-specific respiratory or systemic symptoms in individuals with or without underlying risk factors.
- Diagnosis is contingent upon clinical, microbiological and radiological criteria being met.
- People in whom NTM-PD is suspected or diagnosed should be reviewed and managed by clinicians with appropriate expertise and experience.
- A multidisciplinary approach to management is required, comprising tailored pharmacological intervention, respiratory physiotherapy, dietetic input and nursing support.
- Individuals diagnosed with NTM-PD should be provided with access to relevant support services and signposted to appropriate information resources about their ongoing care.

Declaration of competing interest

All authors are members of NTM Network UK, which is a network of healthcare professionals, researchers and patients from across the UK who have an interest in infections caused by non-tuberculous mycobacteria. TGDC has received non-financial support from Napp and GSK for attendance at ERS conference; TGDC's employer has received payment for his participation in advisory boards or for providing teaching sessions from AstraZeneca, Chiesi, GSK, Novartis, Boehringer Ingelheim, and Insmed, outside the submitted work. CC received non-financial support from GSK for attendance at ERS; CC's employer has received financial support from AstraZeneca through her grant application; CC received payment for her participation in advisory boards or providing teaching from AstraZeneca, Chiesi, GSK and Insmed, outside the submitted work. RH has received consultancy fees from Insmed, outside the submitted work.

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