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Non tuberculous mycobacteria pulmonary disease: patients and clinicians working together to improve the evidence base for care

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ABSTRACT

Non-tuberculous mycobacterial pulmonary disease is on the rise globally. It is often missed, and causes significant morbidity and even mortality. Here, members of a clinical research network and a patient support group discuss some of the current key issues in NTM management.

In addition to the need for research into epidemiology, immunology and treatment, we recommend greater use of patient and clinician networks to: (i) educate primary and secondary care clinicians to develop a high index of suspicion when investigating and treating at risk populations. (ii) promote a multidisciplinary team. (iii) promote shared patient-clinician decision making throughout care. (iv) incorporate use of patient self-report measures to assess progress and outcomes. (v) increase education of patients on their illness and its management. (vi) recruit patients into research projects and registries to improve the clinical evidence base. (vii) increase co-production of research with key stakeholders such as patients and their families, using expert patients and patient groups. (viii) understand more about the psychological, social and economic consequences of the disease.

Introduction

Little is known about the epidemiology, natural history or best management of non-tuberculous mycobacterial pulmonary disease (NTM-PD). Progress requires collaboration between patients and clinicians; and as members of a clinical research network and a patient support group, we discuss some of the current key issues in NTM management, and make recommendations we believe are relevant in these areas.

Increasing prevalence

Almost 200 species of (NTM) exist. They live particularly in soils and water, and are increasingly recognised as a cause of human disease, typically affecting the lungs. NTM-PD is usually seen in people with airways damage such as cystic fibrosis (CF), bronchiectasis or chronic obstructive pulmonary disease (COPD), or when normal lung epithelial ciliary action to clear sputum is impaired, or when immunity is lowered by age, immunosuppressive drugs, inhaled corticosteroids, or HIV infection. Gastro-oesophageal reflux disease may also predispose to infection.

NTM disease is a rare disease as it affects less than 1 in 2,000 people. However, this obscures the fact that NTM pulmonary disease has been increasing in prevalence in recent decades in many countries including China, Korea, Japan, North America, sub Saharan Africa and Europe (Daniel-Wayman et al., 2019; Nishiuchi et al., 2017; Shah et al., 2016). In 2010 its prevalence in the US overtook that of tuberculosis (Daniel-Wayman et al., 2019).

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Although epidemiological data are incomplete, prevalence varies from 3.3 cases per 100,000 population in Germany (Ringshausen et al., 2016) to 13.9 in the USA (Donohue and Wymer, 2016) and 29 in Japan (Izumi et al., 2018). *Mycobacterium avium* complex (MAC) accounts for almost half of NTM infections worldwide (Lande et al., 2018), though several other NTM species are relatively common causes of disease. People with CF are particularly susceptible to rapidly growing *M. abscessus* (Bryant et al., 2016).

Although the commonest risk factor for NTM-PD is bronchiectasis, why patients acquire NTM remains unknown (Daniel-Wayman et al., 2019). Infection may signal dysregulated host immunity. Prevalence increases as populations age and therapies that impair immune function become commoner. Individual immune response and background lung structure produce different patterns of lung disease including nodular-bronchiectasis, fibro-cavitary disease and hypersensitivity pneumonitis (Ratnatunga et al., 2020).

We need accurate data on prevalence, where NTM infection is increasing and why (Cowman et al., 2019). Although there is little evidence for human-to-human transmission, recently there have been reports of global transmission of *M. abscessus* in CF patients (Bryant et al., 2016) as well as spread of *M. chimaera* infection via contaminated water heater-cooler systems in cardiac bypass machines (Kohler et al., 2015). Given the success in making NTM lung disease a public health reportable infection in Wisconsin and Queensland, we believe that enhanced surveillance programmes could help public health experts study disease trends and spread within populations (Thomson et al., 2017).

Recognition by clinicians

The early symptoms of NTM disease are often non-specific but later, patients complain of a worsening productive cough, breathlessness on exertion, fatigue and impaired quality of life (Mehta and Marras, 2011). The infection may be missed when symptoms are attributed to COPD, bronchiectasis, recurrent chest infections of unknown cause, or tuberculosis. In many areas of the world where tuberculosis is prevalent, the diagnosis is mainly based on symptoms, chest X-ray and the detection of acid-fast bacilli in a sputum smear. This procedure may not distinguish NTM from tuberculosis and thus inappropriate treatment may be given (Nishiuchi et al., 2017).

Applying machine-learning methods to primary and secondary care clinical notes can improve detection of NTM-PD over random testing by almost a thousand fold (Doyle et al., 2020). Clinician education should focus on the possibility of NTM in patients presenting with frequent or persistent pulmonary infections that respond poorly to standard antibiotics, or where gastrointestinal reflux seems to promote respiratory exacerbations (Henkle et al., 2016).

Making a diagnosis and planning medical treatment

Specific mycobacterial cultures need to be requested to make the diagnosis but hospital physicians and general practitioners are not necessarily familiar with NTM disease. This can cause considerable delays in diagnosis: – the median time from symptom onset to diagnosis has been estimated to be at least two years (Ahmed et al., 2020). Current guidelines recommend tests for NTM infection in patients with bronchiectasis (Haworth et al., 2017), but this is performed in less than a fifth of patients (Finch et al., 2019). Thus, many are failed by services that miss detecting NTM earlier in its natural history and so allow progression to chronic symptoms and lung damage often associated with prolonged NTM-PD. Effective clinical education and focussed clinical guidelines relevant to different medical settings will help to change this.

Nevertheless, unless there are multiple isolates, it can be hard to decide whether culture of NTM species in sputum or bronchoscopy washings is a chance finding or a sign of active infection. Bronchiectasis may precede or follow the onset of NTM infection (Larsson et al., 2017). There is no simple distinction between coloniser and pathogen; rather a gradient of disease may depend on exposure and host related factors (Stout et al., 2016). There have even been suggestions that the presence of NTM is merely a signal for a distinctive pulmonary microbiome that is causing the inflammatory lung disease (Sulaiman et al., 2018). In low income settings, NTM-PD may be mistaken for drug-resistant tuberculosis if adequate species identification is not available (Sarro et al., 2018; Stout et al., 2016).

The role of NTM drug sensitivity testing (DST) is some way behind that for tuberculosis. This is due to the small number of drugs used to treat NTM that demonstrate a clear-cut relationship between *in vitro* testing and *in vivo* outcome. In this regard, macrolides are the single most important antibiotic group; and DST is recommended for *M. avium* complex, *M. kansasii* and *M. abscessus* (Daley et al., 2020) for this drug class. Amikacin (again for *M. avium* complex and *M. abscessus*) and Rifampicin (for *M. kansasii*) are also drugs where DST is helpful to guide drug selection.

Some subspecies of *M. abscessus* have an inducible erythromycin resistance methylase (erm) gene that results in resistance to macrolides. This can be measured *in vitro* by prolonged (14 day) culture in the presence of the drug, or using molecular techniques. Given the clinical significance of resistance with this NTM family, it

Table 1
Strength of evidence of recommendations in ATS/ERS/ESCMID/IDSA Clinical Practice Guideline (Daley et al., 2020): Treatment of NTM-PD.

Strength of GRADE evidence	Number of recommendations within each GRADE category	Comment (31 Recommendations were developed for 22 PICO Questions)
Strong recommendation, moderate certainty in estimates of effect	1	Use ALIS in refractory MAC
Strong recommendation, very low certainty in estimates of effect	3	(1) Use macrolide in macrolide-sensitive MAC; (2) Don't routinely use IV aminoglycosides in *M. kansasii*; (3) Use macrolide-containing multidrug regimen in *M. abscessus* with no inducible or mutational resistance
Conditional recommendation, moderate certainty in estimates of effect	1	Use IV aminoglycosides in cavitary or severe or macrolide-resistant MAC
Conditional recommendation, very low certainty in estimates of effect	25	All other recommendations
Insufficient evidence	1	Susceptibility testing in *M. xenopi*

Note: ALIS – Amikacin Liposome Inhalation Suspension; GRADE - Grading of Recommendations Assessment, Development, and Evaluation; IV – intravenous; MAC - *Mycobacterium avium* complex; PICO – Problem, Intervention, Comparison, Outcome.

is important to ensure that services have access to these tests and associated specialist microbiological advice when planning drug treatment (Haworth et al., 2017).

Medical treatments for NTM-PD and whether or not they are effective

Although a number of clinical guidelines are in use (Haworth et al., 2017; Daley et al., 2020), almost all recommendations are based on the lowest levels of evidence, often consensus clinical opinion or clinical case description (Table 1). Treatment is more akin to that for drug-resistant rather than drug-sensitive tuberculosis, involves multiple drugs including injectable agents for a minimum of 12 months and often longer (Haworth et al., 2017) and has numerous adverse effects (Cowman et al., 2019). Thus, many experienced physicians prefer a "wait and see" approach in the absence of clinically significant progression of disease or radiological features of severe disease such as cavities on chest radiography.

The commonest treatments for NTM-PD are a macrolide (azithromycin or clarithromycin) in combination with rifampicin and ethambutol (Haworth et al., 2017). However, antibiotic treatments for NTM-PD have not generally been subjected to rigorous clinical trials. As an example of the low level of current knowledge, research is underway to assess whether rifampicin adds anything to azithromycin plus ethambutol (e.g. the MAC2v3 trial https://www.clinicaltrials.gov/ct2/show/NCT03672630?term=rifampicin&cond=Mycobacterium+Avium&draw=2&rank=1). Specialist monitoring is needed as adverse effects are frequent, patients are generally older and may have multiple other conditions, and patient concordance with treatment uncertain.

Cure on treatment depends on the NTM species, the patient's age and other comorbidities (Ratnatunga et al., 2020); but rarely achieves the success seen in tuberculosis. Although many patients have a positive clinical and radiological outcome, recurrence is common (Stout et al., 2016).

Disease-specific mortality from NTM-PD is difficult to establish due to lack of research, and also that patients are often older with important comorbidities. However, one well-conducted 15-year study of 1445 newly diagnosed patients in South Korea indicates that old age, male sex, low body mass index, chronic pulmonary aspergillosis, pulmonary or extrapulmonary malignancy, chronic heart or liver disease and raised erythrocyte sedimentation rate were poor prognostic factors. On chest radiographic imaging, the non-cavitary, nodular bronchiectatic form seemed to have the best prognosis (Jhun et al., 2020).

Given this treatment complexity and uncertain clinical outcome, NTM-PD is an area in which high clinician-patient concordance is vital. Thus, patients, clinicians and researchers can fruitfully collaborate in seeking to advance the most effective disease management.

Other treatments and case management

Patients may be offered anti-NTM medication without promotion of other approaches. Chest physiotherapy is often crucial, in particular airways clearance, which removes accumulating sputum and helps prevent NTM re-establishing itself or replicating extensively. However, only about 50% of patients use airways clearance, many desist within a year of starting (EMBARC and ELF, 2020) and high quality evidence that it contributes to clinical outcomes is lacking (Basavaraj et al., 2020). Maintenance of a healthy body weight is also important, given that a lower abdominal fat ratio is a strong predictor of progression of infection (Kim et al., 2017).

To coordinate this complex clinical management, services must establish an infrastructure managed by a specialist physician with considerable experience of NTM and its treatment, aided by a specialist nurse to coordinate injectable and nebulised treatment, together with input from a pharmacist, physiotherapist, psychologist and dietitian (Haworth et al., 2017). Similar to drug resistant tuberculosis in the UK, this could be with the support of specialist regional centres and a national clinical advisory group (https://mdrtb.brit-thoracic.org.uk/WebPages/Login/frmLogin.aspx).

Research priorities

Priorities for patients are prevention, timeliness to diagnosis, vaccine development, newer drugs and drug combinations with fewer side effects, greater expert-patient involvement in research, the place of chest physiotherapy in management, and tools to measure quality of life, disease-specific activity and assessment of severity (EMBARC and ELF, 2020; Henkle et al., 2016; Riggare, 2020). Priorities for specialists are epidemiological and molecular drivers of transmission and course of infection, use of drugs and vaccines to boost immune function, and development of NTM specific vaccines, drugs, and diagnostics specifically tailored to the hosts and pathogens (Abe et al., 2020; Daniel-Wayman et al., 2019). Bioengineered bacteriophages are of increasing interest, especially in drug resistant NTM (Dedrick et al., 2019). Given its current prevalence, collaborative clinical trial expertise across countries is required.

We call for greater use of clinical databases to provide vital information on natural history, response to treatment and impact on quality of life. Also essential is clinical and laboratory-based research for new diagnostics, prognostics, and treatments (Ratnatunga et al., 2020). What constitutes a successful treatment outcome and when to stop may be unclear, beyond an arbitrary recommendation of culture negativity over 12 months (Haworth et al., 2017). Patient-reported outcome tools tailored for NTM-PD may assist patients and clinicians to agree an endpoint for treatment (Satta et al., 2014). Crucially, we need expert patient groups to advise on research priorities.

Patient networks, support groups and expert education

Many patients are challenged by the concordance needed for effective treatment, the uncertainties of outcome and how to ensure that they receive high-quality clinical care. Patients want to know how to explain their infection to close family and others in the face of public fears about tuberculosis. The standard answers at present are that most persons with normal lungs do not suffer the infection and that person-to-person transmission of NTM is rare. However are we always right to assume that clusters of NTM infections in families are simply attributable to shared genetic factors? (Colombo et al., 2010; Stout et al., 2016).

Patients welcome access to a network of experts to whom they can turn to for advice or even treatment (Henkle et al., 2016). Nevertheless, their clinician's advice is often not their sole source of information on how they might be treated (Hashem and Merritt, 2018) and they also seek the support of peers. In recent years a key source of help and support for patients with a range of disorders has come from network groups, particularly those where patients with the same disease can interact and exchange information and advice (Nimmon and Regehr 2018). Clinicians, too, value the role of social media, particularly discussion forums and collaborative projects, in facilitating their patients' self-management of chronic disease (De Angelis et al., 2018).

Patient online health networks, for example the US-based MAC Lung Disease Group on Facebook, are growing exponentially but most are isolated from clinical expertise and thus can be uncertain

authorities on sources of help and guidance. Specialist networks could help to fill this uncertainty as well as capitalise on the views coming from patient networks in coordinating joint education and improving clinician-patient communication (Nimmon and Regehr, 2018). One recent example of such joined up thinking is the current "Rare Barometer Voices" survey that is ongoing in Europe and into which the patients can respond and take part in surveys (https://www.eurordis.org/voices).

Patient networks can also help in efforts to educate general practitioners and hospital physicians, as well as paramedics. A pioneer example in the field is NTM Info and Research (NTMir https://ntminfo.org/), which started in 2004 in the US as a patient website. After *Time Magazine* ran an article on NTM and NTMir, it evolved into a not-for-profit patient advocacy group, which subsequently funded pre-clinical research and epidemiological studies, published a patient pamphlet, expanded the network of patient support groups, and held regular patient/physician education conferences. A number of us have recently established a UK website for patients with NTM (https://www.ntmpatientcare.uk) that is a source of information and guidance. It has links to a clinician-based NTM network (https://www.ntmnetworkuk.com/), which itself is associated with the European NTM registry EMBARC NTM (https://www.bronchiectasis.eu/Contents/Item/Display/939). We aim to work together to enhance education and treatment services, and so improve the lot of people with this increasingly common disease.

Recommendations

NTM-PD is on the rise globally. It is often missed, and causes significant morbidity and even mortality. In addition to the need for research into epidemiology, immunology and treatment,

We recommend greater use of patient and clinician networks to:

1) educate primary and secondary care clinicians to develop a high index of suspicion when investigating and treating at risk populations, such as those with recurrent chest infections and bronchiectasis.
2) promote a multidisciplinary team approach involving medicine, nursing, microbiology, pharmacy, immunology, chest physiotherapy, psychology and dietetics.
3) promote shared patient-clinician decision making at each stage of the process from diagnosis, to treatment, to long term follow up.
4) incorporate use of patient self-report measures to assess progress and outcomes.
5) increase education of patients on their illness and its management.
6) recruit patients into research projects and registries to improve the evidence base for prevention, treatment and clinical outcomes of NTM lung disease.
7) increase co-production of research with key stakeholders such as patients and their families, using expert patients and patient groups.
8) understand more about the psychological, social and economic consequences of the disease.

Conflict of interest

Marc Lipman — Trustee, NTM Patient Care UK; Chair, NTM Network UK.

Heinke Kunst — Management Committee, NTM Network UK.

Michael R Loebinger — Steering Committee, EMBARC; Steering Committee, NTM Network UK.

Heather J Milburn — Trustee, NTM Patient Care UK; Member, NTM Network UK.

Michael King — Trustee, NTM Patient Care UK.

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