Diagnosis and treatment of lung infection with nontuberculous mycobacteria

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Purpose of review

Pulmonary infections caused by nontuberculous mycobacteria (NTM) are diagnosed with increasing frequency, in part due to growing at-risk populations but also as a result of improved awareness and diagnostic facilities. This review summarizes recent literature regarding epidemiological, clinical, diagnostic and therapeutic aspects of NTM lung infections.

Recent findings

The number of species known to cause NTM infections has increased due to the extended use of molecular techniques. The number of recognized risk factors, including newly discovered inherited immunological disorders and novel types of immunomodulating drugs such as antagonists of tumor necrosis factor-α is also growing. Revised diagnostic criteria for NTM lung infection are available but the decision whether to treat a patient remains a matter of careful individual evaluation taking into account the NTM species, extent of disease, general condition and underlying disorders. No major breakthrough has been made with regard to treatment. Antibiotic treatment of NTM infection is complicated by the necessary long duration and the adverse toxicity profile of many of the potentially effective drugs while there is an uncertain correlation between in-vitro susceptibility and in-vivo effectiveness except for two drug–NTM species combinations. The role for novel antibiotics in the treatment of NTM infection is still uncertain.

Summary

Much remains unknown regarding treatment of NTM lung infections. In order to provide optimal care, the recommendations provided in the 2007 American Thoracic Society/Infectious Diseases Society of America statement should be taken as a starting point and there should be a low threshold to seek expert consultation.

Keywords

lung infection, nontuberculous mycobacteria, review

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Introduction

Nontuberculous mycobacteria (NTM) associated with human disease comprise a genetically highly divergent group of over 120 different species omnipresent in our environment. They are typically opportunistic pathogens that cause disease in patients with preexisting pulmonary disease or immune suppression. This brief review aims to highlight some of the trends and insights that have been published in this field in the past years, without the intention of completeness due to space limitations. More comprehensive information has been published recently [1•,2•,3••,4].

Epidemiology

NTM are ubiquitous in the natural and man-made environment worldwide. Many species are recognized opportunistic pathogens but most have not yet been associated with human disease. There is a spectrum of virulence from primary pathogens such as *Mycobacterium kansasii* that can cause disease in presumably healthy individuals, via *M. avium* associated with preexisting lung disease or defects of cellular immunity, to species such as *M. gordonae* that are rarely associated with disease.

Classically, NTM are divided into slow growing and rapid growing species and this remains an important classification system with relevance for treatment. In the USA, *M. avium-intracellulare* complex (MAC) is the most frequent pulmonary isolate, followed by *M. kansasii*, but the species distribution may be different in other geographical areas [3••]. Interestingly, although the designation '*M. avium*' suggests that these are derived from birds, molecular typing has pointed out that *M. avium* strains causing lymphadenitis in The Netherlands represent the

M. avium hominissuis subgrouping that is mainly found in humans and slaughter pigs but not in birds [5,6]. The number of different *Mycobacterium* species that have been identified has more than doubled over the past 10 years [3••,7•], mainly due to the higher discriminative power of molecular techniques such as 16S rRNA gene sequencing. The clinical relevance of rarely or newly identified species should be assessed critically [8]. *M. microti*, which is in fact part of the *M. tuberculosis* complex and not an NTM, is generally considered nonpathogenic for humans but has been recognized as a rare cause of infection presenting as pulmonary tuberculosis [9]. Two NTM with characteristic clinical presentations but that are typically not associated with pulmonary disease even in immunocompromised hosts are *M. marinum* [10,11], the causative agent of fish tank granuloma, and *M. ulcerans* causing Buruli ulcer disease for which new insights suggest that insects may serve as vector [12,13].

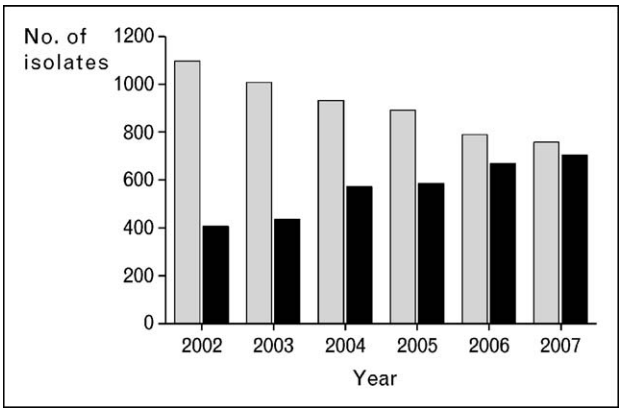
Although NTM lung disease is not reportable and the precise incidence is thus not exactly known, an increase in the number of NTM pulmonary isolates has been observed in many settings. This is most likely due to a combination of increased awareness, improved diagnostic standards and imaging techniques and an increase of at-risk populations [1•,3••]. In industrialized countries, where the incidence of tuberculosis has decreased or stabilized, rates of NTM lung infections now exceed those of tuberculosis (Fig. 1). In contrast, recent studies in African countries where the prevalence of HIV infection is high indicate that NTM may play a much larger role in tuberculosis-like disease than was previously assumed [14]. NTM infection may, therefore, confuse the diagnosis of tuberculosis as the tools for culture and identification of mycobacteria are often not available in that setting.

That there could be an increase in exposure to NTM was suggested by a comparison of skin test surveys performed in the USA in 1971–1972 and 1999–2000, respectively, showing that the prevalence of sensitization to *M. intracellulare* increased from one in nine individuals (11.2%) to one in six (16.6%) [15]. Possibly, NTM contamination of tap water in association with behavioral changes such as the increased use of showers may contribute to increased NTM exposure.

Risk factors for nontuberculous mycobacteria lung infection

Patients with HIV or those otherwise severely immunosuppressed due to genetic disorders in the cellular immune system or treatment with immunosuppressive drugs more frequently present with disseminated NTM disease, with or without pulmonary involvement, whereas isolated NTM lung infection is observed mostly in older patients with chronic pulmonary disease. This indicates that systemic immunity is essential in controlling NTM dissemination, while the lung may provide a more permissive site to allow establishment of NTM infection. An improved standard of care has prolonged survival of patients with chronic lung disorders such as chronic obstructive pulmonary disease (COPD) or cystic fibrosis. In addition, the total number of immunosuppressed patients is increasing steadily and these can present with NTM lung infection alone or as part of disseminated disease.

Figure 1 Trend in the yearly number of patients with positive culture of *Mycobacterium tuberculosis* or nontuberculous mycobacteria in The Netherlands



MTB, *Mycobacterium tuberculosis;* NTM, nontuberculous mycobacteria. □, MTB complex; ■, NTM. Data from the National Institute of Public Health and the Environment, Bilthoven, The Netherlands.

Host defense of the lung against NTM involves both anatomical and functional integrity of the airways system and specific cellular immune responses. Lung diseases associated with NTM infection include, for example, cystic fibrosis, immotile cilia syndrome, bronchiectasis, COPD, cavitary disease, for instance due to previous infection and pneumoconiosis. Certain body habitus such as pectus excavatum or scoliosis have been associated with NTM lung infection, although the causative role of the abnormal anatomy is uncertain.

Disorders of the cellular immune system that are associated predominantly with disseminated NTM infection include HIV infection, treatment with immunosuppressive drugs for inflammatory disorders, transplantation or graft-versus-host disease. Antagonists of tumor necrosis factor-α (TNF-α) constitute a relatively novel class of drugs that has been associated with an increased risk of tuberculosis as well as of other opportunistic infections with intracellular pathogens [16,17,18••]. Sporadic cases of NTM infections have been reported in this population [7•,19,20] but the incidence of NTM infections during

treatment with infliximab or etanercept was many-fold lower than that of tuberculosis [21]. However, in a recent survey in the USA, the number of NTM infections exceeded that of tuberculosis [22•], which may reflect improved screening for latent tuberculosis infection in that setting [18••,23–27]. Of note, reported NTM infections in patients using TNF antagonists were characterized by rapid progression, in contrast to the more insidious course in other populations, and by an immune reconstitution inflammatory syndrome following withdrawal of the TNF antagonist analogous to that observed in HIV patients on highly active anti-retroviral treatment [28,29] or in patients who develop tuberculosis while using a TNF antagonist [30–32].

Patients with genetic deficiencies in the interleukin-12/interleukin-23/interferon (IFN)-γ system are unusually susceptible to NTM, which has highlighted the essential role of this signaling pathway in the innate and adaptive cell-mediated host defense against intracellular pathogens (See [33] for an excellent review of currently recognized genetically determined defects in the cell-mediated immunity associated with infections caused by NTM and other intracellular microorganisms. It provides a useful flowchart for guiding immunological and genetic examination for the most common type 1 axis defects). Some acquired deficiencies such as those with autoantibodies to IFN-γ similarly confer high susceptibility to NTM disease [33]. Apart from the innate or acquired immune deficiencies and abnormal lung anatomy or function as mentioned above, it is likely that additional host genetic factors play a role in susceptibility to NTM, especially in the absence of recognized risk factors [33]. These may affect bioactivity of the epithelial mucosa (e.g. α-1 antitrypsin anomalies; cystic fibrosis transmembrane regulator mutations) or components of the innate immune response such as Toll-like receptors or human natural resistance-associated macrophage protein (NRAMP1/SLC11A1) [34–37].

Clinical presentation

There are three prototypical forms of NTM lung infection [4,38•]: a tuberculosis-like pattern presenting with infiltrates with or without cavitation in the upper lobes, which is observed mainly among older men with COPD who are smokers; presentation with nodules or nodular bronchiectasis as can be seen in slender older female nonsmokers and which has become known as the 'Lady Windermere syndrome' [39,40]; and a hypersensitivity pneumonitis associated with exposure to water-containing systems such as hot tubs or baths. Many patients, however, will have more varied or mixed presentations that do not fit into these prototypic categories. A recent review compared the clinical and epidemiological features of NTM lung infection in immunocompetent hosts for eight NTM species, illustrating the considerable overlap [38•]. Clinical symptoms of NTM lung infection are nonspecific and reflect the type and extent of disease, the underlying condition and comorbidities. Chronic cough is common, whereas fever and sweats occur less frequently; dyspnea is mainly a feature of hypersensitivity pneumonitis, whereas hemoptysis and systemic symptoms suggest advanced disease. The presence of disseminated NTM disease is strongly suggestive of an impaired cellular immune status and in the absence of a recognized risk factor justifies an evaluation of genetic deficiencies as some of those, such as a dominant partial IFN-γ receptor 1 deficiency, can first manifest later in life [41].

Diagnosis

NTM are ubiquitous in the environment and may contaminate clinical samples from nonsterile sites. In order to differentiate between infection and contamination or colonization, a diagnosis of NTM pulmonary disease should be based on a combination of clinical, radiological, histological and bacteriological criteria [1•,3••]. In brief, the diagnosis requires the presence of symptoms, radiographic abnormalities and either two or more sputum isolates or at least one positive culture from bronchial washing or lavage, or a transbronchial or other biopsy with acid-fast bacilli and/or granulomata in association with a positive culture result from the biopsy, washing or sputum as well as the exclusion of other diagnoses. Of note, semi-quantitative reporting of smear positivity has been omitted from the revised diagnostic criteria [3••] as compared with the 1997 American Thoracic Society (ATS) criteria [42]. The value of diagnostic criteria was illustrated by a recent large study among 505 patients with positive NTM cultures of whom only 119 (24%) met the criteria for NTM disease [43•]. Negative histology or staining can be due to sample error or impaired immune responsiveness and does not exclude the presence of invasive disease.

Radiology

When plain radiography does not provide compelling information, high-resolution computerized tomography (CT) scanning allows better differentiation between colonization and invasive infection. In general, there are no characteristic radiographic patterns for individual NTM species, but patients with MAC infection more often had severe bronchiectasis and more nodules on CT compared with other NTM species [44,45]. Patients with HIV infection and *M. kansasii* lung disease presented most commonly with consolidation and nodules predominantly located in the mid and lower lung zones in contrast to the upper-lobe cavitary presentation as seen in patients without HIV infection [46]. Comparing MAC and *M. abscessus*, lobar volume loss, nodules, airspace consolidation and thin-walled cavities were more

frequently seen with MAC [47]. In a study aimed to differentiate between tuberculosis, multidrug-resistant tuberculosis (MDR TB) and NTM, the presence of multiple cavities, young age and previous tuberculosis treatment implied MDR TB, whereas extensive bronchiectasis and old age were suggestive of NTM disease [48]. Pleural effusions are uncommon with NTM.

Immunological techniques

Skin testing based on tuberculins of *M. tuberculosis* and specific NTM species has limited value due to broad cross-reactivity [49] and a lack of validated criteria for interpretation of test results, although skin testing was highly discriminative in children with NTM lymphadenitis [50]. Proof of concept that a species-specific skin test may have diagnostic potential was recently shown for the *M. tuberculosis*-specific antigen ESAT-6 [51•]. Novel blood tests have been developed that measure IFN-γ production in response to antigens that are highly specific for *M. tuberculosis* [52,53,54•,55•]. The potential of IFN-γ release assays (IGRAs) to differentiate between tuberculosis and NTM infection is debatable, however. First, the limited and variable sensitivity of IGRs for active tuberculosis implies that a negative result does not rule out tuberculosis [56,57]. In addition, IGRAs cannot differentiate between active and latent tuberculosis infection and a positive IGRA result may thus reflect latent tuberculosis in a patient with actual NTM lung disease. Finally, the antigens included in IGRAs are also present in *M. kansasii*, *M. marinum* and *M. szulgai*, which may be a cause of false-positive responses [58,59,60]. Among 100 patients with NTM infections, 13 had a positive IGRA result, six of whom were infected with *M. kansasii* or *M. marinum* [61].

Microbiological techniques

The sensitivity of acid-fast staining depends on the concentration of mycobacteria per volume. Fluorochrome staining is the preferred method, being most sensitive. Appropriate clinical specimens are crucial for the diagnosis. In children with suspected mycobacterial lung infection or adults who either do not produce sputum or cannot be instructed, gastric lavage fluid is a relevant sample that should be collected immediately in appropriate buffer in order to neutralize gastric acid. Use of both solid and liquid media is recommended for culture [3••], the former allowing precise identification and the latter faster results. The field of molecular-based diagnostic techniques such as gene probing and PCR is evolving [62].

Drug-susceptibility testing

The role of susceptibility testing remains a point of uncertainty and debate because the correlation between in-vitro susceptibility and in-vivo effectiveness has not been demonstrated except for clarithromycin-based treatment of MAC and for rifampin-based treatment of *M. kansasii*. Routine susceptibility testing is, therefore, recommended only for these specific combinations, whereas for the rapid growing mycobacteria a wide array of different antibiotics should be tested, even though there is no evidence to support a correlation between in-vitro susceptibility and in-vivo effectiveness [1•,3••,63]. In patients with lack of response to first-line drug treatment, persistent infection or with a relapse, drug-susceptibility testing may be valuable as well.

The Clinical and Laboratory Standards Institute (CLSI) recommends liquid medium methods for drug-susceptibility testing of slow and rapid growing NTM [64]. In the Netherlands, a Middlebrook 7H10 agar dilution method has been used for over a decade with favorable results for *M. tuberculosis* complex isolates [65]. These techniques have highlighted the therapeutic potential of the macrolides, linezolid and tigecycline for treatment of NTM disease. In a recent study of 40 isolates of rapid growing NTM, amikacin was the most effective antimicrobial agent; clarithromycin and imipenem showed good activity against *M. fortuitum* and *M. abscessus* but not against *M. chelonae*, whereas quinolones were only effective against *M. fortuitum* [66], illustrating that species identification is relevant for treatment. Results from a large study on drug-susceptibility testing of a wide variety of clinical NTM isolates may further elucidate the therapeutic value of antituberculosis and second-line drugs (J. van Ingen *et al.*, submitted).

Treatment

Treatment of NTM lung infection can include medical and/or surgical therapy or observation. Determining treatment should be guided by the pattern of disease, the causative species, extent of disease and the patient's immune status, comorbidity and general condition.

Medical treatment

Since the newer macrolides were introduced, there have been no significant additional treatment advances for drug treatment of NTM lung disease [1•,67]. Guidelines for initial medical treatment and dosing are available [1•,3••,38•,67], but failure rates remain high and relapses can occur after apparently successful therapy following guidelines [68]. Addition of 3 months of streptomycin to a standard regimen for MAC infection led to a higher rate of sputum conversion at the end of treatment but no difference in relapse rate [69]. Apart from poor susceptibility of rapid growing mycobacteria, the effectiveness of multidrug treatment is limited by the presence of bronchiectasis, cavitation or collapsed areas that limit the penetration of antibiotics. Moreover, treatment regimens are difficult to adhere to because of their long duration, adverse effects and interactions with comedication. If

applicable and possible, the immune status should be improved by treatment of HIV infection or lowering immune suppression. In contrast to the limited success of treatment of NTM lung infection, the hypersensitivity-like pneumonitis can be managed effectively with corticosteroids and avoidance of the exposure, whereas the role of antibiotics is uncertain.

Monitoring during treatment includes monthly sputum cultures, as treatment duration is until at least 12 months following the conversion to negative culture. Molecular techniques provide no information on whether viable bacteria are present and thus have limited value for follow-up.

Choice of antibiotic regimens

The susceptibility to first-line drugs used for tuberculosis is generally limited, except for *M. kansasii* and related species. Appropriate regimens by species are available from the literature [3••,38•] and are only summarily mentioned here. *M. kansasii* and *M. szulgai* should be treated with a regimen of rifampin and ethambutol with an uncertain role of isoniazid, with the dosage of ethambutol at the higher end of the dose range during the initial 2 months. A shorter duration is not generally advocated. Treatment of MAC is based on a combination of rifampin with ethambutol and clarithromycin, with or without streptomycin during the first months. Intermittent dosing three times weekly may improve tolerability and may be preferred for limited disease but response rates were lower in patients with cavitary disease, those previously treated or with COPD [70]. There is no evidence supporting a preference for clarithromycin or azithromycin. The development of macrolide resistance is an adverse prognostic occurrence that was found to be more frequent in regimens without ethambutol [71], suggesting that efforts should be directed toward optimizing the first treatment attempt.

Rapid growing mycobacteria such as *M. fortuitum*, *M. chelonei* and *M. abcessus* are generally unresponsive to standard treatment and the choice of drugs could be guided by susceptibility testing, even though evidence is lacking. Infection with *M. abscessus* is the most difficult to treat medically and there are no regimens with proven efficacy. If possible, treatment can include surgical resection of localized disease followed by antibiotic treatment or intermittent brief periods of treatment to alleviate symptoms. In patients with limited clinical symptoms, follow-up with no treatment may be the wisest choice. There is limited clinical experience with newer agents such as linezolid or tigecycline to which mycobacteria can be susceptible *in vitro*. For all NTM species, the duration of treatment should cover at least 12 months following conversion to a negative culture.

In view of the limited effectiveness, together with the long duration and side effects of currently available drug regimens, novel and more effective antibiotics are needed, but this field is clearly no research priority. It can only be hoped that the more topical search for novel drugs for the treatment of MDR TB will yield some that are effective against NTM [72,73].

Surgery

A recent retrospective review covering a 23-year period studied early outcome of lung resection as part of a multimodality treatment program for NTM infection in 236 consecutive patients with focal persistent lung damage amenable to surgical resection [74•]. Patients were predominantly white women, few were immunocompromised and all received 2–6 months of preoperative antibiotic treatment as well as a thorough multidisciplinary preoperative assessment. Overall operative mortality was 2.6%, with a clear decline over time from 7.1% in the 1980s to 0.6% in the period between 2001 and 2006. Morbidity was high at 18.5%, of which 4.2% was due to bronchopleural fistulas. In a smaller series of 23 patients from Korea, half of whom were infected with *M. abscessus*, the rate of postoperative complications was 35%, including two bronchopleural fistulas, but all surviving patients converted to culture negative [75]. Thus, lung resection can play a role in selected patients, but there is a high risk of complications and a multidisciplinary approach executed by dedicated clinicians is needed that should include optimal medical pretreatment and preoperative evaluation.

Immunotherapy

Adjunctive cytokine treatment of NTM infections with IFN-γ or other cytokines may have a place in patients with an identified inherited cellular immune deficiency [76–79]. In patients with tuberculosis, the use of cytokines or immunomodulating drugs such as thalidomide or antagonists of TNF-α had a variable effect on outcome [80,81]. At present, the role of immunotherapy for NTM infections in other settings is completely unclear.

Preventive measures

It is generally thought that NTM infections are the result of primary infection or colonization and not of reactivation. Transmission between patients has not been documented and isolation of patients is not required. Regarding the ubiquitous nature of NTM, it is not possible to avoid exposure completely, but exposure of nonintact skin or medical equipment to tap water should be avoided as this is a known source of NTM and NTM can resist standard disinfection. The use of indoor hot tubs could be discouraged for patients with risk factors.

Topics for further study

Further studies toward a better understanding of NTM should include comparative genomics, which may shed more light on the biology of the NTM life-cycle and contribute by identification of species-specific antigens for diagnostic and epidemiological purposes, analogous to recent developments in tuberculosis and leprosy [51•,82,83]. Studies on animal models and human populations suggest that NTM infection can interfere with protective efficacy of bacillus Calmette–Guerin (BCG) vaccine [84]. A better understanding of the impact of NTM infection on vaccine-induced responses is an important topic for future investigation, especially in relation to the development of novel tuberculosis vaccines [85,86••].

Conclusion

Large gaps still remain in the knowledge regarding most aspects of NTM infections and recommendations have mostly been based on expert opinion rather than on evidence obtained from actual studies. Therefore, the diagnosis and treatment of NTM lung infections should be an individualized process that requires close communication between various disciplines and for which expert consultation should have a low threshold.

References and recommended reading

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