Pulmonary Disease Caused by Non-Tuberculous Mycobacteria

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Key Words

Europe · Mycobacterium · *Mycobacterium avium*/intracellulare complex · Non-tuberculous mycobacteria · Pulmonary disease

Abstract

Non-tuberculous mycobacteria (NTM) include more than 160 ubiquitous, environmental, acid-fast-staining bacterial species, some of which may cause disease in humans. Chronic pulmonary infection is the most common clinical manifestation. Although patients suffering from chronic lung diseases are particularly susceptible to NTM pulmonary disease, many affected patients have no apparent risk factors. Host and pathogen factors leading to NTM pulmonary disease are not well understood and preventive therapies are lacking. NTM isolation and pulmonary disease are reported to rise in frequency in Europe as well as in other parts of the world. Differentiation between contamination, infection, and disease remains challenging. Treatment of NTM pulmonary disease is arduous, lengthy, and costly. Correlations between results of in vitro antibiotic susceptibility testing and clinical treatment outcomes are only evident for the *Mycobacterium avium* complex, *M. kansasii*, and some rapidly growing mycobacteria. We describe the epidemiology of NTM pulmo-

nary disease as well as emerging NTM pathogens and their geographical distribution in non-cystic fibrosis patients in Europe. We also review recent innovations for the diagnosis of NTM pulmonary disease, summarize treatment recommendations, and identify future research priorities to improve the management of patients affected by NTM pulmonary disease.

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Introduction

Non-tuberculous mycobacteria (NTM) are ubiquitous environmental bacteria. Humans are frequently in contact with NTM, as the bacteria live in the soil as well as natural and engineered water systems [1–3]. Most NTM species are non-pathogenic, but some are able to cause human disease [4]. Pulmonary manifestations account for 80–90% of all NTM-associated diseases [4]. In contrast to pulmonary tuberculosis (TB), direct human-to-human transmission of NTM has infrequently been reported [5–7]. *Mycobacterium abscessus*, *M. avium* complex, *M. kansasii*, *M. malmoense*, and *M. xenopi* are the clinically most important species. Depending on the causative NTM species, the clinical course and treatment

response of NTM pulmonary disease (NTM-PD) can be very variable [8]. During the last three decades, an increasing incidence of pulmonary NTM isolation has been observed in Europe and several other regions worldwide [8–13]. The increase seems to be associated with the declining incidence of TB in countries with a higher socioeconomic standard [14]. Several factors may contribute to the emergence of NTM-PD, including an aging population with chronic lung diseases and advances in radiological diagnostics that have improved the identification of pulmonary abnormalities [15]. Population-based studies focusing on the demographic change in NTM-PD remain scarce.

In this review we portray NTM-PD from a European perspective, concentrating on the epidemiology and description of NTM species as emerging pulmonary pathogens in non-cystic fibrosis patients. Consensus recommendations for the management of NTM in individuals with cystic fibrosis have recently been published [16, 17]. We review recent diagnostic innovations and advances in NTM-PD case management which are not specific to Europe alone. Disseminated NTM diseases [as e.g. in people living with human immunodeficiency virus (HIV)], NTM-associated lymphadenitis in children, or other extrapulmonary manifestations of NTM infections are not the focus of this review.

Methods

A review of the available literature was accomplished by searching electronic databases including MEDLINE and PubMed, using the following key words: ‘non tuberculous mycobacteria’, ‘nontuberculous mycobacteria’, ‘*Mycobacterium avium* complex’, ‘*M. abscessus*’, ‘*M. kansasii*’, ‘*M. xenopi*’, and ‘*M. malmoense*’. In addition, reference lists from review articles and guidelines were hand-searched for relevant articles.

Epidemiology and Emerging Pathogens

The genus *Mycobacterium* was introduced in 1896, a decade after the discovery of *M. tuberculosis* as the causative pathogen of TB [18]. A total of 182 taxa (169 species and 13 subspecies) have been assigned to the genus so far [2], including several heterotypic synonyms. Excluding synonymic taxa, 165 species and 8 subspecies can be distinguished. Some taxa are phylogenetically closely related and are referred to as ‘complexes’. It is important to note that those complexes are taxonomically poorly defined, and different authors might subsume different taxa under

the respective complex denominations. However, with a certain degree of consensus, most microbiologists consider the *M. avium/intracellulare* complex (MAC) to consist of at least 10 species, i.e. *M. avium*, *M. intracellulare*, *M. arosiense*, *M. bouchodurhonense*, *M. chimaera*, *M. colombiense*, *M. marseillense*, *M. timonense*, *M. vulneris*, and *M. yongonense*, as well as 4 subspecies, i.e. *M. avium* subsp. *avium*, *M. avium* subsp. *silvaticum*, *M. avium* subsp. *hominissuis*, and *M. avium* subsp. *paratuberculosis*, which have high genetic similarity [19–22]. Thirty to 60 NTM species are repeatedly recovered from clinical specimens, while the majority of NTM have only rarely if ever been observed in clinical settings [23]. As NTM isolation or disease is not notifiable to public health authorities in Europe, epidemiological surveys are not routinely performed for NTM-PD.

In some cases, differentiation of species and subspecies may have a clinical impact. For example, it has been demonstrated that specific MAC species may have varying degrees of virulence leading to different clinical courses [24]. *M. bolletii* and *M. massiliense* were proposed as 2 new species of the *M. abscessus* complex in 2006 [25], but in 2011 it was suggested that both species be reunified under the single subspecies *M. abscessus bolletii* [26]. Both species and subspecies denominations are valid today. For clinicians, however, the identification of *M. abscessus* subsp. *massiliense* (former *M. massiliense*) is helpful. While both of the other *M. abscessus* subspecies harbour the inducible erythromycin ribosome methyltransferase 41 (*erm41*) gene, which enables them to intracellularly inactivate macrolides leading to various degrees of resistance after exposure to these antibiotics, the gene is not functional in *M. abscessus* subsp. *massiliense*. Consequently, this species is generally susceptible to macrolides [27, 28].

M. goodnae is among the *Mycobacterium* species most frequently recovered from environmental samples worldwide. Recovered from a clinical sample, it is mostly considered not to be clinically relevant, even though disease may occur. Online supplementary table S1 (see www.karger.com/doi/10.1159/000445906 for all online supplementary material) gives examples of the differential relevance of some *Mycobacterium* species if isolated from clinical specimens [29].

MAC is by far the most frequently encountered group of pathogens of NTM-PD in European countries [30–32], with *M. avium* subsp. *hominissuis* being the predominant subspecies recovered from human biospecimens [33, 34]. A recent international prevalence survey showed marked regional differences in the isolation of mycobacterial spe-

cies [30]. MAC was the species most frequently recovered in the majority of European countries, though *M. xenopi* was more commonly isolated in Hungary (49 vs. 16%) and *M. kansasii* in Poland and Slovakia (35 and 36% vs. 23 and 28%, respectively). Rapidly growing *Mycobacterium* species were more common in the UK and in Greece as compared to MAC (44 and 46% vs. 22 and 36%, respectively). In London, UK, the predominant NTM species related to disease in HIV-seronegative individuals was *M. kansasii* [35]. This is in contrast to the high prevalence of *M. abscessus* complex on the North American, Asian, and Australian continents, where it is the second most frequent NTM after MAC causing NTM-PD [36–38]. In the majority of European countries, *M. xenopi* (which represents <0.01% of isolated NTM), followed by *M. kansasii* and *M. malmoense*, is more frequently encountered in NTM-PD than is *M. abscessus* in non-cystic fibrosis patients [8, 9, 39–42].

The prevalence of NTM species has changed over time in Europe [34]. For example, during the past decades, infections with *M. xenopi* have increasingly been observed in Central, Southern, and Western Europe, while they appear to be almost absent in Northern Europe [34]. In contrast, in Northern Europe *M. malmoense* infections are emerging [30, 34, 39, 43]. It appears that specific environmental factors related to soil and water increase the risk of pulmonary NTM disease [32, 44], but they do not comprehensively explain the geographic variation of different species [45].

Incidence rates of NTM-PD in Europe range from 0.2 to 2.9/100,000 population. In Croatia, the overall estimated age-standardized annual incidence of probable NTM-PD was 0.2/100,000 population (2006–2010), with a difference between the coastal (0.4/100,000) and the continental region (0.2/100,000) [40]. In Scotland, the mean incidence rate of NTM episodes was reported to be 2.4/100,000 population, with no clear trend over the years 2000–2010 [41], while increasing NTM isolation incidence rates were observed in another study from the UK, rising from 0.9 to 2.9/100,000 population (1995–2006), and the incidence of NTM-PD rose in the English region of Leeds from 0.8 to 2.0/100,000 population (1995–1999) [9, 46]. In Denmark, the NTM-PD incidence increased from 0.6 to 1.5/100,000 population-years from 2003 to 2008 [39]. In Germany, the overall age-adjusted rates of pulmonary NTM infection-associated hospitalizations increased from 0.7 to 1.1/100,000 population [11]. Increases in the incidence of NTM-PD in different parts of Europe are likely related to demographic changes with accompanying risk factors for lung health [8].

Population Structure

Pre-existing chronic lung diseases, especially COPD, asthma, and bronchiectasis, are the main risk factors for NTM-PD in Europe [39, 47–50]. In contrast to the USA, fibrocavitary disease or consolidating infiltrates are more common than nodular bronchiectatic NTM-PD in Europe [47, 51]. A considerable proportion of patients with NTM-PD in Europe have no detected underlying lung disease or immunodeficiency [9, 39, 52].

Clinical Presentation

Clinical symptoms in patients with NTM-PD may be indistinguishable from TB or other respiratory diseases, including lung cancer [4]. Patients typically present with fatigue, fever, weight loss, asthenia, and/or anorexia [4, 47]. Respiratory symptoms may consist of cough, sputum production, haemoptysis, or dyspnoea and can be secondary to various respiratory tract or parenchymal diseases [4, 47]. A plain chest radiograph may be inadequate for evaluating radiological features. High-resolution computed tomography scans more precisely demonstrate the extent of parenchymal lung damage, particularly by visualization of nodular bronchiectatic or small cavitory lesions [4, 53].

Recent studies have suggested that the nodular bronchiectatic pattern is the predominant form of MAC-induced disease, accounting for approximately 50% of cases and ranging from 43 to 79% in Canada, the USA, Korea, and Japan. In contrast, the rates of fibrocavitary and unclassified forms in the same studies ranged from 17 to 40% and from 6 to 39%, respectively [54–57]. Few studies from Europe used the same radiopathological classifications, and comparative studies of the clinical spectrum of NTM-PD manifestations between Europe and other areas of the world are missing.

It appears that the majority of cases with MAC-PD in Europe fulfil neither the criteria for fibrocavitary nor for nodular bronchiectatic disease, and that the manifestations of the disease vary. Van Ingen et al. [47] reported that patients with MAC-PD more often had cavitory than nodular bronchiectatic disease in the Netherlands. Among patients with MAC-PD in France [47, 52] there were lower rates of fibrocavitary than of nodular bronchiectatic disease, which is similar to the results of recent surveys in the USA and South East Asia [53–58]. Coinfection with MAC and *M. abscessus* subsp. *abscessus* occurs and may be associated with new or enlarged cavities in

Fig. 1. Thoracic CT images from patients with NTM-PD. **a** A 48-year-old non-smoking woman with pectus excavatum and a 4-month history of fever and night sweats, a small cavitation in the right upper lobe (**a1**) and nodular bronchiectatic infiltrates in the right (**a2**) and left (**a3**) upper lobes. Acid-fast bacilli were detectable on sputum smears. Sputum culture repeatedly grew *M. intracellulare*. **b** A 63-year-old woman with a smoking history of >50 pack-years of cigarettes, COPD GOLD stage 3 lung disease, chronic productive cough, night sweats, and weight loss. Fibrous scarring and traction bronchiectasis can be seen in both upper lobes (**b1**, **b2**), as can centrilobular emphysema (**b2**, **b3**). Acid-fast bacilli were detectable on sputum smears, and sputum cultures grew *M. abscessus* on 2 different occasions. **c** A 57-year-old woman with a

smoking history of 45 pack-years of cigarettes and COPD GOLD stage 3 lung disease. She presented with productive cough, night sweats, and weight loss. Acid-fast bacilli were detectable on sputum smears. Sputum and bronchoalveolar lavage cultures grew *M. malmoense*. Thoracic imaging revealed pleural thickening (**c1**), dense infiltrates (**c1**), and a cavity (**c2**) in the upper right lobe, as well as peripleural nodular infiltrations in the left upper lobe. No further abnormalities were seen on thoracic CT (representative image: **c3**). Although all 3 images series are typical for NTM-PD, species identification is not possible by radiological imaging. Clinical and microbiological information is required together with imaging results to arrive at a decision for treatment.

case of additional *M. abscessus*-PD [59]. This underlines the necessity of regular microbiological and clinical follow-ups to determine which patients truly have *M. abscessus*-associated lung disease during the course of MAC-PD.

In several studies from different regions, infections with rapidly growing mycobacteria were less frequently and infections with *M. kansasii*, *M. malmoense*, or *M. xenopi* more frequently associated with fibrocavitary disease [43, 44, 54, 55, 58, 60–65] (fig. 1), demonstrating a

Table 1. Wolinsky's clues: support for the diagnosis of NTM-PD [adapted from 75]

Clue	Supporting a diagnosis of NTM-PD	Commentary
1 Quantity of growth	Moderate or heavy bacillary growth from sputum or BAL specimen	Relevant to NTM-PD, since moderate or heavy growth of mycobacteria from bronchopulmonary specimens is usually associated with disease
2 Repeated isolation of the same species	Repeated isolation of the same organisms	Single, random isolations often connote contamination; the indication for treatment of NTM-PD should not be based on one unconfirmed isolation of an NTM species
3 Site of positive specimen	Isolation of NTM from a sterile body site, e.g. lung tissue	Less relevant to NTM-PD, since the diagnosis is mostly based on BAL or sputum examinations
4 Identified NTM species	Isolation of <i>M. abscessus</i> , <i>M. kansasii</i> , and <i>M. malmoense</i> from a bronchopulmonary specimen is usually related to PD	<i>M. gordonae</i> is among the NTM species most frequently isolated from bronchopulmonary specimens but is almost always not related to NTM-PD; treatment of <i>M. gordonae</i> infection should only be initiated if other clues are present
5 Host risk factors	Risk factors for NTM-PD include bronchiectasis, COPD, and other chronic lung diseases	Cave: chronic lung disease also predisposes to colonization with NTM

BAL = Bronchoalveolar lavage.

species dependency of the different forms of NTM disease.

Hypersensitivity pneumonitis due to mycobacteria (also called 'hot tub lung') is a hypersensitivity reaction occurring in patients who are exposed to MAC antigens, e.g. from sources such as indoor hot tubs [66] or colonized showers [67, 68]. Occupational exposure to *M. immunogenum* has also been described [69, 70]. The diagnosis is established based upon clinical, radiological, and immunological criteria plus the optional presence of corresponding mycobacteria in the respiratory system. There is a continuing debate on optimal management of these patients [71]. The fact that a high rate of patients have been reported to be cured by avoidance of the antigen and/or corticosteroid therapy without antimycobacterial therapy suggests that hot tub lung is more likely a form of hypersensitivity pneumonitis than an infectious disease [72–74].

Diagnosis

In the early 1980s, Emanuel Wolinsky, a pioneer in the field of NTM diseases, proposed 5 criteria to distinguish clinically relevant NTM disease from presence of NTM without relevant clinical correlates; those were (1) medi-

um-to-heavy growth of NTM in culture, (2) repeated isolation, (3) an origin of a positive specimen from sites with little or no contact with the environment, (4) a medium-to-high probability that the isolated NTM species causes disease, and (5) the presence of risk factors predisposing to NTM disease (table 1) [75]. The American and British Thoracic Societies proposed 3 similar though simplified criteria for the establishment of the diagnosis of NTM disease: (1) compatible correlates in a radiograph or CT scan of the thorax, including bronchiectasis, infiltrates, multiple nodules, multifocal bronchial disease, and cavities, *plus* (2) compatible clinical symptoms and exclusion of other diseases with similar symptoms and radiological signs, including TB, *plus* (3) at least 2 sputum samples which are positive on culture from 2 separate expectorated samplings *or* 1 positive culture from at least 1 bronchial wash or lavage (both of which are only relevant for patients with nodular bronchiectatic disease, who do not expectorate sputum) *or* isolation of mycobacteria from a sterile site, including lung tissue obtained by transbronchial or open lung biopsy (online suppl. table S2) [4, 76]. It should be noted that these diagnostic criteria were developed with respect to disease caused by MAC, *M. kansasii*, or *M. abscessus* and may have to be further adapted to nodular bronchiectatic as compared to fibrocavitary disease.

In addition to the current diagnostic guidelines [4, 76], molecular tests for species identification and antibiotic susceptibility testing (AST) should be part of any diagnosis of NTM-PD where available [24, 77]. Smear microscopy of respiratory secretions yields positive results in approximately half of patients with probable or ascertained disease [38, 47, 78]. Acid-fast bacilli are more likely to be visible in patients fulfilling the ATS criteria; they can be regularly detected in patients presenting with cavities and are only rarely seen in patients with nodular bronchiectatic NTM-PD [58]. Smear microscopy is particularly valuable in combination with nucleic acid amplification tests (NAAT) for *M. tuberculosis*. All commercial, CE-marked (a mandatory conformity marking for certain products sold within the European Economic Area) NAAT for TB share negative predictive values higher than 99.5% in smear-positive samples under low-TB prevalence conditions [79, 80]. Consequently, NTM are identified with very high probability in cases with acid-fast bacilli observable on sputum smear microscopy and negative *M. tuberculosis* NAAT results from the same sample (online suppl. table S3).

Few CE-marked commercial NAAT allow for the direct detection of NTM DNA in respiratory secretions, including *artus*[®] Mycobac. diff. LC PCR (Qiagen, Hilden, Germany), Speed-oligo[®] Direct Mycobacterium tuberculosis (Viracell, Granada, Spain), Geno-Sen's MTC/MOTT Real Time PCR (Corbett Research, Mortlake, N.S.W., Australia), and GenoType[®] Mycobacteria Direct (Hain Lifescience, Nehren, Germany). While the *artus*[®] assay differentially detects DNA of only the *M. tuberculosis* and *M. avium* complexes on a real-time PCR platform, Speed-oligo[®] and Geno-Sen's detect *M. tuberculosis* complex and the genus *Mycobacterium* by reverse hybridization of PCR products in a dipstick format and a real-time PCR assay, respectively, and GenoType[®] Mycobacteria Direct detects the genus *Mycobacterium* plus 4 NTM species [81]. By the end of 2016, the last assay will most likely be replaced by a new generation of GenoType[®] CM, a line probe assay which will be adjusted for direct detection of up to 13 NTM species in clinical specimens (Hain Lifescience, pers. commun.). Some other assays like the CapitalBio Mycobacteria Real-Time PCR Detection Kit (CapitalBio Corporation, Beijing, China) or the REBA Myco ID (YD Diagnostics, Yongin, South Korea) are offered by Eastern Asian companies and are not yet CE marked. The REBA Myco ID assay was developed for the differentiation of 20 species in culture, but it was demonstrated also to be a useful tool for the identification of NTM in smear-positive specimens with 98%

overall concordance with culture [82]. Due to the ubiquity of NTM, all these assays suffer from the same shortcoming, i.e. that the qualitative detection of NTM DNA in the respiratory tract does not prove any causal association of NTM with disease. That is most likely why none of these assays has ever reached widespread acceptance. But following Wolinsky's postulates [75], the rapid identification of those species which are most likely associated with clinical correlates should be considered as evidence of NTM-PD. Therefore, molecular assays directly applied to clinical specimens should be able to detect the most relevant *Mycobacterium* species.

Most NTM grow under the same culture conditions as *M. tuberculosis*. While British guidelines demand the combination of a liquid medium [e.g. Middlebrook 7H9 in MGIT[®] (Becton, Dickinson and Company, Franklin Lakes, N.J., USA), BactAlert (bioMérieux, Marcy l'Etoile, France), or VersaTrek (Trek Diagnostic Systems, Independence, Ohio, USA)] with either Löwenstein-Jensen or a Middlebrook agar (7H10 or 7H11), German guidelines demand 2 solid media (Löwenstein-Jensen or Ogawa *plus* Middlebrook agar or Stonebrink or Gottsacker or Colet-sos medium) [76, 83, 84]. Whereas a benefit from the combination of a solid and a liquid medium for the sensitivity (>10% increase) of culture has been proven in previous studies, the combination of 2 solid media might be more useful for growth of *M. bovis* than of NTM [85]. The automated reader of the Bactec MGIT 960 machine might fail to detect some fastidious NTM species [86]. German guidelines claim to address this weakness by (1) visual control of every negative MGIT tube for faint growth, (2) prolonged incubation of negative cultures if smear microscopy has been positive, and (3) molecular tests for the presence of NTM in culture if the clinical signs are typical of mycobacteriosis but culture remains negative [84]. Some NTM species such as *M. genavense* or *M. haemophilum*, though practically always pathogenic when isolated from clinical specimens, only grow in culture after a prolonged incubation time or after the addition of special growth factors [87, 88]. Once growth is detected, *M. tuberculosis* should immediately be excluded by use of antigen-based rapid tests [e.g. the Capilia TB assay (TAUNS, Izunokuni, Japan) or the MGIT TBc ID Test (Becton, Dickinson and Company), PCR, or line probe assays [89]. If NTM are identified, they should be taxonomically differentiated to the level of complex, species, or subspecies depending on their clinical relevance. Most European laboratories initially use reverse hybridization line probe assays such as Genotype CM/AS (Hain Lifescience) or InnoLiPA Mycobacteria (Innogenetics,

Ghent, Belgium), which allow for the differentiation of up to 13 species in one assay. Very recently, new commercially available spectral reference libraries have been issued for the differentiation of NTM using matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry [90]. In this recent evaluation, the results correlated in 97.4% of the cases with the genetic taxon identification based on 16S rRNA gene and subsequent *rpoB* or *hsp65* sequencing. The preparation protocol of the test matrix as requested by the manufacturer is quite labour intensive. A new, much easier protocol has been validated rendering this method more feasible for routine practice [91]. While molecular tests, i.e. line probe assays, gene sequencing, and PCR assays, are all in the same range of costs depending on the on-site staff and equipment available, cost-efficiency studies of MALDI-TOF for the differentiation of mycobacteria are still pending. In virtually all European laboratories, molecular assays have displaced biochemical tests or mycolic acid chromatography for the differentiation of mycobacteria [92]. Consequently, the degree of taxonomical diversification is much higher in contemporary studies, rendering comparative observations with regard to the emergence or disappearance of certain species unreliable.

A variety of methods have been proposed for AST of NTM, including micro- and macrodilution tests, the E test, and proportional- and absolute-concentration methods [93, 94]. While the American Clinical and Laboratory Standards Institute (CLSI) provides clear guidelines as to when and how to use AST of NTM and how to interpret minimal inhibitory concentrations, British guidelines do not mention AST, the European Committee on Antimicrobial Susceptibility Testing (EUCAST) provides breakpoints only for 2 antimycobacterial drugs (delamanid and bedaquiline) which are not recommended for the treatment of NTM-PD at present, and German guidelines advise caution with reference to missing evidence for the clinical relevance of AST results from large cohorts [76, 84, 95–97]. Following CLSI standards, evidence of in vitro susceptibility and clinical outcome is satisfactory for MAC, *M. kansasii*, *M. marinum*, and *M. abscessus* subsp. *massiliense* as long as broth microdilution AST are used. E tests suffer from high intra- and inter-laboratory variability, and the proportional method on solid media or in MGIT has its breakpoints not yet defined for NTM. In view of the emergence of NTM-PD with *M. abscessus* complex, European authors recommend determination of the inducibility of the *erm41* gene by exposing *M. abscessus* isolates to clarithromycin for 14 days [93]. Yet, with the increasing clinical importance of NTM disease,

evaluation of the clinical relevance of AST results from NTM should receive greater attention by both mycobacteriology research centres and grant donors of respective clinical trials.

Management

In clinical practice, patients with severe and/or progressive NTM-PD are considered candidates for antibiotic multidrug therapy [4, 76]. The ATS/IDSA diagnostic criteria help to differentiate between patients requiring and patients not requiring treatment, but they are probably better applicable to patients with nodular bronchiectatic disease than to those with fibrocavitary disease. Particularly in the USA, where the nodular bronchiectatic form of NTM disease predominates, a substantial proportion of more than 40% of patients with NTM might require antimycobacterial treatment based on the individual judgement of the physician in charge [98]. When patchy consolidation is the only presentation on thoracic imaging, the decision to initiate treatment is less stringent.

Treatment recommendations are mostly based on expert opinions and traditions [99]. The scientific evidence base for most recommendations is narrow and is largely derived from retrospective cohort studies, drug susceptibility surveys, or animal experiments [100–102]. Only one prospective, placebo-controlled clinical trial on pulmonary infections caused by MAC is available, which compares the treatment outcome of pulmonary MAC infection with and without additional aminoglycoside in addition to the standard treatment regimen [103]. This trial is particularly interesting for European countries, since half of these patients presented with fibrocavitary disease. Clinical improvement was better in the streptomycin group with regard to microbiological findings, underlying respiratory diseases, and radiological findings, but the difference was not significant [103].

Surgery is an important option for patients with severe NTM-PD who have a poor response to medical therapy, localized cavitation, or severe nodular bronchiectatic disease; however, the complication rate can be high [54]. Two different retrospective analyses showed a persistent sputum culture conversion rate after surgery and postsurgical medical treatment in 81 and 88% of patients, respectively [54, 104]. If surgery is feasible, it should be considered for patients with persistent culture positivity after 6 months of medical treatment [104].

An important shortcoming of management of patients with NTM-PD is that standardized endpoints for treatment outcomes are lacking [105]. Outcome objectives may vary from sputum culture conversion to simple improvement of clinical and radiological signs.

The cornerstones of most anti-NTM drug regimens are macrolides, but there are exceptions such as *M. kansasii*-PD. Table 2 lists the drugs used in treatment of NTM-PD. Suggested treatment regimens are shown in table 3. Clarithromycin and amikacin are the only drugs with a shown correlation between in vitro drug susceptibility and in vivo efficacy in MAC-PD [106–109]. Clarithromycin is usually combined with some rifamycin and with ethambutol [4]. No data are available that suggest any superiority of either clarithromycin or azithromycin in the treatment of pulmonary MAC disease [110]. For MAC-PD, far more data are available for clarithromycin than for azithromycin, but in clinical practice azithromycin is frequently used due to its preferable dosing schedules and better gastrointestinal tolerance. Azithromycin also is considered less prone to interaction with rifamycins than is clarithromycin [111].

Induction of cytochrome P450 by rifampicin may lower macrolide blood levels below inhibitory concentrations [111]. It is not well understood, however, why patients with NTM-PD might still respond clinically [112, 113]. Whether therapeutic drug monitoring improves treatment outcomes in MAC-PD is currently under investigation [113, 114].

In HIV-seropositive individuals, rifabutin is often preferred over rifampicin because of less frequent drug-drug interactions with antiretroviral therapies. In case of treatment with rifabutin, azithromycin should be the macrolide of choice [115, 116].

In nodular bronchiectatic MAC-PD, intermittent (3-times-weekly) therapy with a macrolide, a rifamycin, and ethambutol has been suggested as a reasonable initial treatment regimen [117, 118]. This treatment is common in the USA but less popular in Europe. In case of MAC in vitro drug resistance or adverse effects, the alternative drugs are amikacin, streptomycin [119], or, with less clinical evidence, clofazimine [120, 121]. Patients with severe MAC-PD or fibrocavitary disease in particular might profit from aminoglycoside treatment in addition to the standard regimen in the intensive treatment phase [103, 122].

Results from recent trials support inhalation of aerosolized amikacin [123], especially liposomal amikacin [124]. In vitro synergistic activity against NTM was reported for clofazimine and amikacin [125]. The impact of

linezolid on treatment outcome in NTM-PD remains unclear [126, 127]. A high frequency of adverse drug events in long-term therapy restricts the use of linezolid as part of a treatment regimen for patients with severe disease and distinct patterns of antibiotic resistance or intolerance to other drugs [128].

Rifampicin is the backbone of treatment for *M. kansasii*-PD (table 3) [129]. The preferred combination partners for multidrug regimens are ethambutol plus either isoniazid or a macrolide [130]. Some authors have proposed to shorten the treatment period for *M. kansasii*-PD to 12 [130] or even 9 months [76, 131] compared to the 12 months after sputum culture conversion recommended by the ATS/IDSA [4]. Patients with rifampicin-resistant *M. kansasii*-PD might require a 3- to 4-drug regimen based on in vitro susceptibilities, including isoniazid, moxifloxacin, ethambutol plus a macrolide or aminoglycoside. Some experts suggest extending the duration of treatment to 18 months in this situation.

The results of various treatment regimen evaluations for *M. malmoense*-PD were inconclusive in 2 trials conducted by the British Thoracic Society [132, 133]. The current recommendation for the treatment of *M. malmoense*-PD is a combination therapy including a rifamycin, ethambutol, and a macrolide, with moxifloxacin being an alternative to the macrolide in case of adverse events or failing therapeutic response (table 3) [119].

In the absence of sufficient data on clinical outcomes of *M. xenopi* infections upon antimycobacterial therapy, recommendations must be formulated with caution (table 3). A combination therapy with a rifamycin and ethambutol together with a macrolide (possibly also adding moxifloxacin) for 12 months beyond the date of culture conversion has been proposed [119]. An ongoing randomized clinical trial in France compares the efficacy and tolerance of moxifloxacin- and clarithromycin-containing regimens.

While *M. simiae* infection relatively often leads to PD in some parts of the USA, this is much less commonly the case in Europe. As with many other mycobacteria causing NTM-PD, the optimal treatment regimen for *M. simiae*-PD is not known. In vitro DST reveals an antibiotic drug resistance against many different compounds. The choice of drugs for treatment should be based on DST results. Combination drug regimens often include amikacin in association with 2–3 other drugs [134]. A combination of amikacin and clofazimine has synergy in vitro against *M. simiae* isolates, suggesting the use of these 2 drugs as part of a regimen [135]. Trimethoprim/sulfamethoxazole is sometimes part of a treatment regimen in *M. simiae*-PD.

Table 2. Dosages and common adverse events of drugs used for the treatment of NTM-PD

Substance Abbreviation Drug class	Route	Adult dosage	Child dosage ^a	GFR <10%	Hepatic impairment	Most common adverse events	Commentary
Amikacin Amik <i>Aminoglycosides</i>	i.m., i.v., inhal.	10–15 mg/kg o.d. 5–7 days per week (<i>M. abscessus</i>) 25 mg/kg o.d. 3 times per week (max. daily dose 1 g) (MAC/ <i>M. abscessus</i>) for 2–4 months or until culture conversion	15 mg/kg o.d. 5–7 days per week for 2–4 months or until culture conversion	Not recommended in severe renal impairment HD: 12–15 mg/kg/dose after dialysis 2–3 times weekly	No adjustment, probably safe	Electrolyte abnormalities, nephrotoxicity, ototoxicity	Standard drug for <i>M. abscessus</i> subsp. and <i>M. simiae</i> -PD treatment; should also be considered for treatment intensification for MAC-PD, consider nebulized amikacin as alternative treatment for MAC and <i>M. abscessus</i> subsp.-PD; patients should have a central venous catheter with subcutaneous reservoir implanted for i.v. therapy; monitor renal function, electrolytes, and audiology exam
Azithromycin Azt <i>Macrolides</i>	p.o., i.v.	250–500 mg o.d. or 500 mg o.d. 3 times a week	10–16 years: 12 mg/kg/day (max. 500 mg)	Use with caution in patients with GFR <40 ml/min	Use with caution	GI disturbances (diarrhoea, nausea), pruritus, skin rash, vaginitis i.v.: local inflammation, pain at injection site	Standard drug for MAC, <i>M. kansasii</i> , <i>M. malmoense</i> , and <i>M. xenopi</i> -PD treatment; in the absence of inducible macrolide resistance: standard drug for <i>M. abscessus</i> subsp., possible drug for <i>M. simiae</i> , alternative drug for <i>M. kansasii</i> ; monitor QTc interval
Cefoxitin Cef <i>Cephalosporins</i>	i.v.	2–4 g t.i.d. (max. 12 g/day)	>3 months: 40 mg/kg q.i.d. (max. 12 g/day)	GFR 5–9 ml/min: 0.5–1 g every 12–24 h GFR <5 ml/min: 0.5–1 g every 24–48 h HD: LD 1–2 g after each HD; maintenance dose as noted above based on GFR	No adjustment	GI disturbances (diarrhoea)	Intensive-phase treatment option for <i>M. abscessus</i> subsp.-PD; patients should have a vena cava superior catheter with subcutaneous reservoir implanted for daily i.v. therapy
Ciprofloxacin Cfx <i>Fluoroquinolones</i>	p.o., i.v.	400–750 mg b.i.d.	10–20 mg/kg b.i.d., max. 750 mg b.i.d. (limited data on children 1–5 years of age)	50% of usual dose b.i.d. HD: 250–500 mg o.d. after HD	Use with caution in severe impairment	Dizziness, insomnia, nervousness, somnolence, headache (i.v.), restlessness (i.v.; ++ in children), skin rash, GI disturbances, increased serum AST, ALT, injection site reactions (i.v.; children more prone to adverse effects)	Possible drug for continuation phase of <i>M. abscessus</i> subsp.-PD treatment; QTc interval prolongation may be potentiated with other drugs; close monitoring recommended when used with other drugs that prolong the QTc interval
Clarithromycin Clr <i>Macrolides</i>	p.o., i.v.	500 mg b.i.d.	7.5 mg/kg b.i.d. (max. 500 mg)	500 mg o.d.	No adjustment, probably safe	Disturbance/loss of smell and/or taste, headache, nausea and vomiting, tinnitus	Standard drug for MAC, <i>M. kansasii</i> , <i>M. malmoense</i> , and <i>M. xenopi</i> -PD treatment; in the absence of inducible macrolide resistance: standard drug for <i>M. abscessus</i> subsp., possible drug for <i>M. simiae</i> , alternative drug for <i>M. kansasii</i> ; monitor QTc interval
Clofazimine Cfz <i>Iminophenazines</i>	p.o.	100–200 mg o.d.	1 mg/kg o.d. (limited data)	No adjustment	Use with caution, 100 mg o.d. or less in severe liver diseases	GI disturbances, skin discoloration	Possible drug for continuation phase of <i>M. abscessus</i> subsp.-PD treatment; alternative drug for MAC, possible drug for <i>M. simiae</i> therapy; in case of severe skin discoloration, dose reduction to 5 times a week; monitor QTc interval
Doxycycline Dox <i>Tetracyclines</i>	p.o., i.v.	200 mg o.d. LD, then 100 mg o.d. or b.i.d.	≥8 years: 4 mg/kg o.d. LD, then 2 mg/kg o.d.	No adjustment	Use with caution in severe impairment	GI disturbances, phototoxicity	Possible drug for continuation phase of <i>M. abscessus</i> subsp.-PD therapy (avoid concomitant application with tetracycline)
Ethambutol Emb <i>1,2-amino alcohols</i>	p.o., i.v.	15–25 mg/kg o.d.	15 mg/kg o.d.	15 mg/kg 3 times weekly	No adjustment, probably safe	Optic neuropathy	Standard drug for MAC, <i>M. kansasii</i> , <i>M. malmoense</i> , and <i>M. xenopi</i> -PD treatment; visual disturbance is often rapid in onset and may begin with loss of red-green discrimination; monitor visual acuity

Table 2 (continued)

Substance Abbreviation Drug class	Route	Adult dosage	Child dosage ^a	GFR <10%	Hepatic impairment	Most common adverse events	Commentary
Imipenem/ cilastatin Imp Carbapenems	i.v.	As imipenem component: 1,000 mg b.i.d.-t.i.d.	20 mg/kg t.i.d. (40 mg/kg t.i.d. in severe infections)	500 mg b.i.d. HD; drug administration after dialysis	Rarely associated with elevated transaminases, probably safe	Exanthema, GI disturbances, hypersensitivity, leucopenia, thrombocytopenia	Intensive-phase treatment option for <i>M. abscessus</i> subsp.-PD; patients should have a vena cava superior catheter with subcutaneous reservoir implanted for daily i.v. therapy; possibly similar effectivity to meropenem
Isoniazid Inh Pyridine carboxylic acids	p.o., i.v.	5 mg/kg o.d.	<30 kg: 7–15 mg/kg o.d. ≥30 kg: 4–6 mg/kg o.d. (max. 300 mg/ day)	No adjustment	Use with caution	Hepatotoxicity (predominantly parenchymatic hepatitis with ALT and APT elevation), neurotoxicity, polyneuropathy	Standard drug for <i>M. kansasii</i> -PD therapy; monitor for hepatotoxicity; give with pyridoxine
Linezolid Lzd Oxazolidinones	p.o., i.v.	600 mg o.d. or b.i.d.	10 mg/kg t.i.d.	No adjustment	Rarely associated with elevated transaminases	Anaemia, neuropathy, thrombocytopenia	Possible drug for continuation phase of <i>M. abscessus</i> subsp.-PD therapy; possible drug for <i>M. simiae</i> -PD treatment; severe adverse events are frequent in long-term therapy; close monitoring of blood count and awareness of peripheral neuropathy is mandatory; give with pyridoxine
Moxifloxacin Mfx Fluoroquinolones	p.o., i.v.	400 mg o.d.	7.5–10 mg/kg o.d.	No adjustment	Rarely associated with hepatotoxicity, no adjustment in mild-to-moderate hepatic impairment	Headache, dizziness, GI disturbances, insomnia	Alternative drug for MAC, <i>M. kansasii</i> , <i>M. malmoense</i> , and <i>M. xenopi</i> -PD therapy; possible drug for <i>M. simiae</i> treatment; QTc interval prolongation may be potentiated with other drugs; close monitoring recommended when used with other drugs that prolong the QTc interval
Prothionamide Pto Thioamides	p.o.	10–15 mg/kg (usually 750 mg o.d. or 2–3 divided doses)	10–15 mg/kg (usually in 2–3 divided doses) (max. daily dose 1 g)	No adjustment	Use with caution	Depression, GI disturbances, hepatotoxicity, hypothyroidism	In vitro DST suggests that slow-growing NTM as well as <i>M. fortuitum</i> and related species are susceptible to prothionamide; however, clinical data are not available
Rifabutin Rbt Rifamycins	p.o.	5 mg/kg o.d. (up to 450 mg o.d. sometimes used)	5 mg/kg o.d.	No adjustment	Use with caution	Anaemia, discolouration of body fluids, hepatotoxicity (predominantly cholestatic hepatitis with γGT and AP elevation), lymphopenia, rash, thrombocytopenia	Alternative drug for MAC, <i>M. kansasii</i> , <i>M. malmoense</i> , and <i>M. xenopi</i> -PD therapy; monitor for hepatotoxicity; dose adjustments may be necessary when dosing with interacting drugs (e.g. ART)
Rifampicin Rif Rifamycins	p.o., i.v.	10 mg/kg o.d. (max. 600 mg)	10–20 mg/kg o.d.	No adjustment	Use with caution	Anaemia, discolouration of body fluids, hepatotoxicity (predominantly cholestatic hepatitis with γGT and AP elevation), lymphopenia, rash, thrombocytopenia	Standard drug for MAC, <i>M. kansasii</i> , <i>M. malmoense</i> , and <i>M. xenopi</i> -PD therapy; monitor for hepatotoxicity; dose adjustments may be necessary when dosing with interacting drugs (e.g. ART)
Streptomycin Sm Aminoglycosides	i.m., i.v.	15 mg/kg o.d. 5–7 days per week (<i>M. abscessus</i>) 15 mg/kg o.d. 3 times per week (MAC, <i>M. abscessus</i>) (max. daily dose 1 g)	15 mg/kg o.d. 5–7 days per week (max. daily dose 1 g)	Not recommended in severe renal impairment HD: 12–15 mg/kg/dose after dialysis 2–3 times weekly	No adjustment, probably safe	Electrolyte abnormalities, nephrotoxicity ototoxicity	Treatment intensification for MAC-PD; patients could have a central venous catheter with subcutaneous reservoir implanted for i.v. therapy; monitor renal function, electrolytes, and audiology exam

Table 2 (continued)

Substance Abbreviation Drug class	Route	Adult dosage	Child dosage ^a	GFR <10%	Hepatic impairment	Most common adverse events	Commentary
Tigecycline	i.v.	Initially, 100 mg single dose; maintenance dose: 50 mg b.i.d.	8–11 years: 1.2 mg/kg b.i.d., max. dose: 50 mg ≥12 years: 50 mg every 12 h	No dosage adjustment necessary	Mild-to-moderate hepatic impairment (Child-Pugh class A or B): no dosage adjustment necessary Severe hepatic impairment (Child-Pugh class C): initially 100 mg single dose, maintenance 25 mg every 12 h	Use antiemetic premedication, as there are often GI disturbances (++) nausea, vomiting; localized phlebitis, headache, dizziness, skin rash, hyponatraemia, increased amylase, anaemia, hypoproteinaemia, increased serum transaminase and cholestase parameters; infection, abscess, weakness, increased blood urea nitrogen	Intensive-phase treatment option for <i>M. abscessus</i> subsp.-PD; patients should have a vena cava superior catheter with subcutaneous reservoir implanted for daily i.v. therapy
Trimethoprim/sulfamethoxazole Timp/Smz Dihydrofolate reductase inhibitors/sulfonamides	p.o.	960 (800 + 160) mg b.i.d.	≥6 years: 480 (400 + 80) mg b.i.d.	GFR 15–30 ml/min: half of the dose GFR <15 ml/min: contraindicated	Use with caution in severe impairment	Allergic reactions (exanthema, pruritus, purpura, photodermatitis, erythema nodosum, very rarely SJS, TEN), GI disturbances, thrombo-/leucopenia in long-term use	Possible drug for <i>M. simiae</i> -PD therapy; optimal dosing not known; monitor blood count in long-term use

o.d. = Once daily; b.i.d. = 2 times a day; t.i.d. = 3 times a day; q.i.d. = 4 times a day; LD = loading dose; GFR = glomerular filtration rate; γGT = γ-glutamyltransferase; HD = haemodialysis; GI = gastrointestinal; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis; ART = antiretroviral therapy. * There are limited data available on the dosing of antibiotics in children. Daily dosages should not exceed the maximum dose recommended for adults.

In *M. abscessus*-PD, sustained culture conversion and clinical improvement can often not be achieved with any presently available drugs independently of the chosen regimen [136]. Symptom control and microbial suppression may be the best achievable goal of therapy.

In vitro drug resistance to multiple antimycobacterial antibiotics is common in *M. abscessus* [136]. The mechanisms leading to intrinsic or acquired resistance are particularly complex and not necessarily induced by previous exposure to antibiotics [137, 138]. Because of its variability in susceptibility and its potential to induce macrolide resistance [27], AST is generally recommended. Still, the in vitro-in vivo correlation between drug resistance testing and clinical outcome in *M. abscessus*-PD is poor [139], and the role of AST in achieving successful treatment remains uncertain [119, 140, 141]. Several studies applying molecular tools to distinguish *M. abscessus* subsp. *abscessus* from *M. abscessus* subsp. *massiliense* have shown a better outcome for patients infected with *M. abscessus* subsp. *massiliense* treated with a macrolide [44, 141–143]. Measuring inducible macrolide resistance has become a standard laboratory test, based on either *erm41* gene sequence analysis or phenotypic testing with prolonged incubation. Currently, there is no consensus on *M. abscessus* complex treatment, except for the use of a macrolide in the absence of resistance, e.g. due to the *erm41* gene. A possible recommendation for the treatment of *M. abscessus*-PD consists of two phases [4, 119, 144]. The first one is the intensive phase, with at least two injectable agents (amikacin plus cefoxitin, imipenem, or tigecycline) plus three orally administered drugs (e.g. ciprofloxacin, doxycycline, and linezolid). Following culture conversion, treatment is usually continued with the orally available drugs only. Clofazimine should be considered as an alternative drug in the treatment of *M. abscessus* complex disease [144]. In vitro studies have shown a promising synergistic effect when used concomitantly with amikacin [125, 145]. In a small case series, bedaquiline had a non-sustained treatment effect against *M. abscessus* [146]. If the results of prolonged DST suggest a susceptibility of *M. abscessus* species to macrolides, one of the macrolides, preferably azithromycin, should always be part of the drug regimen. Clarithromycin might induce macrolide resistance in the *M. abscessus* complex more frequently than azithromycin [147], but this finding is not consistent [148]. The choice of companion drugs that will protect the macrolide from resistance is controversial. If feasible, surgery should always be considered for *M. abscessus*-PD [140].

Table 3. Drug treatment of NTM-PD [adapted from 119, 144]

	Recommended regimen	Alternative drugs
<i>M. abscessus</i> subsp. <i>abscessus</i> and subsp. <i>bolletii</i> (consider inducible macrolide resistance)	2 drugs i.v. (IP only): amikacin <i>plus</i> either cefoxitin <i>or</i> imipenem <i>or</i> tigecycline <i>plus</i> 3 drugs p.o. (IP and CP) of the following: macrolide ¹ (in case of absence of inducible macrolide resistance), clofazimine, linezolid, ciprofloxacin, doxycycline (not together with tigecycline)	Consider nebulized (liposomal) amikacin (IP and CP)
<i>M. abscessus</i> subsp. <i>bolletii</i> , former subsp. <i>massiliense</i> (usually no inducible macrolide susceptibility)	2 drugs i.v. (IP only): amikacin <i>plus</i> either cefoxitin <i>or</i> imipenem <i>or</i> tigecycline <i>plus</i> 3 drugs p.o. (IP and CP): macrolide ¹ (in case of absence of inducible macrolide resistance) <i>plus</i> 2 of the following: clofazimine, linezolid, ciprofloxacin, doxycycline (not together with tigecycline)	Consider nebulized (liposomal) amikacin (IP and CP)
<i>M. avium</i> complex	3 drugs p.o.: macrolide ¹ , rifamycin ² , ethambutol	Amikacin (IP), consider nebulized application; streptomycin (IP); moxifloxacin; clofazimine
<i>M. kansasii</i>	3 drugs p.o.: rifampicin, ethambutol, isoniazid <i>or</i> a macrolide ¹	Moxifloxacin
<i>M. malmoense</i>	3 drugs p.o.: macrolide ¹ , rifamycin ² , ethambutol	Moxifloxacin
<i>M. simiae</i>	Amikacin (IP only): <i>plus</i> 2–3 drugs p.o. (IP and CP) of the following: clofazimine, macrolide ¹ , moxifloxacin, linezolid, trimethoprim/sulfamethoxazole	Effective drug regimen for <i>M. simiae</i> is unclear; in vitro DST shows generally extensive drug-resistance
<i>M. xenopi</i>	3 drugs p.o.: macrolide ¹ , rifamycin ² , ethambutol	Moxifloxacin

The choice of drugs for a treatment regimen should be based on the results of DST, if possible. IP = Intensive phase; CP = continuation phase. ¹ Macrolide: azithromycin or clarithromycin. ² Rifamycin: rifampicin or rifabutin; if rifabutin is used, prefer azithromycin over clarithromycin.

Treatment durations:

- Recommendations for the duration of treatment have a low level of evidence
- IP, usually in *M. abscessus* therapy, occasionally in severe MAC or *M. simiae*-PD: 1–3 months or until sputum/bronchoalveolar lavage culture conversion; CP, with orally available drugs only: 12 months beyond the time of sputum/bronchoalveolar lavage culture conversion
- For MAC-PD: in case of mild nodular bronchiectatic disease, an intermittent treatment 3 times per week with rifampicin, ethambutol, and a macrolide has been suggested
- General recommendation: if eradication of the NTM causing PD is not achieved by 6 months of therapy despite an appropriate choice of drugs, consider the option of surgery; if surgery is not possible, the goal of treatment, including the decision on the duration of treatment should focus on symptom control; short-course pulse treatments including i.v. therapy or continuous oral therapy/inhalation therapy to suppress mycobacterial growth may be appropriate treatment options

A treatment duration of 12 months after sputum culture conversion is generally recommended for most NTM-PD [4], but it is very well possible that any standardized treatment recommendation is inadequate in the majority of cases [149]. Evidence-based individualization of treatment duration is not available, mainly due to the lack of biomarkers which would indicate treatment success and could guide physicians to discontinue antibiotics at a more appropriate time. It was shown in multidrug-

and extensively drug-resistant TB that shortened therapy durations of 9–12 months can, under certain circumstances, be as effective as the recommended 20-month treatment duration [150], and this could apply to diseases caused by other mycobacteria as well. Due to the complexity of the therapy of patients with NTM infections, treatment should be coordinated by physicians with sufficient experience and in constant consultation with respective reference centres.

Table 4. Suggested research priorities to improve the management of NTM-PD

Priority measures
1. Development of interventions to prevent the development of NTM-PD in risk groups
2. Establishment of the relationship between in vitro DST and the in vivo efficacy of drugs used for the treatment of NTM-PD
3. Development of novel drugs for the treatment of NTM-PD
4. Development of adjunctive immunotherapies to improve treatment outcomes in NTM-PD
5. Identification of biomarkers to guide the decision on when to initiate NTM-PD therapy
6. Evaluation of synergistic/antagonistic effects of drugs used for combination antimycobacterial therapy
7. Identification of biomarkers that allow the prediction of treatment failure or success early in the course of antimycobacterial therapy
8. Ascertaining the value of therapeutic drug monitoring to optimize treatment outcomes in NTM-PD
9. Identification of biomarkers that allow individualization of the duration of treatment for NTM-PD
10. Finding an international consensus definition of treatment outcomes in NTM-PD

Conclusions and Outlook

NTM-PD belongs to the group of orphan diseases. Still, the demographic changes in Western societies might probably lead to a further increase in the incidence of NTM-PD in Europe and other industrialized regions. At present, clinical decisions affecting patients with NTM-PD heavily rely on expert opinion rather than on good clinical evidence. Care for affected patients can only be improved if research priorities (table 4) are recognized and addressed and better evidence for the management of NTM-PD is generated by basic and clinical research.

Evidence for the clinical management of patients with NTM-PD will require the collaboration of many colleagues from different clinical centres to generate reliable data together. Existing European networks such as the NTM-NET, a branch of the Tuberculosis Network European Trials group (TBNET), the ESCMYC [European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Study Group on Mycobacteria], and the European Respiratory Society (ERS) Assembly for Respiratory Infections provide platforms for conducting such international multicentre studies, hopefully leading to a better understanding and management to improve the care for patients with NTM-PDs in the future.

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